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Tesi di Laurea:

A Prospective Study for Liver Transplantation in septuagenarian Patients

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Index

Abstract - English

Background

Although European and international guidelines do not specifically contraindicate Liver Transplantation (LT) in elderly patients, emphasizing the importance of the clinical picture and physiological age over chronological age, many Transplant Centers and Institutions worldwide have established a maximum age limit (ranging from 65 to 70 years). The literature lacks specific selection criteria for elderly patients; therefore, this study proposes an evaluation model for liver transplant candidates over 70.

Materials and Methods

In 2019, we introduced a protocol to assess liver transplant suitability for candidates aged 70-75 with cirrhosis or HCC. The protocol includes liver transplants only from deceased donors and is limited to patients undergoing their first liver transplant for chronic liver disease or hepatic neoplasia. Considering a geriatric assessment (in terms of the Multidimensional Prognostic Index, MPI) and accounting for both hepato-related and non-hepato-related risk factors, patients with an MPI score of 2 or less were deemed eligible for transplantation.

The primary endpoint evaluated was the one-year overall survival (OS). The secondary endpoints included: the one-year survival of the transplanted graft, post-operative complications (expressed as the Comprehensive Complication Index, CCI), and duration of hospital and ICU stays. The minimum planned sample size was 18.

The prospective cohort was then compared with a retrospective cohort of patients aged over 70 who had previously undergone their first liver transplantation at our Center. The two populations were assessed and found to be comparable. Subsequently, we retrospectively compared the merged cohorts of patients over 70 with the general population, those under 70 years old, who underwent liver transplantation in our Center for chronic liver disease or hepatic neoplasia from 2016 to 2022.

ClinicalTrials.gov ID: NCT06382740

Results

In this prospective study, among the 31 patients over 70 enrolled from 2019 to 2024, 71% were male, and 81% suffered from Hepatocellular Carcinoma (HCC). The median Model for End-Stage Liver Disease (MELD) score was 16.0 (IQR: 11.0, 21.0). The one-year overall survival (OS) rate was 88.7%, thus achieving the primary endpoint. The one-year graft survival rate was 84.2%, and the median Comprehensive Complication Index (CCI) for complications was 20.5 (IQR: 8.7, 42.0). The median hospital stay was 16 days (IQR: 11, 33.5), while the median stay in the intensive care unit (ICU) was 5 days (IQR: 3, 9).

The comparison of 'In protocol' and 'Out protocol' patients over 70 years old shows statistically significant differences regarding the waiting list times. The 'In protocol' patients had a shorter median time (5.1 vs. 21.3 months) and a slightly higher median age (71.8 vs. 70.6 years). Follow-up duration was shorter for 'In protocol' patients (13.0 vs. 31.2 months). The only significant postoperative differences were a lower median Comprehensive Complication Index (CCI) for 'In protocol' patients (20.5 vs. 26.9) and a longer ICU stay (5.0 vs. 4.0 days).

Comparing the global ‘Over 70’ cohort, which included both ‘In protocol’ and ‘Out protocol’ populations, with the ‘Under 70’ group, no difference in terms of primary and secondary endpoints was observed, except for the CCI, which revealed a statistically significant lower median value for the ‘Over 70’ patients, with a median of 20.9 (IQR: 8.7, 42.6), compared to 29.6 (IQR: 20.9, 49.3) for their younger counterparts.

Conclusions

Liver transplantation is a viable therapeutic option for elderly patients, and age should not be considered an absolute contraindication. The increasing life expectancy and the expanding donor pool necessitate a shift towards considering biological rather than chronological age for transplantation

eligibility. This prospective study proposes a pre-listing evaluation model for transplantation based on a scoring scale defined by geriatric assessment as well as liver-related and non-liver-related risk factors.

Abstract - Italiano

Background

Nonostante le linee guida europee e internazionali non controindichino specificamente il Trapianto di Fegato (LT) nei pazienti anziani, enfatizzando l'importanza del quadro clinico e dell'età fisiologica rispetto all'età anagrafica, molti Centri di Trapianto e Istituzioni in tutto il mondo hanno stabilito un limite di età massimo (che varia dai 65 ai 70 anni). In letteratura non vi sono criteri di selezione specifici per i pazienti anziani; pertanto, questo studio propone un modello di valutazione per i candidati al trapianto di fegato ultrasettantenni.

Materiali e Metodi

Nel 2019, abbiamo introdotto un protocollo per valutare l'idoneità al trapianto di fegato per candidati di età compresa tra 70 e 75 anni con cirrosi o HCC. Il protocollo include trapianti di fegato solo da donatori deceduti ed è limitato ai pazienti che si sottopongono al loro primo trapianto di fegato per malattia epatica cronica o neoplasia epatica. Considerando una valutazione geriatrica (in termini di Multidimensional Prognostic Index, MPI) e tenendo conto sia dei fattori di rischio epato-correlati che non epato-correlati, i pazienti con un punteggio MPI di 2 o meno sono stati ritenuti idonei per il trapianto.

Il principale endpoint valutato è stato la sopravvivenza complessiva (OS) ad un anno. Gli endpoint secondari includevano: la sopravvivenza ad un anno del graft trapiantato, le complicanze post-operatorie (Comprehensive Complication Index, CCI), e la durata dei soggiorni ospedalieri e in terapia intensiva (ICU). La dimensione campionaria minima è stata stimata a 18.

La coorte prospettica è stata quindi confrontata con una coorte retrospettiva di pazienti di età superiore ai 70 anni che avevano effettuato il loro primo trapianto di fegato presso il nostro Centro. Le due popolazioni sono state valutate come comparabili. Successivamente, quindi, abbiamo retrospettivamente confrontato la coorte di pazienti ultrasettantenni con la

popolazione generale di pazienti, sotto i 70 anni, che presso il nostro Centro hanno subito un trapianto di fegato per malattia epatica cronica o neoplasia epatica dal 2016 al 2022.
ID ClinicalTrials.gov: NCT06382740

Risultati

In questo studio prospettico, tra i 31 pazienti di età superiore ai 70 anni arruolati dal 2019 al 2024, il 71% erano maschi, e l'81% soffriva di Carcinoma Epatocellulare (HCC). Il punteggio mediano Model for End-Stage Liver Disease (MELD) era 16 (IQR: 11, 21). Il tasso di sopravvivenza complessiva (OS) ad un anno si è dimostrato essere dell'88.7%, raggiungendo così l'endpoint primario. Il tasso di sopravvivenza del graft ad un anno era dell'84.2%, e il Comprehensive Complication Index (CCI) mediano era 20.5 (IQR: 8.7, 42.0). La degenza ospedaliera mediana era di 16 giorni (IQR: 11, 33.5), mentre la permanenza mediana in terapia intensiva (ICU) era di 5 giorni (IQR: 3, 9).
Il confronto tra i pazienti 'In protocol e 'Out protocol' ultrasettantenni mostra alcune differenze statisticamente significative rispetto ai tempi di attesa. I pazienti 'In protocol' avevano un tempo mediano inferiore (5.1 vs. 21.3 mesi). La durata del follow-up era più breve per i pazienti 'In protocol' (13.0 vs. 31.2 mesi). L'età mediana si è dimostrata leggermente superiore nel gruppo 'In protocol' (71.8 vs. 70.6 anni). Le uniche differenze postoperatorie significative erano un CCI mediano inferiore per i pazienti 'In protocol' (20.5 vs. 26.9) e un soggiorno più lungo in ICU (5 vs. 4 giorni).
Confrontando la coorte globale 'Over 70', che includeva sia le popolazioni 'In protocol' che 'Out protocol', con il gruppo 'Under 70', non è stata osservata alcuna differenza in termini di endpoint primari e secondari, eccetto per il CCI, che ha rivelato un valore mediano significativamente inferiore per i pazienti 'Over 70', con una mediana di 20.9 (IQR: 8.7, 42.6), rispetto a 29.6 (IQR: 20.9, 49.3) per i loro omologhi più giovani.

Conclusioni

Il trapianto di fegato rappresenta una valida opzione terapeutica per i pazienti anziani e l'età non deve essere considerata una controindicazione assoluta. Con l'incremento dell'aspettativa di vita e il numero crescente di donatori, diventa fondamentale valutare l'età biologica rispetto a quella anagrafica nel determinare l'idoneità al trapianto. Questo studio prospettico propone un modello di valutazione pre-listing per i trapianti, che si basa su una scala di punteggio definita dalla valutazione geriatrica e da fattori di rischio correlati e non correlati al fegato.

1. Introduction

Liver transplantation is a surgical procedure that involves, in its various execution possibilities, the retrieval of an organ (graft), whether whole or partial, from a "donor" patient and its subsequent implantation in a "recipient" patient, to treat a primary or, in some cases, secondary liver disease.

The types of transplantation, indications, post-operative therapy, and surgical technique have seen a constant evolution throughout the 20th century, thanks to progress both in technological and pharmacological fields.

1.1. Historical background

The origins of liver transplantation date back to the 1950s of the 20th century, particularly to the experiments of C. Stuart Welch, who performed the first auxiliary liver transplant in a dog in Albany in 1955 (1), and of Jack Cannon, who described the first orthotopic liver transplant performed on a dog in 1956 at the University of California, Los Angeles (UCLA) (2). It is also worth mentioning the contribution of Vittorio Staudacher (1913–2005), Professor of General Surgery and head of Emergency Surgery at the Ospedale Maggiore in Milan, to whom, according to a 2012 study, the first description of orthotopic liver transplant in a dog could be attributed, although it was little recognized by subsequent historiography, dated 1952 (3).

These early experiments paved the way for Thomas Starzl to perform the first orthotopic liver transplant in humans in 1963 in Denver, about 10 years later (4).

However, the technical ability to perform the transplant was not associated with favorable outcomes: following the deaths of the first 7 patients who underwent transplantation (2 intraoperative deaths, 5 within 23 days of transplantation), the pioneers themselves decided to discontinue the liver transplant program (5).

It would be necessary to wait until the end of what Starzl called "the frustrating period between 1969 and 1979" to achieve the first tangible results, mainly due to the introduction of cyclosporine, discovered in 1976 by Jean-Francois Borel and first adopted by Roy Calne in the field of transplantation (6). The subsequent momentum was significant: given the results obtained, since 1983 liver transplantation was no longer defined as an "experimental procedure" but as "clinical practice" (7).

The following years were characterized by the progressive evolution of immunosuppressive therapy and the optimization of intra- and postoperative patient management, resulting in improved medium-to-long-term outcomes. This improvement became so evident as to shift the focus of the discussion: the main issues are no longer exclusively represented by clinical management but by the management of the limited resources of grafts and the progressive expansion of transplant indications.

1.2. Liver transplant indications

Liver transplantation historically finds indications in end-stage liver diseases, particularly in conditions where the patient's life expectancy in the absence of transplantation is less than one year, or in conditions where transplantation can provide a drastic improvement in quality of life. Over the years, the indications, as described below, have been progressively expanded, mainly in the oncological field. In the early series historically highlighted in the literature, the indication for liver transplantation was very heterogeneous, including terminal liver cirrhosis, congenital diseases, and primary or secondary liver neoplasms. The common element was represented by poor prognosis, in the absence of further possible treatments (8).

The main indication for liver transplantation today remains liver cirrhosis, with various etiologies depending on the geographical areas considered: in Europe, the 2018 report of the European Liver Transplant Registry revealed that cirrhosis, regardless of the underlying disease, was the most frequent indication for LT (50%), followed by Hepatocellular carcinoma (17%), and cholestatic liver diseases (9%) (9).

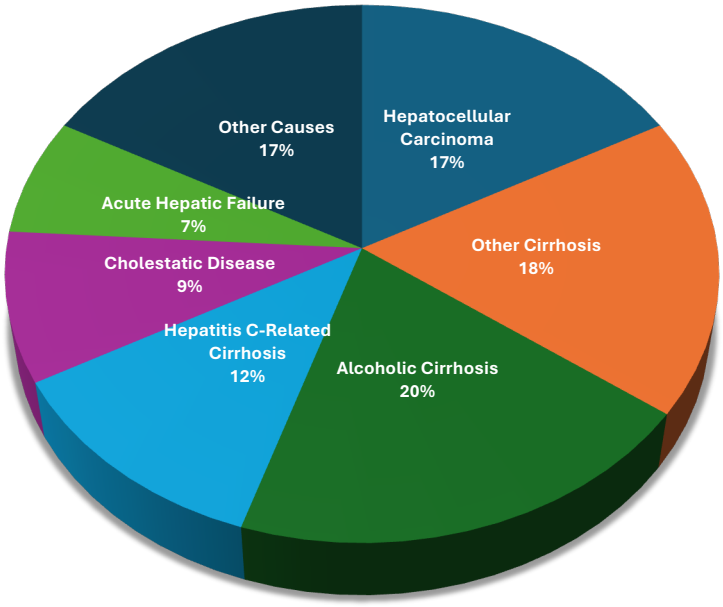


Figure 1. Primary diseases leading to liver transplantation in Europe. ⁄Others: metabolic disease: 6%, Congenital Biliary Disease 5%, Other liver tumors 3%, other liver disease 3%. (10)

1.2.1. Acquired non-oncological indications

Complicated liver cirrhosis represents the most common indication for liver transplantation worldwide. According to the EASL (European Association for the Study of the Liver) guidelines, the transplant process should be evaluated in every patient with liver disease who has a life expectancy of less than a year or in cases of unacceptable quality of life due to the same liver pathology (10). The etiology of liver cirrhosis is progressively evolving with the evolution of available therapies and lifestyle changes: in Europe and North America, alcohol is the leading cause of liver transplantation for cirrhosis. The spread of HBV vaccination and the effectiveness of antiviral drugs against HCV is the basis for the progressive reduction of viral etiology, while cases of cirrhosis based on NASH/NAFLD are constantly and progressively increasing (10,11).

Merely having cirrhosis does not warrant a liver transplant. Generally, a transplant becomes a consideration when cirrhosis is accompanied by complications such as portal hypertension, hepatorenal syndrome, or other signs of deteriorating liver function, including variceal bleeding, ascites, and encephalopathy (10,12).

Patients with cirrhosis are typically candidates for liver transplantation once their biological score of the Model for End-Stage Liver Disease (MELD) is ≥15 (10,12). Nonetheless, there are several exceptions to MELD, including pulmonary complications of cirrhosis, hepatic encephalopathy, amyloidosis, primary hyperoxaluria, etc. In these cases, extra points could be attributed to patients to give them priority for transplantation (10,13). Another exception to MELD is HCC. Waiting list time-dependent points can be added to laboratory MELD to give priority to patients with HCC. Additional points can be added depending on the type of tumor (size, number of nodules, alpha-fetoprotein [AFP] level, waiting time, and response to downstaging procedures). MELD score is driving the allocation of grafts in many countries in Europe. However, the final decision for allocation is frequently based on multiple parameters besides MELD including the match with the donor, but also local/regional priorities (10).

In addition to complicated liver cirrhosis, among the acquired non-oncological indications, particular importance, especially regarding the urgent allocation of grafts, is attributed to acute liver failure.

