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Sex-based disparities in liver transplantation: Evidence from a nationwide Italian cohort

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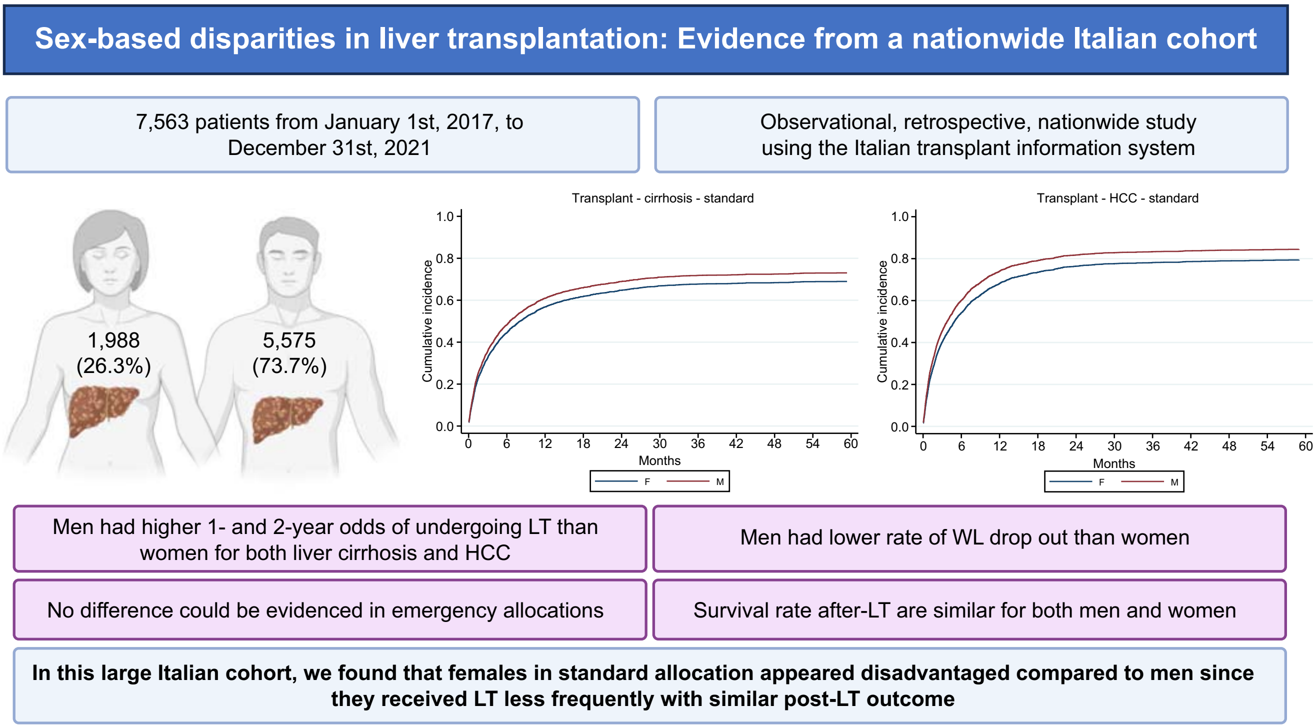
Graphical abstract



Sex-based disparities in liver transplantation: Evidence from a nationwide Italian cohort

7,563 patients from January 1st, 2017, to December 31st, 2021

Observational, retrospective, nationwide study using the Italian transplant information system

Men had higher 1- and 2-year odds of undergoing LT than women for both liver cirrhosis and HCC

Men had lower rate of WL drop out than women

No difference could be evidenced in emergency allocations

Survival rate after-LT are similar for both men and women

In this large Italian cohort, we found that females in standard allocation appeared disadvantaged compared to men since they received LT less frequently with similar post-LT outcome

Highlights:

- Sex-based disparities in LT have been acknowledged for several years, particularly in studies in the USA.
- Female standard allocation patients in Italy appeared to be at a disadvantage compared with their male counterparts.
- The existence of allocation mechanisms other than the standard allocation can mitigate these disparities.
- The introduction of scores to better counteract this disparity, is expected to improve allocation equity.

Impact and implications:

Although sex-based disparities in the LT setting have been acknowledged for several years, particularly in studies conducted in the USA, few data are available in Europe. Our study provides an exhaustive overview regarding the disadvantage facing women outside the USA in accessing LT. By detailing these differences, it provides solid arguments for developing equitable health policy. Given that these differences are affected by the national scenario, having local data is crucial for defining possible targeted actions.

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Research article

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Sex-based disparities in liver transplantation: Evidence from a nationwide Italian cohort

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Background & Aims: Although sex-based disparities in the liver transplantation (LT) setting have been acknowledged for several years, particularly by studies conducted in the USA, data from European countries are scarce.

Methods: We conducted a nationwide, retrospective, observational study on candidates identified for LT in Italy between January 2017 and December 2021 using national registry data with follow-up until June 2023. The primary aim was to assess sex-based differences in LT access, analyzing delisting, retransplantation, and mortality rates. Patients were monitored from waitlist admission to transplant, removal, or death, with competing risks modeled (Fine and Gray) multivariable analysis. Survival outcomes were evaluated using Kaplan–Meier estimates, time-dependent Cox models, and stratified log-rank tests.

Results: In total, 7,563 patients were included in the analysis, 5,575 (73.7%) of whom were men. Men had higher 1- and 2-year probabilities of undergoing LT compared with women for both liver cirrhosis (subdistribution hazard ratio [sHR] 1.13, 95% CI 1.02–1.26, $p = 0.02$ and sHR 1.12, 95% CI 1.01–1.24, $p = 0.03$, respectively) and hepatocellular carcinoma (HCC) (sHR 1.20, 95% CI 1.07–1.36, $p = 0.003$ and sHR 1.21, 95% CI 1.08–1.35, $p = 0.001$, respectively). The wait list (WL) dropout rate in men did not differ significantly to that for women (12.6% *vs.* 13.9%, $p = 0.14$) except when the indication to LT was HCC (10.6% *vs.* 14.2%, $p = 0.035$). In addition, men had a lower wait list (WL) mortality rate compared with women (7.0% *vs.* 8.5%, $p = 0.04$). Post-LT survival rates were similar for both sexes.

Conclusions: In this large Italian cohort, female standard allocation patients appeared to be at a disadvantage compared with men, because they received LT less frequently, but with similar post-LT outcomes.

Introduction

Sex-based disparities in liver transplantation (LT), which were first documented more than 20 years ago, continue to be described at all stages of the LT cascade, from evaluation, to access to the wait list (WL), and through to transplantation.[1,2] Data from the USA have showed that, since the introduction of the Model for End-stage Liver Disease (MELD) allocation policy, women are 11–30% less likely to undergo LT.[3]

The MELD score is a mathematical algorithm based on the evaluation of total bilirubin, creatinine, and the international normalized ratio (INR) for prothrombin time, which is adopted to estimate WL mortality within 90 days.[4] Regardless of the undeniable benefits of using the MELD score,[5] several contributing factors have been analyzed to explain this disparity between men and women in LT access and prioritization. These include differences in liver disease etiology and eligibility for MELD exception points.[6] Furthermore, the MELD score has been criticized for being systematically biased because it includes serum creatinine, which is known to put women at a disadvantage given their lower muscle mass.[1] Smaller size has also been found to disadvantage allocation for women.[7] Different models have been proposed to eliminate the sex-based disparity in access to LT resulting from the MELD and MELD-Na allocation policy. The first attempt was made by Allen *et al.* in 2018.[8] The authors proposed allocating one additional MELD point to all female patients, which would increase access to LT, with the greatest benefit in patients with a MELD score of 20–29.[8] In 2021, Kim *et al.*[9] proposed MELD 3.0, which included two new variables in the score (female sex and serum albumin) and reduced the creatinine ceiling from 4 mg/dl to 3 mg/dl. Application of the final model resulted in a significant reduction in number of WL deaths among female patients compared with MELD-Na alone ($p = 0.02$) in the simulated allocation analysis.[9] Subsequently, the Gender Equity Model for Liver Allocation (GEMA) and the GEMA-Na, which replaced creatinine with the

