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Temporal trends of waitlistings for liver transplantation in Italy: The ECALITA (Evolution of IndiCAtion in LIver transplantation in ITAly) registry study

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ABSTRACT

Background: Over the last decades relevant epidemiological changes of liver diseases have occurred, together with greatly improved treatment opportunities.
Aim: To investigate how the indications for elective adult liver transplantation and the underlying disease etiologies have evolved in Italy.
Methods: We recruited from the National Transplant Registry a cohort comprising 17,317 adults patients waitlisted for primary liver transplantation from January-2004 to December-2020. Patients were divided into three Eras:1(2004–2011),2(2012–2014) and 3(2015–2020).
Results: Waitlistings for cirrhosis decreased from 65.9% in Era 1 to 46.1% in Era 3, while those for HCC increased from 28.7% to 48.7%. Comparing Eras 1 and 3, waitlistings for HCV-related cirrhosis decreased from 35.9% to 12.1%, yet those for HCV-related HCC increased from 8.5% to 26.7%. Waitlistings for HBV-related cirrhosis remained almost unchanged (13.2% and 12.4%), while those for HBV-related HCC increased from 4.0% to 11.6%. ALD-related cirrhosis decreased from 16.9% to 12.9% while ALD-related HCC increased from 1.9% to 3.9%.
Conclusions: A sharp increase in liver transplant waitlisting for HCC and a concomitant decrease of waitlisting for cirrhosis have occurred In Italy. Despite HCV infection has noticeably decreased, still remains the primary etiology of waitlisting for HCC, while ALD and HBV represent the main causes for cirrhosis.

There has been a consistent change in the indications for liver transplantation (LT) around the world in the last decades. Thanks to effective vaccination programs and extended use of nucleoside/nucleotide analogs [1], a progressive decrease in LT waitlisting for Hepatitis B Virus (HBV) related cirrhosis has occurred, at least in Western countries [2,3]. The availability of Direct Antiviral Agents (DAAs) has enabled 95% of patients with HCV to be cured, resulting in decreased LT for HCV-related end-stage liver disease (ESLD) in many countries [4]. The worldwide spread of obesity, and the associated increase of metabolic syndrome, has resulted in more LT candidates with metabolic-associated fatty liver disease (MAFLD) [5]. Similarly, the proportion of LT candidates listed due to alcohol-related liver disease (ALD) has increased sharply, both in the US [6] and in Europe [7], with greatest burden in Northern countries. In contrast, LT registrations for cholestatic liver disease showed a decreasing trend, accounting for less than 10% of LT indications in the US [8], Australia, and New Zealand [9], while being more frequent in the United Kingdom [10].

In Southern Europe, few studies have explored the impact of the changing epidemiology of liver disease on LT activity. We aimed to investigate the evolution of LT indications and the underlying disease etiologies based on registry data from the Italian National Transplant Center (CNT).

1. Material and methods

Since January 1, 2004, data referring to all adult LT candidates from 22 Italian Transplant Center were prospectively collected from the electronic Transplant Informative System (TIS) developed by CNT [11]. Initially, limited data from transplant candidates were collected (first name, surname, age, sex), together with definite clinical variables (reason for listing, underlying disease etiology, model for end-stage liver disease [MELD], AB0 group, listing date) [12]. From May 2012, a revised form of TIS was implemented that included more comprehensive clinical records of candidates and organ donors. The revised TIS was based on an XML protocol (Simple Object Access Protocol, SOAP) (13].

The two principal aims of this study were to analyze the yearly changes occurred in Italy in: 1) the primary indications for LT waitlisting; 2) the etiologies of underlying liver diseases of LT candidates.

The study was approved by the ethics committee of the promoting center (Policlinico Tor Vergata; N: 256.20).

1.1. Database, inclusion criteria, and data encoding

Data were recruited from the TIS database, appropriately categorized following revision of possible conflicting data. *The study cohort* included: adults (age ≥ 18 years) waitlisted for primary LT in Italy between January 1, 2004, and December 31, 2020 with no missing/uncertain data on indication at waitlisting. Pediatric patients, candidates with acute hepatic failure, and adults requiring combined transplantation or re-transplantations were excluded.

We analyzed the following variables: primary indication for LT, etiology of underlying liver disease, date of listing, MELD score, age at listing, sex, blood group, Body Mass Index (BMI), and the presence of dyslipidemia, diabetes, or arterial hypertension.

The primary indications for LT were categorized as follows: a) cirrhosis; b) hepatocellular carcinoma (HCC); b) MELD exceptions; c) non-HCC malignancies; d) “other indications” (Supplement Table 1). Patients waitlisted for HCC were identified by cross-matching all available records. Whenever the term HCC was mentioned in the TIS, HCC was considered as primary indication. The MELD exceptions category included liver diseases qualifying for MELD exception points, as indicated by the evolving CNT rules during the study period [May 2007; April 2011; and March 2017 statements] [14].

The underlying disease etiologies were categorized as follows: a) virus related; b) alcoholic/Laennec; c) idiopathic; d) autoimmune; e) drug-related; f) hereditary/genetic; g) MAFLD; h) other metabolic liver disease and i) “other etiology” (Supplement Table 2). Concerning HCV and HBV infections, LT candidates were categorized after cross-matching the information on disease etiology with the presence of one or more virological blood markers (HBV-DNA, HCV-RNA, HBsAg, HBsAb, HBcAb, HCV-Ab). In case of multifactorial etiologies, HCV infection was considered the leading underlying disease etiology. In the absence of HCV, HBV infection and alcohol were considered as leading etiologies in hierarchical order.