Acute liver failure is characterized by the development of severe acute liver injury with encephalopathy and compromised synthetic function in a patient without pre-existing cirrhosis or liver disease. While the time course that differentiates acute from chronic liver failure varies among reports, a commonly used cutoff is a disease duration of less than 26 weeks. Although there are numerous causes of acute liver failure, viral hepatitis, and drug-induced liver injury are the most common causes of acute liver failure in adults (14).

Patients with acute liver failure are assigned the highest priority for liver transplantation in the USA and Europe (10,15). Without a liver transplant, patients with acute liver failure will either fully recover liver function or succumb to the condition (16), and approximately 40 percent of patients will survive without needing liver transplantation (17). However, since it can be challenging to predict whether a particular patient will recover, those with acute liver failure are generally directed to a liver transplant center as soon as possible and evaluated by prognostic models, developed to help identify patients who are unlikely to recover spontaneously (14).

1.2.2. Congenital non-oncological indications

Malformative liver pathologies, particularly biliary atresia, account for 40.9% of pediatric liver transplants in the USA in 2021 (11) and represent the main etiology behind pediatric liver transplants. The progressive improvement in transplant outcomes has allowed for the expansion of indications to metabolic diseases such as glycogen storage diseases or defects in the urea cycle like oxaluria, conditions in which liver transplantation, while not eliminating the genetic defect, allows for the clinical treatment of the patient (11). Other genetically determined conditions, such as Wilson's disease or hemochromatosis, rarely constitute a transplant indication in pediatric age, more often leading to a condition of manifest liver cirrhosis later in adulthood (18).

1.2.3. Oncological indications

While liver transplantation for hepatocellular carcinoma (HCC) has long been a shared indication (19,20) and is included in international guidelines, there are still no shared indications in other areas. For example, regarding cholangiocarcinoma, the 2013 AASLD (American Association for the Study of Liver Diseases) guidelines and the EASL guidelines differ: in the AASLD guidelines, it is a contraindication to transplantation, while in the EASL guidelines, cholangiocarcinoma is described as a possible indication for transplantation (10,12).

In general, the following indications can be considered in the field of transplant oncology:

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC), while it can manifest in up to 20% of cases in patients without underlying liver pathology, is closely associated with liver cirrhosis, to the extent that it is sometimes considered a complication of liver disease. The indication for liver transplantation for HCC has been modified over time to better select transplant candidates, minimizing the risk of post-transplant disease recurrence. The Milan Criteria, which were defined in

1996 by Mazzaferro's group, although re-evaluated and updated, remain a reference point for liver transplantation indication in HCC (20). They define transplant eligibility for patients with a single HCC nodule under 5cm in diameter or a maximum of three nodules, each under 3cm in diameter. Within these parameters, liver transplantation has been characterized by an 83% recurrence-free survival at four years (20). Subsequent updates, though validated in the literature, have attempted to modify the purely numerical and dimensional criteria set by the Milan Criteria (21). Others have tried to include the assessment of the biological aggressiveness of the disease (expressed through alpha-fetoprotein, AFP) in defining transplant indications (22).

Criteria	Description	Biopsy Necessary
Milan Criteria (1996)	- Single nodule ≤ 5cm OR Up to 3 nodules, each ≤ 3cm - No vascular invasion - No extrahepatic disease	No
UCSF Criteria (2001)	- Single nodule ≤ 6.5cm OR Up to 3 nodules, largest < 4.5cm, - Total tumor volume (TTV) ≤ 8cm	No
Hangzhou Criteria (2008)	- Total tumor diameter (TTD) < 8cm OR TTD > 8cm - AFP < 400 ng/ml	Yes
Up-to-seven Criteria (2009)	- Size of the largest nodule (in cm) + number of nodules ≤ 7 - No vascular invasion	Yes
Toronto Criteria (2016)	- No limit on lesion size or number - No extrahepatic disease, no venous/biliary tumor thrombosis - No cancer-related symptoms - Biopsy required for nodules beyond Milan Criteria, exclude if poor differentiation	Yes

Figure 2. Criteria for Liver Transplantation Indication for HCC

The evolution of the criteria for liver transplantation, as reported in Figure 2, reflects the scientific community's intention to extend these indications. This is also evident in the evolution of the BCLC (Barcelona Clinic Liver Cancer) Criteria, with the original edition from 1999 (23) and the latest update in 2022 (24).

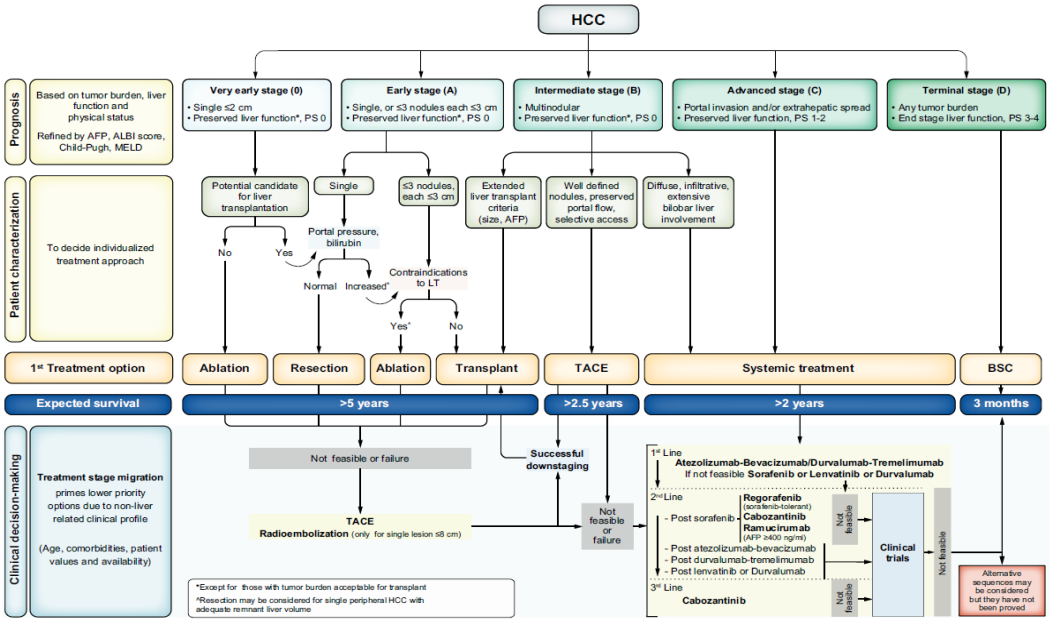


Figure 3. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update.

Currently, in the treatment of HCC, it is increasingly evident that liver transplantation represents the best therapeutic chance, in cases where it is possible to resort to it (25). Based on this evidence, new approaches have been proposed, beyond the BCLC system or the Milan Criteria, aimed at offering the patient the best possible treatment based on their characteristics. This is the principle of the Therapeutic Hierarchy recently described by Vitale et al. (25), whose algorithm is shown in Figure 4.

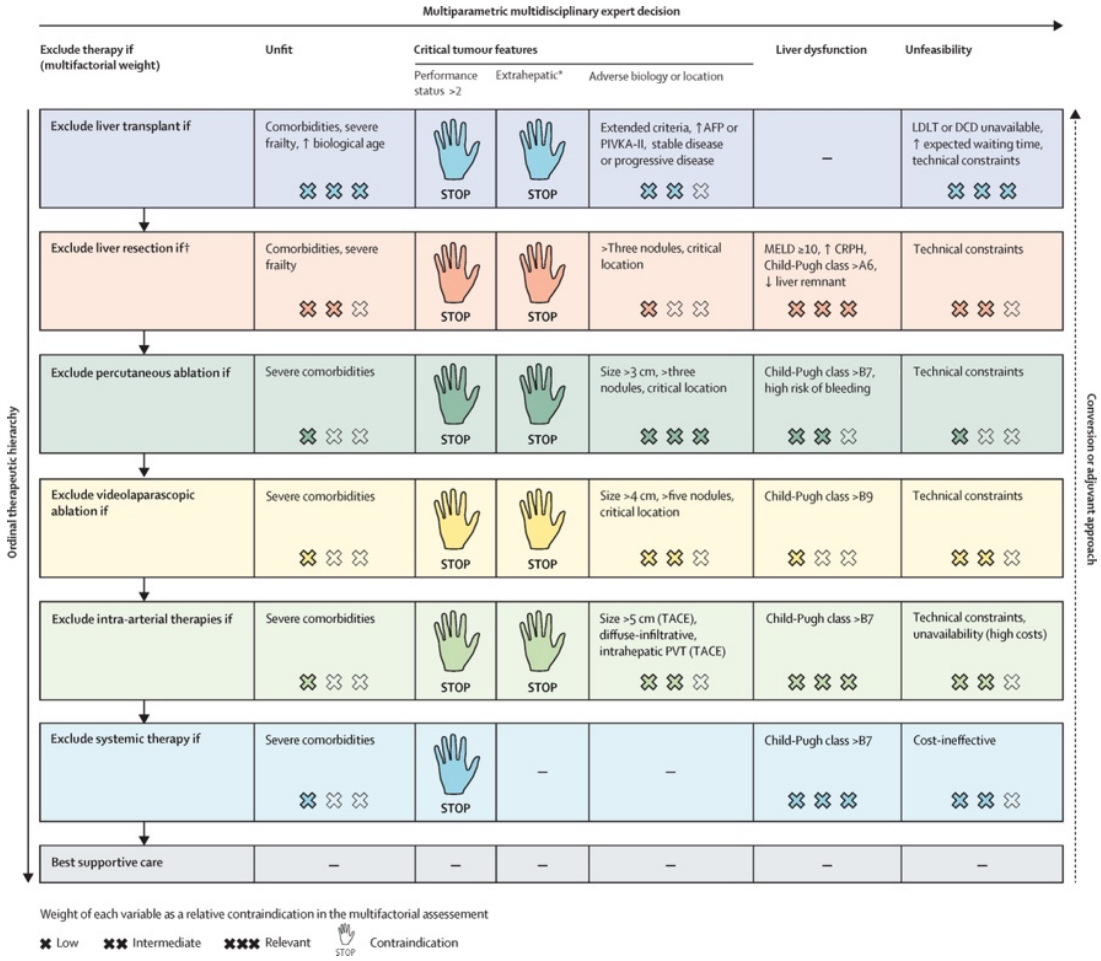


Figure 4. The Therapeutic Hierarchy, Vitale et al.

However, the expansion of transplant indications sees a limit due to the still-existing gap between the availability of grafts and the demand. The issue of the correct allocation of available resources has become increasingly important. In Italy, during a special Consensus Conference in 2015, the issue was addressed by adopting the concepts of transplant urgency, transplant benefit, and transplant utility, with the declared aim of ensuring the ethics of the allocation of available grafts (26).

Cholangiocarcinoma (CAA)

Liver transplantation for cholangiocarcinoma remains a debated option in the literature to this day. However, it is necessary to consider peri-hilar cholangiocarcinoma (pCCA) and intrahepatic cholangiocarcinoma (iCCA)

as two distinct entities. In the case of distal cholangiocarcinoma, due to its location, there is no possible indication for transplantation.

pCCA: Peri-hilar cholangiocarcinoma originates from the epithelium of the extrahepatic bile duct, in the segment between the confluence of the cystic duct and the common hepatic duct and the first-order right and left hepatic ducts. The literature defines a well-established survival rate of 71% at 5 years following liver transplantation (in conjunction with chemotherapy and radiotherapy) according to the very restrictive criteria introduced by De Vreede in 2000 (27). The effectiveness of liver transplantation for pCCA has been validated over time in American series (28) and European ones (29), allowing many countries to include pCCA in the indications for liver transplantation.

Selection Criteria	Exclusion Criteria
Biopsy/Cytology obtained during cholangiography procedure, OR Ca19.9 > 100 U/ml in the absence of cholangitis and radiological evidence of "mass forming" obstruction	Not eligible for orthotopic liver transplantation
No evidence of distant metastasis, intrahepatic or lymph node metastases	Patient previously underwent hepatic resection, chemotherapy, or radiotherapy for peri-hilar cholangiocarcinoma (pCCA)
Non-resectable neoplasia with diameter < 3cm	Patient with ongoing infections

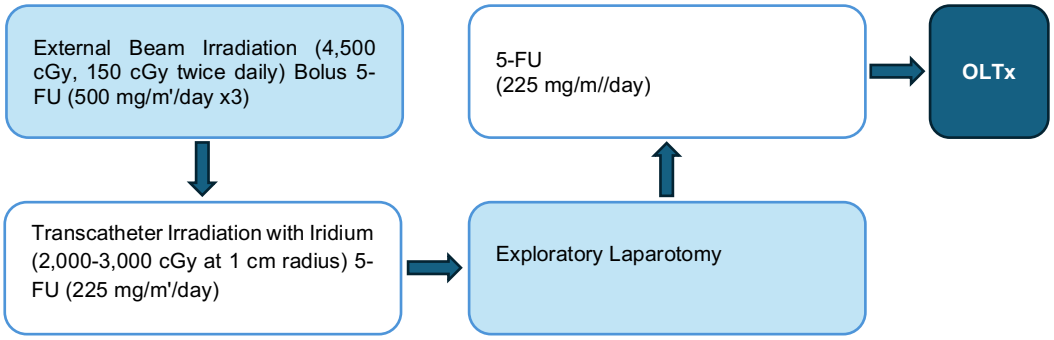


Figure 5. Mayo Protocol for liver transplant for pCCA (27)

iCCA: Intrahepatic cholangiocarcinoma originates from the epithelium of the intrahepatic bile ducts and represents 10-20% of the total CCA. Unlike pCCA, which has been established as a possible transplant indication within the already described protocols, iCCA remains a controversial indication due to the finding of a high rate of post-transplant recurrence, with a survival rate of 2 years less than 40% (30). However, there is evidence in the literature, obtained from retrospective studies by the group of Sapisochin in 2014 (considering patients with a radiological diagnosis of HCC but with a post-transplant anatomopathological finding of iCCA), that the post-transplant survival of patients with “very early” iCCA (single nodule, <= 2cm) would be 73% at 5 years (31). Also considering these results, to date, liver transplantation for iCCA can only be an indication within clinical trials (30,32).

Within the innovative realms of pCCA and iCCA research, the LITALHICA and LIRICA studies, respectively, aim to outline a more nuanced approach to liver transplantation. This approach has the potential to establish new standards for treating these complex malignancies. The studies are designed to evaluate the impact of chemotherapy on patients’ overall survival and quality of life post-transplantation. Furthermore, they aim to identify prognostic biological markers and clinical factors prior to transplantation that may predict improved postoperative outcomes. Additionally, the research investigates the efficacy of preoperative PET-MRI in precisely staging pCCA and iCCA, with a special emphasis on lymph node involvement. The studies also plan to juxtapose these imaging results with the histopathological findings following hilar lymphadenectomy (33,34).

Hepatic metastases from colorectal neoplasia (CRLMs)

Liver transplantation for metastases from colorectal neoplasia is currently under evaluation in the literature. The first case series in the literature (35) reported a 5-year survival of 12%, which led to the discontinuation of the

experience in the early '90s. More recently, trials have been initiated in Scandinavian countries, thanks to the relative availability of grafts, which exceeds the needs. The SECA-I trial (36) indeed demonstrated a 5-year survival of 60% in 2013. Currently, there are various trials in different European countries aimed at defining the effectiveness of liver transplantation in patients with CRLM. However, as of today, there are still various uncertainties, as reported in a recent paper by Mazzaferro's group (37), which do not allow a clear indication for liver transplantation in patients with CRLMs, still limited to clinical trials.

