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The role of an integrated referral program for patients with liver disease: A network between hub and spoke centers

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Abstract

Introduction: Access to Liver transplantation (LT) can be affected by several barriers, resulting in delayed referral and increased risk of mortality due to complications of the underlying liver disease.

Aim: To assess the clinical characteristics and outcomes of patients with acute or chronic liver disease referred using an integrated referral program.

Materials and Methods: An integrated referral program was developed in 1 October 2017 based on email addresses and a 24/7 telephone availability. All consecutive adult patients with liver disease referred for the first time using this referral program were prospectively collected until 1 October 2021. Characteristics and outcomes of inpatients were compared with a historical cohort of patients referred without using the integrated referral program (1 October 2015—1 October 2017). Patients were further divided according to pre- and post-Covid-19 pandemic.

Results: Two hundred eighty-one referred patients were considered. End stage liver disease was the most common underlying condition (79.3%), 50.5% of patients were referred as inpatients and 74.7% were referred for LT evaluation. When inpatient referrals ($n = 142$) were compared with the historical cohort ($n = 86$), a significant increase in acute liver injury due to drugs/herbals and supplements was seen ($p = 0.01$) as well as an increase in End stage liver disease due to alcohol-related liver disease and NASH, although not statistically significant. A significant increase in referrals for evaluation for Trans-jugular intrahepatic portosystemic shunt placement was seen over time (5.6% vs. 1%; $p = 0.01$) as well as for LT evaluation (84.5% vs. 81%; $p = 0.01$). Transplant-free survival was similar between the study and control groups ($p = 0.3$). The Covid-19 pandemic did not affect trends of referrals and patient survival.

Conclusions: The development of an integrated referral program for patients with liver disease can represent the first step to standardize already existing referral networks between hub and spoke centers. Future studies should focus on the timing of referral according to different etiologies to optimize treatment options and outcomes.

KEYWORDS
acute, chronic, end stage liver disease, hub, liver disease, liver transplantation, mortality, OLT, referral program, spoke

INTRODUCTION

Liver disease accounts for approximately 2 million deaths per year worldwide, especially due to viral hepatitis, cirrhosis and hepatocellular carcinoma (HCC).[1] Liver disease is also associated with extrahepatic co-morbidities, increased healthcare costs and impairment in quality of life.[2,3] Liver transplantation (LT) represents an effective therapeutic option for a relevant number of patients with end-stage liver disease (End stage liver disease (ESLD)) and acute liver failure (ALF). Current guidelines define access to LT as a quality measure for the management of patients with ESLD.[4–6] However, high heterogeneity exists in terms of indications and timing of referral, often resulting in delayed referral to LT centers and increased risk of mortality.[7–9] Several patients with advanced liver disease may remain stable for a long time after their first decompensation episode, and are therefore referred only if a second acute decompensating event occurs. Similarly, patients with hepatocellular carcinoma (HCC) may be treated locally without considering LT as a therapeutic option.

In this setting, pilot programs involving peripheral and tertiary hospitals have been developed worldwide, offering integrated care for patients with ESLD, especially if potential LT candidates.[10–12]

Nevertheless, published data on indications, timing and methods for referring patients with liver disease to LT centers are heterogeneous, mainly because of several differences in LT programs internationally,[13] but also at the local level, where epidemiological, ethical and cultural disparities, as well as differences in indications for LT exist.[14–17]

In Italy, an effort to define criteria and timing of referral for patients with acute and chronic liver disease has recently been proposed by a panel of transplant hepatologists appointed by the Italian Association for the study of the Liver,[18] however no data have yet been published on the availability of referral systems. Therefore, the aim of this study was to assess characteristics and outcomes of patients with liver disease referred to the Multivisceral Transplant Unit, Padua University Hospital, using an integrated referral program, and to compare outcomes with those of a historical cohort of patients referred before the introduction of this referral program.

Key summary

Established knowledge on this subject

- Heterogeneity exists in terms of indications and timing of referral to liver transplantation.
- In patients with liver disease delayed referral often results in increased risk of mortality.
- Available data on indications, timing and methods for referring patients with liver disease to liver transplant centers are heterogeneous.

Significant new findings of this study

- The implementation of the integrated referral program standardized a common clinical practice, previously based on personal contacts.
- More clinicians working in spoke hospitals can have access to the referral system.
- This program can help in the organization of care needs such as number of dedicated beds, personnel required.

MATERIAL AND METHODS

Integrated referral program

An integrated referral program was developed from 1 October 2017 at the Multivisceral Transplant Unit, Padua University Hospital (Italy). A dedicated email address with an electronic format and a 24/7 telephone availability were implemented, allowing referring hospitals to contact the Multivisceral Transplant Unit to refer patients with acute and chronic liver disease and with potential indication for LT. Each case was further discussed directly with referral clinicians , and in selected cases, patients were referred back to the referring hospital with a plan for combined management.