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Royal Free Hospital glomerular filtration rate (RFH-GRF) formula, was found to perform better than the MELD, MELD-Na, and MELD 3.0 scores in predicting mortality within 3 months from WL admission.[10] The GEMA-Na score, the first score to be validated outside of the USA, appears to have a better discrimination capacity in the female population, where it is estimated that one in eight deaths might be avoided if it is used.[10,11] Although these disparities are well established in studies conducted in the USA and scarce, albeit increasing, evidence on sex-based disparities is available for Europe, there are no comprehensive data from Italy. Europe has national or macro-national (e.g., Eurotransplant) allocation systems, which are generally based on the MELD-Na score, but allow for flexibility by introducing alternative scoring systems to prioritize conditions that are not adequately rated using this score alone.[12–14] A recent, extensive study across Eurotransplant countries confirmed that women are at a disadvantage when it comes to accessing LT, mainly as a result of the effect size,[15] while a comprehensive analysis from Spain confirmed the superiority of MELD 3.0 and GEMA-Na in addressing sex-based disparities in LT access.[16] To increase the body of evidence across Europe, this study evaluated, in the Italian LT setting, the potential existence of sex-related disparities in the probability of undergoing LT and of WL dropout and analyzed the differences in post-LT survival rates.

Methods

Objectives and outcomes

We conducted a retrospective observational study on LT candidates admitted to the LT-WL in Italy between January 1, 2017 and December 31, 2021.

The primary objective of the study was to determine whether there were any differences in access to LT in Italy, considering biological sex as the main variable, as well as to analyze the delisting, retransplant, and mortality rates. To do so, LT candidates were monitored from the time of WL admission to LT, removal from the WL or death, whichever occurred earliest. Reasons for WL removal included being too sick to receive a transplant, achievement of significant clinical improvement, or LT refusal. WL dropout because of clinical deterioration was considered to be a competitive event with death. Relisting as a result of graft failure was analyzed separately and considered as a secondary outcome. We additionally provide data on the survival rate in LT recipients stratified by biological sex and matched for the sex of the donor.

Study population

Consecutive adult patients listed for LT in Italy between January 1, 2017 and December 31, 2021, and included in the Transplant Information System (Sistema Informativo Trapianti; SIT) of the Italian National Transplantation Center (Centro Nazionale Trapianti; CNT) registry, were enrolled in this study. The patients were followed until June 30, 2023. Multiorgan transplantation was considered an exclusion criterion, whereas relisting and re-LT resulting from graft failure were evaluated separately in the analysis. Indications for LT were divided into three groups: liver cirrhosis (LC); hepatocellular carcinoma (HCC); and all other conditions resulting in LT (*e.g.* other tumors, other liver diseases, and subacute liver failure). Patients waitlisted for HCC were identified by crossmatching all available records. Whenever the term ‘HCC’ was mentioned in the SIT, HCC was considered the primary indication.

In addition, in accordance with the Italian allocation system protocol, we classified allocation urgency into ‘national emergency’ and ‘macro-regional emergency’. The former, which applies to United Network for Organ Sharing (UNOS) status 1 cases and exemptions deemed worthy of such urgency by the CNT board, speeds up the allocation process by issuing a nationwide call for compatible donation offers. By contrast, the latter is an allocation scheme shared by neighboring regions (Fig. 1) that applies to MELD-Na scores of up to 28 and waivers evaluated by the CNT board. Standard allocation is followed in non-urgent cases by the regions pertaining to the individual transplant centers and is based on the Italian Score for Organ allocation (ISO),[17] which is derived from the MELD-Na score but is enhanced with extra points relating to the etiology of the liver disease and the indication to equate the multiple conditions resulting in LT (Supplementary section S1).[17] Each allocation group was analyzed separately to respect the peculiarities of each allocation using different rules, while still gaining insights into each of these models. The allocation policy was consistent throughout the study.

Ethical aspects

The study complied with the ethical guidelines set forth in the Declaration of Helsinki. The SIT, which was established by Italian Law no. 91 of April 1, 1999 as part of the New Health Information System, is an IT infrastructure for the management of data relating to the activities of the Italian transplant network with the purpose of ensuring the transparency and traceability of donation, procurement, and transplantation processes. The patient data extracted from the SIT database were anonymized before statistical analysis, to ensure that subjects could not be re-identified, in accordance with European and Italian regulations (Article 6[e], Article 9[g], and Article 89 of Regulation [EU] 2016/679; Article 2-*sexies* and Article 106 of Italian Legislative Decree 196/2003; Article 1 of Italian Ministerial Decree 3/3/2017; and the Ethical Rules Governing Processing for Statistical or Scientific Research Purposes, provided for in Article 20[4] of Legislative Decree no. 101 of 10/10/2018). As a result, the study did not apply for Ethics Committee approval, but it was otherwise revised and approved by the CNT Scientific Committee.

Statistical analysis

Continuous variables were expressed as mean ± SD and the categorical variables as frequencies and percentages. Data were compared using the Student *t* test and Wilcoxon rank sum test, or Fisher’s exact test in the case of sparse tables.

We analyzed the probability of undergoing a LT (at 1 and 2 years) using the cumulative incidence function (CIF) with the competing risks death, being too sick for LT, and improvement with permanent removal from the WL. A similar approach was adopted when evaluating deterioration in condition/death while on the WL (concurrent events: LT or improvement). For LT probabilities and delisting rates, the ‘sex’ factor was estimated by adjusting for demographic and clinical covariates (*i.e.* age, BMI, MELD-Na) by performing Fine and Gray multivariable analysis for concurrent events. A sample calculation was not

Fig. 1. Map of Italy depicting the organization of the LT centers and regions and macro-regions that share the organs. DDLT, deceased donor liver transplantation; HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation; LT, liver transplantation.

performed, but the entire available cohort was analyzed by interpreting the results according to the 95% CIs for the estimated parameters.

In the intention to treat (ITT) analysis, we considered the first WL date as Day 0 and calculated survival from this time point. Patients were followed until death or censoring analysis at the end of follow-up, regardless of LT or relisting for LT status. Mortality rates starting from the listing and 1- and 5-year ITT survival were estimated using the Kaplan–Meier method. Given that the LT variable is, by definition, time dependent, a time-dependent covariate Cox model was implemented in the ITT multivariable analysis. A 90-day censoring analysis was also conducted.

Post-LT patient and graft survival was then analyzed for patients receiving LT using the Kaplan–Meier method (with a univariate log-rank test) and Cox regression and by stratifying by sex and donor covariates (age, cause of death, and BMI).

Plots and statistical tests based on the Schoenfeld residuals were calculated to investigate violation of the Cox model assumptions: no violation was found for the covariates in the stratified analysis (by LT indication and patient status on WL; Figs. S1 and S2); $p \leq 0.05$ was considered statistically significant. Statistical analysis was carried out with Stata/SE 17 (StataCorp LLC, College Station, TX, USA).