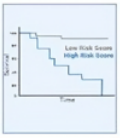
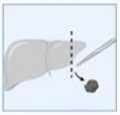
	Available evidence	Open Issues
 **Post-transplant survival**	Disease free-survival after LT seems to be comparable to progression-free survival after chemotherapy, however LT seems to offer better long-term survival to patients with unresectable CRLM than any available chemotherapeutic regimen.	• No randomized controlled trial on chemotherapy versus transplantation • No data on quality of life after LT versus "chronic" chemotherapy
 **Prognostic factors**	Some selection criteria for LT are now considered well-established. LT should be avoided in patients with • Progressive disease • Extrahepatic dissemination • BRAF mutation	Many potential prognostic factors and selection criteria have been identified through retrospective analyses, however those results may change with the emergence of prospective evidence and larger datasets.
 **Transplant vs resection**	Retrospective studies have identified LT as superior to LR in case of high tumor burdens requiring portal vein embolization.	Some patients with tumors that are technically resectable may benefit from LT. No comparison has been made between parenchymal-sparing resection and LT. The definition of resectability is not univocal.
 **Endpoints**	Recurrence-free survival may not be an appropriate endpoint. Recurrence is common after LT, however overall survival may be excellent also after recurrence.	Establishing appropriate trial endpoints is going to be crucial if CRLM become an established indication for LT. Overall survival and transplant benefit may be candidate endpoints.
 **Ethical considerations**	The current number of patients eligible to LT for CRLM is low and unlikely to have a substantial impact on a waiting list. Patients who have been on systemic chemotherapy for 1-2 years are likely to be stable enough to wait 3-4 months for LT without progressing and dropping out of the waitlist. For now, prioritization should be tailored on the local situation.	• The number of eligible patients would dramatically increase if resectable patients were included • Whether LDLT is an acceptable option for this indication remains to be established • The RAPID procedure may be an option, however the risk of tumor diffusion between the two steps needs to be investigated
 **Medical management**	Patients should remain on maintenance chemotherapy while on the waiting list. Most trials involved an immunosuppressive switch to mTOR.	There is limited evidence of the effect of different immunosuppressive regimens on post-LT outcomes.
 **Treatment of recurrent disease**	Post-recurrence survival can be good in case of curative-intent treatment. Post-LT recurrences should be managed aggressively.	Treatment of post-LT recurrence should follow oncological principles.

Figure 6. Maspero Liver Transplantation for Hepatic Metastases from Colorectal Cancer (37)

Hepatic metastases from neuroendocrine neoplasia

The treatment of choice for liver metastases from neuroendocrine tumors is represented by hepatic resection. In patients with unresectable metastases, liver transplantation can represent, in some cases, a possible treatment.

According to the ENETS guidelines (European Neuroendocrine Tumor Society), liver transplantation can be considered in highly selected patients with carcinoid syndrome and extensive hepatic involvement, with pathology refractory to multiple lines of systemic therapy (38). The NANETS guidelines (North American Neuroendocrine Tumor Society) define the indication for liver transplantation as controversial, considering the option feasible, however, if, in addition to the European criteria, the disease falls within the Milan Criteria (39).

The indication for liver transplantation in abdominal neoplasms, excluding hepatocellular carcinoma, remains generally controversial to this day and subject to numerous uncertainties, the foremost being the actual relevance of disease recurrence and the consequent cancer-related mortality. The need for an immunosuppressive therapeutic regimen can lead to a reduction in the body's immunological surveillance. Moreover, regarding secondary tumors, these do not represent a local pathology but are the expression of a systemic disease: our ability to identify distant disease locations is limited by the resolving power of current technology. Finally, the biological characteristics of neoplasms are not completely identifiable with biopsy sampling alone today, preventing proper patient stratification (40). Despite these issues not finding an answer in the literature to date, the results described above show how liver transplantation may, in the future, represent a therapeutic option also in secondary liver neoplasms, as in the case of hepatocellular carcinoma and perihilar cholangiocarcinoma, the definition of multimodal treatment and the implementation of patient selection protocols could allow the achievement of satisfactory results in terms of disease-free and overall survival.

1.3. Graft shortage

The expansion of the indications for liver transplantation, as mentioned in the previous section, has led to a corresponding increase in the demand for organs available for transplantation. According to data provided by the National Transplant Center (CNT) (41), in Italy in 2023, there were 1,646 liver transplants performed; the number of patients on the list as of 10/31/2023 was 940 (as of 03/05/2024, there are 932).

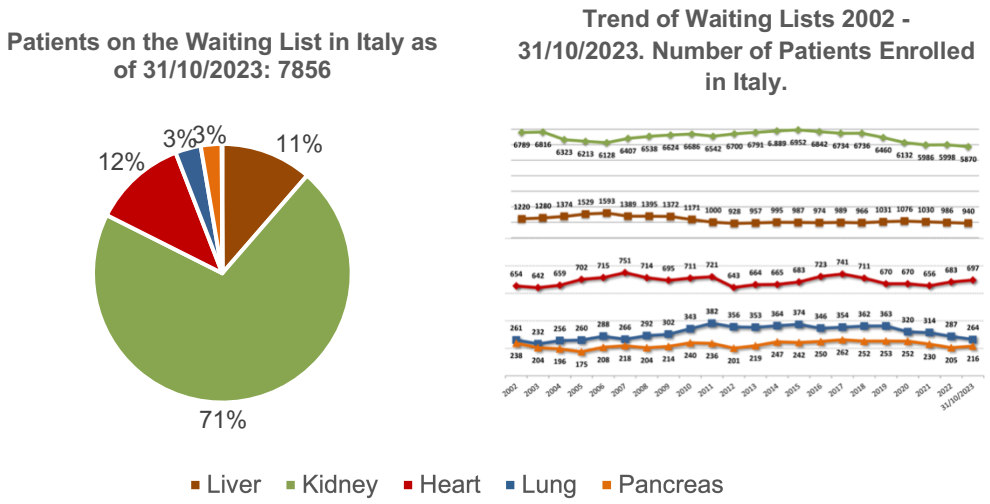


Figure 7. Waiting List, National Transplant Center, Italy (41)

The average waiting time on the transplant list (defined as the average registration time on the waiting list for patients) is, as of 5/03/2024, it is 1.7 years (41). The average waiting time for a transplant (the time elapsed, on average, between registration on the list and the liver transplant) is 0.4 years. The mortality rate on the waiting list is 5.1% (41). These numbers, although progressively decreasing compared to previous years, clearly represent the imbalance present between demand and supply, in contrast to the increase in transplant indications.

To increase the number of available grafts, over the years, different countries have implemented various policies to raise awareness about organ donation. Technical and technological progress has also allowed for an increase in the pool of available organs, particularly thanks to:

Implementation of living donor transplantation (LDLT)

Liver donation from a living donor is globally less common than from a deceased donor. According to data provided by the Global Observatory on Donation and Transplantation (42), in 2022, there were 37,436 liver transplants performed worldwide, of which 28,343 (76%) were from deceased donors and 9,061 (24%) from living donors. Considering countries like India or South Korea, a predominant role is attributed to living donor liver transplantation (respectively 80,9% and 76.1% of the total transplants performed). In Italy, in 2022, of the 1,479 liver transplants performed, only 32 (2.2%) were from living donors. This trend towards a greater diffusion of living donation in the countries of the Eastern world can be attributed to various factors, including socio-cultural elements opposed to the donation of organs from the deceased. The living donation, in addition to better post-transplant graft function results, is nevertheless progressively expanding, also thanks to the spread of minimally invasive techniques and the reduction of postoperative complications in the donor.

Increase in the use of grafts from marginal donors (ECD)

Marginal donors, also defined as 'extended criteria donors' (ECD), are so defined due to the presence of certain characteristics that could determine a suboptimal functioning of the organs harvested post-transplant. The criteria defined by EASL in 2016 to characterize the marginal donor are reported in Fig.8 (10).

Criteria for the definition of a marginal donor:	
Age >65 years	Transaminases >3 times the limit
Hepatic steatosis >30%	Bilirubin >2 mg/dl
Donors with cardiovascular risk factors	Serum sodium >165 mEq/L
BMI >30 mg/dl	Liver from terminally ill donors (DCD)

Figure 8. Extended Criteria Donors definition, (10)

The 2016 EASL guidelines are the only ones to provide an indication based on specific criteria for the definition of an extended criteria donor. In a recent meta-analysis (43), it is highlighted that the criteria present in literature for defining an ECD are not uniform among various authors, particularly concerning age, with cut-offs variably established at 65, 70, or 80 years. Concerning the donor's age, older age is correlated with a higher incidence of biliary complications, but not with different overall survival at 1 and 5 years after transplantation.

Implementation of transplantation from non-heart-beating donors (DCD)

The harvesting of organs from non-heart-beating donors (donor after circulatory death, DCD) in Italy has historically been complicated by the need to wait 20 minutes from the cessation of cardiac activity to declare the death of a potential donor (44). In other countries, for example, the United Kingdom, death can be legally declared in significantly less time (5 minutes), clearly reducing the warm ischemia time to which potential grafts are subjected. However, in recent years, the harvesting of organs from DCD has also been implemented in our country: according to data from the National Transplant Center, in 2022, there were 114 liver transplants from DCD, a significant increase compared to 68 in 2021 and 45 in 2020 (41). This result is mainly due to the implementation of type III DCD, according to the Maastricht Classification (45). In the literature, the data regarding short-term outcomes are comparable to those obtained with grafts from DBD (46). However, there is evidence showing a higher risk of ischemic cholangiopathy (ITBL, due to the longer duration of warm ischemia) and lower graft survival compared to DBD grafts (donor after brain death) (47,48). These data, as highlighted by a retrospective study on a large English case series, must, however, be interpreted considering the prolonged waiting list for DBD transplantation: despite the evidence of lower graft survival in the case of DCD donors, the overall survival of patients on the list is nevertheless increased, more evident in patients with advanced

liver cirrhosis (49). Furthermore, the role of perfusion machines must be considered, with more concrete evidence in the literature regarding hypothermic ones, which are increasingly common in clinical practice and able to condition the graft pre-transplant, reducing the incidence of primary non-function, ischemic cholangiopathy, and increasing the long-term survival of the grafts themselves (50).

1.4. Resource allocation

In the current context, characterized by a gap between the progressive extension of transplant indications and the reduced pool of organs available for transplantation, the process of allocating available resources assumes primary importance. Historically, in the '80s and '90s of the last century, the allocation criterion in the USA was based exclusively on urgency, with priority for patients in intensive care. Subsequently, a temporal criterion was introduced to assign relevance to the duration of the waiting list stay, in which the patient was placed based on their Child-Pugh score (15). Since 2002 in the USA (and from 2006 in Italy), the MELD (Model for End-Stage Liver Disease) has been adopted as the base score for organ allocation in liver transplantation. However, differences persist between countries: especially in geographical areas with a high rate of organ donation, such as Portugal and the Scandinavian countries, there is a center-based regional allocation, to allow locally the best donor-recipient match. In countries like Spain and Canada, the assignment system is dual and based on MELD and local assignment. The United Kingdom, on the other hand, since 2018 has changed its allocation system, focusing on the concept of survival benefit, identifying the UKELD score that performed better than the MELD score in predicting survival. This context, extremely variable based on socio-cultural, political, and legislative elements, does not allow today to define the correct allocation, especially concerning marginal grafts (51).

In Italy, as already mentioned, the Institutional Organ controlling the transplant network is the National Transplant Center, which collaborates both directly and through interregional institutions (consider, for example,

the North Italy Transplant program, NITp) with the individual Transplant Centers (21 in total). The allocation of organs is national for pediatric transplants and emergencies (primary non-function, MELD > 40, acute liver failure), while it is interregional (macro areas) for patients with MELD ≥ 30 and regional for other patients (51). In 2015, during a multidisciplinary Consensus Conference (26), the system was re-evaluated to allow the allocation of available organs also in case of pathologies not directly related to a MELD score, in particular HCC, based on the principles of urgency, utility, and benefit already described in 2009 in Lancet by Persad et al (52). Figure 9 reports the indications considered as exceptions to MELD, while the allocation scheme is described in Figure 10. The goal, expressed during the same Consensus Conference, is to arrive at an allocation as close as possible to the ideal model represented in Figure 11 (26).

Priority and sharing	LT indication
P1 (Macro area sharing after serving those with MELD>30)*	Rendu–Osler–Weber Hepatoblastoma (young adult) Hemangioma (if Kasabach Merritt syndrome) Acute late ReLT FAP (if domino)
P2 (Sharing at regional level)	Hepato-pulmonary syndrome PPH Refractory hydrothorax Chronic late ReLT Hepato-renal syndrome (if not automatically equated to MELD) Previous severe infections
P3 (Sharing at regional level)	Refractory ascites FAP Wilson's (with compensated cirrhosis and initial neurological symptoms) NET metastases Hemangioendotheliomas
P4 (Sharing at regional level)	PSC or PBC with intractable pruritus Polycystic disease Complicated adenoma Hemangiomas
P Multidisciplinary (Center-based)	Hepatic encephalopathy Fibrolamellar HCC Liver adenomatosis (not complicated) Hilar cholangiocarcinoma CRC metastases

Figure 9. Agreed on priority strata for MELD exceptions and corresponding organ-sharing areas (26)

Priority	PTS Category	Points	Allocation area
Super-Urgent	FHF, early reLT	(first come, first served)	Nationwide
Urgent	MELD >30	Biochemical MELD	Macro area
Urgent	EXCEPTIONS P1	30	Macro area
Standard	EXCEPTIONS P2	25 + 1/month	Region
Standard	Bioch MELD 15–29	Biochemical MELD	Region
Standard HCC Stratum 1	HCC: TT_{DR}-TT_{PR} (downstaged patients or partial responders to bridge therapies)	HCC-MELD[19] + extra points for time or MELD 22 at entry + extra points for time (at regional board's discretion)[§] Cap at 29	Region
Standard HCC Stratum 2	HCC: TT_{FR} (first presentation or late recurrence)	HCC-MELD[19] Criteria for awarding extra points for longer waits and priority class migration on disease progression will be set regionally (regional board approval)[#]	Region
Standard HCC Stratum 3	HCC: $T0_C$–T1-$T0_L$ (complete responders or T1 tumors)	Biochemical MELD	Region
Standard	EXCEPTIONS P3	20 + 1 every 2 months	Region
Standard	EXCEPTIONS P4	15 + 1 every 2 months	Region

Figure 10. Proposed and agreed national waiting list prioritization policies and geographical distribution of organ allocation for patients with or without HCC and those considered MELD exceptions (26)

