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Waiting list mortality and 5-year transplant survival benefit of patients with MASLD: An Italian liver transplant registry study

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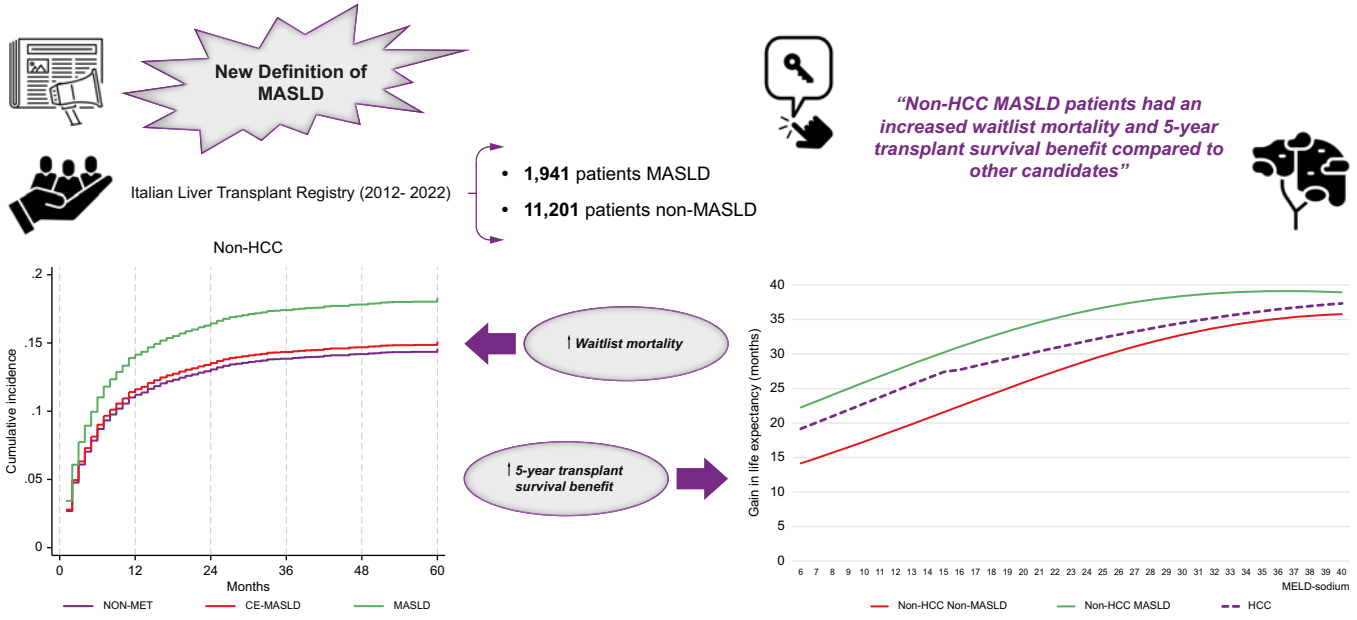
Graphical abstract



Highlights:

- The proportion of liver transplantation candidates with MASLD increased from 2012 to 2022.
- MASLD prevalence as an indication for liver transplantation in Italy is rising and will soon surpass HCV.
- MASLD is associated with an increased risk of death for waitlisted patients without HCC.
- Transplant benefit is greater in patients with MASLD, especially without HCC.

Impact and implications:

The present research addresses the critical need to understand the evolving landscape of liver transplantation indications, mainly focusing on metabolic dysfunction-associated steatotic liver disease (MASLD) in Italy. Given the significant rise in MASLD cases, these findings highlight that patients with non-HCC MASLD face increased waitlist mortality and benefit more from liver transplantation within 5 years compared with other candidates. The significance of these results lies in their emphasis on the necessity of focusing on patients with MASLD on waiting lists to improve outcomes. By tailoring transplant eligibility criteria and resource allocation, the study provides actionable insights to improve patient survival and optimise liver transplantation practices.

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Waiting list mortality and 5-year transplant survival benefit of patients with MASLD: An Italian liver transplant registry study

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Background & Aims: International consensus has recently introduced a new definition of metabolic dysfunction-associated steatotic liver disease (MASLD). We sought to analyse epidemiological trends, prognostic features, and transplant survival benefits of patients with MASLD and without MASLD waiting for liver transplantation (LT) in Italy.

Methods: Using the Italian Liver Transplant Registry database, we analysed data from adult patients listed for primary LT attributable to end-stage chronic liver disease between January 2012 and December 2022. Independent multivariable waiting lists and post-transplant survival models were developed for patients with and without hepatocellular carcinoma (HCC). A Monte Carlo simulation was used to create 5-year transplant benefit distributions based on the presence of MASLD, HCC, and model for end-stage liver disease (MELD)-sodium values.

Results: A total sample of 1,941 patients with MASLD and 11,201 patients without MASLD was considered. A significant increase in the prevalence of MASLD as an indication for LT was observed from 2012 to 2022, for both cohorts with HCC (from 17.7 to 30%) and without HCC (from 9.5 to 11.8%) cohorts. Projections suggest that, as early as next year, MASLD will overcome HCV as the second most common indication for transplantation after alcoholic liver disease in Italy. According to univariate and multivariate analyses, MASLD was not an independent predictive factor for patient survival after transplantation. However, it increased the risk of death for patients on the waiting list without HCC (hazard ratio 1.62, p <0.001). At the same MELD-sodium, the 5-year transplant benefit was higher in patients with non-HCC MASLD, followed by patients with HCC, whereas it was lower in patients without HCC and without MASLD.

Conclusions: Patients with non-HCC MASLD had an increased waitlist mortality and 5-year transplant survival benefit compared with other candidates.

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Introduction

Non-alcoholic steatohepatitis (NASH) represents a rising indication for liver transplantation (LT) worldwide.[1–3] In the USA, NASH now stands as the second leading cause of LT, following alcohol-related liver disease (ALD).[1] A similar trend has emerged in Europe, albeit with a lower prevalence of NASH. The proportion of patients with NASH undergoing LT has steadily risen in Europe, climbing from 1.2% in 2002 to 8.4% in 2016.[4] Moreover, different trends have been shown in the populations of patients with and without hepatocellular carcinoma (HCC). Despite NASH being the fastest-growing cause of HCC globally,[5] recent studies indicate that HCV-related HCC remains the primary indication for HCC-related LT in the USA,[6] albeit with a gradual decline. NASH is the second cause with an increasing trend and is also progressively emerging as an indication for LT in patients without HCC, only second in growth to ALD.[6]

A recent international consensus, achieved through the Delphi method, introduced a new definition of steatotic liver diseases (SLDs), replacing the previous definitions of NAFLD and metabolic-[dysfunction] associated fatty liver disease (MAFLD). SLD is an umbrella term encompassing all diseases in which patients exhibit hepatic steatosis, documented through biopsy

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or imaging. Conversely, metabolic dysfunction-associated steatotic liver disease (MASLD) represents a subcategory of SLD, wherein patients exhibit documented hepatic steatosis and positivity for at least one of five well-defined cardiometabolic criteria, excluding other possible causes of steatosis [7]. SLD and MASLD imply an inclusive diagnosis, avoiding stigmatising patients while accurately describing the underlying pathophysiological process.[7]

In parallel to these significant epidemiologic and terminological evolutions, relevant changes have occurred in LT allocation policies. A novel allocation principle known as the transplant benefit has recently been introduced in some countries' clinical practice.[8,9] This innovative principle, proposed for both patients with and without HCC, holds the potential to create an ideal balance between urgency-based (focused on averting the patient's risk of dying without transplant) and utility-based principles (aimed at preventing a poor post-LT outcome).[10]

To our knowledge, studies assessing the prevalence and prognosis of MASLD (based on the new definition and diagnostic criteria) still need to be included among candidates for LT. With the present study, we aim to analyse the recent and future trends in waiting list (WL) inscriptions and LTs in Italy from 2012 to 2022, focusing on MASLD-related cirrhosis. In addition, we explored the demographic features of patients with MASLD compared with those with other liver diseases. Finally, we estimated the transplant survival benefit of candidates with MASLD *vs*. without MASLD.