Results

General characteristics of the study population

In total, 7,563 patients were enrolled in the study, of whom 5,575 (73.7%) were men. The main demographic and clinical characteristics of the study population are presented in Table 1. At listing, men were older (mean age 56 *vs.* 54 years, $p = 0.05$) and had a higher BMI (mean BMI 26.3 *vs.* 24.6 kg/m^2, $p < 0.001$) compared with women. In particular, male patients were more often overweight (25.0 <BMI <29.9; 40.8% *vs.* 29.3%, $p = 0.09$) or obese (30.0 <BMI <34.9; 17.0% *vs.* 10.8%, $p = 0.03$). No significant differences were observed in the MELD score at listing.

Indications for LT

The most common indication for LT was LC for women (56.5% *vs.* 45.9%, $p < 0.001$) and HCC for men (49.1% *vs.* 24.4%, $p < 0.001$). Other indications for LT (8.7% of the study cohort) were more common in women (19.1% *vs.* 5.0%, $p = 0.001$) and included indications for both benign (3.6% *vs.* 0.5%, $p = 0.001$) and malignant tumors (2.8% *vs.* 1.0%, $p = 0.001$) and for other liver diseases (11.9% *vs.* 3.1%, $p < 0.001$). The distribution across the three groups is summarized in Fig. 2. Distribution across the etiologies grouped for LC and HCC is summarized in Table 1.

ITT analysis

Of the 7,563 patients listed, 5,905 (78.1%) underwent LT (5,870 [77.6%] from deceased donors and 35 [0.46%] from living donors; Table S1), 982 (13.0%) dropped out from the list, 377 (5.0%) were delisted for other causes (clinical improvement, voluntary removal from the list, and social reasons) and 299 (3.95%) were still on the WL as of June 30, 2023. Patient flow on the WL, classified by indications for LT, is detailed in Fig. 2.

Over the entire study period, men received LT more often than did women (79.4% *vs.* 74.2%, $p < 0.001$), regardless of the indication considered. In terms of liver disease etiologies, men underwent LT most frequently for HCV infection (33.8% of men *vs.* 18.4% of women; $p < 0.001$), followed by alcohol-related liver diseases (20.9% of men *vs.* 12.8% of women, $p < 0.001$), whereas autoimmune liver disease was more common among women (3.8% of men *vs.* 14.0% of women, $p < 0.001$).

Men were less likely to drop out of the WL than were women (12.6% *vs.* 13.9%, $p = 0.14$), a difference that became significant when the indication for LT was HCC (10.6% *vs.* 14.2%, $p = 0.035$). Men also had significantly lower WL mortality (7.0% *vs.* 8.5%, $p = 0.04$), whereas women were more frequently delisted because of clinical improvement (3.8% *vs.* 2.2%, $p < 0.001$) for all indications.

In terms of the time spent on the WL before LT for patients in the standard allocation system, there was no difference in the median wait time between men and women with LC (222.8 days *vs.* 209.0 days, $p = 0.07$), whereas, in patients with HCC, women underwent LT 42 days later compared with men (206.2 days *vs.* 164.1 days, $p < 0.04$).

Probability of receiving LT under the standard allocation system

In the competitive risk analysis, we assessed the cumulative probability of receiving a LT by adopting the above-mentioned stratification, namely indications (LC and HCC) in the standard allocation. We found no difference between men and women at 1-month listing for the LC group (men 19.2 %, 95% CI 17.6–20.9 *vs.* women 15.9%, 95% CI 13.6–18.4, $p = 0.27$). Starting from 90 days, there were differences at 1 year (men 61.2%, 95% CI 59.1–63.2 *vs.* women 56.3%, 95% CI 53.0–59.5, $p = 0.01$) and 2 years (men 68.7%, 95% CI 66.7–70.6 *vs.* women 65.5%, 95% CI 62.3–68.5, $p = 0.04$), respectively (Fig. 3A). By contrast, for the HCC group, the cumulative probability of undergoing LT was 19.1% for women and 24.5% for men at 1 month (95% CI 15.7–22.9 and 95% CI 22.9–26.1, respectively; $p = 0.013$), 67.8% for women and 74.0% for men at 1 year (95% CI 63.4–71.9 and 95% CI 72.3–75.7, respectively, $p = 0.01$) and 75.7% (95% CI 71.5–79.4) for women and 81.9% (95% CI 80.3–83.3) for men at 2 years ($p = 0.03$) (Fig. 3B). The 90-day subdistribution hazard ratio (sHR) of undergoing LT was higher for men than for women for both LC and HCC (Table S2A).

In the adjusted model, using etiology of liver disease, MELD-Na, age, and BMI as covariates, the sex-based sHR of undergoing LT showed that men in the LC group were 13% more likely to undergo LT than were their female counterparts (sHR 1.13, 95% CI 1.02–1.26, $p = 0.02$). These data were confirmed at 2 years (sHR 1.12, 95% CI 1.01–1.24, $p = 0.03$), but were non-significant at 5 years (sHR 1.29, 95% CI 0.85-1.96, $p = 0.23$). The same situation was observed for HCC, where men had a 20% advantage of undergoing LT 1 year after listing compared with women (sHR 1.20, 95% CI 1.07–1.36, $p = 0.003$), a finding that was strongly confirmed at 2 years and again at 5 years (sHR 1.21, 95% CI 1.08–1.35, $p = 0.001$ and 1.67, 95% CI 0.98–2.83, $p = 0.059$, respectively).

Probability of WL dropout under the standard allocation

The probabilities of WL dropout at last follow-up estimated by the CIF for LC and HCC are summarized in Table S3. No significant differences in the probability of WL dropout (delisting for clinical deterioration or death) were observed between men and women in the LC group. Men with HCC appeared to have a benefit in terms of a low risk of dropout at 1 and 2 years (sHR 0.76, 95% CI 0.57–0.99, $p = 0.046$ and 0.76, 95% CI 0.58–1.00, $p = 0.046$, respectively). However, there were no significant differences in the probability of dropout at 90 days (Table S2B). When analyzing the cause of dropout, no differences were observed between women and men in terms of disease progression (9.1% in women and 7.4% in men, $p = 0.2$), but there was a difference for organ complications, which occurred more frequently in women (4.3% in women and 2.4% in men, $p = 0.02$). In addition, dropout causes reported as non-compliance and unspecified reasons were observed in 0.2% of both men and women and in 9.1% of the entire population, respectively.

Survival analysis and risk factors stratified by sex under the standard allocation

In the Cox regression model adjusted for age, etiology, MELD-Na, and BMI, no sex-based disparities were observed in terms of survival. Stratifying for sex, no significant statistical differences were observed in patients with HCC; by contrast, in patients with LC, MELD-Na scores of up to 20 and being underweight were identified as risk factors for lower survival among men (HR 2.84, 95% CI 1.73–4.65, $p < 0.001$ and 1.63, 95% CI 1.21–2.19, $p = 0.001$), whereas obesity was found to be

Table 1. General characteristics of the study population.