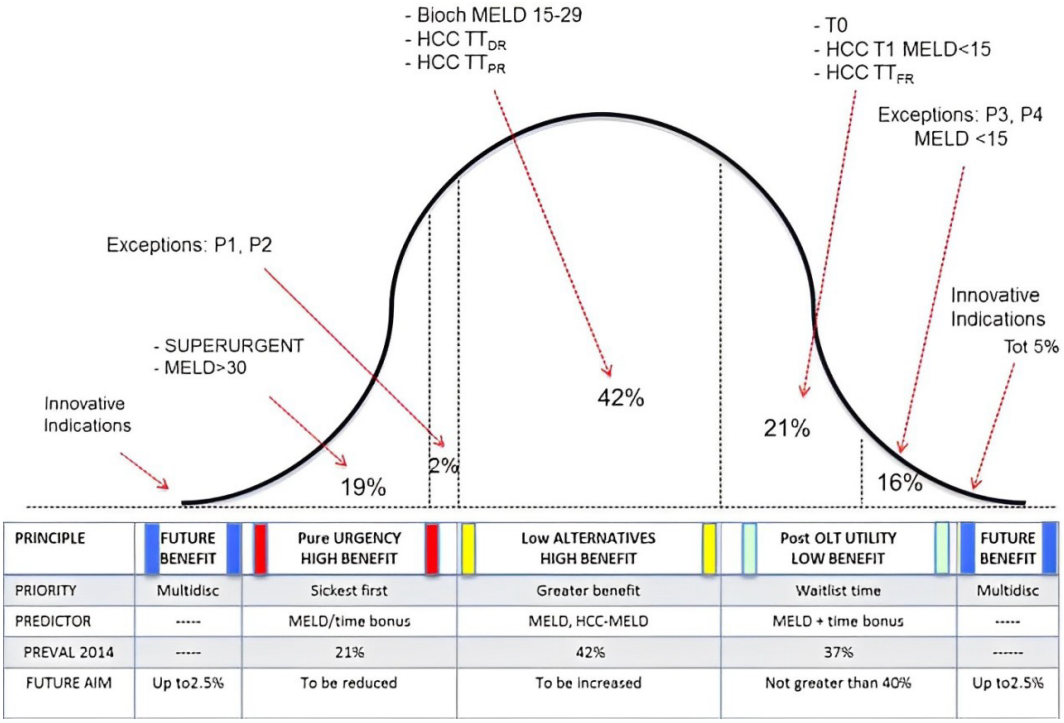


Figure 11. Ideogram of donor resource distribution among the main liver allocation principles in Italy (26)

1.5. Age and liver transplantation

The increase in average life expectancy, especially in Western countries, has led to a new uncertainty in the field of transplantation. The age of presentation and diagnosis of liver diseases is increasingly advanced: already in 2009 in the USA, 28% of the diagnoses of alcoholic liver cirrhosis and 26% of the metabolic forms involved patients over 60 years old. In the case of autoimmune cholestatic forms, the age of the first presentation of the disease reached 65 years in some cases (53). Furthermore, considering the higher incidence of NAFLD liver disease and HCC in individuals over 65 years old (54), it is understandable why, especially in high-volume centers, there is an increasingly common referral of patients over 70 years old. Chronological age, according to EASL and AASLD guidelines, cannot be considered a criterion for exclusion from liver transplantation (10,12). The same guidelines indicate, without providing a decisive indication, that it is more appropriate to evaluate the general clinical picture, comorbidities, and physiological age. Generally, most Transplant Centers worldwide have an upper age limit for liver transplantation indications, 65 years (in some cases 70).

However, the literature does not lack retrospective case series related to the results of liver transplantation in elderly patients. It is necessary to emphasize, however, that there is no uniformity in the definition of elderly: some works consider patients over 60 years old, while in other cases the cut-off to define the patient as elderly is considered at 65 or 70 years old. The results of the studies present in the literature are characterized, however, by contrasting results. In the first meta-analysis of 2016, no difference is reported in the overall survival and graft survival of patients over 70 years old, compared to patients under 70 years old (55). In a second meta-analysis of 2022, a significantly reduced 1-, 3-, and 5-year overall survival is highlighted in patients ≥ 70 compared to younger patients (56). The mortality of elderly patients undergoing liver transplantation appears (57) to be mainly due to cardiovascular events, de novo cancers, and chronic kidney disease (CKD). These elements indicate the need,

expressed both in the context of the SITO consensus conference (Italian Society of Organ Transplantation) of 2017 (58) and in the anesthesiological field (59), to identify states of frailty and comorbidities that may determine an inadequate transplant benefit.

2. Rational of the study

As described in the previous sections, liver transplantation is indicated for acute or chronic 'terminal' liver diseases where medical therapies are ineffective, with a clear indication when the patient's life expectancy, without transplantation, is less than a year or when transplantation can guarantee a drastic improvement in quality of life.

According to EASL and AASLD guidelines, chronological age should not be used as a criterion for excluding patients from liver transplantation (10,12). These guidelines state that there are no age limits for liver transplantation eligibility. However, a multidisciplinary evaluation is necessary to rule out significant comorbidities (10). It is the physiological age, rather than the chronological age, that determines whether an elderly patient can be considered a candidate for transplantation (12).

However, worldwide, and specifically in Italy, in the absence of specific CNT regulations regarding age limitations in patients to be considered for liver transplantation, Transplant Centers and interregional bodies have established formal age limits for listing patients. Initially, this limit was set at 65 years, but more recently, it has been raised to 70 years.

The progressive aging of the general population is reflected in an increase in referrals of patients with end-stage liver cirrhosis and HCC over the age of 70 to the specialist departments of the Hospital of Padua. The Padova Transplant Center has historically chosen to consider 70 years as the age limit for transplantation indication, without however, defining a strict cut-off and subjecting to liver transplantation also patients over 70 years old, when listed before reaching such age, after collegial evaluation and thorough study of the general clinical picture.

The progressive increase in patients evaluated over 70 and the absence in the literature of shared criteria for the selection of patients to be considered for liver transplantation highlighted the need to define parameters capable of allowing a comprehensive evaluation of the patient.

In this scenario, Our Padova Transplant Center decided to develop a specific liver transplantation evaluation protocol for patients over 70. A

decision-making algorithm in subsequent steps was defined, providing clinical and laboratory evaluations in the first instance. In the second and third instances, without clear contraindications, more in-depth and economically impactful instrumental assessments are carried out. The declared purpose is to select patients over 70 years old upstream of the listing process, identifying major exclusion criteria (anamnestic, clinical-laboratory, or instrumental) capable of determining a score based on which to define the continuation with second and third-level evaluations or the early termination of the evaluation process. This algorithm differs from the one currently used for patients potentially eligible for transplantation, where a complete panel of first and second-level exams is performed by all patients, with the only subsequent decision, during a Multidisciplinary Meeting, on the suitability for inclusion in the waiting list for liver transplantation.

Therefore, the expected advantages, in addition to the correct selection of over 70 patient candidates for liver transplantation, also concern the optimization of economic resources for the National Health System.

3. Materials and Methods

3.1. Prospective Study, Cohort

This prospective observational study was conducted on a cohort of patients over seventy years old who were potentially eligible for liver transplantation. For patient selection, the following criteria were considered (valid at the start of evaluation for transplantation):

Inclusion Criteria:

- Age above 70 but below 75 years;
- Indication for liver transplantation due to chronic liver disease or hepatocellular carcinoma;
- Indication for liver transplantation from a deceased donor;
- First-time liver transplant.

Exclusion Criteria:

- Age ≤ 70 years or > 75 years;
- Liver transplant from a living donor;
- Previous liver transplant;
- Liver transplant for acute hepatic failure.

3.1.1. Selection protocol

The proposed selection protocol was structured into three levels, initially involving low-cost clinical and laboratory evaluations at the first level, and only more in-depth clinical and instrumental assessments at the second and third levels, which come at a higher cost.

The first-level evaluation includes the initial surgical or hepatological outpatient visit and a geriatric evaluation. In Figure 12, the identified risk factors are listed, which, when combined to yield an overall score > 2, allow for early exclusion of patients either during the initial visit or subsequent geriatric evaluation.

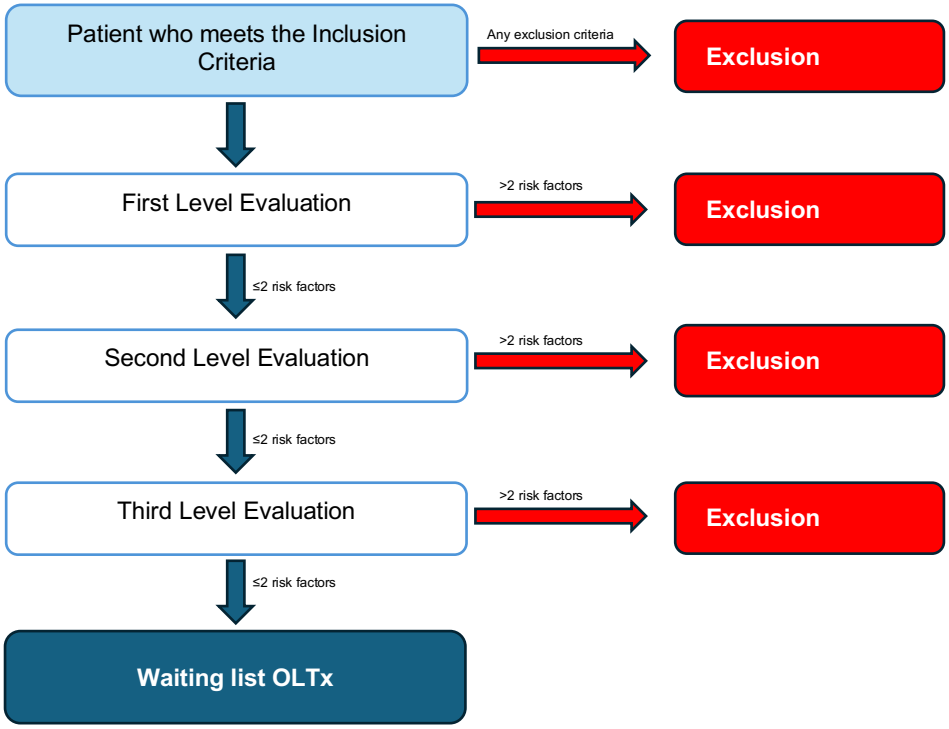
In this protocol, geriatric assessment plays a crucial role in providing an overall evaluation of the patient through the definition of the Multidimensional Prognostic Index (MPI) (60). Calculated using a

mathematical algorithm that incorporates information from 8 domains (basic and instrumental activities of daily living, cognitive status, nutritional status, pressure ulcers, mobility, comorbidities, polypharmacy, and housing status), the MPI was validated and used in geriatric settings to predict one-year mortality, fall risk, estimated hospitalization duration, need for home care, and risk of developing depression. Ultimately, it expresses the multidimensional frailty level of the elderly patient (61,62).

The MPI is expressed as a continuous numerical index ranging from 0 (no risk) to 1 (maximum risk), with the possibility of identifying three risk classes: low (0 – 0.33), medium (> 0.33 – 0.66), or high (> 0.66).

The second-level evaluation includes instrumental and specialized cardiology, pneumology, and anesthesiology evaluations. These assessments will allow for a more in-depth understanding of the overall clinical picture and the identification of any risk factors that may not have emerged during the initial evaluation. At the end of the second-level assessments, if the risk score was >2, the patient will be excluded from transplantation evaluation.

The third-level analysis includes completing the standard evaluation for liver transplantation, which includes instrumental and specialized radiological, neurological, and urological/gynecological examinations. At the end of the evaluation process, the patient's case, as already implemented at Our Center for standard patients undergoing liver transplantation assessment, requires multidisciplinary transplant discussion for definitive confirmation of inclusion on the transplant list.



First-level evaluation (1st surgical/hepatological visit + geriatric evaluation)		
Liver related risk factors (1pt) - MELD-Na > 25 - Prior laparotomic liver surgery - Complete/incomplete portal thrombosis	**Non-Liver related risk factors (1pt)** - Diabetes - BMI>30 - Cardiac disease - Pulmonary disease - Renal disease - Tumor (<5 years) - Debilitating osteoporosis	**Frailty (MPI)** - Low risk, MPI < 0.33 **(0pt)** - Medium risk, MPI 0.33 – 0.66 **(1pt)** - High risk, MPI > 0.66 **(3pt)**

Second-level clinical-instrumental evaluation
- Cardiological evaluation (echocardiography + ECG + visit) - Pneumological evaluation (pulmonary function test + blood gas analysis + visit) - Nephrological evaluation - Anesthesiologic evaluation

Third-level clinical-instrumental evaluation
- Completion of all tests required for placement on the waiting list for OLTx (including CT scans, scintigraphy, and other relevant examinations) - Multidisciplinary discussion

Figure 12. Selection Protocol

3.1.2. Primary and Secondary Endpoints

In our prospective study's protocol, the following outcome measures were used to evaluate the septuagenarian patients:

- The primary endpoint focuses on assessing the overall patient survival (OS) at 12 months following liver transplantation.

The secondary endpoints include:

- The one-year survival of the transplanted graft;
- Post-operative complications, expressed as the Comprehensive Complication Index (CCI);
- Duration of hospital and ICU stays.

3.1.3. Sample Size

This prospective study was designed as a Phase 2 study with the following hypotheses: The inactivity "cut-off" was equal to 50%, while the activity "cut-off" was equal to 80%. Therefore, the hypotheses of interest were H0: $r \leq 50\%$ versus HA: $r \geq 80\%$, where r was the proportion of patients who survived 12 months after liver transplantation. The type I error rate (α, the probability of accepting a treatment that is not sufficiently active, accepting a false positive result) was set at 5% The type II error rate (β, the probability of rejecting an active treatment, obtaining a false negative result) was set at 20%. Based on these hypotheses, 18 patients were required for the study. The efficacy evaluation of the treatment was determined by the number of patients who survived 12 months after liver transplantation. If at most 13 patients survived, the treatment was declared not sufficiently active. Conversely, if at least 14 patients survived, the treatment was considered sufficiently active.

3.2. Retrospective Study, Cohort

This retrospective study analyzed a historical cohort of patients who underwent liver transplantation at our center from 2016 to 2024, after reaching the age of 70. For patient selection, we applied the same criteria retrospectively that were used in the prospective observational study.

The study began by assessing and categorizing two patient subgroups as comparable: those who participated in the prospective study and those who did not. The non-participating group consisted of patients who were either listed for transplantation after the age of 70 but before the initiation of the prospective study, or those who underwent transplantation upon turning 70, even though they had been listed before exceeding that age limit.

For the control group, we selected a cohort of 483 transplant recipients under the age of 70. These individuals met the same selection criteria outlined earlier (except for age) and underwent hepatic transplantation at our institution between 2016 and 2022.

3.2.1. Statistical analysis

Values for categorical variables were expressed as totals and percentages whereas for continuous variables they were described as medians and interquartile ranges (IQR). Statistical analyses were performed using Pearson's chi-squared or Fisher's test for categorical variables and the Wilcoxon rank sum test for continuous variables.

The length of follow-up was calculated from the date of the liver transplant to the date of patient death (overall survival—OS) or the latest follow-up.

Graft survival was calculated from the date of the liver transplant to the date when the transplanted liver failed or ceased to function properly. This can be due to rejection, disease recurrence, or other complications.

The duration of follow-up and survival was expressed as median (interquartile ranges). Survival curves were calculated using the Kaplan–Meier technique and compared with the log-rank test.