Patients and methods

Patients

We performed a retrospective cohort analysis of patients entering the WL for LT in Italy using the Informative Transplant System (SIT). SIT is a national registry that prospectively collects LT data from 21 Italian LT centres, and its entries are regularly checked for consistency by the National Transplant Centre. The National Transplant Centre is the technical–scientific institution of the Italian Ministry of Health responsible for coordinating the National Transplant Network.[11] The National Transplant Centre Scientific Committee reviewed and approved a study request. SIT registry management conforms to Italian legislation regarding privacy, and the present study conforms to the ethical guidelines of the Declaration of Helsinki.

Among 16,215 patients consecutively entering the WL for LT in Italy between 1 January 2012 and 31 December 2022, for this study, we analysed only adult patients with chronic liver disease listed for primary LT (n = 13,142; Fig. 1).

Patients were classified according to primary aetiology of underlying chronic liver disease into main aetiologic categories: HCV, for patients positive for serum anti-HCV antibody and codified as HCV cirrhosis by the enrolling centre; HBV, for carriers of HBsAg (±HDV) and codified as HBV cirrhosis by the enrolling centre; and ALD, in the presence of daily ethanol intake exceeding 20 g for women and 30 g for men, for more than 10 years, in the absence of any other cause of liver injury and codified as ALD by the enrolling centre. The 'other' category included a miscellaneous of rare indications such as autoimmune hepatitis, primary sclerosing cholangitis, primary biliary cholangitis, polycystic liver disease, Wilson disease, hereditary haemochromatosis, and alpha-1-antitrypsin deficiency.

As in other registry studies,[4,12] metabolic variables needed to be better represented in the SIT database. A NASH diagnosis or cryptogenic cirrhosis defined candidates with MASLD plus at least one of the following: overweight/obesity (BMI >25), type 2 diabetes, clinical history of arterial hypertension, or clinical history of dyslipidaemia.

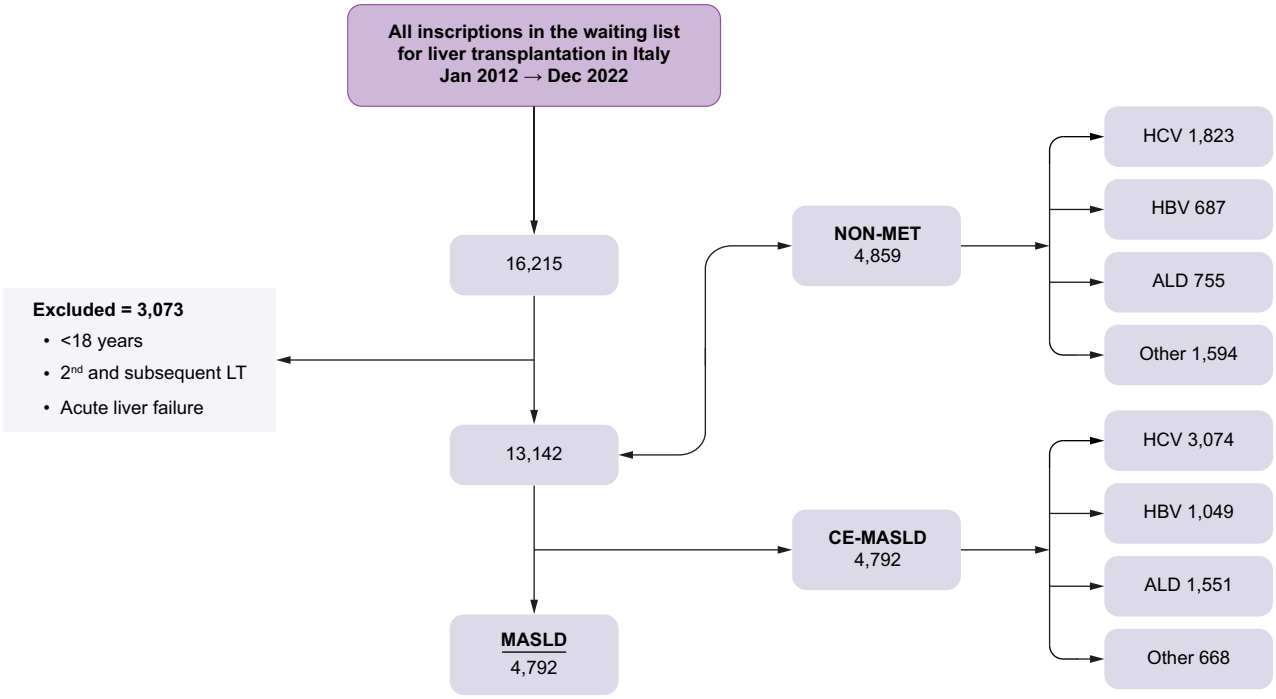

Fig. 1. Flow chart of case selection from the SIT database. ALD, alcohol-related liver disease; CE-MASLD, combined aetiology MASLD; LT, Liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; NON-MET, non-metabolic aetiologies; SIT, Informative Transplant System.

The absence of any aetiological and metabolic factors defined actual cryptogenic LT candidates (CC).

We then stratified other cases into two groups:

- CE-MASLD (combined aetiology MASLD): This includes patients who met any of the cardiometabolic criteria[7] with an additional potential cause(s) of steatosis (*i.e.* HCV, HBV, and at-risk alcohol intake).
- NON-MET (non-metabolic aetiologies): This includes patients with cirrhosis or HCC not associated with metabolic disorders.

In Italy, we do not have a shared nationwide protocol suggesting a specific BMI cut-off as an exclusion criterion for patient inclusion in the WL. Recipient variables include age, sex, BMI, type 2 diabetes, hypertension dyslipidaemia, blood group, primary liver diagnosis, presence of HCC, and model for end-stage liver disease (MELD)-sodium score. For patients with HCC, additional variables were recorded: T stage, the diameter of the largest nodule, the sum of diameters, the number of nodules, alpha-foetoprotein level, and previous therapy. MELD-sodium and HCC variables were recorded during the WL inscription and LT. Donor factors include age, BMI, and blood group. For each enrolled patient, WL status at the end of follow-up was recorded and classified as underwent transplantation, still on the WL, dropout caused by tumour progression; death resulting from liver-related causes; and death resulting from non-liver-related causes. There were no unknown causes of WL removal in the SIT database.

Study design

The objectives of this study were to compare the epidemiology, clinical characteristics, and the transplant survival benefit of patients entering the transplant WL in Italy for MASLD and those listed for other indications (non-MASLD). Therefore, three primary analyses were set. First, we compared the epidemiological trends of MASLD and non-MASLD groups by frequency across years within the study period and explored future trajectories of main aetiologic categories. Second, we compared patients with MASLD and without MASLD regarding recipient and donor characteristics. Third, we calculated the survival benefit of LT in MASLD and non-MASLD patients.

Statistical analysis

Epidemiological trends were graphically represented, and the statistical significance of differences was evaluated using a linear regression model and ANOVA. Linear regression models were also used to explore future trajectories of patients with MASLD and without MASLD.

Continuous variables were summarised using the median and IQR, and the Mann–Whitney *U* test was used to compare groups. Categorical variables were summarised with frequencies and percentages, and the Chi-square test was used to compare groups.

When study covariates' missing data involved less than 10% of patients, they were estimated using the maximum likelihood estimation method.[13] Only univariable analyses were performed when missing data involved more than 10% of patients.