Referred patients were stratified according to the timing of referral (urgent vs. non-urgent) and type of requested evaluation

(out-patient vs. in-patient). Patients were also divided according to underlying liver disease: ESLD, acute liver injury (ALI), ALF. Patients with ESLD were further classified according to the presence of acute decompensation (AD) or acute-on-chronic liver failure (ACLF). Patients with ALF were granted immediate admission, whereas patients with severe ALI,[19] ACLF and selected cases of AD (e.g., patients with acute variceal bleeding) were considered urgent and therefore transferred as soon as possible, within 48 h from the referral request. Clinical meetings between referring clinicians and transplant hepatologists were planned at fixed time points (i.e., every 6 months) in order to evaluate the outcomes of referred patients.

Study design

This was an observational, retrospective study of prospectively collected data. All adult patients with liver disease who were referred for the first time to the Multivisceral Transplant Unit from 1 October 2017 to 1 October 2021 using the integrated referral program were prospectively collected. For each patient, the following clinical characteristics were collected: age, gender, etiology and severity of liver disease (according to the current guidelines[19,20]), presence/absence of HCC. The timing and type of referral of each patient were further considered. Outcomes were evaluated in terms of Transplant-free survival (TFS) (TSF), death, and need for Intensive Care Unit (ICU) admission until October 2022. In-patient characteristics and outcomes were compared with those of a historical cohort of patients who were referred to the Multivisceral Transplant Unit 2 years before the introduction of the above-mentioned integrated referral program (1 October 2015—1 October 2017), and defined as the control group.

Statistical analysis

Variables were reported as frequencies or median (IQR), as appropriate. Categorical and continuous variables were compared using Fisher's exact test, Pearson's test, or Mann Whitney *U* test, as appropriate. Transplant-free survival and post-LT survival was assessed using Kaplan–Meier estimates; survival curves were compared using the log-rank test. Statistical significance was assessed for p values < 0.05. Data analysis was performed using SPSS version 19 (Chicago, Illinois, USA).

RESULTS

Study population

332 patients were referred for the first time to the Multivisceral Transplant Unit using the integrated referral program. Amongst these, 15.3% patients were not considered for referral due to the following reasons: improvement of clinical conditions (45%), death (37%), medical contraindications (10%), and patients' refusal (8%). Therefore, 281 referred patients (males 61.2%, median [IQR] age 55.1 years [47.5–62.8 years]) were considered for this study (Table 1). 240/281 patients were referred from hospitals of the Veneto Region, and 23/281 patients were referred from hospitals of other Italian Regions. 42% were considered urgent referrals, and 50.5% were referred for in-patient evaluation (Figure 1).

TABLE 1 Clinical characteristics of 281 referred patients.

	***n* (%)**
Gender, male, *n* (%)	172 (61.2)
Age, years, median (IQR)	55.1 (47.5–62.8)
Source of referrals, *n* (%)	
Veneto region	240 (85.4)
Other regions	41 (14.6)
Underlying liver disease at referral, *n* (%)	
ESLD	223 (79.4)
ALI	34 (12.1)
ALF	14 (4.9)
Chronic hepatitis/NCPH	10 (3.6)
Child pugh score[a], median (IQR)	9 (8–11)
Child pugh score[a], class, *n* (%)	
A	29 (13)
B	93 (41.7)
C	101 (45.3)
MELD score[a], median (IQR)	18.2 (13.5–24.6)
MELD-Na[a], median (IQR)	22.5 (16.5–27.5)
HCC, yes, *n* (%)	30 (10.7)
Timing of referral, *n* (%)	
Urgent	119 (42.3)
Standard	162 (57.7)
Type of referral, *n* (%)	
Out-patient	139 (49.5)
In-patient	142 (50.5)
Indications for referral, *n* (%)	
Evaluation for LT	210 (74.7)
Evaluation for TIPS placement	28 (10)
Clinical management	36 (12.8)
Treatment of HCC	7 (2.5)

Abbreviations: ALF, acute liver failure; ALI, acute liver injury; ESLD, end-stage-liver-disease; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; NCPH, non cirrhotic portal hypertension; TIPS, Trans-jugular intrahepatic portosystemic shunt.

[a]only for patients with ESLD.

