Digestive and Liver Disease 56 (2024) 1343–1349

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Trends in liver transplantation for primary sclerosing cholangitis

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ARTICLE INFO

Article history:
Received 18 September 2023
Accepted 8 January 2024
Available online 16 January 2024

Keywords:
Cholangiocarcinoma
Liver transplantation
PSC recurrence

ABSTRACT

Background: Primary sclerosing cholangitis is a cholestatic disease with a low prevalence in Italy. Indications for liver transplantation and the time of listing are not stated.
Aim: We performed a national survey to investigate the listing criteria, comorbidities, and outcomes.
Methods: In April 2022, we surveyed liver transplantation in primary sclerosing cholangitis nationwide for the last 15 years.
Results: From 2007 to 2021, 445 patients were included on waiting lists, and 411 had undergone liver transplants. The median age at transplantation was 46 years (males 63.9%); 262 patients (59%) presented an inflammatory bowel disease. Transplants increased over the years, from 1.8 % in 2007 to 3.0 % in 2021. Cholangitis (51%) and hepatic decompensation (45%) were the main indications for listing. The disease recurred in 81 patients (20%). Patient survival after the first transplant was 94 %, 86% and 84% at one, five, and ten years. Twenty-four died in the first year (50% surgical complications, 25% infections); 33 between one to five years (36% recurrence, 21% cholangiocarcinoma recurrence) and nine after five years (56% de novo cancer, 44% recurrence).

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https://doi.org/10.1016/j.dld.2024.01.175

Conclusions: Primary sclerosing cholangitis has been an increasing indication for transplantation in Italy. Cholangitis and decompensation were the main indications for listing. Recurrence and cancer were the leading causes of death.

1. Introduction

Primary sclerosing cholangitis (PSC) is a cholestatic chronic liver disease characterised by bile ducts inflammation and progressive peribiliary fibrosis, intra- and extra-hepatic bile duct damage and stenosis leading to recurrent cholangitis, decompensated cirrhosis and liver failure or cholangiocarcinoma (CCA). It is predominant in males and strongly associated with inflammatory bowel disease (IBD), mainly ulcerative colitis [1]. PSC is a rare disease, with the lowest prevalence in the Mediterranean regions of Europe and the highest in the Scandinavian regions; in Italy, the crude incidence rate between 2012 and 2014 was 0.10 per 100,000 individuals [2]. In a recent systematic review aiming to quantify the epidemiology of PSC, incidence and prevalence appeared to rise across Europe and North America, alongside reported increases in PSC liver transplantation (LT) activity [3]. Patients with PSC-IBD have a four-fold higher risk of colorectal cancer (CRC). PSC also increases the risks of cholangiocarcinoma (CCA) (hazard ratio, HR:28.46), hepatocellular carcinoma (HR:21.00), pancreatic cancer (HR: 5.26), and gallbladder cancer (HR:9.19) [4]. At present, there is no medical therapy that can modify the natural history of the disease, and LT is the only effective treatment option. Among all the indications for LT, PSC has the highest long-term survival with reported five- and ten-year survival rates of 79% and 70%, respectively [5]. Recurrence of PSC (rPSC) occurs in almost 25% of LT recipients and negatively impacts survival; usually, it appears within five years after transplantation, and the main symptoms are cholangitis, itching and liver failure with cholestasis.

Due to its rarity, indications for LT and the timing of listing PSC patients are not clearly defined overall, particularly in countries with a low prevalence, such as Italy. In addition, controversy exists among centres regarding the choice of immunosuppressive therapy and management of post-transplant PSC-specific complications.

To investigate the listing criteria and timing for LT in PSC, we performed a national survey including most of the LT centres in Italy. We evaluated the pre-transplant management of PSC-related comorbidities, the post-transplant outcome, and the approach to post-transplant prevalent complications.

Finally, one of the aims was to compare the features of patients with rPSC with those without recurrence after transplantation.