For survival benefit analysis, patients were subdivided into cohorts defined by the presence or absence of concomitant HCC. As in previous studies,[14,15] for each study population, we created two independent survival models for patients on the WL (WL group) and for those undergoing LT (LT group). In the first model, the baseline visit was considered the day of inclusion in the WL; in the second model, it was the day of LT. The WL survival analysis calculated survival from the day of listing until death before LT, transplantation, or the latest follow-up (which continued after withdrawal until the latest follow-up or death). In the post-LT survival analysis, survival was calculated from the day of LT until death or the latest follow-up.

The intention-to-treat survival analysis calculated survival from the day of listing until death or the latest follow-up before or after LT.

Follow-up data were collected until 30 March 2023, when our initial data analysis was performed.

Because under the current Italian allocation system,[8] and more generally under all systems based on MELD score, patients at the highest risk of WL dropout/death also typically have the highest transplant rate, in the WL model, we used the competing risk method of Fine and Gray[16] using LT and death/dropout as competing events. A conventional multivariable Cox survival analysis was used for the LT model.

We also performed an intention-to-treat survival explorative analysis using Kaplan–Meier curves.

WL and post-LT multivariable models were used to calculate monthly death probabilities (mdp) according to the adjusted DEALE formula:[17] $mdp = 1 - e^{(\ln S(t))/t}$, where t is time expressed in months and S is the survival probability.

The model assessment was performed graphically with cumulative sums of martingale residuals. Following a previously published methodology,[14] a multistate model converted monthly death probabilities (derived from WL and post-LT survival models) into life expectancy values. The survival benefit of LT (gain in life expectancy) at 60 months was calculated by subtracting the no-LT life expectancy predictions from the post-LT life expectancy predictions. A Monte Carlo simulation was used to understand the impact of MELD-sodium, MASLD, HCC, and other covariates on the model survival benefit results and to estimate the level of uncertainty that can be placed in analysing such results. The uncertainty of life expectancy estimations was calculated assuming a triangular distribution for MELD-sodium, MASLD, and other covariate hazard ratios (with their relative confidence intervals). Using the Monte Carlo simulation, we obtained a list of 10,000 outcomes (5-year survival benefit expressed as life expectancy in months) for each population (HCC and non-HCC) based on covariate distributions. This analysis allowed us to describe the correlation between 5-year transplant survival benefit and main study covariates. For this study, we focused our survival benefit analysis on MASLD *vs*. non-MAFLD aetiology, the presence of HCC, and MELD-sodium values.

Finally, because we were interested not only in survival benefit predictions but also in evaluating the role of MASLD in influencing different causes of WL death/dropout (*i.e.* HCC progression *vs*. liver-related death *vs*. non-liver-related death) and different causes of post-transplant death (*i.e.* transplant-related *vs*. HCC-related *vs*. cardio/cerebrovascular *vs*. other causes of

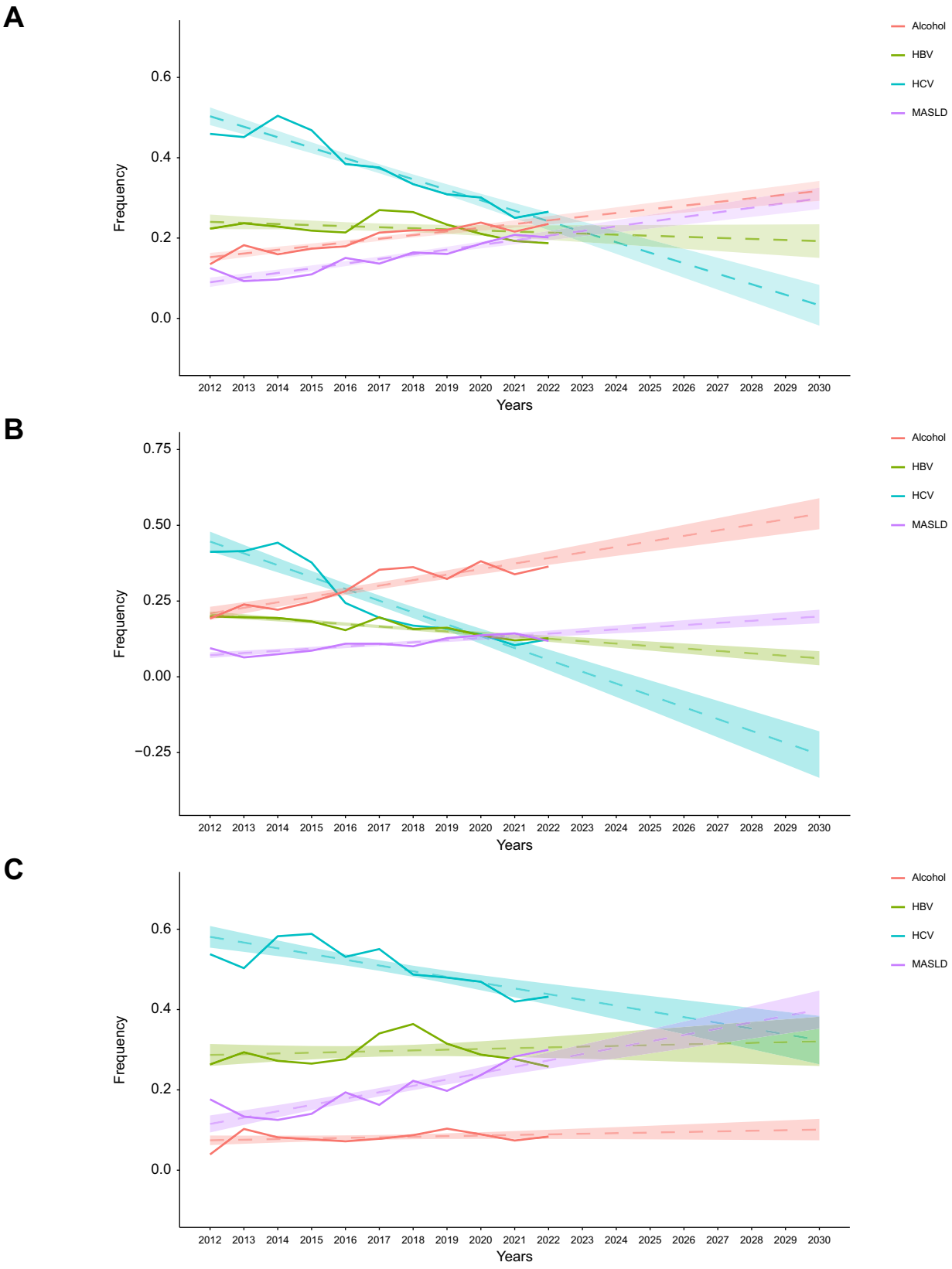

Fig. 2. Epidemiological trends and future trajectories of waiting list inscriptions for liver transplantation in Italy according to main aetiologies of liver disease, period 2012–2030. (A) Whole population, (B) patients without HCC, and (C) patients with HCC. Epidemiological trends were graphically represented, and the statistical significance of differences was evaluated using a linear regression model and analysis of variance. Linear regression models were also used to explore future trajectories of patients with MASLD and without MASLD. HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease.

death), we also used a cause-specific hazard estimation model, as in a recent paper evaluating WL dynamics.[18,19]

A two-tailed p value <0.05 was considered statistically significant. Statistical calculations were performed using JMP® Pro 17.0.0 (2022 SAS Institute Inc., Cary, NC, USA), STATA/SE 18.0 (1985–2023 StataCorp LP, College Station, TX, USA), and TreeAge Pro v2013 (TreAge Software, Williamstown, MA, USA).