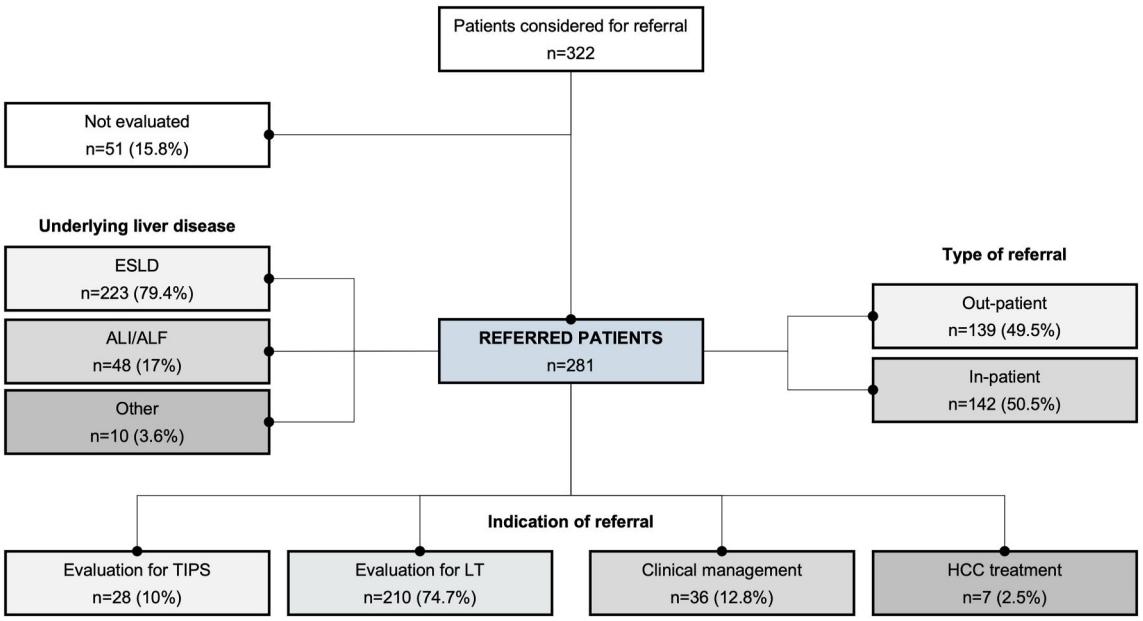

FIGURE 1 Indications for referral during the study period. ALF, acute liver failure; ALI, acute liver injury; ESLD, end-stage-liver-disease; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; NCPH, non cirrhotic portal hypertension; TIPS, Trans-jugular intrahepatic portosystemic shunt.

Although a detailed registry of all the received calls is not available, the majority of referrals were performed during the working hours. However, patients with ALF, ALI, variceal bleedings not responding to endoscopic treatment and urgent medical complications in LT patients were also referred during nights or during the week-end.

In-patient referrals

One hundred and forty-two patients were referred for an in-patient evaluation. Amongst these, 69% patients were referred for ESLD, 29.6% for ALI/ALF, and 1.4% for non-cirrhotic portal hypertension. The median (IQR) time between referral and patient admission was 2[1–4] days. Indications for referral were evaluation for LT (84.5%), evaluation for TIPS (5.6%), and clinical management (9.9%) (Table 2).

Among the 14 patients referred for ALF, 4 patients were referred during the week-end, 2 patients were referred during the night and 8 patients during working hours.

Referrals for TIPS placement were 8 (28.6%) urgent and 20 (71.4%) standard. Amongst urgent referrals, 100% were referred for variceal bleeding refractory to endoscopic treatment, whereas amongst standard referrals, 11 patients had refractory ascites and 9 patients were referred for prophylaxis of variceal bleeding.

In-patient referrals for ESLD

Considering 98 patients referred for ESLD, alcohol-related disease was the predominant etiology (61.2%), followed by viral disease (9.2%). Fifty (51%) patients presented ACLF, and 49% AD. At admission, the median (IQR) Child–Pugh, MELD and MELD-Na scores were 11,[9–12] 24.6 (19.1–30) and 27.3 (22.8–32.2). The majority of patients were referred for LT evaluation (84.7%), whereas 6.1% were referred for TIPS placement, all of these after an episode of acute variceal bleeding.

After a median (IQR) follow-up time of 8[1–27] months, 37.7% of patients died without LT, 41.8% were still alive, 20.4% underwent LT. Overall, 28.6% of patients required admission to the ICU during their first hospitalization. They presented a significantly higher cumulative mortality if compared to patients who did not require admission to the ICU (82% vs. 30%; $p < 0.001$).

Amongst patients admitted for ACLF, 48% of patients presented a grade 1, 30% with grade 2% and 22% with grade 3. When patients were stratified according to ACLF or AD at admission, significant differences were found in the severity of liver disease and outcomes (Table 3). ACLF patients showed higher median (IQR) MELD score (29.6 [25–32.6] vs. 20.7 [15.2–23.6]; $p = 0.001$) and MELD-Na score (31.5 [27.2–34.5] vs. 23.6 [18.5–27.3]; $p = 0.001$) at admission, higher rate of ICU admission for liver related complications (44% vs. 12.5%, $p < 0.001$) and lower 1, 3, 12-month TSF (45%, 33% and 18% vs. 85%, 80% and 66%; $p < 0.001$).

In-patient referrals for ALI and ALF

Forty-two patients were admitted for ALI. Of these, two patients fulfilled the criteria for ALF at the time of referral, whereas the other 12 referred for ALI developed ALF during the hospital stay. The majority of patients with ALI were admitted for DILI (35.7%), followed by AIH (28.6%) and viral etiology (21.4%). Similarly, half of the patients with ALF were admitted for DILI (50%), followed by a virus

TABLE 2 Patient characteristics according to the type of referral (out-patients vs. in-patients).