2. Materials and methods

In April 2022, a web-based survey was sent to all LT centres in Italy. The questionnaire included the clinical feature, indications, and outcomes after LT of patients affected by PSC listed and transplanted from January 2007 to December 2021. Moreover, immunosuppression protocols, follow-up and management of post-transplant procedures were also registered. Criteria for diagnosis of rPSC after LT were all age patients affected recurrence of disease, according to the established Mayo criteria: cholangiography (Magnetic Resonance Cholangiopancreatography) (MRCP) or Endoscopic Retrograde Cholangiography) (ERC) showing intrahepatic and/or non-anastomotic extrahepatic biliary strictures, occurring >90 days after LT or a liver histology showing fibrous cholangitis or fibro-obliterative lesions in the absence of artery thrombosis or stenosis, chronic rejection, or ABO incompatibility [6]. Dominant strictures were defined as a stenosis ≤1.5 mm in diameter of the common bile duct and/or ≤ 1.0 mm of the right or left hepatic duct [7]. The 40-question survey was fully reported in supplementary Table 1. Research Electronic Data Capture (REDCap) web software was used for building, managing online survey and database, finally securely downloaded the responses. Descriptive analyses were performed for the PSC study cohort.

We performed the Kaplan-Meier survival graph, displaying the overall patients' survival in the study cohort.

This study was conducted in accordance with ethical guidelines of the World Medical Association's Declaration of Helsinki [8].

3. Results

Seventeen out of 21 (81%) Italian LT centres completed the survey. A total of 14,709 LTs have been performed by the 17 centres, with a median number of transplants per centre of 627 (range 200–2089). From 1 January 2007 to 31 December 2021, 445 patients with PSC were listed for LT, and 411 were transplanted, accounting for 3% of all transplants. The main indication for LT was recurrent cholangitis in 51% of patients, followed by decompensated cirrhosis in 45%, dominant strictures with brush cytology suspicious for malignancy in 2%, and finally, CCA in the remaining 2% of cases. We listed the main features of the study population in Table 1. Over 15 years, PSC-transplants increased progressively from 20 to 42 per year, representing 1.8 % in 2007 and 3.0 % in 2021 of all LT performed, respectively (Fig. 1). The median age at the listing was 46 years (range 18–73), with a prevalence of males (63.9%). Fig. 2 represents the number of patients listed and transplanted for each single centre and the age distribution at the time of the listing.

3.1. Patients' comorbidities and complications before LT

Regarding comorbidities, 262 patients (59%) presented with inflammatory bowel disease. IBD was more frequent in males (67%) than in females (40%), while other immune diseases such as rheumatoid arthritis, thyroiditis or sicca syndrome were more frequent in females (41%) than in males (17%).

Pre-LT IBD treatment included mesalazine (93.8%), steroids (87.5%), azathioprine (62.5%), and biologics (56.3%).

Drop-outs or deaths on the waiting list involved 27 out of 445 patients (6%), and the principal causes were infections in 25% of cases, too sick for LT in 37%, CCA occurrence in 25%, and CRC in 8%. At that time, eight (1.8%) recipients were currently on the waiting list or had been removed for clinical improvement.

Perihilar CCA was an uncommon LT indication and accepted only by 5 out of 17 (29%) centres; all those five centres applied the pre-LT Mayo protocol [9]. In the presence of a new "relevant stricture," detected on MRCP and defined as any stricture of the common hepatic duct or hepatic ducts associated with signs or symptoms of obstructive cholestasis and/or bacterial cholangitis or suspected for CCA, 88% of the centres used ERC with brushing to rule out biliary dysplasia or CCA; 52% of the centres also performed a choledochoscopy-guided biopsy with micro-sampling for histopathology. Incidental CCA was found in the explanted liver of 19 (4.6% of LT for PSC) patients; 11 out of 19 cases were extrahepatic CCA (57%).

Table 1
Main features of patients with PSC listed and transplanted from 2007 to 2021.