	Female		Male		Total		p value
	N	%	N	%	N	%	
Characteristics	**1,988**	**26.3**	**5,575**	**73.7**	**7,563**	**100**	**<0.001†**
Indication for LT							
LC	1,123	56.5	2,557	45.9	3,680	48.7	<0.001
Alcohol	253	12.7	1,029	18.5	1,282	17.0	<0.001
HCV	150	7.5	556	10.0	706	9.3	0.0014
HBV	249	12.5	394	7.1	643	8.5	<0.001
Autoimmune	273	13.7	203	3.6	476	6.3	<0.001
MASH	77	3.9	215	3.9	292	3.9	0.97
Other	121	6.1	160	2.9	281	3.7	<0.001
HCC	485	24.4	2,738	49.1	3,223	42.6	<0.001
Alcohol	26	1.3	202	3.6	228	3.0	<0.001
HCV	217	10.9	1,294	23.2	1,511	20.0	<0.001
HBV	96	4.8	555	10.0	651	8.6	<0.001
MASH	31	1.6	203	3.6	234	3.1	<0.001
Autoimmune	9	0.5	5	0.1	14	0.2	NA
Other	106	5.3	479	8.6	585	7.7	<0.001
Other	380	19.1	280	5.0	660	8.7	0.001
Other tumor	128	6.4	81	1.5	209	2.8	0.001
Benign liver tumor	72	3.6	26	0.5	98	1.3	<0.001
Other malignant tumor	56	2.8	55	1.0	111	1.5	<0.001
Other liver disease	237	11.9	172	3.1	409	5.4	0.001
Acute/subacute	15	0.8	27	0.5	42	0.6	0.2
National urgency	124	6.2	148	2.7	272	3.6	<0.001
Macro-regional urgency	235	11.8	416	7.5	651	8.6	<0.001
Age at listing							
Mean	54		56		56		0.05*
SD	11.2		9.3		10.0		
BMI (kg/m^2) at listing							
Mean	24.6		26.3		27.3		<0.001*
SD	4.5		5.7		6.5		
BMI (kg/m^2) at listing group							
≤18.5	98	4.9	71	1.3	169	2.2	<0.001
18.5 to <24.9	1,067	53.7	2,226	39.9	3,293	43.5	<0.001
25.0 to <29.9	583	29.3	2,274	40.8	2,857	37.8	0.09
30.0 to <34.9	215	10.8	950	17.0	1165	15.4	0.03
>35.0	9	0.5	13	0.2	22	0.3	0.18
ND	16	0.8	41	0.7	57	0.8	0.9
MELD-Na at listing							
Mean	22.9		21.75				<0.001*
SD	7.8		7				
MELD-Na at listing group							
15–24	793	39.9	1,940	34.8	2,733	36.1	<0.001
25–28	46	2.3	95	1.7	141	1.9	0.1
29+	335	16.9	610	10.9	945	12.5	<0.001
NA	814	40.9	2,930	52.6	3744	49.5	<0.001
MELD-Na at listing (LC)							
Mean	20.5		20.2				0.49*
SD	5.1		4.9				
MELD-Na group (LC)							
15–24	576	51.0	1,328	51.9	1,904	51.7	0.44
25–28	38	3.4	79	3.1	117	3.2	0.16
29+	228	20.2	455	17.8	677	18.4	<0.001
NA	287	25.4	695	27.2	982	26.7	0.03
Transplant (June 30, 2023)							
Deceased donor transplant	1,464	73.6	4,406	79.0	5,870	77.6	<0.001
Living donor transplant	12	0.60	23	0.41	35	0.46	0.28
Total	1,476	74.2	4,429	79.4	5,905	78.1	<0.001
Dropout	277	13.9	705	12.6	982	13.0	0.14
Mortality	169	8.5%	392	7.03	561	7.4	0.04
Delisted other causes	132	6.7	245	4.4	377	5.0	<0.001

Data are reported as mean ± SD, counts (proportion). Chi square unless indicated: *Student *t* test, †two-sample test of proportions; *p* ≤0.05 indicates a statistically significant difference. HCC, hepatocellular carcinoma; LC, liver cirrhosis; LT, liver transplant; MASH, metabolic dysfunction-associated steatohepatitis; MELD-Na, model for end-stage liver disease-sodium.

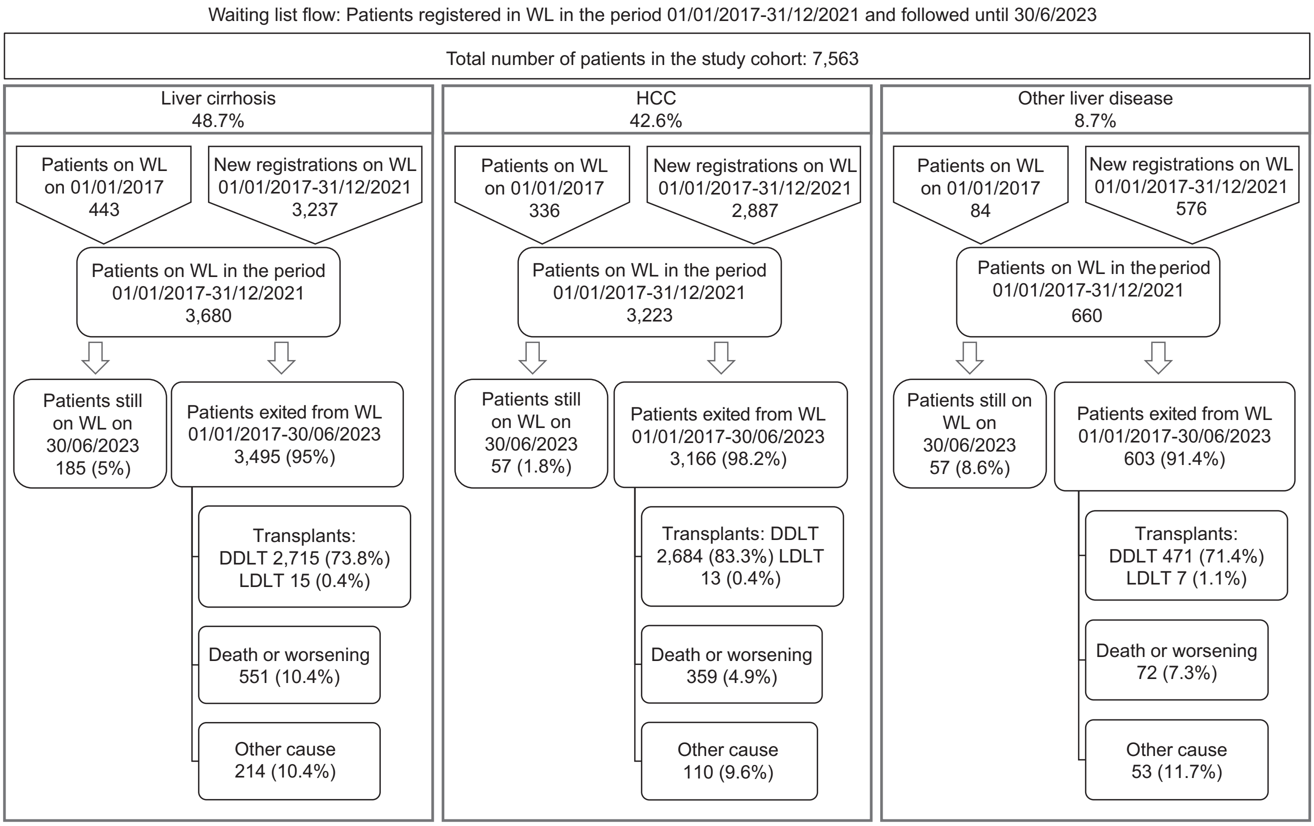

Fig. 2. Flow chart of the study population divided among the three groups. WL, wait list.

a risk factor for women (HR 1.73, 95% CI 1.01–2.98, *p* = 0.046). Finally, older age was a risk factor for both men and women (HR 1.69, 95% CI 1.20–2.37, *p* = 0.02 and HR 2.03, 95% CI 1.26–3.26, *p* = 0.004, respectively), with a linear trend for women (Table 2). We constructed an additional model to analyze risk factors at 90 days and 1 year by adding height, creatinine, and portal hypertension complications (grouped as P2 exception and comprising refractory ascites, hepatic encephalopathy, hepatopulmonary syndrome, hepatorenal syndrome, and portopulmonary hypertension). Thus, we were able to confirm that these complications were additional risk factors, but in a way that did not differ between men and women. More specifically, in the ITT analysis, 90-day HR was higher for increased creatinine and MELD-Na levels for both LC and HCC (data not shown). We also observed the same for increasing age, but only for LC recipients. This confirmed that the cirrhosis complications associated with extra points were a risk factor in LC recipients at 90 days (Table 3).