LT candidates were categorized as being affected by MAFLD, a term introduced in 2020 [5], when one or more of the following terms were registered: NASH (non-alcoholic steatohepatitis), cryptogenic cirrhosis with a BMI ≥30, etiology not available but a BMI ≥30, dysmetabolic/metabolic syndrome with a BMI <30 associated with dyslipidemia, diabetes or both, dysmetabolic/metabolic syndrome regardless of BMI and dyslipidemia, cryptogenic (cirrhosis) with a BMI <30 associated with dyslipidemia, diabetes or both, or an unavailable etiology with a BMI <30 associated with dyslipidemia, diabetes or both.

The study cohort was grouped into three eras: Era 1 from 2004 to 2011, Era 2 from 2012 to 2014, and Era 3 from 2015 to 2020. These intervals were chosen due to the implementation of the TIS database in 2012 and the opportunity to treat HCV-infected patients with DAAs from early 2015.

Among LT candidates with HCC, 23.3% of cases had missing data on the underlying etiology. As the majority of these (67.7%) were waitlisted between 2004 and 2011, we choose to restrict the complete analysis of the HCC group to the period January 2012-December 2020, when missing data were less than 10%.

1.2. Statistical analysis

Most variables showed skewed distributions with significant departures from the normal density; therefore, a non-parametric approach was preferred in the analysis. Continuous variables were summarized by median, first and third quartiles. Categorical variables were described by absolute frequencies and percentages.

For categorical variables, to compare groups we used the χ^2 test (or Fisher exact test in the case of sparse tables). For continuous varaibles, comparison of 2 groups was based on Student *t*-test (or Wilcoxon rank-sum test when a significant departure from normality was detected); in case of more than 2 groups classical ANOVA was used (Kruskal-Wallis test when a significant departure from normality was detected).

To predict the probability of patients to be waitlisted according to different indications and disease etiologies until 2025, a nominal logistic model was used, adjusted for age and sex, where the LT indications were grouped only as cirrhosis HCC and "other". Generalized logits were chosen as a link function. Parameters were estimated by the maximum likelihood method and analysis of variance. Predicted probabilities were obtained by back-transforming the corresponding estimated values for the linear predictor. The Confidence limits are based on the profile-likelihood function. Analyses were conducted using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA) and R, version 3.4 (The R Foundation for Statistical Computing).

2. Results

Of the 24,021 patients who passed through the LT waiting list from January 01, 2004, to December 31, 2020, 17,317 [median age: 55 (IQR=49–61) years, males: 13,115 (75.7%)] represented the study cohort.

Over the entire period, the primary indications for LT were as follows: cirrhosis in 9586 cases (55.4%), HCC in 6868 (39.7%), other indications in 520 (2.9%), MELD Exceptions in 222 (1.3%), non-HCC malignancies in 131 (0.7%). The median MELD score at listing in registrants with cirrhosis and HCC was 16 (IQR=13–21) and 11 (IQR=8–14), respectively. The predominant underlying disease etiologies were hepatitis virus infections (HCV; $n = 6767$ [43%] and HBV; $n = 3332$, [21.2%]), followed by ALD ($n = 2533$ [16.1%]), autoimmune diseases ($n = 964$ [6.1%]), idiopathic diseases ($n = 531$ [3.4%]) and MAFLD ($n = 513$ [3.3%]). Age was significantly different among different etiologies ($p<0.0001$): patients waitlisted with MALFD were the oldest (median age: 59 [IQR=54–64] years), those with non-HCC malignancies (median age: 47 [IQR=37–55] years) or other metabolic liver diseases (median age: 42 [IQR=29–53] years) were the youngest. The median age was similar in patients with HCV (55 years [IQR= 50–60]) and HBV infection (57 years [IQR=50–62]) and with ALD (55 years, IQR=49–60).

2.1. Temporal trends of waitlistings according to the primary indication for LT

Significant changes were observed in the indications for LT across the 3 Eras ($p<0.0001$). There was a marked decrease of cirrhosis and a concomitant increase of HCC as primary indications for LT waitlisting over the study period (Fig. 1). Cirrhosis was involved in 4491 (65.9%) of candidates in Era 1; 1764 (53.8%) in Era 2; and 3331 (46.1%) in Era 3. Conversely, LT waitlistings with HCC as primary indication were 1956 (28.7%) in Era 1; 1396 (42.6%) in Era 2, and 3516 (48.7%) in Era 3 (Table 1). These dramatic temporal changes are best exemplified by comparing 2004 (74.6% of waitlistings for cirrhosis and 20.1% for HCC) with 2020 (46.2% and 46.7% of new registrations, respectively).

In more recent years there was a trend to waitlist older patients. Among patients with HCC the median age was 56 years in Era 1 (IQR=51–61) and 59 years in Era 3 (IQR=54–64), $p<0.0001$; among those with cirrhosis it was 53 years in Era 1 (IQR=47–59) and 55 years in Era 3 (IQR=49–61), $p<0.0001$ (Table 2). There was also a trend to waitlist sicker patients with cirrhosis in both Era 2 and Era 3 (median MELD=17 [IQR=14–22] compared to Era 1 (median MELD=15 [IQR=12–19]), $p<0.0001$. Conversely, among patients with HCC, the median MELD at listing significantly decreased from 12 (IQR=9–17) in Era 1, to 11 (IQR=8–14) in Era 2, and 10 (IQR=8–14) in Era 3, $p<0.0001$ (Table 2). The number of new waitlistings due to MELD exceptions or non-HCC malignancies did not show relevant changes during the study period, consistently accounting for less than 2% (Fig. 1).

2.2. Temporal trends of LT waitlistings according to the underlying disease etiology

In the study cohort, the complete data on the underlying disease were available in 15,718 patients (Table 3). Significant differences were observed in the 3 Eras ($p<0.0001$). HCV infection was the predominant etiology in Era 1 and 2. In 2014, prior to the availability of DAAs, HCV was recorded in 53.2% of new yearly registrations. During Era 3, the etiology relating to HCV began to decrease, dropping to 33% of new registrations in the year 2020 (Fig. 2A).