	Out-patients *n* = 139	In-patients *n* = 142	*p*-value
Gender, male, *n* (%)	84 (60.4)	88 (62)	0.79
Age, years, median (IQR)	56.9 (51.7–64.1)	53.9 (44.8–61.8)	0.002
Source of referral, *n* (%)			
Veneto region	131 (94.2)	109 (76.8)	<0.001
Other regions	8 (5.8)	33 (23.2)	
Underlying liver disease, *n* (%)			
ESLD	125 (89.9)	98 (69)	<0.001
ALI	6 (4.3)	28 (19.7)	
ALF	0 (0)	14 (9.9)	
Chronic hepatitis/NCPH	8 (5.8)	2 (1.4)	
Etiology of ESLD, *n* (%)			
Viral	21 (16.8)	9 (9.2)	0.26
ALD	67 (53.6)	60 (61.2)	
Viral + ALD	18 (14.4)	8 (8.2)	
NAFLD/NASH	8 (6.4)	5 (5.1)	
Cholestatic and autoimmune diseases	5 (4)	7 (7.1)	
Other	6 (5)	9 (9.2)	
Etiology of ALI/ALF, *n* (%)			
Drugs/herbals/supplements	1 (16.7)	17 (40.5)	0.04
Viral	0 (0)	8 (19)	
Autoimmune	5 (83.3)	8 (19)	
Mushrooms	0 (0)	2 (4.8)	
Other/unknown origin	0 (0)	7 (16.6)	
HCC, yes, *n* (%)	23 (16.5)	7 (4.9)	0.002
Child pugh score[a], median (IQR)	8 (7–9)	11 (9–12)	<0.001
MELD[a], median (IQR)	15.3 (10.9–18.7)	24.6 (19.1–30)	<0.001
MELD-Na[a], median (IQR)	18.9 (14–22.9)	27.3 (22.8–32.2)	<0.001
Timing of referral, *n* (%)			
Urgent	4 (2.9)	115 (81)	0.001
Standard	135 (97.1)	27 (19)	
Indications for referral, *n* (%)			
Evaluation for LT	90 (64.7)	120 (84.5)	<0.001
Evaluation for TIPS placement	20 (14)	8 (5.6)	
Clinical management	22 (15.8)	14 (9.9)	
Treatment of HCC	7 (5)	0 (0)	

Abbreviations: ALD, alcoholic liver disease; ALF, acute liver failure; ALI, acute liver injury; ESLD, end-stage-liver-disease; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NCPH, non cirrhotic portal hypertension; TIPS, Trans-jugular intrahepatic portosystemic shunt.

[a]only for patients with ESLD.

TABLE 3 Clinical characteristics and outcomes of in-patients according to the presence of acute decompensation or acute-on-chronic liver failure.

	AD $n = 48$ (%)	ACLF $n = 50$ (%)	p-value
Gender, male, *n* (%)	34 (70.8)	33 (66)	0.6
Age, years, median (IQR)	52.8 (45.2–60.8)	55.3 (44.5–62)	0.7
Underlying etiology, *n* (%)			
Viral	4 (8.4)	5 (10)	0.3
ALD	26 (54.2)	34 (68)	
Viral + ALD	4 (8.3)	4 (8)	
NAFLD/NASH	2 (4.2)	3 (6)	
Cholestatic and autoimmune diseases	6 (12.5)	1 (2)	
Other	6 (12.5)	3 (6)	
Hepatocellular carcinoma, yes, *n* (%)	4 (8.3)	3 (6)	0.6
Child pugh score, median (IQR)	10 (8–11)	12 (10–13)	<0.001
MELD, median (IQR)	20.7 (15.2–23.6)	29.6 (25–32.6)	<0.001
MELD-Na, median (IQR)	23.6 (18.5–27.3)	31.5 (27.2–34.5)	<0.001
CLIF-AD score, median (IQR)	59.5 (56.8–72.3)	-	-
ACLF grade at hospitalization, *n* (%)			
I	-	24 (48)	-
II		15 (30)	
III		11 (22)	
CLIF-C ACLF score, median (IQR)	-	45 (39.5–53.5)	-
Timing of referral, *n* (%)			
Urgent	35 (72.9)	50 (100)	<0.001
Standard	13 (27.1)	0 (0)	
Reason for referral, *n* (%)			
Evaluation for LT	37 (77.1)	46 (92)	0.1
Evaluation for TIPS placement	4 (8.3)	2 (4)	
Clinical management	7 (14.6)	2 (4)	
Hospital stay, days, median (IQR)	10 (7–19.3)	14 (7–25)	0.1
ICU admission, yes, *n* (IQR)	6 (12.5)	22 (44)	0.001
Outcome of hospital admission, *n* (%)			
Alive without LT	41 (85.4)	27 (54)	0.002
Dead	7 (14.6)	19 (38)	
LT	0 (12)	4 (8)	

Abbreviations: ACLF, acute on chronic liver failure; AD, acute decompensation; ALD, alcoholic liver disease; ESLD, end-stage-liver-disease; HCC, hepatocellular carcinoma; ICU, intensive care unit; LT, liver transplantation; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; TIPS, Trans-jugular intrahepatic portosystemic shunt.

(14.3%). The median (IQR) MELD and MELD-Na scores at admission were 22.9 (20.1–28.3) and 24.4 (22–29.2), and all patients were referred for urgent evaluation for LT. The median (IQR) hospital stay was 10 (6–17.5) days and 9 (64.3%) patients with ALF required admission to the ICU. At the end of follow-up (October 2022), 74% patients were alive, 19% had died for liver-related complications, and 7% had undergone LT.