Prognostic survival factors were identified through univariate and multivariate analyses using the Cox proportional hazards model. Some

variables were not balanced within the two study groups thus, to make the two populations more homogeneous a “propensity score matching” (PSM) analysis was carried out. The analysis was performed with MatchIt, which made pairing, subset selection, and subclassification to create treatment groups balanced on included covariates. The matching method was "subclass" and the distance measure was computed by logistic regression with a probit link function. The covariates included: ETOH, NASH, HCC, Pre-Transplant Abdominal Surgery, MELD, Cirrhosis, Donor Age, and ECD. A p-value < 0.05 indicated statistical significance; variables with a p-value < 0.1 were considered of marginal statistical significance. Statistical analyses were performed using R, RStudio 4.4.0 (2024).

4. Prospective Study, Results

From 2019 to 2024, 31 patients eligible for liver transplantation were recruited according to the previously described inclusion criteria (later referred to as ‘In protocol’ patients), reaching and exceeding, therefore, the planned minimum sample size. The follow-up during the waiting list period was similar for each patient to the one that currently happens in place at Our Center for standard patients. Post-transplant, the patients were evaluated during outpatient visits in a manner identical to what is currently planned for standard patients and based on clinical needs.

4.1. Population Description

The population's median age was 71.8 years (IQR: 71.4, 73.2), with males constituting 71% (22/31) of the group. The body mass index (BMI) averaged 25.4 (IQR: 24.5, 26.7). Diabetes was present in 39% (12/31) of the subjects, and chronic kidney disease (CKD) was observed in 26% (8/31).

Regarding liver function scores, the Model for End-Stage Liver Disease (MELD) and MELD-Na scores were both at a median of 16.0 (IQR: 11.0, 21.0, and 11.0, 21.5, respectively). The Child-Pugh score was recorded at a median of 9.0 (IQR: 6.0, 11.0), indicating this population's severity of liver disease.

A significant prevalence of cirrhosis was observed, with 97% (30/31) of the individuals affected. The most prevalent underlying condition was non-alcoholic steatohepatitis (NASH), occurring in 32% (10/31) of cases. Infections with Hepatitis C virus (HCV) and Hepatitis B virus (HBV) were identified in 19% (6/31) and 26% (8/31) of the cases, respectively. Alcohol-related liver disease (ETOH) was affecting 9.7% (3/31) of the population. Cryptogenic causes accounted for 13% (4/31) of the cases. There were no reported instances of cholestatic liver disease. Hepatocellular carcinoma (HCC) was notably prevalent, with 71% (22/31) of the patients diagnosed with this condition. The maximum lesion size was recorded at an average of 1.6 cm (IQR: 0.1, 2.9), with an average number of lesions at 3.0 (IQR:

1.0, 4.0). The total tumor diameter and volume averaged 1.8 cm (IQR: 0.1, 4.3) and 8.2 cm³ (IQR: 0.0, 39.9), respectively. Alpha-fetoprotein (AFP) levels presented a median value of 6.4 ng/mL (IQR: 4.1, 22.3). All the data are provided in Table 1.

	'In Protocol', N = 31
Age (years)	71.8 (71.4, 73.2)
Gender (Male)	22 / 31 (71%)
BMI	25.4 (24.5, 26.7)
BMI > 30	2 / 27 (7.4%)
Diabetes	12 / 31 (39%)
CKD	8 / 31 (26%)
MELD	16.0 (11.0, 21.0)
MELD-Na	16.0 (11.0, 21.5)
Child-Pugh Score ≥ 7	9 / 25 (36%)
Cirrhosis	30 / 31 (97%)
HCV	6 / 31 (19%)
HBV	8 / 31 (26%)
ETOH	3 / 31 (9.7%)
NASH	10 / 31 (32%)
Cholestatic	0 / 31 (0%)
Cryptogenic	4 / 31 (13%)
HCC	22 / 31 (71%)
Max Lesion Size (cm)	1.6 (0.1, 2.9)
N. Lesions	3.0 (1.0, 4.0)
Total Tumor Diameter (cm)	1.8 (0.1, 4.3)
Total Tumor Volume (cm^3)	8.2 (0.0, 39.9)
AFP	6.4 (4.1, 22.3)

Table 1. 'In protocol' population description

4.2. Outcomes

The primary endpoint, 1-year overall survival probability for the septuagenarian population, was 88.7% (95% CI: 77.3%, 100%), thus

allowing the rejection of the null hypothesis H0. The Kaplan-Meier survival probability curve is shown in Figure 13.

Regarding the secondary endpoints, the 1-year graft survival probability was 84.2% (95% CI: 69.3%, 100%) (Figure 13). The overall hospitalization duration showed median values of 16.0 (IQR: 11.0, 33.5) days, while the intensive care unit (ICU) stay was 5.0 (IQR: 3.0, 9.0) days.

The complications that the patients faced after the transplant were classified using the Clavien-Dindo classification system. Using this data, it has been calculated that the Comprehensive Complication Index (CCI) revealed a median of 20.5 (IQR: 8.7, 42.0). The 90-day mortality was 6.5%. All data are shown in Table 2.

	'In protocol', N = 31
Overall Hospitalization (days)	16.0 (11.0, 33.5)
ICU (days)	5.0 (3.0, 9.0)
CCI	20.5 (8.7, 42.0)
Clavien-Dindo	
0	7 / 31 (23%)
1	9 / 31 (29%)
2	6 / 31 (19%)
3°	1 / 31 (3.2%)
3B	4 / 31 (13%)
4°	2 / 31 (6.5%)
4B	0 / 31 (0%)
5	2 / 31 (6.5%)

Table 2. 'In protocol' population, secondary outcomes

5. Retrospective Study

We compared the ‘In protocol’ patients with a historical cohort of 30 individuals, hereafter referred to as ‘Out protocol’ patients. This group included patients who underwent transplantation after reaching the age of 70, despite being listed before surpassing that age threshold (n = 26), and patients who were listed for transplantation after the age of 70 but before the start of the prospective study, thus not evaluated according to our selection protocol (n = 4).

5.1. Comparison with the ‘Out protocol’ population

The analysis found significant differences regarding the duration of the waiting list and follow-up, which were longer in the ‘Out protocol’ cohort. Furthermore, the median age was significantly younger in the ‘Out protocol’ group compared to the ‘In protocol’ group: 70.6 years (IQR: 70.3, 71.1) vs. 71.8 years (IQR: 71.4, 73.2), as shown in Table 3.

The MELD score was higher in the ‘In protocol’ group, with a median of 16 (IQR: 11, 21), compared to 12.5 (IQR: 9, 18.5). Additionally, the Child-Pugh score was equal to 7, or over, in 71% of the ‘In protocol’ group versus 36% of patients.

	Overall, N = 61	'In protocol', N = 31	'Out protocol', N = 30	p-value
Age (years)	71.2 (70.6, 72.0)	71.8 (71.4, 73.2)	70.6 (70.3, 71.1)	**<0.001**
Gender (Male)	44 / 61 (72%)	22 / 31 (71%)	22 / 30 (73%)	0.84
BMI	25.2 (23.1, 27.1)	25.4 (24.5, 26.7)	24.8 (22.8, 28.4)	0.55
BMI > 30	5 / 52 (9.6%)	2 / 27 (7.4%)	3 / 25 (12%)	0.66
Diabetes	18 / 61 (30%)	12 / 31 (39%)	6 / 30 (20%)	0.11
CKD	13 / 61 (21%)	8 / 31 (26%)	5 / 30 (17%)	0.38
MELD	15.0 (10.0, 20.0)	16.0 (11.0, 21.0)	12.5 (9.0, 18.5)	**0.043**
MELD-Na	15.5 (10.3, 20.0)	16.0 (11.0, 21.5)	14.5 (9.5, 19.0)	0.17
Child-Pugh Score ≥ 7	31 / 56 (55%)	22 / 31 (71%)	9 / 25 (36%)	**0.009**
Cirrhosis	60 / 61 (98%)	30 / 31 (97%)	30 / 30 (100%)	>0.99
HCV	16 / 61 (26%)	6 / 31 (19%)	10 / 30 (33%)	0.21
HBV	16 / 61 (26%)	8 / 31 (26%)	8 / 30 (27%)	0.94
ETOH	8 / 61 (13%)	3 / 31 (9.7%)	5 / 30 (17%)	0.47
NASH	14 / 61 (23%)	10 / 31 (32%)	4 / 30 (13%)	0.079
Cholestatic	2 / 61 (3.3%)	0 / 31 (0%)	2 / 30 (6.7%)	0.24
Cryptogenic	6 / 61 (9.8%)	4 / 31 (13%)	2 / 30 (6.7%)	0.67
HCC	45 / 61 (74%)	22 / 31 (71%)	23 / 30 (77%)	0.61
Max Lesion Size (cm)	1.5 (0.1, 2.5)	1.6 (0.1, 2.9)	1.3 (0.8, 2.0)	0.59
N. Lesions	3.0 (1.0, 5.0)	3.0 (1.0, 4.0)	3.0 (1.0, 5.0)	0.49
Total Tumor Diameter (cm)	1.8 (0.1, 4.0)	1.8 (0.1, 4.3)	1.8 (0.8, 3.9)	0.89
Total Tumor Volume (cm^3)	2.8 (0.0, 18.7)	8.2 (0.0, 39.9)	2.2 (0.4, 7.4)	0.37
AFP	6.9 (3.3, 13.7)	6.4 (4.1, 22.3)	7.0 (3.0, 9.3)	0.71

Table 3. Comparative Cohort Analysis, population description - 'In protocol' vs. 'Out protocol''

There were no statistically significant differences in overall survival, as shown in Figure 13; the 'In protocol' population had a 1-year survival probability of 88.66%, while the 'Out protocol' population had 88.46% (p = 0.79). The graft survival for the 'In protocol' population was 84.21%, and for the 'Out protocol' population, it was 84.00% (p = 0.93). None of the other secondary endpoints showed statistical significance, as highlighted in Table 4.

The two populations can thus be deemed comparable, permitting an analysis alongside another demographic.

	Overall, N = 61	'In protocol', N = 31	'Out protocol', N = 30	p-value
Overall Hospitalization (days)	16.0 (11.0, 31.0)	16.0 (11.0, 33.5)	15.0 (8.0, 28.5)	0.28
ICU (days)	4.0 (3.0, 8.0)	5.0 (3.0, 9.0)	3.0 (2.0, 5.0)	0.089
CCI	20.9 (8.7, 42.6)	20.5 (8.7, 42.0)	24.2 (11.8, 49.9)	0.33
Clavien-Dindo				0.43
0.0	14 / 61 (23%)	7 / 31 (23%)	7 / 30 (23%)	
1.0	11 / 61 (18%)	9 / 31 (29%)	2 / 30 (6.7%)	
2.0	15 / 61 (25%)	6 / 31 (19%)	9 / 30 (30%)	
3A	2 / 61 (3.3%)	1 / 31 (3.2%)	1 / 30 (3.3%)	
3B	9 / 61 (15%)	4 / 31 (13%)	5 / 30 (17%)	
4A	5 / 61 (8.2%)	2 / 31 (6.5%)	3 / 30 (10%)	
5.0	5 / 61 (8.2%)	2 / 31 (6.5%)	3 / 30 (10%)	

Table 4. Comparative Cohort Analysis, Outcomes - 'In protocol' vs. 'Out protocol'

5.2. Comparison 'Over 70' vs 'Under 70'

We have proceeded to evaluate the 'Over 70' population, defined as all patients over 70 who underwent transplantation post-70 years. This demographic comprised 31 'In protocol' patients and 30 'Out of protocol' individuals. For comparison, we analyzed a cohort of 483 transplant recipients who underwent hepatic transplantation at our institution from 2016 to 2022. These recipients were all younger than 70 years old at the time of transplantation and will be referred to hereafter as the 'Under 70' patients.

Compared to the population 'Under 70', the older group exhibited a statistically significant longer waiting list duration: 7.4 (IQR: 4.7, 21.1) months vs. 5.4 (IQR: 2.1, 11.8); and a shorter follow-up time: 17.7 (IQR: 4.5, 33.6) months vs. 30.2 (IQR: 10.4, 50.3).

Regarding the etiology leading to liver transplantation, a significantly lower prevalence of ETOH-related liver disease (13% vs. 34%) was observed, alongside a greater prevalence of NASH (23% vs. 13%), cirrhosis (98% vs. 91%) and HCC (74% vs. 54%), as shown in Table 5.

	Overall, N = 544	'Under 70', N = 483	'Over 70', N = 61	p-value2
Age (years)	59.5 (52.4, 65.9)	57.7 (51.3, 63.4)	71.2 (70.6, 72.0)	**<0.001**
Gender (Male)	416 / 542 (77%)	372 / 481 (77%)	44 / 61 (72%)	0.36
BMI	25.3 (23.2, 28.5)	25.4 (23.2, 28.7)	25.2 (23.1, 27.1)	0.38
BMI > 30	74 / 461 (16%)	69 / 409 (17%)	5 / 52 (9.6%)	0.18
Diabetes	147 / 534 (28%)	129 / 473 (27%)	18 / 61 (30%)	0.71
CKD	82 / 533 (15%)	69 / 472 (15%)	13 / 61 (21%)	0.17
MELD	15.0 (10.0, 21.0)	15.0 (10.0, 21.0)	15.0 (10.0, 20.0)	0.53
MELD-Na	16.0 (11.0, 23.4)	16.9 (11.0, 24.0)	15.5 (10.3, 20.0)	0.25
Child-Pugh Score ≥ 7	7.0 (5.0, 10.0)	8.0 (5.0, 10.0)	7.0 (5.0, 9.0)	0.39
Cirrhosis	498 / 543 (92%)	438 / 482 (91%)	60 / 61 (98%)	**0.046**
HCV	136 / 542 (25%)	120 / 481 (25%)	16 / 61 (26%)	0.83
HBV	127 / 542 (23%)	111 / 481 (23%)	16 / 61 (26%)	0.58
ETOH	172 / 542 (32%)	164 / 481 (34%)	8 / 61 (13%)	**<0.001**
NASH	78 / 542 (14%)	64 / 481 (13%)	14 / 61 (23%)	**0.043**
Cholestatic	36 / 543 (6.6%)	34 / 482 (7.1%)	2 / 61 (3.3%)	0.41
Cryptogenic	28 / 543 (5.2%)	22 / 482 (4.6%)	6 / 61 (9.8%)	0.11
HCC	304 / 544 (56%)	259 / 483 (54%)	45 / 61 (74%)	**0.003**
Max Lesion Size (cm)	1.5 (0.6, 2.2)	1.5 (0.9, 2.2)	1.5 (0.1, 2.5)	0.88
N. Lesions	2.0 (1.0, 5.0)	2.0 (1.0, 5.0)	3.0 (1.0, 5.0)	0.52
Total Tumor Diameter (cm)	1.9 (0.8, 3.4)	2.0 (1.0, 3.4)	1.8 (0.1, 4.0)	0.98
Total Tumor Volume (cm^3)	2.1 (0.2, 10.3)	2.1 (0.3, 8.9)	2.8 (0.0, 18.7)	0.39
AFP	5.7 (3.2, 16.4)	5.4 (3.2, 16.9)	6.9 (3.3, 13.7)	0.58

Table 5. Comparative Cohort Analysis, population description - 'Under 70' vs. 'Over 70'.