Results

Epidemiological trends and trajectories of patients with MASLD and without MASLD

The proportion of candidates with MASLD significantly increased over the study period (Fig. 2A), from 12.54% in 2012 to 20.16% (p <0.001), as well as that of patients with alcohol-

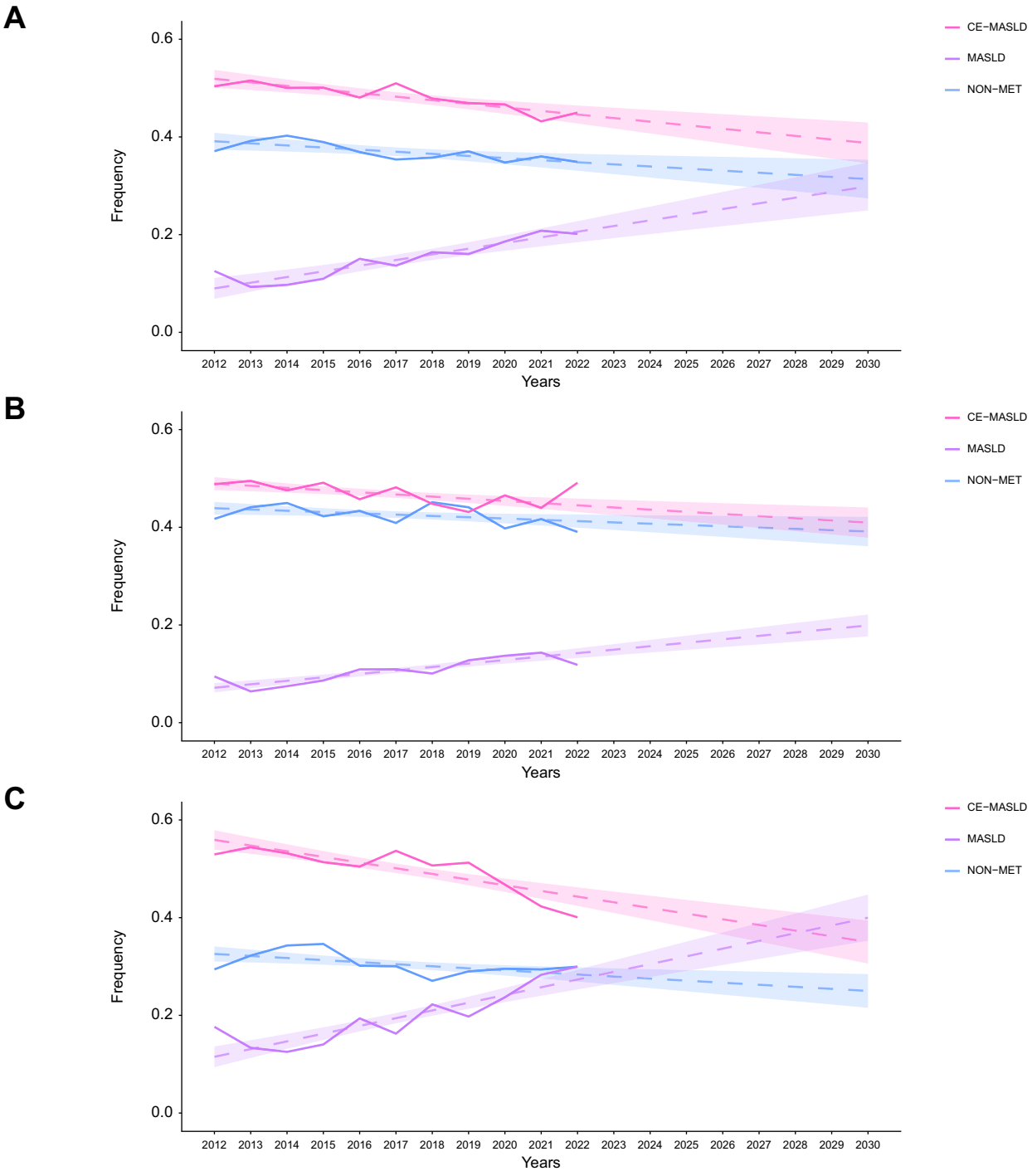

Fig. 3. Epidemiological trends and future trajectories of waiting list inscriptions for liver transplantation in Italy according to metabolic-related liver disease categories, period 2012–2030. (A) Whole population, (B) patients without HCC patients, and (C) patients with HCC. Epidemiological trends were graphically represented, and the statistical significance of differences was evaluated using a linear regression model and ANOVA. Linear regression models were also used to explore future trajectories of patients with MASLD and without MASLD. CE-MASLD, combined aetiology MASLD; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; NON-MET, non-metabolic aetiologies.

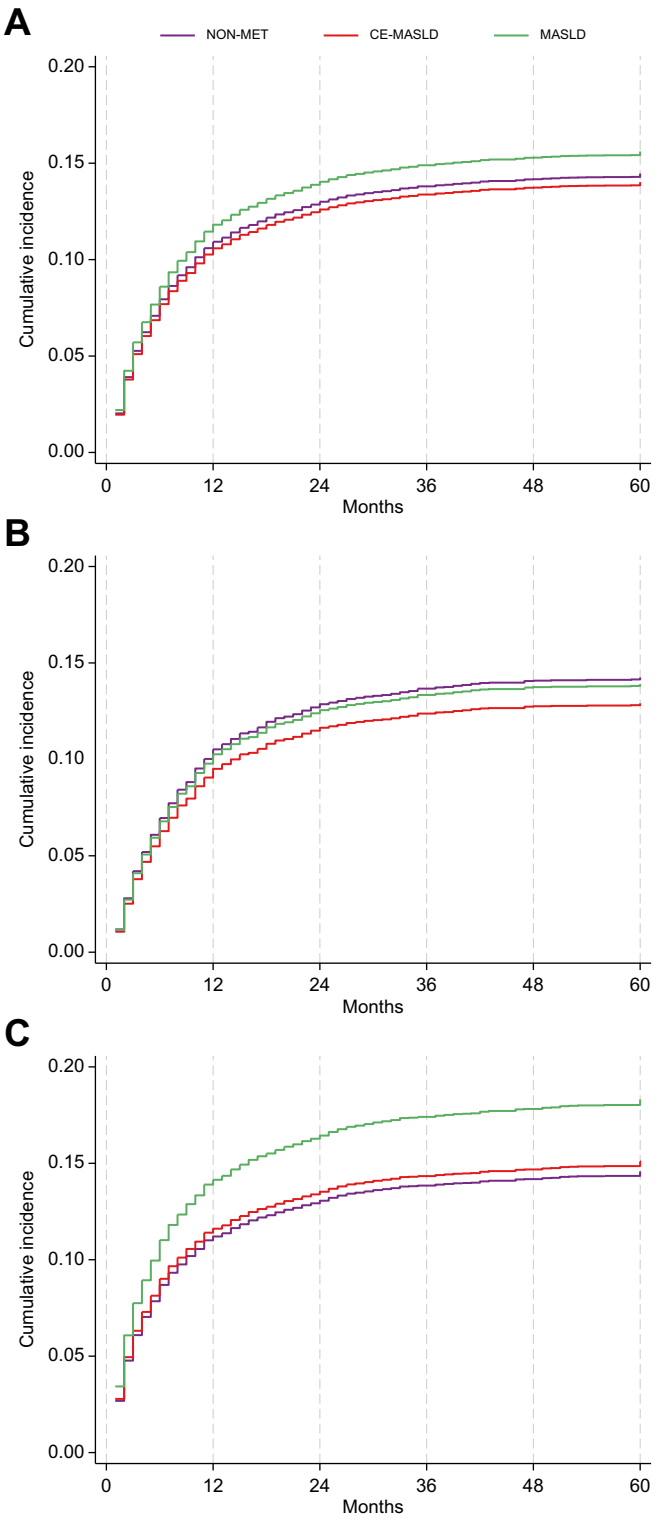

Fig. 4. Waiting list competing risk of death/dropout. (A) Whole population, (B) patients without HCC, and (C) patients with HCC. The competing risk method of Fine and Gray[16] used LT and death/dropout as competing events. The competing risk curves were constructed using estimates adjusted (by a multivariable model) for age, sex, blood group, study period, centre volume, and MELD-sodium. CE-MASLD, combined aetiology MASLD; HCC, hepatocellular carcinoma; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; NON-MET, non-metabolic aetiologies.

related liver disease (from 13.49 to 23.52%, p <0.001). Conversely, the proportions of candidates with HCV (from 45.94 to 26.56%, p <0.001) and CE-MASLD (Fig. 3A; from 50.37 to 44.96%, p <0.001) significantly decreased, whereas that of candidates with HBV and NON-MET (Fig. 3A) remained almost stable.