Patients' features	
N of overall liver transplanted patients	14,709
N of PSC listed patients	445
N/% of PSC transplanted patients	411 (3%)
Median age at listing (y)	46 (18–73)
SEX	
• M	63.9%
• F	36.1%
Primary indication for LT%:	
• Recurrent cholangitis	51%
• Decompensation of liver disease	45%
• CCA	2%
• Dominant strictures suspected for CCA	2%
Patients with IBD (%)	59%
	67%
• M	40%
• F	
Pre-LT IBD treatment:	
• Mesalazine	93.8 %
• Steroids	87.5 %
• Azathiloprine	62.5 %
• Biologics	56.3 %
Dropouts during waiting on the transplant list:	27 (6%)
• Too sick for LT	10 (37%)
• For infections	7 (25%)
• CCA occurrence	7 (25%)
• CRC occurrence	2 (8%)
Acceptance of Perihilar CCA as LT indication	5 Centers (29%)
In case of new "relevant stricture" at MRI centers performed:	
• CA 19-9	94.1%
• MRCP	82.4%
• ERC with brushing	88%
• CT scan	52.9%
• Choledochoscopy-guided biopsy	52%
Incidental CCA at explant:	19 (5%)
Intrahepatic	11 (57%)
Extrahepatic	8 (43%)
Recurrent CCA after LT	10 (52%)
Biliary anastomosis:	
• Roux-en-Y	11 Centres (64.7%)
• Duct-to-duct	6 Centres (35.3%)
Immunosuppressive treatment	
Induction	
• Basiliximab	70%
• Nothing	29%
• Anti-thymocyte globulins	17%
Steroids discontinuation	70% (3–12 months)
Maintenance	
• Tacrolimus	88%
• MMF	76%
• Steroids	58%
• Everolimus	17%
• Azathioprine	17%
• Cyclosporine	12%
• Sirolimus	0%
PostLT follow up	
• Protocol MRCP	82.4% Yes; 17.6% Not
• Protocol liver biopsies	5.9% Yes; 94.1% Not
• Protocol VCTE	47.1% Yes; 52.9% Not
• Protocol colonscopies	88.2% Yes; 11.8% Not
rePSC as indication to retransplantation	87% Yes; 12% Not
Rates of retransplantation for rePSC	22/81 (27%)
Median age between first and second LT (months)	36 (9–108)
Changes in the immunosuppression after retransplantation	14% Yes; 85% Not

Abbreviations: CCA, cholangiocarcinoma; CRC, colorectal cancer; CT, computed tomography; ERC, endoscopic retrograde cholangiography; F, females; IBD, inflammatory bowel disease; LT, liver transplantation; M, males; MMF, mycophenolate mofetil; MRCP, magnetic resonance cholangiopancreatography; N, number; PSC, primary sclerosing cholangitis; RA, rheumatoid arthritis; UC, ulcerative colitis; VCTE, vibration-controlled transient elastography; Y, years.

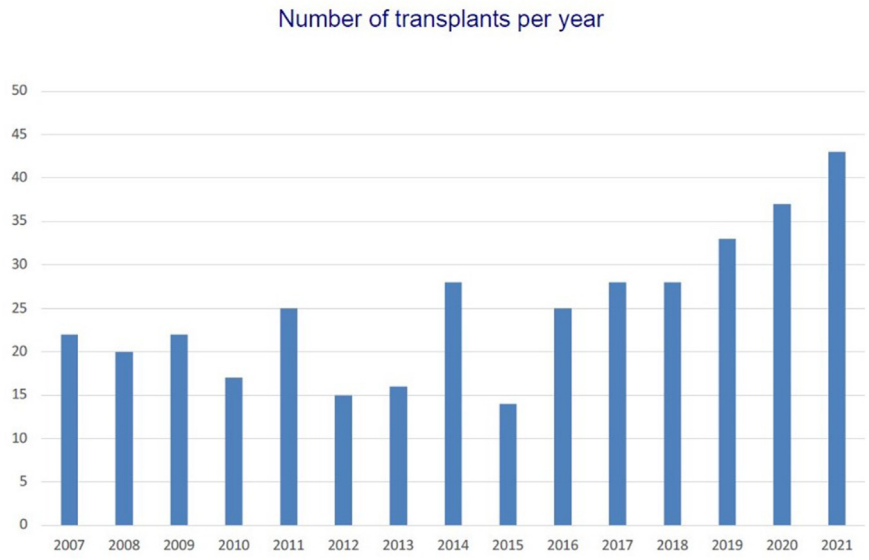


Fig. 1. Trend in the number of liver transplants for PSC from 2007 to 2021.