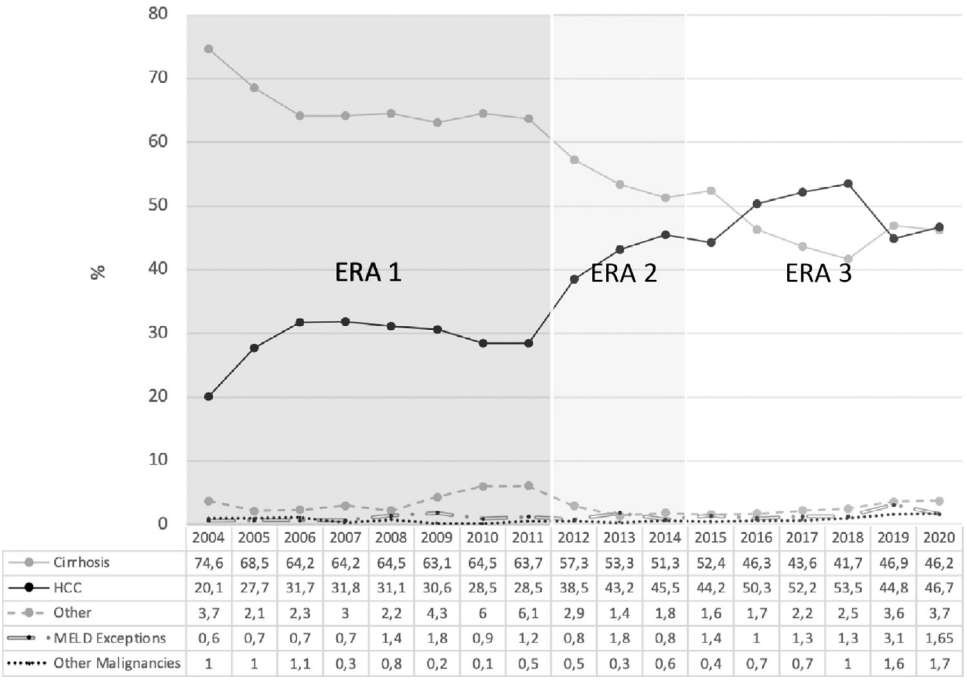
Among the other two most prevalent underlying etiologies, HBV infection increased from 17.2% of all waitlistings in Era 1 to 24% in Era 3 (Table 3; Fig. 2B) while ALD accounted for 18.8% in Era 1, decreased to 11.5% in Era 2, and rised again to 16.0% in Era 3 (Table 3; Fig. 2C).

MAFLD was recognized as underlying etiology in only 0.4% of cases in Era 1 when, however, idiopathic causes accounted for 5% of waitlistings. At the start of Era 2, there was a turnaround between MAFLD and cryptogenic cirrhosis, with MAFLD steadily increasing to reach 5.8% of all etiologies in Era 3, and idiopathic cases dropping to 2.1%.

2.3. Changing trends of primary indications for LT related to different disease etiologies

The indications between the different etiologies are summarize in Fig. 3 and Table 3. By cross-matching the primary indications for LT with the underlying diseases across the 3 Eras, the decrease in HCV-related cases appeared to be prominent only among the waitlisted candidates with cirrhosis, but not among those with HCC. For example, HCV-related cirrhosis represented 26.1% of the indications in Era 2 but only 12.1% in Era 3 representing 9% of overall cirrhosis in 2020. In contrast, waitlistings due to HCV-related HCC increased steadily, accounting for 24% in 2020.

HBV infection continued to represent the second major etiology associated with waitlisting due to both cirrhosis and HCC, with an increasing trend in Eras 2 and 3. ALD gave a considerably lower



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Cirrhosis	74,6	68,5	64,2	64,2	64,5	63,1	64,5	63,7	57,3	53,3	51,3	52,4	46,3	43,6	41,7	46,9	46,2
HCC	20,1	27,7	31,7	31,8	31,1	30,6	28,5	28,5	38,5	43,2	45,5	44,2	50,3	52,2	53,5	44,8	46,7
Other	3,7	2,1	2,3	3	2,2	4,3	6	6,1	2,9	1,4	1,8	1,6	1,7	2,2	2,5	3,6	3,7
MELD Exceptions	0,6	0,7	0,7	0,7	1,4	1,8	0,9	1,2	0,8	1,8	0,8	1,4	1	1,3	1,3	3,1	1,65
Other Malignancies	1	1	1,1	0,3	0,8	0,2	0,1	0,5	0,5	0,3	0,6	0,4	0,7	0,7	1	1,6	1,7

Fig. 1. Indications for waitlistings (Study Cohort, $N = 17{,}317$).

Table 1
Indication to liver transplantation (Study Cohort, $N = 17{,}317$).

YEAR	ERA 1 (2004–2011) $N = 6818$		ERA 2 (2012–2014) $N = 3278$		ERA (2015–2020) $N = 7221$		
INDICATION	*N patients*	*%*	*N patients*	*%*	*N patients*	*%*	*p value*
HCC	**1956**	**28.7**	**1396**	**42.6**	**3516**	**48.7**	**<0.0001**
CIRRHOSIS	**4491**	**65.9**	**1764**	**53.8**	**3331**	**46.1**	**<0.0001**
EXCEPTION TO MELD	**69**	**1.0**	**37**	**1.1**	**116**	**1.6**	**0.0051**
OTHER	**260**	**3.8**	**66**	**2.0**	**184**	**2.6**	**<0.0001**
OTHER MALIGNANT TUMOR	**42**	**0.6**	**15**	**0.5**	**74**	**1.0**	**0.0018**

The waitlisting due to acute liver failure in adults excluded in the present analysis were: 151 in ERA 1, 79 in ERA 2 and 182 in ERA 3.