In Figs 2B and 3B, the epidemiological trends of patients with MASLD were compared with those of patients with HCV-, HBV-, ALD-, CE-MASLD-, and NON-MET-related conditions in the non-HCC group only (n = 7,059). The proportion of patients with non-HCC MASLD increased over the study period, from 9.46% in 2012 to 11.83% in 2022 (p <0.001), as well as that of patients with ALD (from 19.26 to 36.39%, p <0.001). Conversely, the proportion of patients with HCV dramatically decreased (from 41.22 to 12.43%, p <0.001), whereas HBV decreased more slowly than HCV. The proportions of patients with CE-MASLD and NON-MET (Fig. 3B) remained almost stable.

Figs 2C and 3C compare the epidemiological trends of different aetiologies in the HCC group (n = 6,083). Patients with HCC MASLD significantly increased over the study period (from 17.65 to 29.97%, p <0.001), whereas the increase in ALD and the decrease in HCV cases were much less pronounced than in patients without HCC. The proportions of patients with NON-MET remained stable (Fig. 3C), whereas that of patients with CE-MASLD HCC significantly decreased (from 52.94 to 40.07%, p <0.001).

Using linear regression models, we extended to future years the epidemiological trends of MASLD HCV-, HBV-, ALD-, CE-MASLD, and NON-MET-related entries in Italy (Figs 2A–C and 3A–C). We calculated that candidates with MASLD to LT should overcome total candidates with HCV (Fig. 2A) within 2024. For candidates without HCC (Fig. 2B), MASLD aetiology has already overtaken candidates with HCV in 2021. For candidates with HCC (Fig. 2C), we calculated that MASLD should overcome candidates with HCV in approximately 5 years, those with NON-MET within 2023, and those with CE-MASLD in approximately 4 years.

Patient characteristics in the MASLD and non-MASLD groups

Patient characteristics are shown in Table 1. Patients with MASLD were found to be older than patients with CE-MASLD and NON-MET (median age 61 *vs.* 56 *vs*. 55 years, p <0.001) and more frequently male than patients with NON-MET (79.65 *vs*. 65.43%, p <0.001). The prevalence of overweight patients (BMI >25) was significantly higher in patients with CE-MASLD than in patients with MASLD (93.95 *vs*. 91.09%, p <0.001). Conversely, the prevalence of diabetes, dyslipidaemia, and hypertension was higher in patients with MASLD than in patients with CE-MASLD (p <0.001). However, as emphasised in the Patients and Methods section, these values are likely underestimated in both groups. In addition, patients with MASLD had a higher percentage of HCC compared with patients with CE-MASLD and NON-MET, both at the moment of listing for liver transplant (61.51 *vs*. 47.92 *vs*. 38.07%, p <0.001) and at the time of liver transplant (65.03 *vs*. 50.40 *vs*. 40.67%, p <0.001). Median MELD-sodium values were significantly lower in patients with MASLD than in patients with CE-MASLD and

Table 1. Comparison between MASLD, CE-MASLD, and NON-MET populations.

Variables	MASLD (n = 1,941) n (%) or median (IQR)	CE-MASLD (n = 6,342) n (%) or median (IQR)	NON-MET (n = 4,859) n (%) or median (IQR)
Age, years	61 (55–65)	56 (51–62)**	55 (48–61)**
Male sex	1,546 (79.65)	5,103 (80.46)	3,179 (65.43)**
BMI (kg/m^2)	28 (26–30)	27 (26–29)**	22 (21–24)**
BMI >25 kg/m^2	1,768 (91.09)	5,958 (93.95)**	–
Diabetes	822 (42.33)	1,402 (22.10)**	–
Dyslipidaemia	375 (19.31)	540 (8.51)**	–
Hypertension	653 (33.66)	1,461 (23.04)**	–
Main aetiology of liver disease			
HCV	–	3,074 (48.47)	1,823 (37.52)
HBV	–	1,049 (16.54)	687 (14.14)
Alcohol	–	1,551 (24.46)	755 (15.54)
Other (miscellanea)	–	668 (10.53)	1,594 (32.81)
Blood group			
0	809 (41.68)	2,627 (41.42)	1,996 (41.08)
A	740 (38.12)	2,563 (40.41)	1,973 (40.61)
B	290 (14.94)	832 (13.12)	652 (13.42)
AB	102 (5.25)	320 (5.05)	238 (4.90)
Centre volume >50 patients/year	1,397 (71.97)	4,708 (74.24)*	3,582 (73.72)
Year of WL inscription >2016	1,263 (65.07)	3,403 (53.66)**	2,593 (53.57)**
MELD-sodium at WL inscription	14 (10–19)	15 (10–20)*	15 (10–21)*
HCC at WL inscription	1,194 (61.51)	3,039 (47.92)**	1,850 (38.07)**
WL status at the end of follow-up			
Transplants	1,467 (75.58)	4,895 (77.18)	3,575 (73.58)*
Death/dropout	270 (13.91)	811 (12.79)	647 (13.32)*
Still in WL	204 (10.51)	636 (10.03)	637 (13.11)
MELD-sodium at LT	14 (10–20)	15 (10–22)*	15 (10–22)*
HCC at LT	954 (65.03)	2,467 (50.40)**	1,454 (40.67)**
Dual transplants	40 (2.06)	152 (2.40)	166 (3.42)
Liver–kidney	32 (1.65)	148 (2.33)	123 (2.53)
Liver–pancreas	4 (0.21	3 (0.05)	27 (0.56)
Other	4 (0.21)	1 (0.02)	16 (0.33)
Cold ischaemia time (h)	7 (6–8)	7 (6–8)	7 (6–8)
Donor age	63 (50–75)	63 (50–74)	65 (50–76)
Donor blood group			
0	621 (44.26)	2,065 (43.50)	1,472 (42.41)
A	547 (38.99)	1,924 (40.53)	1,464 (42.18)
B	176 (12.54)	571 (12.03)	398 (11.47)
AB	59 (4.21)	187 (3.94)	137 (3.95)
Donor BMI	26 (24–29)	26 (24–28)	25 (23–27)

CE-MASLD, combined aetiology MASLD; HCC, hepatocellular carcinoma; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; NON-MET, non-metabolic aetiologies; WL, waiting list. Continuous variables were summarised using the median and IQR, and the Mann–Whitney *U* test was used to compare groups. Categorical variables were summarised with frequencies and percentages, and the Chi-square test was used to compare groups. *p <0.05; **p <0.001 in the comparisons between MASLD *vs*. CE-MASLD and MASLD *vs*. NON-MET.

NON-MET, both at the moment of listing for liver transplant (14 *vs*. 15 *vs*. 15, p <0.05) and at the time of liver transplant (14 *vs*. 15 *vs*. 15, p <0.05).

In terms of HCC characteristics (Table S1), the populations were very similar, with only some minor differences concerning tumour diameter (more significant in MASLD, particularly *vs*. NON-MET) and prevalence of downstaging procedures (lower in MASLD).

Survival benefit of liver transplantation in patients with MASLD and without MASLD

WL survival model

The impact of MASLD on the risk of WL death/dropout was assessed following multivariate adjustment for age, sex, blood group, study period, centre volume, and MELD-sodium variables.