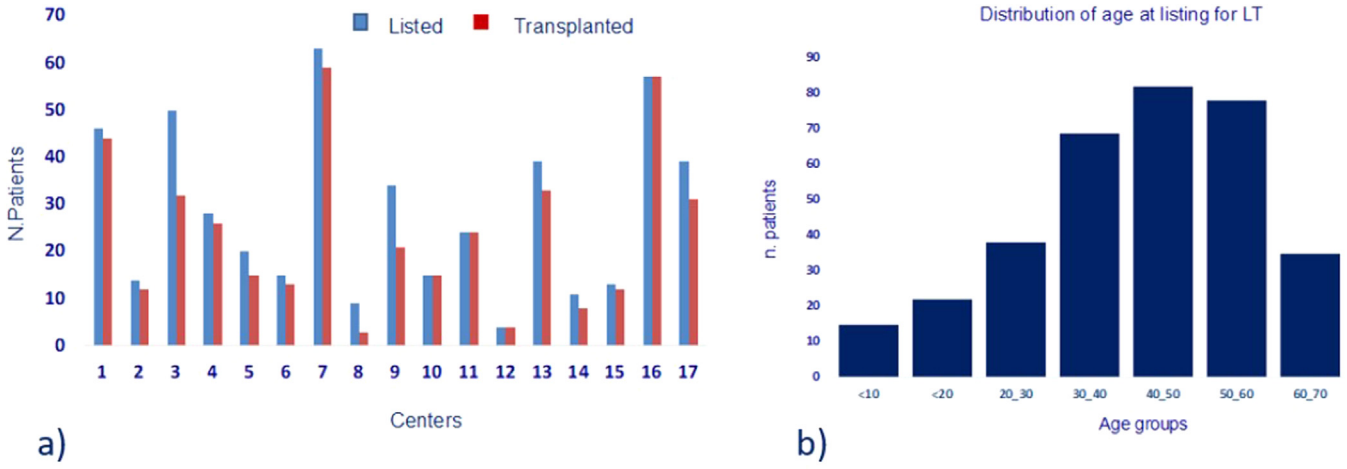


Fig. 2. a) Number of patients respectively listed and transplanted for each single centre; b) the age distribution at the time of the listing.

3.2. Post-transplant management

Sixty-four percent of the centres performed biliary-digestive anastomosis, whereas, when feasible, 36% preferred duct-to-duct anastomosis.

Concerning immunosuppression, most of the centres (12/17, 71%) utilised induction therapy with basiliximab, whereas tacrolimus was the leading immunosuppressive therapy maintained in all but one centre. Tacrolimus plus mycophenolate mofetil (MMF) was the combined therapy of choice in 76% of the centres, whereas only five (29%) continued steroids in the long term.

To detect rPSC, 14/17 (82%) centres performed MRCP protocol, while vibration-controlled transient elastography (VCTE) was applied in 47% to stage fibrosis. Only one centre performed yearly liver biopsies.

For recipients with ulcerated colitis (UC), annual colonoscopies were performed in almost all centres (88%).

IBD flareups after LT occurred in 16 patients. Of these, 25% of cases had graft dysfunction (increased transaminases, indicators of cholestasis or cholangitis).

Transplant centres treated IBD flareups with steroids (87.5%), vedolizumab (31.3%), other biologics (37.5%) and additional therapies (12.5%).