5.3. Donor and Intraoperative Variables

Comparing the 'Over 70' and the 'Under 70' population, the analysis of donor characteristics for liver transplantation shows only a statistically significant difference in age between donors, with median ages, respectively, of 73.5 (IQR: 58.0, 81.0) and 66.0 (IQR: 51.0, 77.0) years, as shown in Table 6

	Overall, N = 544	Under-70, N = 483	Over-70, N = 61	p-value
Donor age (years)	67.0 (52.0, 78.0)	66.0 (51.0, 77.0)	73.5 (58.0, 81.0)	**0.012**
BMI Donor	25.7 (23.0, 28.0)	25.8 (23.0, 28.0)	25.0 (23.0, 28.0)	0.60
Extended Criteria Donor	338 / 544 (62%)	294 / 483 (61%)	44 / 61 (72%)	0.088
Biopsy (Yes/No)	441 / 512 (86%)	386 / 452 (85%)	55 / 60 (92%)	0.19
Macrosteatosis %	5.0 (2.0, 10.0)	5.0 (2.0, 10.0)	5.0 (5.0, 10.0)	0.56
Microsteatosis %	5.0 (1.0, 15.0)	5.0 (1.0, 15.0)	5.0 (4.0, 15.0)	0.93
Fibrosis (Ishak):				0.58
0	426 / 544 (78%)	381 / 483 (79%)	45 / 61 (74%)	
1	109 / 544 (20%)	94 / 483 (19%)	15 / 61 (25%)	
2	7 / 544 (1.3%)	6 / 483 (1.2%)	1 / 61 (1.6%)	
3	2 / 544 (0.4%)	2 / 483 (0.4%)	0 / 61 (0%)	
Donor Category:				0.15
DBD	516 / 536 (96%)	460 / 476 (97%)	56 / 60 (93%)	
DCD	16 / 536 (3.0%)	12 / 476 (2.5%)	4 / 60 (6.7%)	
Living	4 / 536 (0.7%)	4 / 476 (0.8%)	0 / 60 (0%)	
Cause of Donor's Death:				0.051
Anoxia	67 / 529 (13%)	55 / 469 (12%)	12 / 60 (20%)	
Cerebrovascular	369 / 529 (70%)	325 / 469 (69%)	44 / 60 (73%)	
Other	21 / 529 (4.0%)	20 / 469 (4.3%)	1 / 60 (1.7%)	
Trauma	72 / 529 (14%)	69 / 469 (15%)	3 / 60 (5.0%)	
ECD	338 / 544 (62%)	294 / 483 (61%)	44 / 61 (72%)	0.088

Table 6.- Comparative Cohort Analysis, Donor Variables – 'Under 70' vs. 'Over 70'

Among the intraoperative variables, a statistically significant increase in the use of venous grafts was observed in the 'Over 70' group, at 12%, compared to 3.6% in the 'Under 70' group. Furthermore, a higher prevalence of Portal Vein Thrombosis (PVT) was found in the 'Over 70' recipients (25% vs. 13%), with a significantly higher rate of intraoperative diagnosis (9.8% vs. 3.1%). The Balance of Risk Score (BAR) was significantly higher in the septuagenarian patients, with a median of 8 (IQR: 5, 10) vs 6 (IQR: 4, 9).

No statistical difference was observed in terms of surgical techniques. However, there was a statistically significant difference in the type of Arterial Anastomosis used. End-to-end anastomosis was more common in both groups, but in the 'Over 70' group, there was a higher prevalence of Supraceliac anastomosis (8.3% vs. 2.3%). All intraoperative data are shown in Table 7.

	Overall, N = 544	Under-70, N = 483	Over-70, N = 61	p-value
Total Cold Ischemia Time (CIT) (min)	475.0 (410.0, 533.5)	475.0 (410.0, 529.0)	473.5 (407.3, 599.0)	0.24
Total Surgery Time (min)	415.0 (355.0, 487.5)	420.0 (357.8, 490.0)	385.0 (346.5, 450.0)	0.12
Venous graft	24 / 536 (4.5%)	17 / 476 (3.6%)	7 / 60 (12%)	**0.012**
Portal Vein Thrombosis (PVT) Recipient	74 / 510 (15%)	59 / 450 (13%)	15 / 60 (25%)	**0.014**
Intraoperative Diagnosis of PVT	21 / 544 (3.9%)	15 / 483 (3.1%)	6 / 61 (9.8%)	**0.022**
Reperfusion Injury Score (RIS) (L)	6.7 (5.0, 9.0)	6.75 (5.0, 9.0)	6.5 (4.8, 10.0)	0.82
Donor Risk Index (DRI)	2.0 (1.7, 2.1)	2.0 (1.7, 2.1)	2.0 (1.8, 2.2)	0.065
Balance of Risk Score (BAR)	6.0 (4.0, 9.0)	6.0 (3.0, 8.0)	8.0 (5.0, 10.0)	**0.045**
Surgical Technique:				0.81
Classic	93 / 541 (17%)	83 / 480 (17%)	10 / 61 (16%)	
Caval-Preserving Hepatectomy (CPH)	7 / 541 (1.3%)	7 / 480 (1.5%)	0 / 61 (0%)	
CPH + porto-portal anastomosis	6 / 541 (1.1%)	5 / 480 (1.0%)	1 / 61 (1.6%)	
Piggy back	435 / 541 (80%)	385 / 480 (80%)	50 / 61 (82%)	
Arterial Anastomosis:				**0.014**
End-to-end	520 / 539 (96%)	466 / 479 (97%)	54 / 60 (90%)	
Subrenal	3 / 539 (0.6%)	2 / 479 (0.4%)	1 / 60 (1.7%)	
Supraceliac	16 / 539 (3.0%)	11 / 479 (2.3%)	5 / 60 (8.3%)	
Biliary Anastomosis:				0.53
Choledocho-choledochostomy	501 / 539 (93%)	443 / 479 (92%)	58 / 60 (97%)	
External derivation	14 / 539 (2.6%)	14 / 479 (2.9%)	0 / 60 (0%)	
Hepatico-jejunost	24 / 539 (4.5%)	22 / 479 (4.6%)	2 / 60 (3.3%)	

Table 7. Comparative Cohort Analysis, Intraoperative Variables – ‘Under 70’ vs. ‘Over 70’

5.4. Outcomes and Postoperative Variables

The 1-year and 3-year overall survival probabilities for the ‘Over 70’ population were 87.7% (95% CI: 79.5, 96.6) and 84.7% (95% CI: 75.1, 95.4), respectively. The 1-year and 3-year graft survival probabilities were 83.3% (95% CI: 73.3, 94.6) and 78% (95% CI: 66.8, 91.2), respectively. No significant difference in patient and graft survival probabilities was observed compared to the ‘Under 70’ population. The Kaplan-Meier survival probability curves are shown in Figure 13.

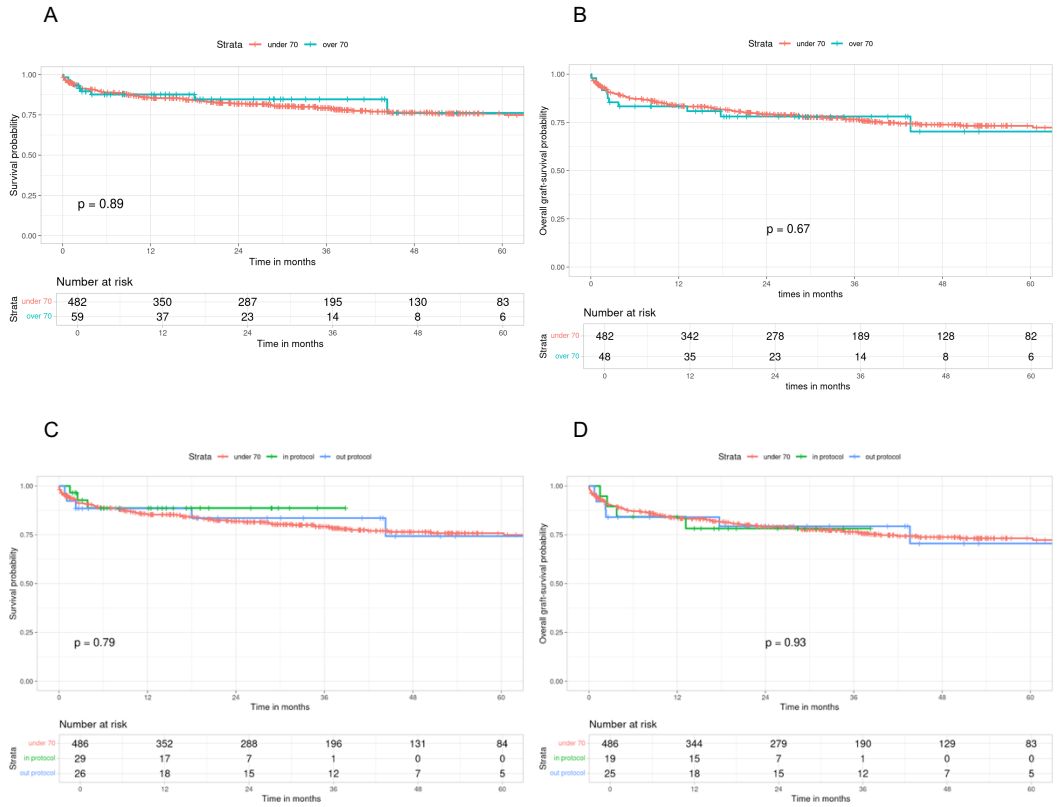


Figure 13. Kaplan-Meier Survival Probability Curves. A: Patient Survival Probability 'Under 70' vs. 'Over 70'. B: Graft Survival Probability 'Under 70' vs. 'Over 70'. C: Patient Survival Probability 'Under 70' vs. 'In protocol' vs 'Out protocol'. D: Graft Survival Probability 'Under 70' vs. 'In protocol' vs 'Out protocol'

The overall hospitalization duration showed no significant difference between the cohorts, with median values of 16.0 (IQR: 11.0, 31.0) days for the older cohort and 17.0 (IQR: 12.0, 34.5) days for the younger; the intensive care unit (ICU) stay was as well not significantly different. The Comprehensive Complication Index (CCI) revealed a statistically significant lower median value for the 'Over 70' patients, with a median of 20.9 (IQR: 8.7, 42.6), compared to 29.6 (IQR: 20.9, 49.3) for their younger counterparts.

During the 90 days following the transplant, further complications were investigated using the Clavien-Dindo complication classification system. The mortality rate associated with liver transplantation was not significantly different, within the 'Over 70' group was 8.2% vs. 8.4% for the 'Under 70'.

Among complications, ascites was significantly more prevalent in the ‘Under 70’ cohort (37% versus 18%). Postoperative data are summarized in Table 8.

	Overall, N = 544	**‘Under 70’, N = 483**	**‘Over 70’, N = 61**	**p-value**
Overall Hospitalization (days)	17.0 (11.0, 33.3)	17.0 (12.0, 34.5)	16.0 (11.0, 31.0)	0.39
ICU stay (days)	3.0 (2.0, 7.0)	3.0 (2.0, 6.0)	4.0 (3.0, 8.0)	0.16
CCI	29.6 (12.2, 48.2)	29.6 (20.9, 49.3)	20.9 (8.7, 42.6)	**0.043**
Clavien-Dindo				>0.99
0.0	59 / 539 (11%)	45 / 478 (9.4%)	14 / 61 (23%)	
1.0	78 / 539 (14%)	67 / 478 (14%)	11 / 61 (18%)	
2.0	156 / 539 (29%)	141 / 478 (29%)	15 / 61 (25%)	
3A	39 / 539 (7.2%)	37 / 478 (7.7%)	2 / 61 (3.3%)	
3B	113 / 539 (21%)	104 / 478 (22%)	9 / 61 (15%)	
4A	42 / 539 (7.8%)	37 / 478 (7.7%)	5 / 61 (8.2%)	
4B	7 / 539 (1.3%)	7 / 478 (1.5%)	0 / 61 (0%)	
5	45 / 539 (8.3%)	40 / 478 (8.4%)	5 / 61 (8.2%)	
Primary Non-Function (PNF)	27 / 508 (5.3%)	25 / 448 (5.6%)	2 / 60 (3.3%)	0.76
Early Allograft Dysfunction (EAD)	122 / 497 (25%)	112 / 437 (26%)	10 / 60 (17%)	0.13
Acute Rejection	91 / 541 (17%)	86 / 480 (18%)	5 / 61 (8.2%)	0.056
Chronic Rejection	7 / 472 (1.5%)	6 / 412 (1.5%)	1 / 60 (1.7%)	>0.99
Biliary complications	122 / 541 (23%)	108 / 480 (23%)	14 / 61 (23%)	0.94
Portal V. Thrombosis	32 / 541 (5.9%)	29 / 480 (6.0%)	3 / 61 (4.9%)	>0.99
Portale V. Stenosis	3 / 494 (0.6%)	2 / 434 (0.5%)	1 / 60 (1.7%)	0.32
Hepatic A. Thrombosis	24 / 541 (4.4%)	20 / 480 (4.2%)	4 / 61 (6.6%)	0.33
Hepatic V. Thrombosis	4 / 477 (0.8%)	4 / 417 (1.0%)	0 / 60 (0%)	>0.99
Hepatic V. Stenosis	4 / 475 (0.8%)	4 / 416 (1.0%)	0 / 59 (0%)	>0.99
Ascites	162 / 464 (35%)	151 / 404 (37%)	11 / 60 (18%)	**0.004**
AKI	147 / 532 (28%)	127 / 471 (27%)	20 / 61 (33%)	0.34
CKD	67 / 513 (13%)	61 / 453 (13%)	6 / 60 (10%)	0.75
Cardiological complications	45 / 541 (8.3%)	42 / 480 (8.8%)	3 / 61 (4.9%)	0.31
Arrhythmias	37 / 544 (6.8%)	34 / 483 (7.0%)	3 / 61 (4.9%)	0.79
Neoplastic Reccurence	15 / 466 (3.2%)	13 / 406 (3.2%)	2 / 60 (3.3%)	>0.99
Re-OLTx	39 / 543 (7.2%)	35 / 482 (7.3%)	4 / 61 (6.6%)	>0.99

Table 8. Comparative Cohort Analysis, postoperative Variables - Under 70 vs. Over 70

5.4. Outcomes and Postoperative Variables after PSM

After the Propensity Score Matching (PSM) analysis, we observed no significant differences in anamnestic variables between the study groups, apart from age.

The 1-year and 3-year overall survival probabilities for the 'Over 70' population were 87.5% (95% CI: 79.2, 96.7) and 84.5% (95% CI: 74.8, 95.4), respectively (p = 0.93). The 1-year and 3-year graft survival probabilities were 82.9% (95% CI: 72.8, 94.5) and 77.7% (95% CI: 66.3, 91.1), respectively (p = 0.63). No significant difference in patient and graft survival probabilities was observed compared to the 'Under 70' population. The Kaplan-Meier survival probability curves are shown in Figure 14. The postoperative variables showed no significant differences between the patient variables, besides those previously observed, as shown in Table 9.