Outcome at the end of follow-up

Considering in-patients, at the end of follow-up (October 2022), 6 patients were lost to follow-up, and 23 underwent LT. Among out-patients, 14 were lost to follow-up and 19 underwent LT, respectively. Therefore, after a median (IQR) follow-up time of 10 (0.8–37) months, the 1, 12, 24-month TSF of in-patients was 71%, 50%, and

47%, respectively. After a median (IQR) follow-up time of 24 (13–43) months, the 1,12 and 24-month TSF was 96%, 76% and 70%, respectively, significantly better than compared with in-patients ($p < 0.001$) (Figure 2).

Comparison of in-patient referral before and after introduction of the integrated referral program

Characteristics and outcomes of in-patients referred after the development of the integrated referral program were compared with those of 86 consecutive patients who were referred during 2 years before the introduction of the integrated program, whose follow-up time was assessed in October 2018. Amongst these, 72% of patients were referred for ESLD, 26.7% for ALI/ALF, and 1.1% for non-cirrhotic portal hypertension. Amongst patients referred for ESLD, the proportion with alcohol-related liver disease was greater in the study group compared with the control group (61.2% vs. 45%), although the difference was not statistically significant. Amongst patients referred for ALI/ALF, the proportion with acute liver disease due to drugs/herbals and supplements was significantly higher in the study group compared to the control group (40.5% vs. 8%, $p = 0.01$). Median (IQR) Child–Pugh and MELD scores were 11[9–12] and 24,[18–28] respectively, with no significant differences in terms of liver disease severity between pre- and post-referral eras (Table 4). Notably, in the referral period, patients were admitted with significantly different indications than before, with an evaluation for TIPS placement having a significant increase over time (5.6% vs. 1%) and LT evaluation having a less significant rising trend (84.5% vs. 81%).

In the pre-referral era, after ruling out 5 (5.8%) patients who were lost at follow-up and 19 (22%) who underwent LT, the 1, 12, 24-month TSF assessed in October 2018 were 77%, 53% and 53%, respectively, after a median (IQR) follow-up time of 13.2 (1.6–22) months. No difference was found when compared with TSF in patients referred after the introduction of the integrated referral program ($p = 0.39$, long-rank test; Figure 3).

Comparison of patient referral before and after the Covid-19 pandemic

In order to investigate the potential role of the Covid-19 pandemic on referral activity, referred patients were stratified according to the pre- and post-Covid-19 pandemic era, considering January 2020 as the time point of the Covid-19 outbreak in Italy. Therefore, 177 and 104 patients were referred in the pre- and in the Covid-19 era, respectively (Table 5). A mean of 5.3 patients/month were referred during the pandemic, compared with 6.3 patients/month in the pre-Covid era (p = ns). Notably, this figure was also confirmed when only in-patient referrals were considered (pre- Covid era vs. Covid era: 2.96 vs. 3.15 patients/month). Patients' clinical characteristics were similar between the eras, as well as the underlying disease, the reason for referral and severity of liver disease at the time of referral (median [IQR] MELD score: 25.4 (17.9–30.9) versus 24.6 (19.5–27.8)). Interestingly, more patients were referred to our Unit for clinical management during the Covid-19 pandemic, perhaps after temporary conversion of some spoke Gastroenterology Units into Covid-19 Facilities. Notably, even with a similar baseline severity of liver disease, there was a trend toward a lower ICU admission rate during the Covid-19 pandemic (19% vs. 32%, $p = 0.07$). Notwithstanding this, the in-hospital mortality was not significantly different between the eras.

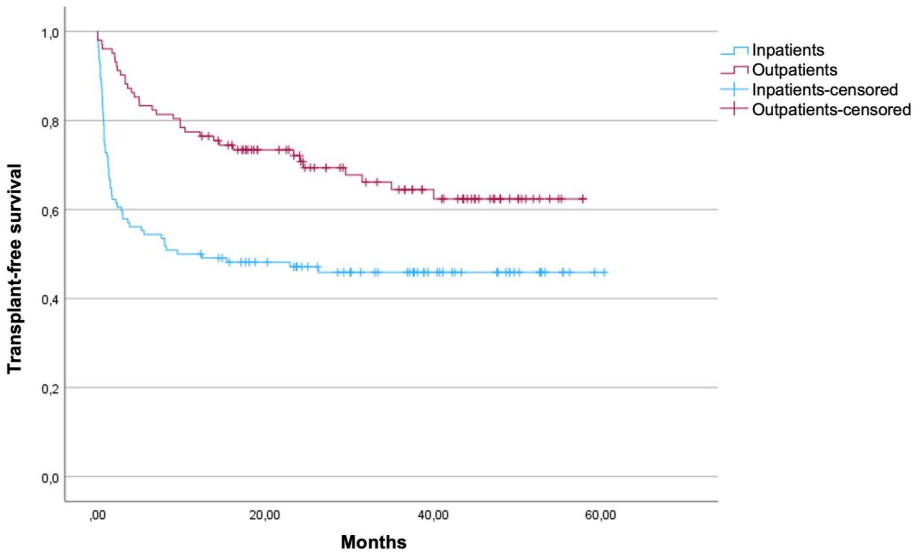

FIGURE 2 Cumulative transplant-free survival of referred patients according to the type of referral (out-patient vs. in-patient).