Table 2
Patients characteristics at liver transplantation waitlisting.

Variables		ERA 1 $n = 6818$	ERA 2 $n = 3278$	ERA 3 $N = 7221$	*p*-value
Age	HCC	56 (IQR=51–61)	57 (IQR=52–62)	59 (IQR=54–64)	<0.0001
	Cirrhosis	53 (IQR=47–59)	53 (IQR=48–59)	55 (IQR=49–61)	<0.0001
MELD	HCC	12 (IQR=9–17)	11 (IQR=8–14)	10 (IQR=8–14)	<0.0001
	Cirrhosis	15 (IQR=12–19)	17 (IQR=14–22)	17 (IQR=14–22)	<0.0001
Sex (M)		5157 (75.64%)	2478 (75.59%)	5480 (75.89%)	0.9213
Nationality	Non Native Italians	435 (6.4%)	305 (9.3%)	893 (12.4%)	<0.0001

contribution to waitlisting for HCC but remained a major cause of waitlisting for cirrhosis. Waitlisting due to MAFLD increased across the three Eras, albeit to a lower extent than virus-related cases, with a similar distribution between cirrhosis and HCC.

2.4. Predicted trends in liver transplant indications in Italy until 2025

The temporal trends of LT waitlisting were modeled until 2025 using a multinomial logistic model, adjusted for sex and age, where the primary indications were grouped only as HCC, cirrhosis, or "Other" indications.

Supplementary Figure 1 summarizes the predicted trends over time for the three indications. Increasing uncertainty is reflected by increasing confidence bands. The data show that the probability of waitlisting for cirrhosis will continue to decrease, reaching 39% in 2025, while the probability of waitlisting for HCC or "other indications" will continue to increase, reaching 55% and 6% in 2025, respectively. The predictive model shows that females will have a higher probability of being waitlisted for cirrhosis and "other indications" compared to males (Supplementary Figure 2). Furthermore, the probability of being waitlisted for cirrhosis or "Other" indications will be higher among younger patients, contrasting the trend to waitlist increasingly older individuals with HCC (Supplement Figure 3). The overall results from the fitted model are summarized in supplement Table 3.

3. Discussion

The study encompasses an extensive period, during which in Italy there has been a substantial change in clinical epidemiology of liver diseases as well as in the indications for LT.

The most relevant finding of this study is the dramatic reciprocal shift that occurred between waitlistings due to cirrhosis and HCC, respectively, as primary indications for LT. Previous studies

Table 3
Underlying disease etiology at waitlisting ($N = 15,718$).

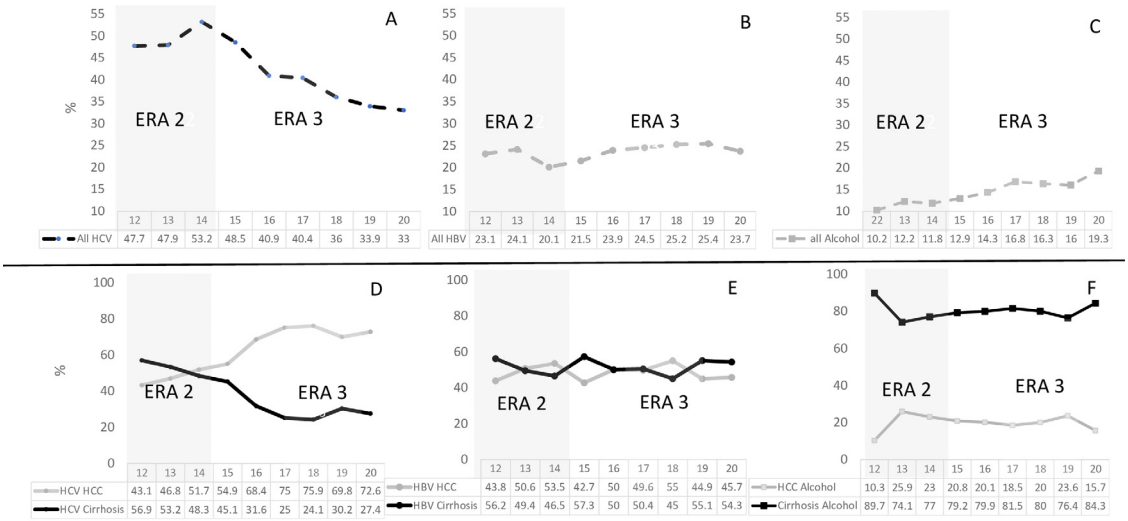
Etiology	Indication	ERA 1 (2004–2011) $N = 5735$		ERA 2 (2012–2014) $N = 3166$		ERA 3 (2015–2020) $N = 6817$		
		N patients	*%*	*N patients*	*%*	*N patients*	*%*	*p*
HCV	**HCC**	**486**	**8.5**	**750**	**23.7**	**1820**	**26.7**	
	Cirrhosis	**2060**	**35.9**	**825**	**26.1**	**826**	**12.1**	
	Other	**–**	**–**	**–**	**–**	**–**	**–**	
	TOT	**2546**	**44.4**	**1575**	**49,8**	**2654**	**38.8**	**<0.0001**
HBV	**HCC**	**231**	**4.0**	**350**	**11.1**	**789**	**11.6**	
	Cirrhosis	**756**	**13.2**	**358**	**11.3**	**848**	**12.4**	
	Other	**–**	**–**	**–**	**–**	**–**	**–**	
	TOT	**987**	**17.2**	**708**	**22.4**	**1637**	**24.0**	**<0.0001**
Alcohol	**HCC**	**111**	**1.9**	**75**	**2.4**	**212**	**3.9**	
	Cirrhosis	**970**	**16.9**	**288**	**9.1**	**877**	**12.9**	
	Other	**–**	**–**	**–**	**–**	**–**	**–**	
	TOT	**1081**	**18.8**	**363**	**11.5**	**1089**	**16.0**	**<0.0001**
MAFLD	**HCC**	**2**	**0.03**	**58**	**1.8**	**197**	**2.9**	
	Cirrhosis	**23**	**0.4**	**39**	**1.2**	**194**	**2.9**	
	Other	**–**	**–**	**–**	**–**	**–**	**–**	
	TOT	**25**	**0.4**	**97**	**3.0**	**391**	**5.8**	**<0.0001**
Idiopathic	**HCC**	**19**	**0.3**	**23**	**0.7**	**34**	**0.5**	
	Cirrhosis	**267**	**4.7**	**78**	**2.5**	**110**	**1.6**	
	Other	**–**	**–**	**–**	**–**	**–**	**–**	
	TOT	**286**	**5.0**	**101**	**3.2**	**144**	**2.1**	**<0.0001**
Autoimmune	**HCC**	**8**	**0.1**	**7**	**0.2**	**20**	**0.3**	
	Cirrhosis	**354**	**6.2**	**148**	**4.7**	**425**	**6.2**	
	Other	**1**	**0.02**	**–**	**–**	**1**	**0.01**	
	TOT	**363**	**6.3**	**155**	**4.9**	**446**	**6.5**	**0.0045**
Other Metabolic liver disease	**HCC**	**4**	**0.1**	**1**	**0.03**	**6**	**0.1**	
	Cirrhosis	**40**	**0.7**	**20**	**0.6**	**32**	**0.5**	
	Other	**12**	**0.2**	**6**	**0.2**	**13**	**0.2**	
	TOT	**56**	**1.0**	**27**	**0.8**	**51**	**0.8**	**0.3827**
Genetic	**HCC**	**9**	**0.2**	**18**	**0.6**	**15**	**0.2**	
	Cirrhosis	**–**	**–**	**–**	**–**	**–**	**–**	
	Other	**210**	**3.7**	**54**	**1.7**	**203**	**3.0**	
	TOT	**219**	**3.9**	**72**	**2.3**	**218**	**3.2**	**0.0004**
Other etiology	**HCC**	**3**	**0.05**	**2**	**0.06**	**19**	**0.3**	
	Cirrhosis	**21**	**0.4**	**8**	**0.3**	**19**	**0.3**	
	Other	**148**	**2.6**	**58**	**1.8**	**157**	**2.3**	
	TOT	**172**	**3**	**68**	**2.2**	**195**	**2.9**	**0.0529**