No significant difference in the WL competing risk of death/dropout (all causes) was observed in patients with MASLD compared with patients with CE-MASLD and NON-MET in the overall population (Fig. 4A; p = 0.140). We further analysed the effect of MASLD on different competing events during the WL, including transplant probability, HCC progression, liver-related death, and non-liver-related death, in the two groups of patients with and without HCC (Table 2). Our findings indicate that the significant prognostic effect of MASLD on the WL risk of death dropout in patients without HCC (Fig. 4B) when compared with patients with CE-MASLD and NON-MET was primarily driven by its impact on liver-related death (Fig. S1-S2 and Table 2). Interestingly, patients with MASLD also had a significantly lower probability of transplant than patients with CE-MASLD and NON-MET (Table 2 and Fig. S1A). Conversely, when MASLD and CE-MASLD were considered together in a unique metabolic (MET) population, we did not find significant differences between MET and NON-MET regarding WL risk of death in patients without HCC (Fig. S3A).

The same analyses performed in patients with HCC did not find any significant difference between the MASLD,

Table 2. Cause-specific (MASLD *vs.* CE-MASLD *vs.* NON-MET) hazard ratios of waiting-list competing events in patients without and with HCC.

WL competing events	Patients without HCC Hazard ratio (95% CI), *p* value	Patients with HCC Hazard ratio (95% CI), *p* value
All causes death/dropout risk		
NON-MET	Reference	Reference
CE-MASLD	1.09 (0.93–1.27), 0.303	0.92 (0.77–1.08), 0.307
MASLD	**1.62 (1.26–2.09), 0.000**	0.99 (0.79–1.23), 0.919
Transplant probability		
NON-MET	Reference	Reference
CE-MASLD	1.05 (0.98–1.12), 0.152	1.01 (0.94–1.09), 0.740
MASLD	**0.86 (0.76–0.98), 0.019**	0.97 (0.87–1.09), 0.605
HCC progression risk		
NON-MET	–	Reference
CE-MASLD	–	1.05 (0.82–1.34), 0.709
MASLD	–	1.03 (0.71–1.50), 0.877
Liver-related death risk		
NON-MET	Reference	Reference
CE-MASLD	1.08 (0.92–1.28), 0.330	0.79 (0.58–1.09), 0.147
MASLD	**1.66 (1.28–2.15), 0.000**	1.05 (0.64–1.74), 0.842
Non-liver-related death risk		
NON-MET	Reference	Reference
CE-MASLD	1.10 (0.61–1.99), 0.742	0.96 (0.33–3.17), 0.959
MASLD	0.94 (0.32–2.80), 0.913	1.03 (0.13–7.97), 0.981

CE-MASLD, combined aetiology MASLD; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; NON-MET, non-metabolic aetiologies; WL, waiting list. Estimates were adjusted for age, sex, blood group, study period, centre volume, and MELD-sodium. A cause-specific hazard estimation model was used to evaluate the role of MASLD in influencing different causes of WL death/dropout (*i.e.* HCC progression *vs.* liver-related death *vs.* non-liver-related death)[18,19] Values in bold denote statistical significance.

CE-MASLD, and NON-MET populations (Fig. 4C, Table 2, and Fig. S2) and between MET and NON-MET populations (Fig. S3B).

Post-transplant survival model and intention-to-treat survival explorative analysis

In the analysis using the Kaplan–Meier curves, no significant differences in post-LT survival were demonstrated between patients with MASLD and other patients (CE-MASLD and NON-MET) in the overall population, with a 5-year survival rate of 86% for the former and 83% for the latter (Fig. 5A). We did not find significant differences in patients without HCC (Fig. 5B; $p = 0.264$). In contrast, a significant difference was confirmed in patients with HCC (Fig. 5C; $p = 0.017$), where patients with CE-MASLD had better survival than patients with NON-MET and MASLD.

The impact of MASLD on different post-LT causes of death was evaluated separately in the two populations of patients with and without HCC after a multivariate adjustment for age, sex, blood group, study period, centre volume, MELD-sodium at transplant, and donor age variables (Table 3).

We did not find a significant impact of MASLD on the post-transplant risk of different causes of death in the two populations of patients with and without HCC (Table 3, Figs S4 and S5).

Moreover, we did not find any significant difference when we compared post-LT survival in patients with MET and NON-MET non-HCC (Fig. S6A) and patients without HCC (Fig. S6B).

An intention-to-treat survival explorative analysis using Kaplan–Meier curves confirmed that in patients without HCC, those with MASLD had significantly lower survival than those with CE-MASLD and NON-MET (Fig. S7A). Conversely, in patients with HCC, MASLD intention-to-survival was similar to that of NON-MET and considerably lower than that of CE-MASLD (Fig. S7B).

Five-year transplant survival benefit model

Because MASLD did not significantly impact either the competing risk of death on the WL (Table 2) or post-transplant survival (Table 3), we assumed that there was no difference in terms of transplant benefit between patients with HCC with and without MASLD.

Using the results from Tables 2 and 3, we calculated the transplant benefit in patients without HCC with and without MASLD and the overall population of patients with HCC.

Fig. 6 describes the results of the transplant benefit analysis. At the same MELD-sodium, the 5-year transplant benefit was higher in patients with non-HCC MASLD, followed by patients with HCC, whereas it was lower in patients without HCC without MASLD.

As MELD-sodium increases, the difference in transplant benefit at 5 years among these three groups diminishes.

Discussion

This comprehensive analysis of the Italian liver transplant registry is the first study applying the new MASLD definition in the context of liver transplant candidates.

This new nomenclature has been endorsed by more than 70 scientific societies and organisations,[7] confirming a broad interdisciplinary consensus within the scientific community and indicating a significant agreement among experts from various disciplines. This support from numerous scientific entities underscores the widespread acceptance and adoption of the new nomenclature in diverse contexts, thereby contributing to the consolidation of its validity and relevance in the scientific landscape. Global recognition facilitates the dissemination of research findings, enables the development of consistent policies, and supports establishing international standards.

Our study confirms the significant increase in the proportion of patients with MASLD on the liver transplant WL occurring in the USA, the European registry,[4] and Italy over recent years,