TABLE 4 Clinical characteristics of in-patients before and after the implementation of the integrated referral program.

	2015–2017 *n* = 86 (%)	2017–2021 *n* = 142 (%)	*p*-value
Gender, male, *n* (%)	58 (67)	88 (62)	0.52
Age, years, median (IQR)	53 (42–63)	53.9 (44.8–61.8)	0.71
Underlying liver disease, *n* (%)			
ESLD	62 (72)	98 (69)	0.25
ALI	17 (20)	28 (19.7)	
ALF	6 (7)	14 (9.9)	
Chronic hepatitis/NCPH	1 (1)	2 (1.4)	
Etiology of ESLD, *n* (%)			
Viral	9 (10)	9 (9.2)	0.19
ALD	38 (45)	60 (61.2)	
Viral + ALD	1 (1)	8 (8.2)	
NAFLD/NASH	3 (3)	5 (5.1)	
Cholestatic disease	10 (12)	7 (7.1)	
Other	1 (1)	9 (9.2)	
Etiology of ALI/ALF, *n* (%)			
Drugs/herbals/supplements	7 (8)	17 (40.5)	0.01
Viral	12 (14)	8 (19)	
Autoimmune	0 (0)	8 (19)	
Mushrooms	0 (0)	2 (4.8)	
Other/unknown origin	4 (5)	7 (16.6)	
Hepatocellular carcinoma, yes, *n* (%)	8 (9)	7 (4.9)	0.17
Child pugh score, median (IQR)[a]	11 (9–12)	11 (9–12)	0.47
MELD, median (IQR)[a]	24 (18–28)	24.6 (19.1–30)	0.46
Timing of referral, *n* (%)			
Urgent	NA	26 (18.3)	-
Standard		116 (81.7)	
Indications for referral, *n* (%)			
Evaluation for LT	70 (81)	120 (84.5)	0.01
Evaluation for TIPS placement	1 (1)	8 (5.6)	
Clinical management	11 (13)	14 (9.9)	
Treatment of HCC	4 (5)	0 (0)	
Hospital stay, days, median (IQR)	14 (7–23)	11 (7–20)	0.13

Abbreviations: ALD, alcoholic liver disease; ALF, acute liver failure; ALI, acute liver injury; ESLD, end-stage-liver-disease; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NCPH, non cirrhotic portal hypertension; TIPS, Trans-jugular intrahepatic portosystemic shunt.

[a]only for patients with ESLD.

DISCUSSION

To our knowledge, this was the first experience of an integrated referral program for out- and in-patients with acute or chronic liver diseases in Italy. As for many other conditions, the institution of this dedicated program may theoretically improve patient's outcomes, rebalance potential inequities, spare healthcare resources, and reduce barriers to LT.[21–23] Recently, an electronic referral system was developed in Italy, but it was dedicated only to the outpatient evaluation of potential candidates for LT.[24]

During a 4-year study, 281 patients were referred to the Multivisceral Transplant Unit (Padua University Hospital) for the first time. Each of these patients received a dedicated care program, shared between hub and spoke Centers, and updated at fixed time points.

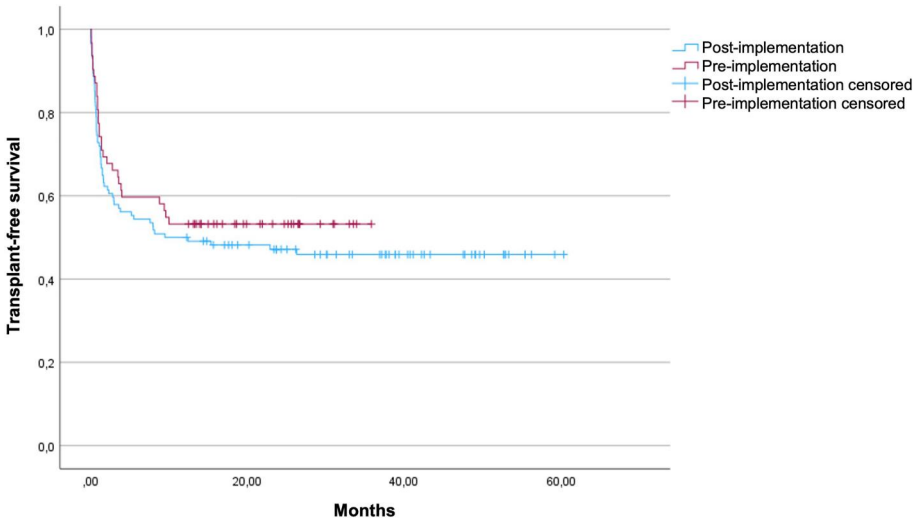

FIGURE 3 Cumulative transplant-free survival of referred in-patients before and after the introduction of the integrated referral program.