already provided robust evidence of the increase in LT performed in Italy in patients with HCC, reported to rise from 18% of all LT before 2002 [15] to 44% in 2005–2007 [16], a much higher figure compared to other Western countries [17,18]. In the present study, analyzing a much wider population, we found that waitlistings with HCC as primary indication increased from roughly 20% in Era 1 to around 50% of cases in Era 3. Notably, the increasing trend of HCC was especially evident in Eras 2 and 3, when the number of missing data was negligible. To our knowledge, this is the highest figure for HCC waitlisting reported worldwide. It is debatable whether these findings result from the changing epidemiology of underlying liver diseases in Italy (about 13,000 new diagnoses of HCC in the year 2020) [19], their more aggressive natural history [20–25], or to the propensity of Italian surgeons to waitlist HCC patients with "extra large criteria" after down-staging procedure [26]. Conceivably, this trend also reflects the CNT-endorsed policy of granting consistent priority to patients with HCC, compared to other LT indications, through the attribution of MELD exception points. Notably, this policy has been further modified in 2015, with the introduction of the Italian Score for Organ Allocation (ISO) score rule [27] (whose results are still under evaluation). Interestingly, our multinomial logistic predictive model shows that the increasing trend to waitlist patients with HCC will further increase until 2025, particularly in older males, together with a continuing decrease of waitlistings due to cirrhosis. Interestingly, the median age for cirrhosis and HCC patients significantly increased across the 3 Eras ($p<0.0001$), likely because of a greater propensity in more recent years to waitlist patients taking in account the "biological" rather than the actual age.

Another relevant finding from this study is the progressive decrease in new waitlistings with an underlying HCV-related etiology. HCV infection represented the predominant underlying etiology in Era 1 and Era 2, reaching a peak of 53.2% of all waitlistings. In Era 3, when DAAs became widely used [28–30], LT due to HCV infection began to decrease, dropping to 33% of waitlistings in 2020. This is a remarkable reduction, yet significantly differs from other countries, such as the UK, where LT registrants with HCV-related diseases have almost disappeared [31]. These results also differ from the US [8] and the Australian [9] Transplant Registry data, both reporting an overall sharper decrease in HCV related-ESLD, to around 15% of the total LT indications in 2019.