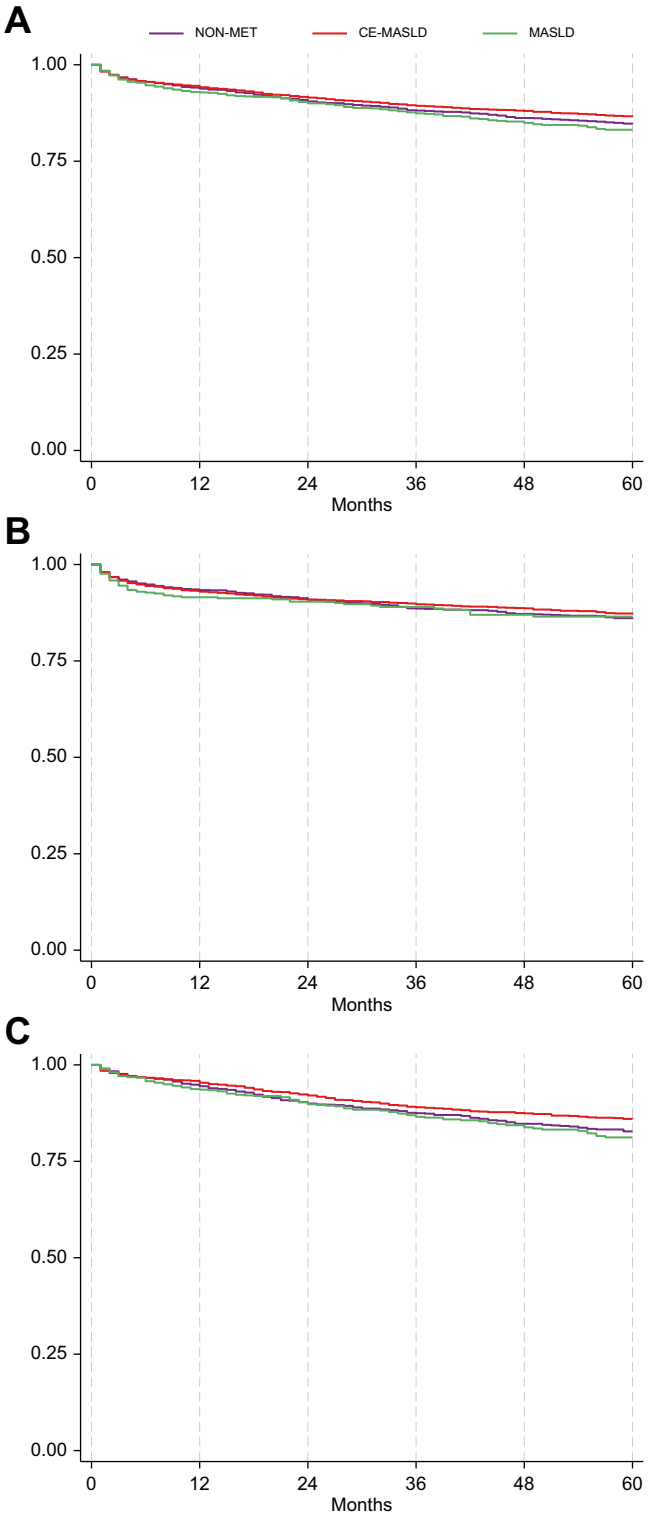

Fig. 5. Post-LT survival Kaplan Meier curves. (A) Whole population, (B) patients without HCC, and (C) patients with HCC. Kaplan–Meier curves were compared using the log-rank test. CE-MASLD, combined aetiology MASLD; HCC, hepatocellular carcinoma; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; NON-MET, non-metabolic aetiologies.

but it introduces two important innovations. Firstly, we focused on WL entries and dynamics, whereas the European study solely assessed liver transplant cases. Secondly, we delved into the prospective trajectories of liver transplant indications in Italy, extending our analysis to 2030. Notably, we discovered that by 2024, MASLD will surpass HCV-related cirrhosis as an indication for transplant, emerging as the second leading indication in Italy after alcoholic liver disease (Fig. 2). Similar trends will likely be observed in other European countries, aligning with recent studies.[20–22]

As observed in other studies,[4,12] we noted that the epidemiological increase in MASLD cases affects both patients with and without hepatocellular carcinoma (HCC) (Fig. 2B and C). In contrast, the epidemiological trajectories of HCV- and alcohol-related cirrhosis exhibited marked differences. Specifically, there was a significant decline in HCV-related cirrhosis and a notable increase in alcohol-related cirrhosis among transplant candidates without HCC. In contrast, these trends were less prominent among candidates with HCC.[4,12,23]

A second noteworthy finding in this study concerns comparing demographic characteristics between patients with and without MASLD. Patients with MASLD captured at the WL registration were older, predominantly male, and more frequently associated with HCC. This result is consistent with findings reported in other studies.[4,12,24] No nationally shared protocol in Italy suggests a specific BMI value as an exclusion criterion for listing patients. However, the relatively low BMI values in patients with MASLD on the transplant WL in Italy (Table 1) suggest that many centres likely applied restrictive criteria for overweight and obese patients in recent years. In addition, it is conceivable that the more severe cardiovascular involvement associated with MASLD[22] may have contributed to the exclusion of older MASLD cases from liver transplantation.

Epidemiological changes in chronic liver diseases, marked by a decline in viral diseases and an increase in alcoholic and metabolic diseases, are to lead liver transplant centres to be less restrictive on this particular aspect in the future. Given that MASLD aetiology will become the second leading indication for liver transplant in Italy (Fig. 2), mirroring trends in other Western countries, the international transplant community should be prepared to reconsider clinical protocols for the evaluation and management of potential transplant candidates based on the evolving population characteristics. Specifically, changes in the transplant population profile may necessitate future resource allocation modifications.

For this reason, we focused on the third and most critical part of our study, which is the survival benefit at 5 years of liver transplant for patients with MASLD compared with those without. Unlike the European research, we also analysed the survival of patients on the WL and found that MASLD significantly reduces WL survival in patients without HCC (Fig. 4B and Table 2). In contrast, as in the European study,[4] our data reveal that patients with metabolic liver disease exhibit a comparable post-transplant outcome to those without MASLD, irrespective of the presence of HCC (Fig. 5 and Table 3). Consequently, we observed that MASLD aetiology significantly enhances the 5-year transplant survival benefit in patients without HCC, whereas it does not substantially impact patients with HCC (Fig. 6). In other words, we are considering that the risk of death without transplant in patients with MASLD without HCC is higher than that of other candidates. At the same time, their post-transplant survival is similar; consequently, the transplant's survival benefit for these patients is more significant. This incremental effect of MASLD on the 5-year transplant

Table 3. Cause-specific (MASLD *vs*. CE-MASLD *vs*. NON-MET) hazard ratios of post-transplant competing events in patients without and with HCC.

Post-transplant competing events	Patients without HCC Hazard ratio (95% CI), *p* value	Patients with HCC Hazard ratio (95% CI), *p* value
Overall patient survival		
NON-MET	Reference	Reference
CE-MASLD	0.89 (0.74–1.06), 0.175	**0.80 (0.67–0.96), 0.017**
MASLD	1.00 (0.75–1.33), 0.985	0.97 (0.77–1.21), 0.767
Transplant-related death		
NON-MET	Reference	Reference
CE-MASLD	0.81 (0.50–1.30), 0.378	0.67 (0.41–1.11), 0.118
MASLD	0.97 (0.45–2.10), 0.947	0.60 (0.29–1.22), 0.160
HCC-related death		
NON-MET	–	Reference
CE-MASLD	–	0.92 (0.66–1.28), 0.621
MASLD	–	0.84 (0.54–1.30), 0.436
Cardio/cerebrovascular death		
NON-MET	Reference	Reference
CE-MASLD	0.86 (0.56–1.32), 0.491	0.88 (0.49–1.60), 0.677
MASLD	1.08 (0.53–2.20), 0.823	1.30 (0.64–2.62), 0.471
Other causes of death		
NON-MET	Reference	Reference
CE-MASLD	0.95 (0.76–1.19), 0.665	0.92 (0.66–1.28), 0.621
MASLD	1.06 (0.75–1.51), 0.735	0.84 (0.54–1.30), 0.436

CE-MASLD, combined aetiology MASLD; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; NON-MET, non-metabolic aetiologies; WL, waiting list. Estimates were adjusted for age, sex, blood group, study period, centre volume, MELD-sodium at transplant, and donor age. A cause-specific hazard estimation model was used to evaluate the role of MASLD in influencing different causes of post-transplant death (*i.e.* transplant-related *vs*. HCC-related *vs*. cardio/cerebrovascular *vs*. other causes of death).[18,19] Values in bold denote statistical significance.

survival benefit persists across different MELD-sodium values, although it appears more pronounced for low MELD-sodium values (Fig. 6). This finding could hold significant implications for future allocation policies. Particularly in countries already implementing the transplant benefit principle for organ allocation,[8,9] our study may suggest an increased transplant priority for patients with MASLD without HCC. To assess whether such prioritisation would be beneficial or harmful, we analysed the specific causes of death/dropout from the WL (Table 3). The significant increase in death/dropout was mainly driven by liver-related events (Table 3).

A recent study analysing the American transplant registry[18] supports the predominant effect of MASLD for low MELD-sodium values. The study underlines increased mortality on the WL for patients with metabolic cirrhosis, particularly evident with lower MELD-sodium values.