Therefore, this integrated referral program represented an easier way to grant patient admission to a tertiary hospital and to strengthen a bidirectional network between Centers. As a matter of fact, there was a rising trend of admissions for LT evaluation after the institution of the integrated referral program (91% vs. 81% previous period). The development of such a program may have increased the awareness of LT as a life-saving therapeutic option for patients with liver disease at a local level, especially those with ESLD. Therefore, the access to an integrated referral program may be considered as an important quality measure for the care of these patients in the future.[6]

Cirrhosis was by far the most common disease at the time of referral, alcohol being the prevalent etiology, with a contemporary low prevalence of viral hepatitis and non-alcoholic fatty liver disease. This pattern probably reflects the current epidemiological scenario in Northern Italy and mirrors the epidemiological changes occurring in Western Countries.[25,26]

Most cirrhotic in-patients were referred having severe clinical conditions, with median (IQR) Child–Pugh and MELD scores equal to 10[8–12] and 24,[18–30] respectively. More than half fulfilled the criteria of ACLF at time of admission (16% with three or more organ failures). Therefore, it was not surprising to observe a high rate of ICU admission, relatively low access to LT, and a poor short-term outcome. A delay in referral could represent the most critical factor to explain these data. Therefore, more efforts to close this gap, especially by precisely defining referral timing according to the type of liver disease, would be advisable in the future, also in order to avoid inequities and spare resources.[27,28] For relatively stable patients with AD, or those who have recovered from an episode of ACLF, the main goal will be to promote an earlier referral, that is, to favor contact with the transplant center before their clinical condition worsens. For the sickest patients with ACLF - a detrimental syndrome with a predictably poor outcome[29,30] - the earlier referral should be associated with an urgent admission to an LT Center, ideally within 24–48 h. Further studies, aiming to evaluate the cost-effectiveness of this system and refine the timing of admission according to the number of organ failures are needed.

The ICU admission rate was higher after the institution of the integrated referral program if compared with the previous 2 years (29% vs. 15%, $p = 0.05$). Considering that liver disease severity was similar between the two groups of patients, we speculated that this difference might be explained by a higher propensity to admit patients with cirrhosis into ICU, in view of a chance of LT[31] and a strengthened interaction with anesthetists for combined care of these patients.

Nevertheless, only a few patients achieved LT, probably because they were considered too sick to be transplanted. Moreover, all these patients were admitted for the first time to the LT Center; thus, some of them died when the evaluation for LT was still ongoing. Allocating an organ to such patients still remains a matter of debate, usually being done after careful evaluation of donor and recipient characteristics, balancing benefit and futility of a transplant.[32,33]

LT coming from referrals accounted for 7% of all LT performed during the study period, and the total number of transplants remained stable over time. A recent study by Tai et al.[12] has shown that a hub-and-spoke network contributed to significantly increasing transplant activity by 160%. However, different organ allocation rules between England and Italy,[13] and the short follow-up time in our study may partly explain this issue.

Considering the comparison with the historical cohort, no significant differences were found in terms of the number of LT performed and in terms of TSF. These data confirm that before the introduction of the integrated referral program, a network for referring patients with acute or chronic liver disease was already established between our Center and spoke hospitals, although it was not regulated and often based on personal contacts. The implementation of the integrated referral program represented an added value to the existing network because it standardized a common clinical practice which was previously based on personal contacts. This allowed more clinicians

TABLE 5 Patient characteristics according to the Covid-19 era.

	Pre-Covid-19 era[c] *n* = 177	Covid-19 era[d] *n* = 104	*p*-value
Gender, male, *n* (%)	108 (61)	64 (61.5)	0.93
Age, years, median (IQR)	51.9 (43.6–61.4)	54.2 (44.7–62.6)	0.74
Source of referral, *n* (%)			
Veneto region	149 (84.2)	91 (87.5)	0.47
Other regions	28 (15.8)	13 (12.5)	
Underlying liver disease, *n* (%)			
ESLD	138 (78)	85 (81.7)	0.45
ALI	21 (11.9)	13 (12.5)	
ALF	8 (4.5)	6 (5.8)	
Chronic hepatitis/NCPH	10 (5.6)	0 (0)	
Etiology of ESLD, *n* (%)			
Viral	16 (11.6)	14 (16.4)	0.11
ALD	85 (61.6)	42 (49.4)	
Viral + ALD	19 (13.8)	7 (8.2)	
NAFLD/NASH	4 (2.9)	9 (10.6)	
Cholestatic and autoimmune diseases	6 (4.3)	6 (7.1)	
Other	8 (5.8)	7 (8.2)	
Etiology of ALI/ALF, *n* (%)			
Drugs/herbals/supplements	11 (44)	6 (35.3)	0.03
Viral	7 (28)	1 (5.9)	
Autoimmune	3 (12)	5 (5.9)	
Mushrooms	2 (8)	0 (0)	
Other/unknown origin	2 (8)	5 (23.5)	
HCC, yes, *n* (%)	15 (8.5)	15 (14.4)	0.11
Child pugh score, median (IQR)[a]	11 (9–12)	11 (9–12)	0.95
MELD, median (IQR)[a]	25.4 (17.9–30.9)	24.6 (19.5–27.8)	0.38
MELD-Na, median (IQR)[a]	28.6 (22.8–32.9)	27.1 (22.7–30.4)	0.20
Timing of referral, *n* (%)			
Urgent	70 (39.5)	50 (48.1)	0.16
Standard	107 (60.5)	54 (51.9)	
Type of referral, *n* (%)			
Out-patient	92 (52)	47 (45.2)	0.27
In-patient	85 (48)	57 (54.8)	
Indications for referral, *n* (%)			
Evaluation for LT	139 (78.5)	71 (68.3)	0.08
Evaluation for TIPS placement	19 (10.7)	9 (8.7)	
Clinical management	13 (7.3)	18 (17.3)	
Treatment of HCC	3 (1.7)	4 (3.8)	
Antiviral treatment	3 (1.7)	2 (1.9)	