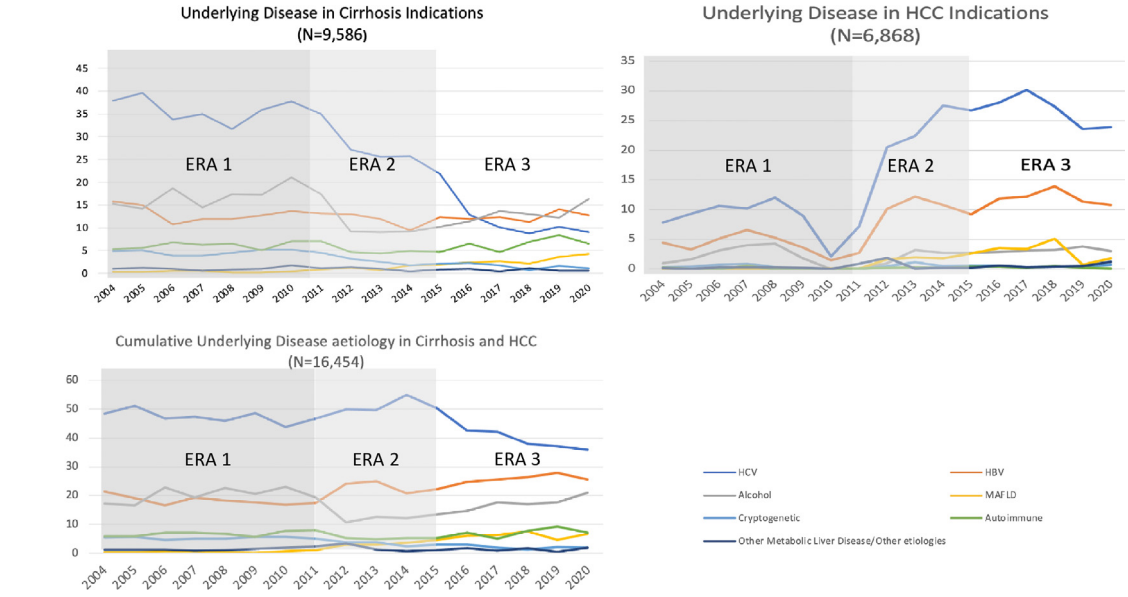
Notably, in our study, HCV-infected patients in Era 3 were mainly represented by candidates with HCC as primary indication for LT (72.6% in the year 2020, Fig. 2D), rather than with cirrhosis (27.4% between HCV and only 9% between all cirrhosis indications in 2020, Figs. 2 and 3), which brings fuel to the debate on the residual risk of HCC in patients with cirrhosis cured of HCV. A similar increase of waitlistings for HCC among HCV-infected patients has been observed, though to a smaller extent, in the US and Australian transplant registries [8,9], again emphasizing the need for stringent surveillance of cirrhotic patients after eradication of HCV infection.

A further relevant result is the rising number of waitlistings due to MAFLD. This is in keeping with US and European data reporting 18% and 9% of MAFLD-related new waitlistings for ESLD and HCC, respectively [8,9]. Collecting precise data on MAFLD is a difficult task since only recently was it fully appreciated that most cases of idiopathic or cryptogenic cirrhosis are indeed due to MAFLD evo-



A, B, C: Trends of all HCV, HBV and Alcohol patients respectively in the Study Cohort (January 2012-December 2020).In cases of multifactorial underlying etiologies, HCV was considered the leading etiology.
D, E, F: The dark and gray solid lines represents the Cirrhosis and HCC distribution in patients with HCV (N=4,221), HBV (N=2,345) and Alcohol (N:1,452) etiologies respectively

Fig. 2. Percentage of HCV, HBV and Alcohol related diseases over time (Study Cohort, January 2012-December 2020, $n = 10{,}503$).



The percentage was calculated on all other indications (for instance in 2020 the waitlistings due to Cirrhosis HCV related was 9% of all other indications and HCC HCV-related was 24%).

Fig. 3. Etiologies trends over the study period in cirrhotic and HCC waitlisted patients.

lution. In agreement with Vitale *et al.* [32], we found that MAFLD-related waitlistings more than doubled, rising to almost 6% of total new registrations in Era 3, a much lower figure compared to European [33] and US data [34–37]. This difference may conceivably reflect a lower prevalence of obesity and associated metabolic abnormalities in Italy compared to other countries. It may be expected, however, that MAFLD will become a more prevalent indication for LT also in Italy, thus careful surveillance of patients with MAFLD is advisable, for both for cirrhosis and HCC.

Our study showed unexpected data concerning the role of HBV infection. During Era 1, HBV infection represented around 17% of disease etiologies among LT waitlistings, a figure which rose to around 24% in Era 2 and 3. This increase was indeed surprising, given the implementation of several health-related interventions, including extensive vaccination programs mandatory in children beginning from the year 1991; stringent measures to prevent mother-to-child transmission; harm reduction services for people who inject drugs; and increased testing and treatment for HBV [38,39]. Why did we not observe an expected decrease of HBV among new LT waitlistings, despite the prevalence of HBV infection in Italy has decreased [40], there are at least two plausible explanations: first, there was a consistent increase in patients with HBV-related HCC listed for LT in more recent years. Indeed, HBV-infected cirrhotic patients receiving nucleos(t)ide antivirals remain at high risk of developing HCC despite their clinical improvement. Second, as shown in Table 2, an increasing number of waitlistings were non-native Italians (accounting for 12.4% in Era 3). Many, in fact, were born in countries where HBV is highly endemic, such as Eastern Europe, Asia, and Africa.

ALD was another relevant disease etiology among LT waitlisted patients, although considerably less frequent than in Northern Eu-

ropean countries [41–44]. In Italy, ALD accounted for around 19% of cases in Era 1, decreasing to 16% in Era 3. Yet, ALD remained the most frequent reason for waitlisting among patients with decompensated cirrhosis in Era 3 while giving a minor contribution to waitlisting for HCC (Figs. 2F and 3).

This large cohort study also allowed us to forecast the probable scenario in the next few years, using a multinomial logistic predictive model, showing that all described trends are expected to continue.

Although the study analyzed the changes that occurred in the last 17 years in the type of adult patients on the waiting list for LT, the results of the study also have an important significance for the activity of pediatric listing and transplantation in consideration of the fact that in Italy most pediatric patients are transplanted with partial grafts obtained with split liver procedures in which the other portion of the liver is transplanted into an adult recipient [45].