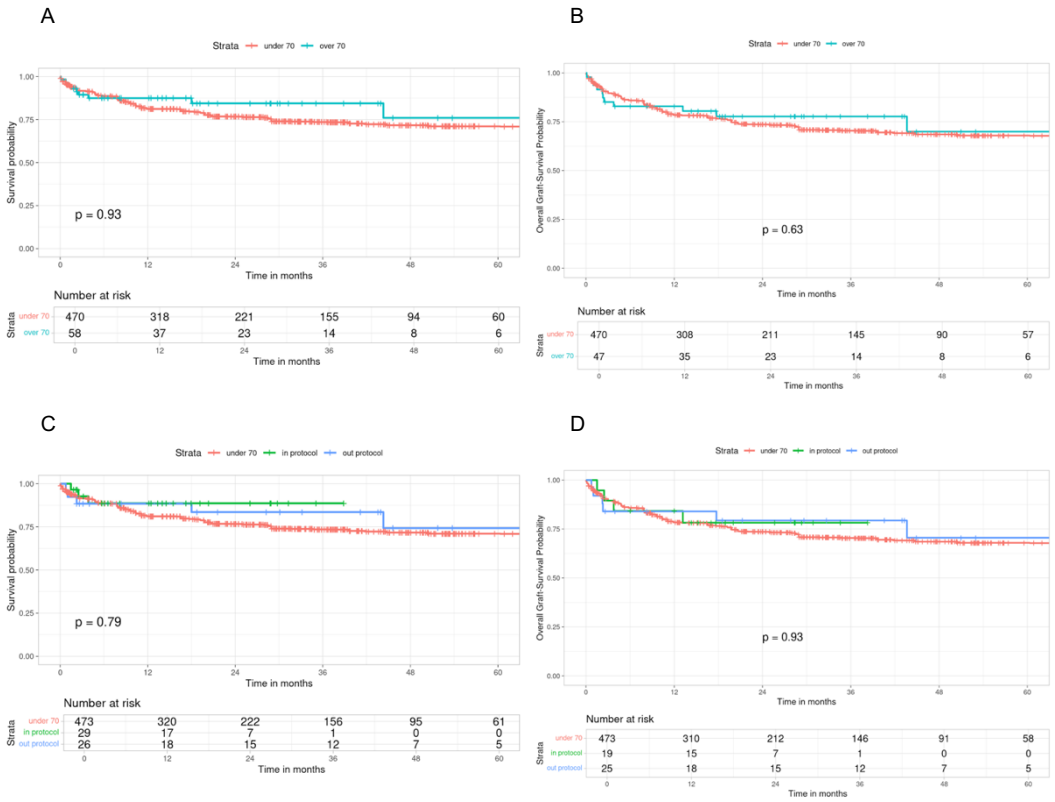


Figure 14. Kaplan-Meier Survival Probability Curves, after Propensity Score Matching analysis. A: Patient Survival Probability 'Under 70' vs. 'Over 70'. B: Graft Survival Probability 'Under 70' vs. 'Over 70'. C: Patient Survival Probability 'Under 70' vs. 'In protocol' vs 'Out protocol'. D: Graft Survival Probability 'Under 70' vs. 'In protocol' vs 'Out protocol'

	Overall, N = 544	'Under-70', N = 483	'Over-70', N = 61	p-value
Overall Hospitalization (days)	17.0 (11.0, 33.0)	17.0 (12.0, 35.0)	16.0 (11.0, 30.3)	0.30
ICU stay (days)	4.0 (2.0, 7.0)	3.0 (2.0, 6.0)	4.0 (3.0, 8.0)	0.16
CCI	29.6 (12.2, 48.2)	29.6 (20.9, 49.0)	20.9 (8.7, 42.7)	**0.05**
Clavien-Dindo				>0.99
0.0	58 / 528 (11%)	44 / 468 (9.4%)	14 / 60 (23%)	
1.0	76 / 528 (14%)	65 / 468 (14%)	11 / 60 (18%)	
2.0	152 / 528 (29%)	138 / 468 (29%)	14 / 60 (23%)	
3A	39 / 528 (7.4%)	37 / 468 (7.9%)	2 / 60 (3.3%)	
3B	111 / 528 (21%)	102 / 468 (22%)	9 / 60 (15%)	
4A	42 / 528 (8.0%)	37 / 468 (7.9%)	5 / 60 (8.3%)	
4B	7 / 528 (1.3%)	7 / 468 (1.5%)	0 / 60 (0%)	
5.0	43 / 528 (8.1%)	38 / 468 (8.1%)	5 / 60 (8.3%)	
Primary Non-Function (PNF)	27 / 501 (5.4%)	25 / 441 (5.7%)	2 / 60 (3.3%)	0.76
Early Allograft Dysfunction (EAD)	122 / 492 (25%)	112 / 432 (26%)	10 / 60 (17%)	0.12
Acute Rejection	88 / 529 (17%)	83 / 469 (18%)	5 / 60 (8.3%)	0.067
Chronic Rejection	7 / 466 (1.5%)	6 / 406 (1.5%)	1 / 60 (1.7%)	>0.99
Biliary complications	120 / 529 (23%)	106 / 469 (23%)	14 / 60 (23%)	0.90
Portal V. Thrombosis	29 / 529 (5.5%)	26 / 469 (5.5%)	3 / 60 (5.0%)	>0.99
Portale V. Stenosis	3 / 487 (0.6%)	2 / 427 (0.5%)	1 / 60 (1.7%)	0.33
Hepatic A. Thrombosis	24 / 529 (4.5%)	20 / 469 (4.3%)	4 / 60 (6.7%)	0.34
Hepatic V. Thrombosis	4 / 470 (0.9%)	4 / 410 (1.0%)	0 / 60 (0%)	>0.99
Hepatic V. Stenosis	4 / 470 (0.9%)	4 / 410 (1.0%)	0 / 60 (0%)	>0.99
Ascites	162 / 458 (35%)	151 / 398 (38%)	11 / 60 (18%)	**0.003**
AKI	147 / 520 (28%)	127 / 460 (28%)	20 / 60 (33%)	0.35
CKD	67 / 501 (13%)	61 / 442 (14%)	6 / 59 (10%)	0.44
Cardiological complications	43 / 529 (8.1%)	41 / 469 (8.7%)	2 / 60 (3.3%)	0.21
Arrhythmias	36 / 530 (6.8%)	34 / 470 (7.2%)	2 / 60 (3.3%)	0.41
Neoplastic Reccurence	15 / 461 (3.3%)	13 / 401 (3.2%)	2 / 60 (3.3%)	>0.99
Re-OLTx	38 / 530 (7.2%)	34 / 470 (7.2%)	4 / 60 (6.7%)	>0.99

Table 9. Comparative Cohort Analysis, after Propensity Score Matching analysis, postoperative Variables - Under 70 vs. Over 70

6. Discussion

The result obtained in the prospective study, regarding 1-year overall survival probability for the ‘In protocol’ population was 88.66%. This figure surpasses the survival rate reported in the most recent meta-analysis (56), yet aligns with the 2016 one (55). It is important to acknowledge that these meta-analyses encompass retrospective studies; the superior outcome observed can be attributed to our selection protocol's effectiveness.

The 1-year graft survival probability stood at 84.21%, which agrees with the findings reported in both meta-analyses. This consistency indicates that our selection protocol may not have contributed to increased graft survival rates. This could be because the protocol needed to integrate innovative approaches beyond standard care to enhance graft survival further.

The median duration of hospitalization, at 16 days, and the median length of ICU stay, at 5 days, were notably less than the durations reported in the 2022 meta-analysis. Unlike the 2022 study, the 2017 meta-analysis did not evaluate these specific parameters. The reduced hospital and ICU stays in our findings further corroborate the efficacy of our selection protocol.

In the retrospective study, the extended waiting list period observed in the ‘Out protocol’ cohort (18.7 months vs. 5.1 months) can be attributed to its composition. Out of the 30 patients, 26 turned 70 years old after being listed for transplants, which most likely indicates a lower urgency criterion for their cases. Because of the same reason, presumably, the median age was slightly lower for the ‘Out protocol’ population. This element could also explain the lower Child-Pugh and MELD scores at transplantation.

The shorter follow-up period observed in the ‘In-protocol’ population may be justified by the relatively recent implementation of the Selection Protocol at our Center in 2019. The lower median value of the CCI for the ‘In Protocol’ patients (20.6 compared to 26.9 in ‘Out Protocol’ patients) could be attributed to the efficacy of our protocol, suggesting that it may be effective in reducing potential complications following liver transplantation.

The comparison between the ‘Over 70’ and ‘Under 70’ cohorts revealed that the older group experienced a more prolonged waiting list duration and a shorter follow-up period than the younger group. These results were likely driven by the ‘Out protocol’ and ‘In protocol’ populations.
In terms of liver disease etiology leading to transplantation, the ‘Over 70’ group’s higher prevalence of NASH, cirrhosis, and hepatocellular carcinoma (HCC) was coherent with data from the United States Scientific Registry of Transplant Recipients (63) and the European Liver Transplant Registry (64). Although the prevalence of Extended Criteria Donors (ECD) was not statistically significant, the donor age was considerably higher among the septuagenarian patients. This last observation aligns with only one study included in the 2017 meta-analysis.
The 1-year OS (Overall Survival) probability for the ‘Over 70’ population was 87.7% ($p = 0.89$), indicating a non-significant difference between the two OS rates. This is consistent with the meta-analysis from 2016 but not with the one from 2022.
The non-significant difference between the 1-year graft survival, overall hospitalization, and ICU stay was coherent with both meta-analyses (55,56).

The CCI revealed a statistically significant lower median value for the ‘Over 70’ patients. This data is likely driven by the ‘In protocol’ subpopulation, confirming the effectiveness of our Selection Protocol in eliminating patients with comorbidities that could potentially lead to significant complications. The perioperative complications were not statistically different in both meta-analyses; however, it should be noted that the two did not report the complications as CCI but rather with a rate of general perioperative complications. Furthermore, the 2016 meta-analysis included only 5 papers that reported data about complications (55,56).

Acknowledging the absence of an in-depth examination of comorbidities in the retrospective study is crucial. The principal limitation of this analysis is the lack of a detailed assessment of comorbidities within the ‘Under 70’

population. These variables are pivotal determinants of the outcome in prospective studies. Consequently, we are advancing our scientific work by collecting more accurate data regarding this aspect to enhance the robustness and validity of our findings.

Regarding the prospective study, a more extensive follow-up is undoubtedly necessary to define the transplant benefit for patients over 70 undergoing liver transplantation.

7. Conclusion

It is possible to affirm that, in selected patients, liver transplantation can represent a therapeutic option even beyond 70 years of age, with satisfactory outcomes in the short and medium term. Although there are no criteria in the literature that allow an evaluation of patients to be considered for liver transplantation, in the elderly patient, an assessment is necessary that considers, in addition to the hepatological picture, also the possible multiple associated comorbidities and the overall state of frailty. Identifying hepato-related risk factors and extra-hepatic factors and evaluating the MPI (Multidimensional Prognostic Index) can allow a first assessment of the patient, enabling both the reduction of resources necessary for the transplant evaluation and the optimization of the selection process. Therefore, this study poses the possibility of using the algorithm developed at Our Center in selecting patients over 70 for liver transplantation, which, however, requires external validation and confirmation on a larger cohort of patients.

8. Bibliography

1. Bull WCT, 1955 undefined. A note on transplantation of the whole liver in dogs. cir.nii.ac.jp [Internet]. [cited 2024 Feb 29]; Available from: https://cir.nii.ac.jp/crid/1571698600164644480

2. Cannon J. Brief Report. JA; 1956.

3. Busuttil RW, De Carlis LG, Mihaylov P V., Gridelli B, Fassati LR, Starzl TE. The first report of orthotopic liver transplantation in the Western world. Am J Transplant [Internet]. 2012 [cited 2024 Feb 29];12(6):1385–7. Available from: https://pubmed.ncbi.nlm.nih.gov/22458426/

4. STARZL TE, MARCHIORO TL, VONKAULLA KN, HERMANN G, BRITTAIN RS, WADDELL WR. HOMOTRANSPLANTATION OF THE LIVER IN HUMANS. Surg Gynecol Obstet [Internet]. 1963 Dec [cited 2024 Apr 15];117:659. Available from: /pmc/articles/PMC2634660/

5. Starzl TE, Fung JJ. THEMES OF LIVER TRANSPLANTATION. Hepatology [Internet]. 2010 Jun [cited 2024 Feb 29];51(6):1869. Available from: /pmc/articles/PMC4507423/

6. Calne RY, Rolles K, Thiru S, Mcmaster P, Craddock GN, Aziz S, et al. Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. Lancet [Internet]. 1979 Nov 17 [cited 2024 Mar 4];2(8151):1033–6. Available from: https://pubmed.ncbi.nlm.nih.gov/91781/

7. National Institutes of Health Consensus Development Conference: liver transplantation. R I Med J. 1984 Feb;67(2):73–6.

8. Starzl TE, Iwatsuki S, Van Thiel DH, Carlton Gartner J, Zitelli BJ, Jeffrey Malatack J, et al. Evolution of liver transplantation. Hepatology [Internet]. 1982 [cited 2024 Mar 4];2(5):614S-636S. Available from: https://pubmed.ncbi.nlm.nih.gov/6749635/

9. Adam R, Karam V, Cailliez V, O Grady JG, Mirza D, Cherqui D, et al. 2018 Annual Report of the European Liver Transplant Registry (ELTR) – 50-year evolution of liver transplantation. Transplant International. 2018 Dec 1;31(12):1293–317.