(Continues)

TABLE 5 (Continued)

	Pre-Covid-19 era[c] *n* = 177	Covid-19 era[d] *n* = 104	*p*-value
Hospital stay, days, median (IQR)[b]	12 (7–21.5)	10 (6–20)	0.88
ICU admission, yes, *n* (%)	28 (32.2)	11 (19)	0.07
Outcome of hospitalization, *n* (%)			
Alive without LT	62 (72.9)	41 (71.9)	0.73
Death	18 (21.2)	14 (24.6)	
LT	5 (5.9)	2 (3.5)	

Abbreviations: ALD, alcoholic liver disease; ALF, acute liver failure; ALI, acute liver injury; ESLD, end-stage-liver-disease; HCC, hepatocellular carcinoma; ICU, intensive care unit; LT, liver transplantation; MELD, model for end-stage liver disease; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NCPH, non cirrhotic portal hypertension; TIPS, Trans-jugular intrahepatic portosystemic shunt.

[a]only for patients with ESLD.

[b]only for in-patients.

[c]Covid-19 era: from 10.2017 to 1.2020.

[d]Covid-19 era: from 2.2020 to 10.2021.

working in spoke hospitals to have access to the referral system , and since it was based on phone and email availability, it allowed that all the liver transplant team (including the head nurse) was constantly updated on the clinical evolution of patients referred. At the same time, this program allowed the evaluation and the analysis of the number of admissions of patients with liver disease according to different eras, different etiologies, and different indications. These data can lastly help in the organization of care needs such as the number of dedicated beds and personnel required, not only at the local but also at the regional level (Figure 4).

In this context, it becomes crucial that such an integrated referral program is supported by an adequate information system based on common platforms, telemedicine and, if applicable also artificial intelligence, in order to simplify the exchange of clinical information.

Lastly, this study showed that the integrated referral program also worked adequately during the Covid-19 pandemic with the same number of patients referred per month as in the pre-Covid-19 era, and with the same outcomes. This represents a positive aspect of this system, which was tested during a national and international healthcare emergency and that could guarantee the preservation of patient referrals in the unlucky event of a new emergency.

Although this study presents some limitations such as the observational design and small number of patients included in the subgroup analysis, it described for the first-time data derived from an integrated referral program for in-patients and out-patients with liver disease in Italy. The current results will be helpful to put in place possible amendments for an improvement of patients' outcomes in the near future. The development of a fully electronic referral format and telemedicine-based consultations will be valuable options in this setting. An improvement of TFS - currently unsatisfactory for specific groups of patients such as those with ACLF - will increase the cost-effectiveness of the entire program. Future efforts will focus on a better patient selection, earlier referral, and faster hospital admission. Lastly, we believe that our network will open the way to the development of similar programs since it would be an important quality measure for the future care of patients with ESLD.

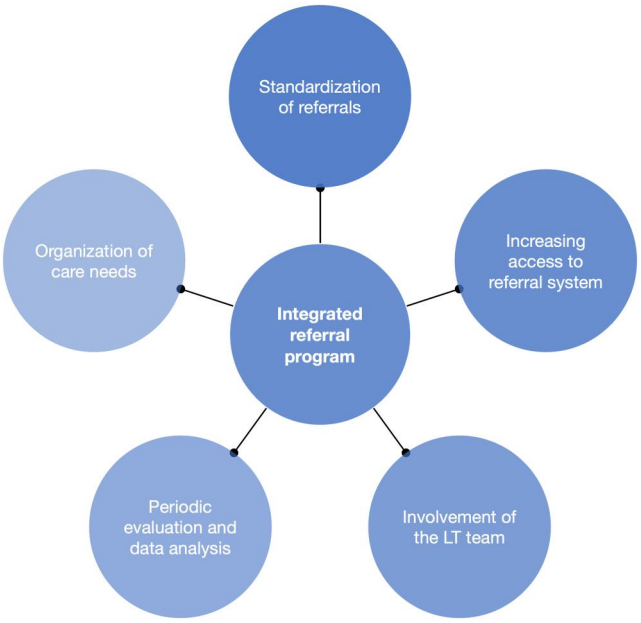

FIGURE 4 Advantages of the implementation of an integrated referral program.

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CONFLICT OF INTEREST STATEMENT

The Authors have nothing to disclose about this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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