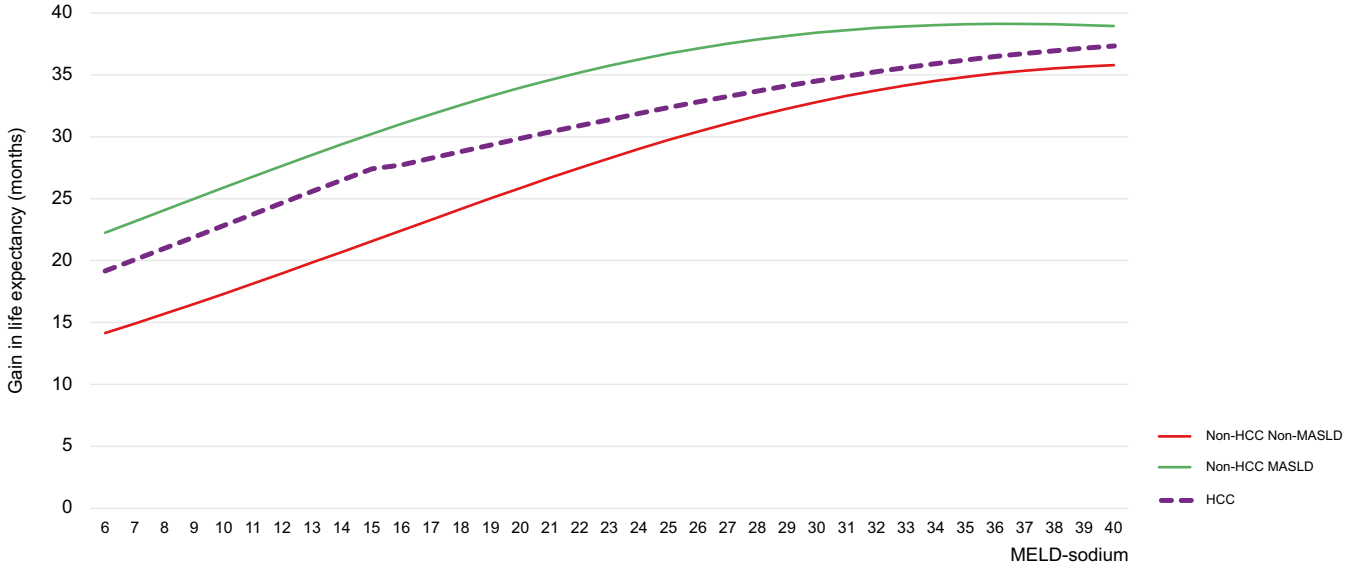

Fig. 6. Five-year transplant benefit (gain in life expectancy months) in patients with HCC, non-HCC MASLD, and non-HCC non-MASLD based on MELD-sodium values. A multistate model converted monthly death probabilities (derived from WL and post-LT survival models) into life expectancy values. The survival benefit of LT (gain in life expectancy) at 60 months was calculated by subtracting the no-LT life expectancy predictions from the post-LT life expectancy predictions. Using the Monte Carlo simulation, we obtained a list of 10,000 outcomes (5-year survival benefit expressed as life expectancy in months) for each population (HCC and non-HCC) based on covariate distributions. This analysis allowed us to describe the correlation between 5-year transplant survival benefit and main study covariates (*i.e.* MASLD *vs*. non-MAFLD aetiology, the presence of HCC, and MELD-sodium values). HCC, hepatocellular carcinoma; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease; WL, waiting list.

Based on the above considerations, increasing priority for patients with non-HCC MALSD patients may be advantageous. However, differentially prioritising aetiologies of cirrhosis, such as MASLD, over other entities could raise ethical issues. Therefore, adjusting priority scores based on aetiology only should be carefully evaluated.

A few limitations of the present study should, however, be acknowledged. Firstly, the study's retrospective nature makes it susceptible to unintentional biases. In addition, similar to other registry-based studies,[4,12] the prevalence data for cardiometabolic factors (diabetes, dyslipidemia, and hypertension) are likely significantly underestimated owing to the non-mandatory inclusion of these data in the transplant registry. Notably, this limitation could result in undervaluing the actual prevalence of metabolic cases among transplant candidates in Italy and Europe, especially in light of the new definitions of MAFLD and MASLD.[7,25] The lack of extensive diabetes data could be particularly critical, considering the importance of diabetes in the transplant context.[22,26] In addition, other variables describing cirrhosis complications, such as varices, ascites, hepatopulmonary syndrome, hepatic encephalopathy, hepatorenal syndrome, and the presence of renal dysfunction, were not available. Although differences in clinical data among cohorts might influence outcomes, the large number of cases is likely to mitigate biases.

Conclusions

In conclusion, our study reveals a significant increase in candidates with MASLD for liver transplants from 2012 to 2022, with the expectation of surpassing the incidence of candidates with HCV in Italy as early as next year. In the case of patients with HCC, although the prevalence of MASLD is still increasing, it will take several more years for it to become the primary indication for transplant in this population because of a slower decline in HCV prevalence compared with patients without HCC. Nevertheless, the proportion of candidates with concurrent MASLD and HCC is rising, reflecting the well-established association of MASLD with HCC. Although MASLD has not been proven to be an independent predictive factor for patient survival after transplant, it significantly influences the WL survival of patients without HCC, increasing their risk of death during their time on the list. Consequently, the survival benefit of transplant in patients with MASLD without HCC surpasses that of other candidates, regardless of the degree of liver dysfunction measured by MELD-sodium (Fig. 6). If externally validated, this result suggests improvements in allocation policies aimed at increasing the priority of patients with MASLD compared with other transplant candidates. Careful evaluation and patient selection for patients with MASLD remains crucial to maintaining an acceptable survival rate for these patients before and after transplant.

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Abbreviations

ALD, alcohol-related liver disease; CE-MASLD, combined aetiology MASLD; HCC, hepatocellular carcinoma; LT, liver transplantation; MAFLD, metabolic-[dysfunction] associated fatty liver disease; MASLD, metabolic dysfunction-associated steatotic liver disease; MELD, model for end-stage liver disease score; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NON-MET, non-metabolic aetiologies; SIT, Informative Transplant System; SLD, steatotic liver disease; WL, waiting list.

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Conflicts of interest

The authors declare no conflicts of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualisation: AV, UC. Methodology: AV, IB, LM, ST, AR, MC. Formal analysis: AV, MO, IB, LM, ST, AR, MC. Data curation: ST, MC, PB, RR, SM, PDS, PC, MC, SF, MCM, LDC, LB, SG, RV, MC, SF, GR, FD, FDB, NDM, AC. Writing—original draft preparation: AV, UC, MO. Writing—review and editing: UC, AV, MO, FPR, GM, PB, RR, SM, PDS, PC, MC, SF, MCM, LDC, LB, SG, RV, MC, SF, GR, FD, FDB, NDM, GB, PR. Supervision: APB, RR, SM, PDS, PC, MC, SF, MCM, LDC, LB, SG, RV, MC, SF, GR, FD, FDB, PR, NDM, LM, GB. Project administration, AV, UC, ST, AR, MC. All authors have approved the submitted version and agree to be personally accountable for the authors' contributions and for ensuring that questions related to the accuracy or integrity of any part of the work, even details in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature.

Data availability statement

Restrictions apply to the availability of these data. Data were obtained from the Informative Transplant System database. This prospective database is managed by the Italian National Transplant Centre (directly from the Italian Health Ministry), where prospectively collected data from each Italian centre are recorded at different time points. The management of this database conforms to Italian privacy legislation. Data are available (http://www.trapianti.salute.gov.it/trapianti/homeCnt.jsp) only with the permission of the Italian National Transplant Centre.

Ethics approval statements

The study was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Ethical review and approval were waived for this study because, according to Italian laws, no specific patient approval is needed for any retrospective analysis, but patients provided written informed consent for every diagnostic and therapeutic procedure (liver transplantation included), as well as for having their clinical data recorded anonymously in the Informative Transplant System database. This prospective database is managed by the Italian National Transplant Centre (directly depending on the Italian Health Ministry), recording prospectively collected data from each Italian centre at different time points. The management of this database conforms to Italian privacy legislation.

Supplementary data

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