We acknowledge that this study has limitations. First, the retrospective nature, as is the nature of registry-based studies. Second, fewer data were collected during Era 1, as a shorter questionnaire was used and there were several missing data on the underlying etiologies, especially among HCC patients. In order to limit potential biasases we choose to restrict a detailed analysis of HCC patients only to those waitlisted after 2012, when the TIS was implemented. Third, this study provides a thorough analysis of the changing trends of LT waitlisting in Italy, yet does not offer data on the actual transplantation activity.

In conclusion, in Italy over the last two decades, there has been a sharp increase of LT indications for candidates with HCC and a concomitant decrease for those with cirrhosis, a trend expected to continue in the coming years. Among the underlying disease etiologies, HCV infection has dramatically decreased yet is and will likely continue to be a primary cause of waitlisting due to HCC. HBV infection remains the second major cause for waitlisting in Italy, mainly for HCC, with no expected trends to decrease. ALD is the major cause of waitlisting due to decompensated cirrhosis, while MAFLD, despite still relatively infrequent, is clearly an increasing indication for LT also in patients with HCC. We feel that these results could be helpful for health policymakers to refine current LT rules in Italy and eventually other Southern European countries, in the attempt to improve overall equity and the opportunity to be transplanted for all categories of patients.

Declaration of Competing Interest

None declared.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2022.08.033.

References

[1] Global health sector strategy on viral hepatitis 2016–2021. Geneva: World Health Organization; 2016. Available from: http://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/ (Accessed on July 13, 2021).
[2] Young K, Liu B, Bhuket T, et al. Long-term trends in chronic hepatitis B virus infection associated liver transplantation outcomes in the United States. J Viral Hepat Sep 2017;24(9):789–96 Epub 2017 May 5. PMID: 28273387. doi:10.1111/jvh.12703.
[3] https://www.who.int/publications/i/item/consolidated-strategic-information-guidelines-for-viral-hepatitis-planning-978-92-4-151519-1 (accessed on July 13, 2021).
[4] https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-c (accessed on July 13, 2021).
[5] Eslam M, Sanyal AJ, George J. International consensus panel. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology May 2020;158(7):1999–2014 e1Epub 2020 Feb 8. PMID: 32044314. doi:10.1053/j.gastro.2019.11.312.
[6] Kitajima T, Moonka D, Yeddula S, et al. Liver transplant waitlist outcomes in alcoholic hepatitis compared with other liver diseases: an analysis of UNOS registry. Clin Transplant 2020.
[7] Adam R, Karam V, Cailliez V, et al. Annual report of the European liver transplant registry (ELTR) - 50-year evolution of liver transplantation. Transpl Int 2018;31(12):1293–317 2018 DecPMID: 30259574. doi:10.1111/tri.13358.
[8] Kwong A, Kim WR, Lake JR, et al. OPTN/SRTR 2018 annual data report: liver. Am J Transplant Jan 2020;20(Suppl s1):193–299 PMID: 31898413. doi:10.1111/ajt.15674.
[9] Australia and New Zealand Liver and Intestinal Transplant Registry. Report on liver and intestinal transplantation activity. 31st Annual Report. ANZLITR. https://www.anzlitr.org (accessed on January 16, 2022).
[10] https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/19867/nhsbt-liver-transplant-report-1920.pdf. (Accessed on January 16, 2022).
[11] Gazzetta Ufficiale n.87, April 15, 1999. Law 1st April 1999, n.91. disposizioni in materia di prelievi e di trapianti di organi e tessuti.
[12] Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. Hepatology Feb 2001;33(2):464–70 PMID: 11172350. doi:10.1053/jhep.2001.22172.
[13] https://www.sciencedirect.com/topics/computer-science/simple-object-access-protocol. (Accessed on January 16, 2022)
[14] http://www.trapianti.salute.gov.it/trapianti/homeCnt.jsp (Accessed on January 16, 2022)
[15] Fagiuoli S, Mirante VG, Pompili M, et al. Monotematica AISF 2000-OLT study group. Liver transplantation: the Italian experience. Dig Liver Dis Sep 2002;34(9):640–8 PMID: 12405251. doi:10.1016/s1590-8658(02)80207-9.
[16] Angelico M, Cillo U, Fagiuoli S, et al. Liver Match, a prospective observational cohort study on liver transplantation in Italy: study design and current practice of donor-recipient matching. Dig Liver Dis Feb 2011;43(2):155–64 Epub 2010 Dec 24. PMID: 21185796. doi:10.1016/j.dld.2010.11.002.
[17] Kim WR, Stock PG, Smith JM, et al. OPTN/SRTR 2011 annual data report: liver. Am J Transplant Jan 2013;13(Suppl 1):73–102 PMID: 23237697. doi:10.1111/ajt.12021.
[18] http://www.eltr.org/Overall-indication-and-results.html accessed on January 16, 2022
[19] I numeri del cancro in Italia 2020, Intermedia Editore, Banca dati AIRTUM, www.medinews.it (accessed on 1st July 2022)
[20] Reig M, Mariño Z, Perelló C, et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol Oct 2016;65(4):719–26 Epub 2016 Apr 13. PMID: 27084592. doi:10.1016/j.jhep.2016.04.008.
[21] Conti F, Buonfiglioli F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol Oct 2016;65(4):727–33 Epub 2016 Jun 24. PMID: 27349488. doi:10.1016/j.jhep.2016.06.015.
[22] Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol Sep 5 2017 S0168-8278(17)32273-0Epub ahead of print. PMID: 28887168; PMCID: PMC5837901. doi:10.1016/j.jhep.2017.08.030.
[23] Calvaruso V, Cabibbo G, Cacciola I, et al. Incidence of hepatocellular carcinoma in patients with HCV-associated cirrhosis treated with direct-acting antiviral agents. Gastroenterology Aug 2018;155(2):411–21 e4Epub 2018 Apr 12. PMID: 29655836. doi:10.1053/j.gastro.2018.04.008.
[24] Hassany M, Elsharkawy A, Maged A, et al. Hepatitis C virus treatment by direct-acting antivirals in successfully treated hepatocellular carcinoma and possible mutual impact. Eur J Gastroenterol Hepatol Aug 2018;30(8):876–81 PMID: 29727383. doi:10.1097/MEG.0000000000001152.
[25] Kanwal F, Kramer J, Asch SM, et al. Risk of hepatocellular cancer in HCV patients treated with direct-acting antiviral agents. Gastroenterology Oct 2017;153(4):996–1005 e1Epub 2017 Jun 19. PMID: 28642197. doi:10.1053/j.gastro.2017.06.012.
[26] Tran NH, Munoz S, Thompson S, Hallemeier CL, Bruix J. Hepatocellular carcinoma down-staging for liver transplantation in the era of systemic combined therapy with Anti-VEGF/TKI and immunotherapy. Hepatology Jun 28 2022 Epub ahead of print. PMID: 35765265. doi:10.1002/hep.32613.
[27] Cillo U, Burra P, Mazzaferro V, et al. A multistep, consensus-based approach to organ allocation in liver transplantation: toward a "blended principle model". Am J Transplant Oct 2015;15(10):2552–61 Epub 2015 Aug 14. PMID: 26274338. doi:10.1111/ajt.13408.
[28] Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med May 16 2013;368(20):1878–87 Epub 2013 Apr 23. PMID: 23607594. doi:10.1056/NEJMoa1214853.
[29] European Association for Study of LiverEASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol Jul 2015;63(1):199–236 Epub 2015 Apr 21. PMID: 25911336. doi:10.1016/j.jhep.2015.03.025.
[30] Poordad F, Schiff ER, Vierling JM, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. Hepatology May 2016;63(5):1493–505 Epub 2016 Mar 7. PMID: 26754432; PMCID: PMC5069651. doi:10.1002/hep.28446.
[31] https://www.odt.nhs.uk/statistics-and-reports/organ-specific-reports/ (accessed on January 20, 2022).
[32] Vitale A, Trapani S, Burra P. Recent trends and intention-to-treat survival of liver transplantation for nonalcoholic steatohepatitis: an Italian liver transplant registry study. Digestive and Liver Disease 2020;52:e16–17.
[33] Haldar D, Kern B, Hodson J, et al. Outcomes of liver transplantation for non-alcoholic steatohepatitis: a European Liver Transplant Registry study. J