Macro-regional and national emergency allocations

To gain further insights into sex-based differences within the Italian allocation system, the same analyses were also performed on the macro-regional and emergency allocation groups. Women were more often allocated for emergency LT under either the national (6.2% *vs.* 2.7%, *p* <0.001) or macro-regional (11.8% *vs.* 7.5%, *p* <0.001) allocations. However, no further sex-based differences emerged in the ITT analysis or the probability of LT for these two allocation types.

Post-transplant survival

Post-LT survival in patients with LC showed no difference at 1 and 5 years (Table 4A). Detailing for indication for LT, recipient sex, and donor–recipient sex-matching, men presented worse adjusted HR compared with women: HR 1.54 (*p* = 0.02) and 1.47 (*p* = 0.01) at 1 and 5 years, respectively. Death was recorded in a total of 733 LT recipients, with a different distribution according to sex and cause of death for neoplastic causes (120 *vs.* 13 deaths, *p* = 0.006) (Table S4).

In patients with LC, compared with women receiving same-sex donations, survival among men was worse, regardless of whether their donor was male or female (HR 1.6, 95% CI 0.99–2.6, *p* = 0.06 and 1.76, 95% CI 1.11–2.77, *p* = 0.02, for female–male and male–male donor matching, respectively). The LC etiologies with the worst 1-year male patient outcomes were alcohol-related liver disease (HR 2.60, 95% CI 0.94–7.22, *p* = 0.07) and HCV (HR 3.54, 95% CI 1.09–11.47, *p* = 0.04).

No differences in post-LT survival were observed among patients listed for HCC. However, for HCC, men showed a higher adjusted HR than did women at 1 year (HR 1.74, 95% CI 1.11–2.72, *p* = 0.02) and at 5 years (HR 1.35, 95% CI 0.99–1.84,

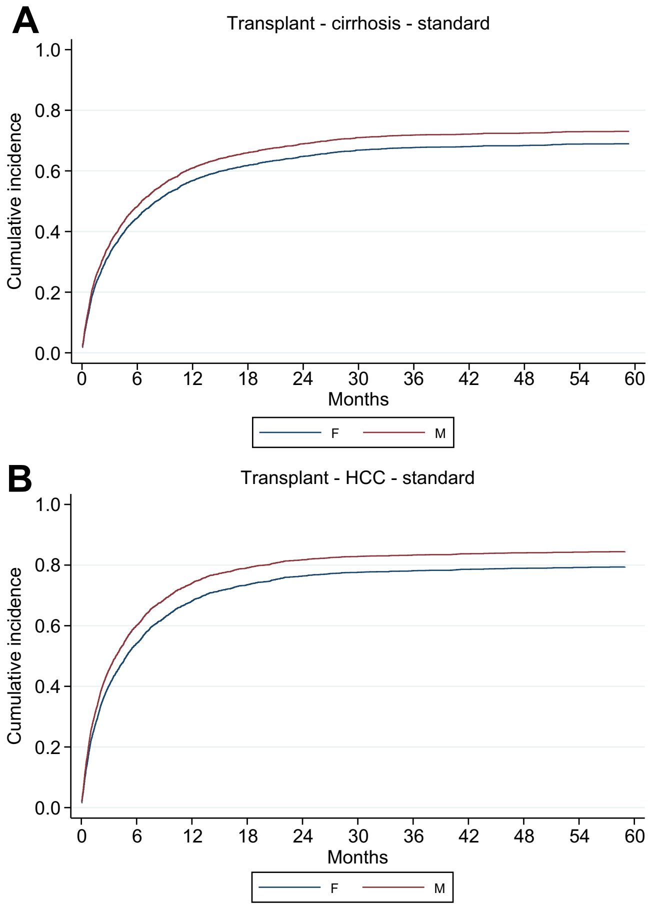

Fig. 3. Cumulative probability of receiving a LT in standard allocation for the (A) LC and (B) HCC group. Data analyzed using cumulative probability with CIF function; p ≤0.05 indicates a statistically significant difference. F, female; HCC, hepatocellular carcinoma; LC, liver cirrhosis; LT, liver transplantation; M, male.

p = 0.06), regardless of donor–recipient sex-matching. Among the HCC etiologies, men with HCV showed poorer survival (HR 1.72, 95% CI 0.86–3.44, p = 0.12, at 1 year). Patient and graft survival curves are summarized in Fig. 4.

Relisting analysis

Of the 5,905 (4,429 male and 1,476 female) LTs performed, graft failure was recorded in 377 (6.4%) LT recipients. Following graft failure, 163 (2.8%) patients died at a median time of 36 days (IQR 9–187 days) from the first LT and 214 (3.6%) were relisted for a second LT. No difference between women and men was observed in terms of death after graft failure (122/4,429, 2.8% *vs.* 41/1,476, 2.8%, respectively) or relisting (168/4,429, 3.8% *vs.* 46/1476, 3.1%, respectively; p = 0.5).

The main causes of relisting were hepatic complications (89.3%), which were equally distributed between men and women (3.3% *vs.* 3%, respectively). Of the patients relisted, 205 (95.8%) underwent a second LT, eight (3.7%) dropped out from the WL, and only one patient was delisted for clinical improvement. The main causes of death after re-LT were infectious complications (61; 37.4%), hepatic complications (53; 32.5%), cardiovascular complications (nine; 5.5%), cerebrovascular complications (two; 1.2%), and neoplastic complications (three; 1.8%), without any differences between men and women.

Discussion

This is the first study to systematically present results of the Italian LT program considering biological sex as the main variable for comparisons, thereby adding a new body of evidence for the existence of sex-based disparities in the LT setting in European countries.

In a cohort of 7,563 patients listed for LT, most patients were men and were more frequently transplanted for HCC and allocated under the standard allocation compared with their female counterparts. Regardless of the indications considered, men received LT more frequently than women, who tended to have longer wait times, and men were less likely to drop out of the WL than women when listed for HCC. Consistently, WL mortality was also lower for men. In the Cox adjusted regression model, men listed for HCC presented a lower risk of 1- and 2-year WL dropout. Furthermore, men listed for LC and HCC in the standard allocation system had a higher probability of receiving LT 1 and 2 years after listing. This advantage was evident for the HCC group as early as the first month on the WL. No difference was observed in allocation systems other than the standard one. Although no differences were observed in overall post-LT survival between the two groups, male recipients with LC in the standard allocation system had worse 1- and 2-year post-LT survival compared with women.

Evidence highlighting the disparities between women and men on the LT-WL was first described in the USA in 2008 by Moylan *et al.*,[3] several years after the introduction of MELD-based allocation. The authors compared the periods before and after the introduction of the MELD system and confirmed that, although race was no longer associated with LT receipt or WL mortality after the implementation of the MELD method, sex-based disparities persisted. Since this seminal work, several studies have confirmed this phenomenon, analyzing, among the various potential factors involved, kidney function expressed through creatinine in the MELD formula,[8,18] etiology of the liver disease,[19,20] and liver size[7] conditioning donor–recipient size mismatch. However, these assumptions have always been inherent in the North American allocation system and were only recently confirmed, albeit only partially, in European cohorts.[15,16] Our study increases the body of evidence in the European setting and provides the first comprehensive analysis from Italy.

The strengths of this study include the fact that it is a comprehensive analysis of the Italian allocation system and considers allocation by types other than the standard one. In line with another study analyzing sex-based differences in acute liver failure in patients listed with a Status-1 exception, in which no clear disparities in LT or WL removal could be identified,[21] we also found that there was no meaningful difference between men and women allocated under the national emergency when adjusted for confounders. In their study, Nephew *et al.*[21] concluded that the broader donor pool and heightened priority might overcome sex-based disparities. This might also explain why, in our study, even the evaluation of macro-regional emergencies did not reveal any sex-based differences, considering that a macro-regional policy strategy is

Table 2. ITT survival analysis in LC and HCC groups.