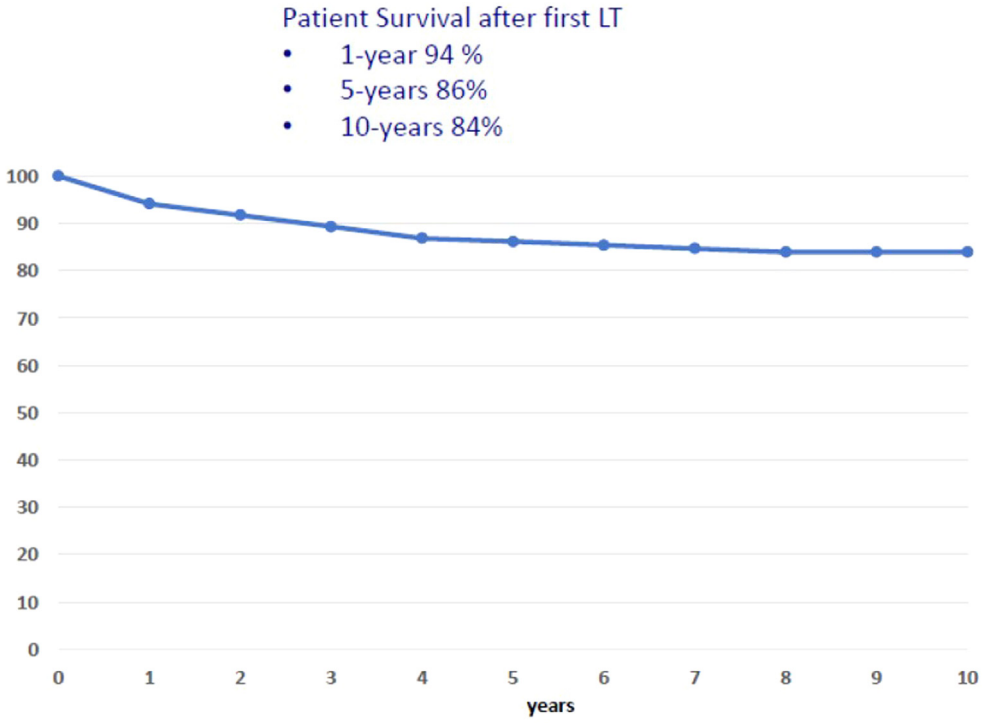
Finally, 17 patients underwent colectomy after LT.

3.3. Outcomes

Patient survival after the first LT was 94 %, 86% and 84% at one, five, and ten years, respectively (Fig. 3).

Overall mortality at 15 years was 66/411 (16%). Twenty-four out of 66 (36%) patients died within the first year following LT, and the leading causes of death were surgical complications (50%) or postoperative infections (25%). Thirty-three patients died between one to five years; rPSC (36%), and occult CCA recurrence (21%) were the leading causes. After five years of LT, nine recipients died, and the most common cause of death was de novo cancer, mainly CRC.

Occult CCA was detected in the explanted liver of 19 patients and 11 (57%) died, 10 patients for tumor progression. rPSC was diagnosed in 81 patients (20%), 24% in the first year, 64% in the first three years, and 91% in the first five years. The prevalence of rPSC varied between centres, according to surveillance proto-



Patients at Risk	411	387	377	367	357	354	351	348	345	345
Patients alive	387	377	367	357	354	351	348	345	345	345

Fig. 3. Kaplan–Meier survival analysis of patients.

cols; the only centre performing procedural liver biopsies reported a higher prevalence than those that did not (24 % vs. 15%).

Recurrence was symptomatic in 69% of the recipients, and the main symptoms were cholangitis (66%), pruritus (86%) and jaundice (60%). rPSC occurred in 84% of patients with IBD-PSC and 16% of patients with PSC alone.

Almost all centres (15 out of 17) accepted rPSC as an indication for retransplantation, and nearly all maintained the same immunosuppressive protocol after the second LT.

The survival rate of the twenty-two patients who underwent a second LT due to PSC recurrence was 63% at five years.

Median time from first e second LT was 36 months (9–108). Regarding the patients undergoing retransplantation for rPSC, 15 out of 22 were alive at the last follow-up, and six had died (two due to sepsis, one due to bile cast syndrome, one due to primary non-function, and two due to new recurrence of PSC).

Four patients who experienced early recurrence after the second LT had to undergo a third transplant; two died, one in the postoperative period and the other for rPSC after five years.