10. Burra P, Burroughs A, Graziadei I, Pirenne J, Valdecasas JC, Muiesan P, et al. EASL Clinical Practice Guidelines: Liver transplantation. J Hepatol [Internet]. 2016 Feb 1 [cited 2024 Mar 4];64(2):433–85. Available from: https://pubmed.ncbi.nlm.nih.gov/26597456/

11. Kwong AJ, Ebel NH, Kim WR, Lake JR, Smith JM, Schladt DP, et al. OPTN/SRTR 2021 Annual Data Report: Liver. Am J Transplant [Internet]. 2023 Feb 1 [cited 2024 Mar 4];23(2 Suppl 1):S178–263. Available from: https://pubmed.ncbi.nlm.nih.gov/37132348/

12. Martin P, Dimartini A, Feng S, Brown R, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Hepatology [Internet]. 2014 Mar [cited 2024 Mar 1];59(3):1144–65. Available from: https://pubmed.ncbi.nlm.nih.gov/24716201/

13. Freeman RB, Gish RG, Harper A, Davis GL, Vierling J, Lieblein L, et al. Model for end-stage liver disease (MELD) exception guidelines: Results and recommendations from the MELD exception study group and conference (MESSAGE) for the approval of patients who need liver transplantation with diseases not considered by the standard MELD formula. Liver Transplantation [Internet]. 2006 Dec 1 [cited 2024 Apr 15];12(S3):S128–36. Available from: https://onlinelibrary.wiley.com/doi/full/10.1002/lt.20979

14. Lee WM, Larson AM, Todd Stravitz R. AASLD Position Paper: The Management of Acute Liver Failure: Update 2011. 2011;

15. UNOS | United Network for Organ Sharing | US Organ Transplantation [Internet]. [cited 2024 Mar 5]. Available from: https://unos.org/

16. Ostapowicz G, Fontana RJ, Schioødt F V., Larson A, Davern TJ, Han SHB, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med [Internet]. 2002 Dec 17 [cited 2024 Apr 15];137(12):947–54. Available from: https://pubmed.ncbi.nlm.nih.gov/12484709/

17. Reuben A, Tillman H, Fontana RJ, Davern T, Mcguire B, Stravitz RT, et al. Outcomes in Adults With Acute Liver Failure Between 1998 and 2013: An Observational Cohort Study. Ann Intern Med [Internet]. 2016 Jun 7 [cited 2024 Apr 15];164(11):724–32. Available from: https://pubmed.ncbi.nlm.nih.gov/27043883/

18. Kerkar N, Rana A. Wilson Disease in Children. Clin Liver Dis [Internet]. 2022 Aug 1 [cited 2024 Mar 4];26(3):473–88. Available from: https://pubmed.ncbi.nlm.nih.gov/35868686/

19. Bismuth H, Chiche L, Adam R, Castaing D, Diamond T, Dennison A. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. Ann Surg [Internet]. 1993 [cited 2024 Mar 4];218(2):145. Available from: /pmc/articles/PMC1242923/?report=abstract

20. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med [Internet]. 1996 Mar 14 [cited 2024 Mar 4];334(11):693–700. Available from: https://pubmed.ncbi.nlm.nih.gov/8594428/

21. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: Expansion of the tumor size limits does not adversely impact survival. Hepatology. 2001 Jun 1;33(6):1394–403.

22. Duvoux C, Roudot-Thoraval F, Decaens T, Pessione F, Badran H, Piardi T, et al. Liver transplantation for hepatocellular carcinoma: A model including α-fetoprotein improves the performance of milan criteria. Gastroenterology. 2012 Oct 1;143(4):986-994.e3.

23. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis [Internet]. 1999 [cited 2024 Mar 4];19(3):329–37. Available from: https://pubmed.ncbi.nlm.nih.gov/10518312/

24. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol [Internet]. 2022 Mar 1 [cited 2024 Mar 4];76(3):681–93. Available from: https://pubmed.ncbi.nlm.nih.gov/34801630/

25. Vitale A, Cabibbo G, Iavarone M, Viganò L, Pinato DJ, Ponziani FR, et al. Personalised management of patients with hepatocellular carcinoma: a multiparametric therapeutic hierarchy concept. Lancet Oncol [Internet]. 2023 Jul 1 [cited 2024 Mar 4];24(7):e312–22. Available from: https://pubmed.ncbi.nlm.nih.gov/37414020/

26. Cillo U, Burra P, Mazzaferro V, Belli L, Pinna AD, Spada M, et al. A Multistep, Consensus-Based Approach to Organ Allocation in Liver

Transplantation: Toward a “Blended Principle Model.” Am J Transplant [Internet]. 2015 Oct 1 [cited 2024 Mar 4];15(10):2552–61. Available from: https://pubmed.ncbi.nlm.nih.gov/26274338/

27. De Vreede I, Steers JL, Burch PA, Rosen CB, Gunderson LL, Haddock MG, et al. Prolonged disease-free survival after orthotopic liver transplantation plus adjuvant chemoirradiation for cholangiocarcinoma. Liver Transpl [Internet]. 2000 [cited 2024 Mar 4];6(3):309–16. Available from: https://pubmed.ncbi.nlm.nih.gov/10827231/

28. Darwish Murad S, Kim WR, Harnois DM, Douglas DD, Burton J, Kulik LM, et al. Efficacy of neoadjuvant chemoradiation, followed by liver transplantation, for perihilar cholangiocarcinoma at 12 US centers. Gastroenterology [Internet]. 2012 [cited 2024 Mar 4];143(1). Available from: https://pubmed.ncbi.nlm.nih.gov/22504095/

29. Mantel HTJ, Westerkamp AC, Adam R, Bennet WF, Seehofer D, Settmacher U, et al. Strict Selection Alone of Patients Undergoing Liver Transplantation for Hilar Cholangiocarcinoma Is Associated with Improved Survival. PLoS One [Internet]. 2016 Jun 1 [cited 2024 Mar 4];11(6). Available from: https://pubmed.ncbi.nlm.nih.gov/27276221/

30. Gringeri E, Gambato M, Sapisochin G, Ivanics T, Lynch EN, Mescoli C, et al. Cholangiocarcinoma as an Indication for Liver Transplantation in the Era of Transplant Oncology. J Clin Med [Internet]. 2020 May 1 [cited 2024 Mar 4];9(5). Available from: /pmc/articles/PMC7290472/

31. Sapisochin G, Rodríguez De Lope C, Gastaca M, Ortiz De Urbina J, Suarez MA, Santoyo J, et al. “Very early” intrahepatic cholangiocarcinoma in cirrhotic patients: should liver transplantation be reconsidered in these patients? Am J Transplant [Internet]. 2014 Mar [cited 2024 Mar 4];14(3):660–7. Available from: https://pubmed.ncbi.nlm.nih.gov/24410861/

32. Abreu P, Gorgen A, Oldani G, Hibi T, Sapisochin G. Recent advances in liver transplantation for cancer: The future of transplant oncology. JHEP Reports [Internet]. 2019 Nov 1 [cited 2024 Mar 4];1(5):377. Available from: /pmc/articles/PMC7005652/

33. LIver Transplantation for Non-Resectable Intrahepatic CholAngiocarcinoma (LIRICA) - Full Text View - ClinicalTrials.gov

[Internet]. [cited 2024 Jun 14]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT06098547

34. LIver TrAnspLantation for Non-resectable Peri-HIlar cholangioCArcinoma (LITALHICA) - Full Text View - ClinicalTrials.gov [Internet]. [cited 2024 Jun 14]. Available from: https://classic.clinicaltrials.gov/ct2/show/NCT06125769

35. Is orthotopic liver transplantation a feasible treatment for secondary cancer of the liver? - PubMed [Internet]. [cited 2024 Mar 4]. Available from: https://pubmed.ncbi.nlm.nih.gov/1989293/

36. Hagness M, Foss A, Line PD, Scholz T, Jørgensen PF, Fosby B, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg [Internet]. 2013 May [cited 2024 Mar 4];257(5):800–6. Available from: https://pubmed.ncbi.nlm.nih.gov/23360920/

37. Maspero M, Sposito C, Virdis M, Citterio D, Pietrantonio F, Bhoori S, et al. Liver Transplantation for Hepatic Metastases from Colorectal Cancer: Current Knowledge and Open Issues. Cancers (Basel) [Internet]. 2023 Jan 1 [cited 2024 Mar 4];15(2). Available from: https://pubmed.ncbi.nlm.nih.gov/36672295/

38. Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Neuroendocrinology [Internet]. 2016 Apr 1 [cited 2024 Apr 17];103(2):172–85. Available from: https://pubmed.ncbi.nlm.nih.gov/26731013/

39. 2022 Edition NANETS GUIDELINES. [cited 2024 Mar 4]; Available from: https://nanets.net/

40. Panayotova G, Lunsford KE, Latt NL, Paterno F, Guarrera J V, Pyrsopoulos N. Expanding indications for liver transplantation in the era of liver transplant oncology. World J Gastrointest Surg [Internet]. 2021 May 5 [cited 2024 Mar 4];13(5):392. Available from: /pmc/articles/PMC8167850/

41. CNT - Sistema Informativo Trapianti [Internet]. [cited 2024 Apr 18]. Available from: https://trapianti.sanita.it/statistiche/report_attivita.aspx

42. countliver - GODT [Internet]. [cited 2024 Mar 5]. Available from: https://www.transplant-observatory.org/countliver/

43. Neri I, Pascale MM, Bianco G, Frongillo F, Agnes S, Giovinazzo F. Age and liver graft: a systematic review with meta-regression. Updates Surg [Internet]. 2023 Dec 1 [cited 2024 Mar 5];75(8):2075–83. Available from: https://pubmed.ncbi.nlm.nih.gov/37695503/

44. Gazzetta Ufficiale [Internet]. [cited 2024 Mar 5]. Available from: https://www.gazzettaufficiale.it/eli/id/1994/01/08/094G0004/sg.

45. Thuong M, Ruiz A, Evrard P, Kuiper M, Boffa C, Akhtar MZ, et al. New classification of donation after circulatory death donors definitions and terminology. Transpl Int [Internet]. 2016 Jul 1 [cited 2024 Mar 5];29(7):749–59. Available from: https://pubmed.ncbi.nlm.nih.gov/26991858/

46. Fallani G, Stocco A, Siniscalchi A, Antonini MV, Stella AP, Amato A, et al. Beyond the Concepts of Elder and Marginal in DCD Liver Transplantation: A Prospective Observational Matched-Cohort Study in the Italian Clinical Setting. Transpl Int [Internet]. 2023 Sep 7 [cited 2024 Mar 5];36. Available from: https://pubmed.ncbi.nlm.nih.gov/37736400/

47. Sasaki K, Nair A, Firl DJ, McVey JC, Moro A, Diago Uso T, et al. Conditional probability of graft survival in liver transplantation using donation after circulatory death grafts - a retrospective study. Transpl Int [Internet]. 2021 Aug 1 [cited 2024 Mar 5];34(8):1433–43. Available from: https://pubmed.ncbi.nlm.nih.gov/33599045/

48. Croome KP, Mathur AK, Aqel B, Yang L, Taner T, Heimbach JK, et al. Classification of Distinct Patterns of Ischemic Cholangiopathy Following DCD Liver Transplantation: Distinct Clinical Courses and Long-term Outcomes From a Multicenter Cohort. Transplantation [Internet]. 2022 Jun 1 [cited 2024 Mar 5];106(6):1206–14. Available from: https://pubmed.ncbi.nlm.nih.gov/34468429/

49. Taylor R, Allen E, Richards JA, Goh MA, Neuberger J, Collett D, et al. Survival advantage for patients accepting the offer of a circulatory death liver transplant. J Hepatol [Internet]. 2019 May 1 [cited 2024 Mar 5];70(5):855–65. Available from: https://pubmed.ncbi.nlm.nih.gov/30639505/

50. Tingle SJ, Dobbins JJ, Thompson ER, Figueiredo RS, Mahendran B, Pandanaboyana S, et al. Machine perfusion in liver transplantation.

Cochrane Database Syst Rev [Internet]. 2023 Sep 12 [cited 2024 Mar 5];9(9). Available from: https://pubmed.ncbi.nlm.nih.gov/37698189/

51. Tschuor C, Ferrarese A, Kuemmerli C, Dutkowski P, Burra P, Clavien PA, et al. Allocation of liver grafts worldwide - Is there a best system? J Hepatol [Internet]. 2019 Oct 1 [cited 2024 Mar 5];71(4):707–18. Available from: https://pubmed.ncbi.nlm.nih.gov/31199941/

52. Persad G, Wertheimer A, Emanuel EJ. Principles for allocation of scarce medical interventions. Lancet [Internet]. 2009 [cited 2024 Mar 5];373(9661):423–31. Available from: https://pubmed.ncbi.nlm.nih.gov/19186274/

53. Frith J, Newton J. Liver transplantation in more elderly age. Transpl Int [Internet]. 2009 Jun [cited 2024 Mar 5];22(6):599–600. Available from: https://pubmed.ncbi.nlm.nih.gov/19490546/

54. Tajir K, Shimizu Y. Liver physiology and liver diseases in the elderly. World J Gastroenterol [Internet]. 2013 Dec 14 [cited 2024 Mar 5];19(46):8459–67. Available from: https://pubmed.ncbi.nlm.nih.gov/24379563/

55. Gómez Gavara C, Esposito F, Gurusamy K, Salloum C, Lahat E, Feray C, et al. Liver transplantation in elderly patients: a systematic review and first meta-analysis. HPB. 2019 Jan 1;21(1):14–25.

56. Mohan BP, Iriana S, Khan SR, Yarra P, Ponnada S, Gallegos-Orozco JF. Outcomes of liver transplantation in patients 70 years or older: a systematic review and meta-analysis. Ann Hepatol [Internet]. 2022 Nov 1 [cited 2024 Mar 5];27(6). Available from: https://pubmed.ncbi.nlm.nih.gov/35835365/

57. Durand F, Levitsky J, Cauchy F, Gilgenkrantz H, Soubrane O, Francoz C. Age and liver transplantation. J Hepatol [Internet]. 2019 Apr 1 [cited 2024 Mar 5];70(4):745–58. Available from: https://pubmed.ncbi.nlm.nih.gov/30576701/

58. Età | S.I.T.O - società italiana trapianti d’organo [Internet]. [cited 2024 Mar 5]. Available from: https://www.societaitalianatrapiantidiorgano.com/eta/

59. De Gasperi A, Petrò L, Cerutti E. Liver Transplantation and the Elderly Candidate: Perioperative Considerations. Anesthesiol Clin

[Internet]. 2023 Sep 1 [cited 2024 Mar 5];41(3):595–611. Available from: https://pubmed.ncbi.nlm.nih.gov/37516497/

60. Pilotto A, Ferrucci L, Franceschi M, D'Ambrosio LP, Scarcelli C, Cascavilla L, et al. Development and validation of a multidimensional prognostic index for one-year mortality from comprehensive geriatric assessment in hospitalized older patients. Rejuvenation Res [Internet]. 2008 Feb 1 [cited 2024 May 30];11(1):151–61. Available from: https://pubmed.ncbi.nlm.nih.gov/18173367/

61. Pilotto A, Custodero C, Maggi S, Polidori MC, Veronese N, Ferrucci L. A multidimensional approach to frailty in older people. Ageing Res Rev [Internet]. 2020 Jul 1 [cited 2024 May 30];60. Available from: https://pubmed.ncbi.nlm.nih.gov/32171786/

62. Warnier RMJ, van Rossum E, van Velthuijsen E, Mulder WJ, Schols JMGA, Kempen GIJM. Validity, Reliability and Feasibility of Tools to Identify Frail Older Patients in Inpatient Hospital Care: A Systematic Review. J Nutr Health Aging [Internet]. 2016 Feb 1 [cited 2024 May 30];20(2):218–30. Available from: https://pubmed.ncbi.nlm.nih.gov/26812520/

63. Stepanova M, Kabbara K, Mohess D, Verma M, Roche-Green A, AlQahtani S, et al. Nonalcoholic steatohepatitis is the most common indication for liver transplantation among the elderly: Data from the United States Scientific Registry of Transplant Recipients. Hepatol Commun [Internet]. 2022 Jul 1 [cited 2024 Jun 27];6(7):1506. Available from: /pmc/articles/PMC9234626/

64. Haldar D, Kern B, Hodson J, Armstrong MJ, Adam R, Berlakovich G, et al. Outcomes of liver transplantation for non-alcoholic steatohepatitis: A European Liver Transplant Registry study. J Hepatol [Internet]. 2019 Aug 1 [cited 2024 Jun 27];71(2):313. Available from: /pmc/articles/PMC6656693/