	Female			Male		
Variable	**HR**	***p* value/*p*>z***	**95% CI**	**HR**	***p* value/*p*>z***	**95% CI**
LC						
Etiology *vs.* other						
Alcohol	0.94	0.838	0.54–1.65	1.35	0.193	0.86–2.14
Autoimmune	0.96	0.895	0.54–1.71	0.80	0.495	0.43–1.51
HBV	0.65	0.177	0.34–1.22	1.35	0.251	0.81–2.24
HCV	1.05	0.874	0.58–1.89	1.19	0.475	0.74–1.91
MASH	0.73	0.449	0.33–1.63	1.12	0.701	0.63–1.98
MELD-Na *vs.* <20						
20–28	1.86	0.228	0.68–5.13	2.84	<0.001	1.73–4.65
>29	1.01	0.959	0.58–1.76	1.63	0.001	1.21–2.19
Age *vs.* <55						
55–59 years	1.60	0.039	1.02–2.50	1.49	0.003	1.15–1.92
60–64 years	1.85	0.009	1.17–2.93	2.21	<0.001	1.70–2.87
≥65 years	2.03	0.004	1.26–3.26	1.69	0.002	1.20–2.37
BMI (kg/m^2) *vs.* normal						
≤18.5	1.16	0.687	0.56–2.43	2.84	0.002	1.49–5.43
25.0 to <29.9	1.04	0.858	0.70–1.52	1.16	0.2	0.93–1.45
>30.0	1.73	0.046	1.01–2.98	1.13	0.463	0.82–1.54
HCC						
Etiology *vs.* other						
Alcohol	1.24	0.741	0.35–4.40	0.95	0.814	0.60–1.50
Autoimmune	1.42	0.739	0.18–10.96	–	–	– –
HBV	1.12	0.778	0.51–2.43	0.83	0.307	0.59–1.18
HCV	1.15	0.668	0.61–2.17	1.03	0.827	0.77–1.39
MASH	1.02	0.974	0.36–2.87	0.94	0.815	0.59–1.52
Age *vs.* <55						
55-59 years	0.58	0.191	0.26–1.31	1.07	0.648	0.81–1.41
60-64 years	0.94	0.851	0.50–1.78	0.98	0.886	0.73–1.31
≥65 years	1.15	0.642	0.63–2.10	1.05	0.76	0.78–1.41
BMI (kg/m^2) *vs.* normal						
≤18.5	0.69	0.717	0.09–5.12	0.54	0.388	0.13–2.19
25.0 to <29.9	0.66	0.133	0.38–1.14	1.10	0.419	0.87–1.39
>30.0	1.22	0.535	0.65–2.32	1.21	0.228	0.89–1.64

Data were analyzed using a Cox regression model; *p value for LC; p>z for HCC; $p \leq 0.05$ indicates a statistically significant difference. HCC, hepatocellular carcinoma; HR, hazard ratio; ITT, intention to treat; LC, liver cirrhosis; MASH, metabolic dysfunction-associated steatohepatitis; MELD-Na, model for end-stage liver disease-sodium.

implemented to increase the donor pool. Macro-regional emergency could share some similarities with the high MELD allocation policy adopted in the USA. In a study evaluating patients with high MELD scores, Cron *et al.*[22] reported that, once patients reached MELD 40, women were less likely to be transplanted (sHR 0.90, p <0.01) and more likely to die or be delisted (sHR 1.14, p = 0.02). Indeed, women had a higher offer refusal rate, resulting partly from donor–recipient size mismatches. In our study, we were unable to support these findings, which suggests that another factor in the Italian emergency allocation system exceeds both MELD score and patient size. These differences could be explained by the segmented nature of allocation, which is managed on a regional basis. Conversely, our study showed that differences do exist, even if they were perhaps less marked than those obtained by the UNOS database studies, among men and women with respect to the standard allocation system, particularly when specific subgroups were analyzed. In line with previous studies, a discrepancy emerged between the indications observed in men and women. In our cohort, a higher proportion of men had alcohol-related disease as indication compared with women, for both HCC (3.6% *vs.* 1.3%, respectively) and LC (18.5% *vs.* 12.7%, respectively). Although no causal inferences can be drawn from this finding, prior research has identified this trend,[20,23] suggesting that the absence of a psychosocial context often accounts for this difference.

In terms of the likelihood of receiving LT for both LC and HCC in the standard allocation system, men had an advantage over women of 13% and 20%, respectively, after 1 year. This difference was particularly marked at the 1- and 2-year timepoints, whereas it was not significant during the first 3 months and lost significance at 5 years. This finding appears to confirm other observations.[6,8,20] In a recent analysis, Cron *et al.*[24] reported that women had a lower 1-year cumulative incidence of receiving LT and a higher 1-year cumulative incidence of death or delisting for health deterioration compared with men. This is in line with our findings. However, when adjusted for height, these differences were no longer significant. The findings of our study are unable to support the size effect. Although we could not find specific risk factors able to account for these differences between men and women in the multivariate analysis, the standard allocation system is essentially based on the MELD score and creatinine level, which are confirmed as general risk factors for poor outcome, suggesting that this score has a role in explaining these disparities.

Considering WL dropout, men listed for HCC were less frequently delisted compared with women at 1 and 2 years. These results could not be entirely explained by considering the natural history of HCC in women.[25] Women with HCC show

Table 3. ITT survival analysis in LC at 90 days and 1 year based on an additional model including also creatinine, weight, and portal hypertension complications.