4. Discussion

According to studies from other countries, the data from the Italian Survey showed an increasing rate of LT for PSC over time, reaching 3% of all indications in 2021 [10]. The principal clinical characteristics of the Italian population were quite similar to those described in the European registries [11]. The leading indication for LT was recurrent cholangitis and decompensated cirrhosis, while stenosis suspected for CCA was uncommon, accounting for 2% of all PSC transplants.

Indication for LT in the presence of stenosis suspicious of malignancy is controversial and differs among centres worldwide. In the Northern European centres, brush cytology with dysplasia on one or repeated brushing, without visible intrahepatic mass, is an accepted indication for LT, reaching 14 % of all transplants in PSC patients [12]. The low rate of transplants for suspected malignant stenosis in the Italian population suggests the need to improve the diagnostic workup of PSC patients to identify pre-cancerous lesions or detect early-stage CCA. CCA in patients with PSC is assumed to develop by gradual progression from normal biliary epithelium via dysplastic changes and finally to malignant transformation. Therefore, a surveillance protocol with MRCP with a hepatobiliary contrast-enhancement agent is recommended annually and in the case of a change in clinical status or concerns for CCA [13]. Regarding the pre-LT period the survey showed a relatively homogeneous behavior etween centres in the pre-LT management of complications. The appearance of a new biliary stricture at MRCP constitutes one of the significant diagnostic and therapeutic dilemmas in the workup of PSC patients because some of them may present asymptomatic stenosis and endoscopic brushing and treatment could trigger complications such as cholangitis or pancreatitis worsening the disease course [14]. Otherwise, some studies showed that endoscopic treatment of stenosis is associated with improvement of symptoms and cholestasis and could detect CCA in an earlier phase [15]. In the present survey, many of the centres opted for an endoscopic diagnosis and treatment of relevant stenosis to improve cholestasis due to stenosis or to rule out the presence of CCA.

Regarding immunosuppression protocol, cyclosporine or tacrolimus has been suggested to impact PSC recurrence. A Nordic multicentre study indicated that cyclosporine had been

associated with a low prevalence of rPSC when compared to tacrolimus [16], while in more recent studies no benefit in the use of cyclosporine has been reported [17]. In the Italian PSC-transplant population, the prevalent immunosuppressive protocol included induction therapy with basiliximab and tacrolimus plus MMF in the maintenance without steroids, only a minority of the centres utilised cyclosporine as primary immunosuppressive therapy. We observe that in our centres PSC recipients received mainly the same immunosuppressive regimens utilised for other indications.

Regarding follow-up after LT to evaluate rPSC, all centres performed MRCP, while only one routinely performed graft biopsies. In this centre, the diagnosis of recurrence was the highest; histological findings of rPSC could anticipate the radiological diagnosis, but it is not clear if an earlier diagnosis could improve the outcome. Compared to other more expansive studies, mortality and dropoutson the waiting list were relatively low in Italy. This may, in part, be related to the high priority given since 2015 to patients with previous serious infections in the organ allocation system in Italy [18,19]. Appearance of CCA or CRC during the waiting list time was the leading cause of dropout along with clinical worsening. In our experience, post-transplant survival in PSC recipients was the highest among all the etiologies, with a good long-term survival (86% at five years).

While technical surgical causes were the primary cause of one-year mortality or retransplantation, rPSC and occult CCA-recurrence were the main causes of mortality in the medium and long-term periods. Notably, we observed many occult CCAs detected in the explanted liver. According to a previous study, mortality was high reaching 57% in one year [20]. In the present study, the death rate for recurrence of occult CCAis relatively high, accounting for 10 out of 19 patients (52.6%). Our data confirm that the diagnosis of CCA on PSC is often challenging to achieve and all the procedures used to date are characterised with low sensitivity, suggesting the need to improve diagnostic workup to exclude CCA before LT. rPSC negatively impacts long-term patient survival; an European Liver Transplant Registry (ELTR) study by Vissern et al. reported a reduced patient survival with an HR of 2.31 among patients with rPSC [5].