Hepatol Aug 2019;71(2):313–22 Epub 2019 May 7. PMID: 31071367; PMCID: PMC6656693. doi:10.1016/j.jhep.2019.04.011.
[34] Flegal KM, Carroll MD, Kit BK, et al. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA Feb 1 2012;307(5):491–7 Epub 2012 Jan 17. PMID: 22253363. doi:10.1001/jama.2012.39.
[35] Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology Jun 2012;55(6):2005–23 PMID: 22488764. doi:10.1002/hep.25762.
[36] Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology Mar 2015;148(3):547–55 Epub 2014 Nov 25. PMID: 25461851. doi:10.1053/j.gastro.2014.11.039.
[37] Goldberg D, Ditah IC, Saeian K, et al. Changes in the prevalence of hepatitis c virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. Gastroenterology Apr 2017;152(5):1090–9 e1Epub 2017 Jan 11. PMID: 28088461; PMCID: PMC5367965. doi:10.1053/j.gastro.2017.01.003.
[38] EASLClinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67(2):370–98 2017 AugEpub 2017 Apr 18. PMID: 28427875. doi:10.1016/j.jhep.2017.03.021.
[39] Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet Feb 9 2013;381(9865):468–75 Epub 2012 Dec 10. PMID: 23234725. doi:10.1016/S0140-6736(12)61425-1.
[40] Brancaccio G, Nardi A, Madonia S, et al. The present profile of chronic hepatitis B virus infection highlights future challenges: an analysis of the Multicenter Italian MASTER-B cohort. Dig Liver Dis 2019.
[41] Burra P, Senzolo M, Adam R, et al. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). Am J Transplant Jan 2010;10(1):138–48 Epub 2009 Dec 1. PMID: 19951276. doi:10.1111/j.1600-6143.2009.02869.x.
[42] Singal AK, Mathurin P. Diagnosis and treatment of alcohol-associated liver disease: a review. JAMA Jul 13 2021;326(2):165–76 PMID: 34255003. doi:10.1001/jama.2021.7683.
[43] Musto JA, Eickhoff J, Ventura-Cots M, et al. The level of alcohol consumption in the prior year does not impact clinical outcomes in patients with alcohol-associated hepatitis (AH). Liver Transpl Jun 10 2021 Epub ahead of print. PMID: 34109723. doi:10.1002/lt.26203.
[44] Belli LS, Perricone G, Adam R, et al. Impact of DAAs on liver transplantation: major effects on the evolution of indications and results. An ELITA study based on the ELTR registry. J Hepatol Oct 2018;69(4):810–17 Epub 2018 Jun 27. PMID: 29940268. doi:10.1016/j.jhep.2018.06.010.
[45] Angelico R, Trapani S, Spada, et al. A national mandatory-split liver policy: a report from the Italian experience. Am J Transplant Jul 2019;19(7):2029–43 Epub 2019 Mar 14. PMID: 30748091. doi:10.1111/ajt.15300.