	Female			Male		
Variable	**HR**	***p* value**	**95% CI**	**HR**	***p* value**	**95% CI**
LC at 90 days						
Etiology *vs.* other						
Alcohol	0.47	0.154	0.17–1.33	1.18	0.437	0.77–1.81
Autoimmune	0.93	0.898	0.33–2.67	0.78	0.421	0.43–1.43
HBV	0.21	0.062	0.04–1.08	1.10	0.714	0.67–1.78
HCV	0.77	0.654	0.24–2.42	1.19	0.442	0.76–1.86
MASH	0.40	0.278	0.07–2.11	1.00	0.987	0.59–1.71
MELD-Na *vs.* <20						
20–28	3.06	0.095	0.82–11.39	2.85	<0.001	1.79–4.51
>29	7.12	<0.001	3.31–15.30	2.26	<0.001	1.66–3.07
Age *vs.* <55						
55–59 years	2.14	0.128	0.80–5.68	1.71	<0.001	1.32–2.21
60–64 years	2.52	0.077	0.90–7.04	2.19	<0.001	1.67–2.87
≥65 years	4.93	0.001	1.90–12.80	2.01	<0.001	1.46–2.75
BMI (kg/m^2) *vs.* normal						
≤18.5	1.33	0.706	0.30–5.94	1.48	0.273	0.74–2.97
25.0 to <29.9	0.83	0.651	0.37–1.85	0.97	0.789	0.78–1.21
>30.0	1.99	0.157	0.77–5.17	1.08	0.600	0.81–1.45
P2 exceptions *vs.* other						
Portal hypertension complications	1.03	0.958	0.39–2.72	1.28	0.14	0.92–1.79
Height *vs.* <160 cm						
160–165	1.07	0.869	0.49–2.32	0.69	0.269	0.36–1.33
166–170	1.18	0.765	0.40–3.48	0.75	0.378	0.40–1.42
171–180	3.50	0.027	1.15–10.66	0.69	0.246	0.37–1.29
>180	–	–	–	0.58	0.112	0.30–1.14
Creatinine *vs.* ≤1 mg/dl						
>1–<1.5	2.92	0.009	1.31–6.54	0.94	0.629	0.73–1.21
≥1.5–2.0	5.81	0.004	1.75–19.29	1.10	0.635	0.74–1.63
≥2.0	2.21	0.199	0.66–7.44	1.57	0.013	1.10–2.25
LC at 1 year						
Etiology *vs.* other						
Alcohol	0.51	0.074	0.25–1.07	1.06	0.823	0.65–1.73
Autoimmune	1.22	0.576	0.61–2.41	0.81	0.559	0.39–1.66
HBV	0.78	0.516	0.37–1.66	1.00	0.991	0.57–1.77
HCV	0.88	0.737	0.43–1.82	1.08	0.772	0.64–1.83
MASH	0.61	0.317	0.24–1.59	0.97	0.921	0.53–1.79
MELD-Na *vs.* <20						
20–28	2.56	0.053	0.99–6.62	4.00	<0.001	2.44–6.54
>29	2.55	0.002	1.40–4.67	2.84	<0.001	2.00–4.04
Age *vs.* <55						
55–59 years	1.81	0.043	1.02–3.23	1.94	<0.001	1.40–2.68
60–64 years	1.78	0.06	0.97–3.26	2.46	<0.001	1.76–3.43
≥65 years	2.83	<0.001	1.59–5.01	2.57	<0.001	1.77–3.74
BMI (kg/m^2) *vs.* normal						
≤18.5	1.56	0.274	0.70–3.49	1.53	0.326	0.66–3.57
25.0 to <29.9	0.92	0.741	0.56–1.50	0.98	0.858	0.75–1.28
>30.0	1.53	0.195	0.81–2.89	1.11	0.556	0.78–1.60
P2 exceptions *vs.* other						
Portal hypertension complications	1.05	0.881	0.55–2.03	1.20	0.388	0.79–1.82
Height *vs.* <160 cm						
160–165	0.81	0.364	0.50–1.29	0.97	0.934	0.41–2.25
166–170	0.73	0.359	0.37–1.43	1.29	0.549	0.57–2.93
171–180	1.20	0.652	0.54–2.68	1.10	0.814	0.49–2.47
>180	–	–	–	0.76	0.531	0.32–1.81
Creatinine *vs.* ≤1 mg/dl						
>1–<1.5	2.06	0.006	1.23–3.47	0.90	0.493	0.66–1.22
≥1.5–2.0	2.56	0.055	0.98–6.69	1.05	0.847	0.64–1.72
≥2.0	2.80	0.007	1.33–5.90	1.54	0.045	1.01–2.35

Data were analyzed using Cox regression model; *p* ≤0.05 indicates a statistically significant difference; HR, hazard ratio; ITT, intention to treat; LC, liver cirrhosis; MASH, metabolic dysfunction-associated steatohepatitis; MELD-Na, model for end-stage liver disease-sodium.

better follow-up compliance rates,[26] tend to have less recurrence after curative treatments,[27] and often have better survival compared with their male counterparts.[28] Therefore, other factors besides strictly biological tumor characteristics could be involved, such as equitable access to down-staging treatments. When analyzing the cause of dropout, no differences

Table 4. 1- and 5-year post-LT survival analysis by sex of patients and by sex matching.

Kaplan–Meier survival analysis with log-rank test

		LC			HCC		
Sex	**Years**	**Survival function**	**95% CI**	**Log-rank test *p* value**	**Survival function**	**95% CI**	**Log-rank test *p* value**
Female	1 year	90.0%	87.3–92.2	0.54	95.7%	92.7–97.5	0.123
	5 years	77.4%	69.2–83.7		74.6%	61.6–83.7	
Male	1 year	90.6%	89.0–91.9		92.2%	90.9–90.3	
	5 years	80.3%	77.0–83.3		76.2%	73.0–79.0	

Multivariable Cox regression model with Wald test

Group		**LC standard allocation**			**HCC standard allocation**		
M (F ref)	**Years**	**Adjusted HR**	**95% CI**	***p* value**	**Adjusted HR**	**95% CI**	***p>z***
	1 year	1.54	1.07–2.22	0.02	1.74	1.11–2.72	0.02
	5 years	1.47	1.08–1.99	0.01	1.35	0.99–1.84	0.06
F/M (F/F ref)	1 year	1.60	0.99–2.60	0.06	1.51	0.90–2.55	0.12
M/F (F/F ref)	1 year	1.31	0.69–2.49	0.41	0.54	0.18–1.63	0.28
M/M (F/F ref)	1 year	1.76	1.11–2.77	0.02	1.48	0.89–2.48	0.13
F/M (F/F ref)	5 years	1.51	1.00–2.29	0.05	1.34	0.92–1.96	0.13
M/F (F/F ref)	5 years	1.36	0.80–2.33	0.25	0.89	0.46–1.75	0.74
M/M (F/F ref)	5 years	1.72	1.17–2.54	0.01	1.28	0.88–1.86	0.19

A statistically significant difference is indicated by $p \leq 0.05$. F, female; HCC, hepatocellular carcinoma; HR, hazard ratio; LC, liver cirrhosis; M, male.

were observed between women and men in terms of disease progression (9.1% and 7.4%, respectively; $p = 0.2$), but were observed in terms of organ complications, which appear to occur more frequently in women (4.3% in women and 2.4% in men, $p = 0.02$). There is literature suggesting that estrogen exposure could represent a protective factor in women of childbearing potential with liver disease, which is later lost during the postmenopausal age.[29–31] In our study, increasing age in patients with LC managed under the standard allocation was a risk factor for mortality in both sexes. However, in