Our experience confirms the results published by Visseren in 2021 regarding the significant impact of rPSC on patient survival. In that study, the appearance of rPSC in the first five years caused a drop in the probability of survival at 15 years from 82 to 64% [5].

However, the same authors showed that the patient survival after the second transplant for rPSC was comparable to retransplantation for other causes and appeared to be an acceptable option [5].

In another ELTR study by Berenguer et al. rPSC was the cause of death in a small minority of cases (1.8%). The reason could be in the different eras considered. To the countrary, Berenguer et al. included LT patients for PSC from three decades earlier; moreover, in the same study, rPSC had a lower impact on patient survival. The reason for this difference is unclear: 25.8% of the death causes were not reported in the ELTR registry; in contrast, in our survey, we registered all causes of death. In addition, the criteria for rPSC diagnoses were established in 1999 [6]; therefore, this could have been underestimated in patients who died before this year.

Retransplantation remains a controversial option in those patients.

Additionally, in Italy, most of the centres accepted rPSC as an indication for retransplantation, and our data confirms lower patient survival compared to the first transplant (63% at five years vs. 86 % respectively).

Unfortunately, we do not have survival data for LTs in the Italian centres that participated in the survey due to causes other than PSC.

However, the data published by the National Transplant Center on patient survival in the adult population of LT recipients between 2000 and 2020 showed a one-year and five-year survival of all transplants performed in Italy (data including PSC) of 87.2% and 72.8%, respectively.

Even if the observation period we considered in this survey is slightly different (2007–2021), it is the data closest to Italian real life [21].

These results suggest that PSC has an overall better outcome than other etiologies in Italy (94 and 86% at one and five years, respectively).

In conclusion, our study confirms the trend of increasing indication for LT in PSC, with high long-term patient survival. CCA diagnosis during waiting list time or as occult CCA in the liver explant is the leading cause of mortality pre-transplant or in the short-term period after LT, thus underlying the absence of high-sensitivity diagnostic strategies to intercept early CCA or high-grade dysplasia.

The survey, moreover, indicated a relative homogeneity in the pre- and post-transplant management of PSC patients among LT centres in Italy. rPSC remained the principal cause of morbidity and mortality in the long term. However, data derived from our experience, although limited, seem to support that retransplantation is an affordable option for these patients.

The limitations of our study include that although the surveys provide essential information, some questions were multiple choice, so there were no alternative options or free text comments. However, to our knowledge, this is the first study of its kind on the Italian PSC population undergoing LT.

Another limitation of the survey regards the lack of information regarding the type of IBD associated with PSC, the timing of colectomy after the LT, and the features regarding maintenance of therapy to prevent flareups of IBD.

However, at present, there is no data to support routine pre-vs. post-LT colectomy timings regarding the safety and efficacy of the colonic resection. Subjects with liver cirrhosis could be considered at greater risk of morbidity and mortality after gut surgery [22].

In this national multicentre cohort, rPSC occurred in 84% of patients with IBD-PSC and 16% of patients with PSC alone.

Consequently, subjects, carriers of PSC and IBD, should have more intensive follow-up due to a higher risk of rPSC.

Finally, we will use the data from the survey to conceptualise prospective studies to determine risk factors for the rPSC on LT.

Collaborators

Other members of PSC-LiTra study group.

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Funding statement

This manuscript has not been funded.

Availability of data and material

All data are available in the electronic archives of the IRCCS Azienda Ospedaliero-Universitaria di Bologna.

Conflict of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

Acknowledgments

The authors thank the heads of the Hepatobiliary Surgery and Liver Transplantation Units of Italian centres involved in the survey for their valuable contribution to patient management:

Paolo De Simone, Umberto Baccarani, Umberto Cillo, Lucio Caccamo, Salvatore Agnes, Giuseppe Tisone, Renato Romagnoli, Giovanni Vennarecci, Francesco Tandoi, Marco Vivarelli, Fabrizio Di Benedetto, Enzo Adorno, Luciano De Carlis, Amedeo Carraro, Giuseppe Maria Ettorre, Matteo Cescon, Michele Colledan, Fausto Zamboni.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2024.01.175.

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