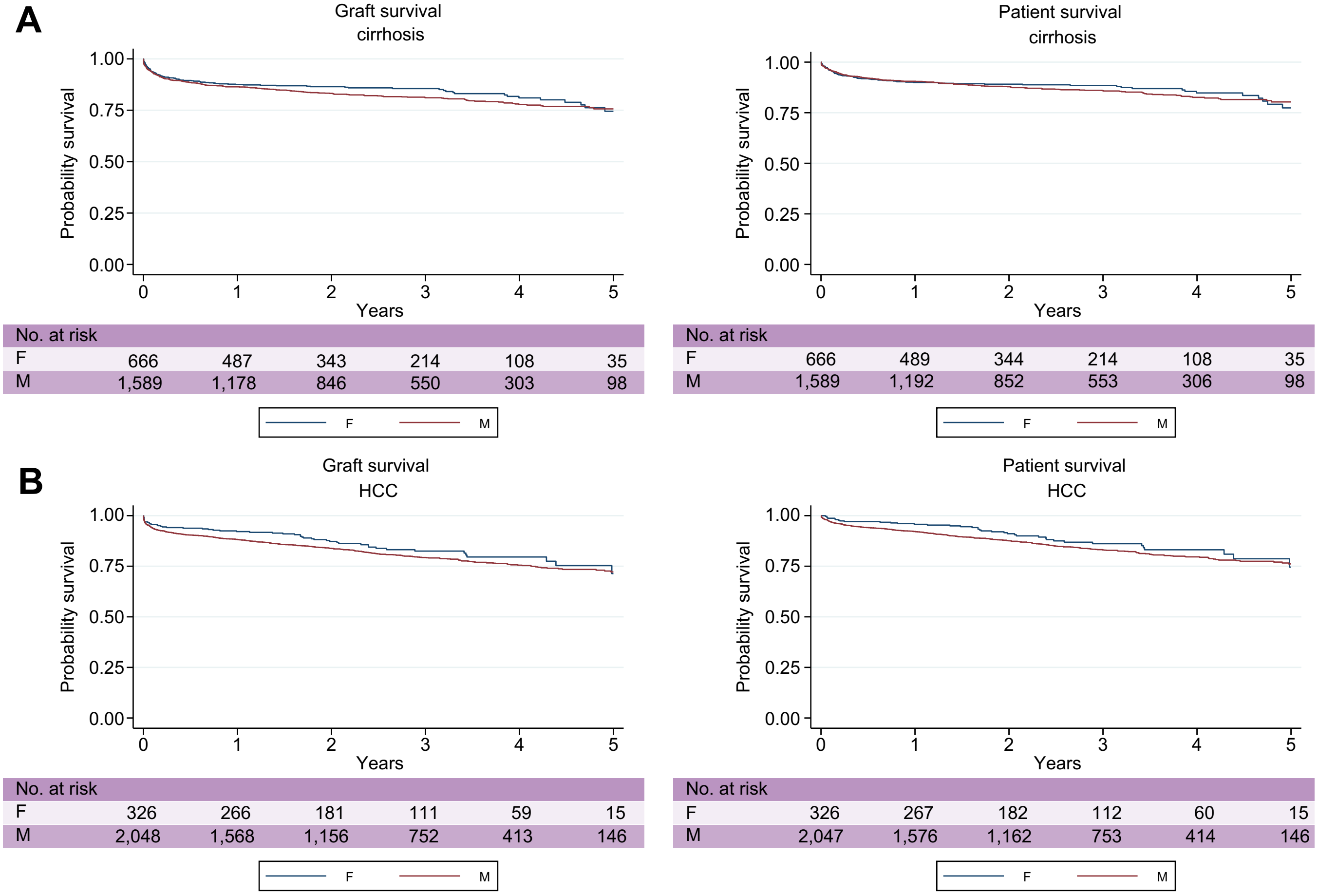

Fig. 4. Graft and patient post-LT survival in patients with (A) LC or (B) HCC. Data were analyzed using Kaplan–Meier survival analysis; $p \leq 0.05$ indicates a statistically significant difference. F, female; HCC, hepatocellular carcinoma; LC, liver cirrhosis; LT, liver transplantation; M, male.

women after 55 years of age, the risk trend was linearly incremental (Table 2), whereas this was not observed in men, where the highest risk coincided with the 60–65-year age group. However, these are only assumptions and robust conclusions cannot be established based on the available data.

The finding of non-inferior post-LT survival rates in women is in line with several worldwide reports.[32–36] In the study by Germani *et al.*,[36] donor–recipient sex mismatch was significantly associated with a lower post-LT survival rate in men (HR 1.12, 95% CI 1.04–1.2, $p = 0.003$). In our study, we showed that women had a better prognosis in the LC group in the absence of donor–recipient mismatch.

Our study presents some limitations. First, this was a retrospective study with data from a national registry and, therefore, lacks granularity. In particular, only a limited number of covariates were included in the multivariate analysis, limiting the possibility of drawing complex causal relationships that could explain our results. In addition, data on albumin and urea were not mandatory fields, and clinical data on ascites were not always available, limiting the validation of the alternative proposed scores (*i.e.* MELD 3.0 and GEMA). However, the availability of up-to-date, complete, and national data, such as those contained in the SIT, does make it possible to obtain a comprehensive picture of the Italian allocation system with an exhaustive sample size. Second, the adopted groupings of patients (*i.e.* LC, HCC, and other tumors) might have led to an oversimplification of the complex Italian allocation system, thus limiting the possibility of emphasizing certain nuances that could have influenced our results; however, this approach was necessary to produce a numerically meaningful analysis. In addition, the absence of a formal sample size calculation and the predetermined width of the 95% CIs could have diminished the reliability of clinically meaningful comparisons. However, analyzing the entire Italian cohort resulted in a sample size comparable to that used in the existing literature.[10]

One of the strengths of our study was the confirmation that sex-based differences also exist in the allocation systems outside North America. Eurotransplant recently released an analysis of data for the period 2007–2019 on biological sex differences in patients waitlisted for LT.[15] The findings highlighted a disparity to the detriment of women that is not associated with MELD scores but rather with smaller body size, which appears to put women at a disadvantage. Although our study showed that BMI had an impact on survival in patients with LC, these findings do not support the size effect hypothesis. Instead, they highlight the detrimental impact of sarcopenia and malnutrition, particularly in men.[37] Recently, Tejedor *et al.*[38] published the first report of the Spanish Liver Transplant Registry analyzing data for the period 2000–2022 with a sex-oriented perspective, and concluded that, even outside the USA and in countries with short wait times, women are disadvantaged in the LT setting. They found that women were significantly less likely to receive LT than were men (odds ratio 0.78, 95% CI 0.63–0.97, $p = 0.022$) and waited longer (198.6 ± 338.9 *vs.* 173.3 ± 285.5 days, $p < 0.001$). The Spanish study analyzed patients over a long time period, during which several factors might have affected the results. Moreover, the MELD score was available for 5,475 of the 14,385 patients included. Yet, in the Spanish context, which is characterized, similarly to Italy, by a high rate of cadaveric donations and a relatively short WL, Rodríguez-Perálvarez *et al.*[16] recently demonstrated that MELD 3.0, and GEMA-Na even more so, might correct sex disparities in access to LT, and reported a 57% increased risk of mortality or delisting due to disease within 90 days for women. These rates are significantly higher than those observed in our experience, a discrepancy that might be partially attributable to the approach adopted in our study, which analyzed different indications for LT separately, for example by making a distinction between LC and HCC, where the impact of the MELD score differs. Nevertheless, the rates observed in the Italian cohort, while reflecting this context of disparity, also showed more moderate differences. Our study corroborates the results of these Spanish studies and, by narrowing the period of the analysis and evaluating the entire allocation system, highlights how the use of MELD exceptions to the standard allocation model can act as a mitigator of sex-based disparities.

To conclude, this retrospective nationwide study shows that women are at a disadvantage compared with men, because they receive LT less frequently and, when listed for HCC, tend to wait longer and are less protected against WL dropout. Conversely, the existence of allocation mechanisms other than the standard one can mitigate the existence of these disparities. With the introduction of scores (MELD 3.0, GEMA, etc.) that have been seen to be better suited to counteracting this disparity, we expect greater equity in allocation in the future.[11,39]

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Abbreviations

CNT, *Centro Nazionale Trapianti* (National Transplantation Center); cumulative incidence function (CIF)GEMA, Gender Equity Model for Liver Allocation; HCC, hepatocellular carcinoma; INR, international normalized ratio; ISO, Italian Score for Organ allocation; ITT, intention to treat; LC, liver cirrhosis; LT, liver transplantation; MASH, metabolic dysfunction-associated steatohepatitis; MELD, model for end-stage liver disease; Na, sodium; RFH-GRF, Royal Free Hospital glomerular filtration rate; sHR, subdistribution hazard ratio; SIT, *Sistema Informativo Trapianti* (Italian Transplant Information System); UNOS, United Network for Organ Sharing; WL, wait list.

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Conflicts of interest

The authors declare no conflicts of interest that pertain to this work.

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

Authors' contribution

Conceptualization, data revision, drafting the protocol and article: CB, STrapani. Data collection, data analysis: LM, STesta, FP. Literature revision, drafting the article: FDA, LL, VC, MG, MCilla. Editing and revision of the final draft for critical intellectual content: MM, FM, FI, EC, PT. Data curation: MCardillo, GF. Conceptualization, supervision, revision of the final draft for critical intellectual content: PB.

Data availability statement

Data are available from the corresponding author upon reasonable request.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2025.101387.

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Author names in bold designate shared co-first authorship

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