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# Fairness and pitfalls of the Italian waiting list for elective liver transplantation: The ECALITA registry study

Tommaso Maria Manzia[a], Silvia Trapani[b], Alessandra Nardi[c], Andrea Ricci[b], Ilaria Lenci[d], Bruno Sensi[a], Roberta Angelico[a,*], Tullia Maria De Feo[e], Salvatore Agnes[f], Enzo Andorno[g], Umberto Baccarani[h], Amedeo Carraro[i], Matteo Cescon[j], Umberto Cillo[k], Michele Colledan[l], Domenico Pinelli[l], Luciano De Carlis[m], Paolo De Simone[n], Davide Ghinolfi[n], Fabrizio Di Benedetto[o], Giuseppe Maria Ettorre[p], Salvatore Gruttadauria[q,r], Luigi Giovanni Lupo[s], Francesco Tandoi[s], Vincenzo Mazzaferro[t], Renato Romagnoli[u], Giorgio Rossi[v], Lucio Caccamo[v], Massimo Rossi[w], Marco Spada[x], Giovanni Vennarecci[y], Marco Vivarelli[z], Fausto Zamboni[aa], Giuseppe Tisone[a], Massimo Cardillo[b], Mario Angelico[d]

[a] *Department of Surgical Science, University of Rome Tor Vergata, Hepatobiliary and Transplantation Unit, Policlinico Tor Vergata [Tor Vergata General Hospital], Rome, Italy, 00133*
[b] *Italian National Transplant Centre, National Institute of Health, Rome, Italy, 00161*
[c] *Department of Mathematics, University of Rome Tor Vergata, 00133, Rome, Italy*
[d] *Hepatology and Transplant Unit, Fondazione Policlinico Tor Vergata [Tor Vergata General Hospital Foundation], 00133*
[e] *North Italy Transplant program (NITp). Transplant Coordination Unit, Fondazione IRCSS Cà Granda Ospedale Maggiore Policlinico [Cà Granda General Research Hospital], Milan, Italy, 20122*
[f] *Department of Surgery, Transplantation Service, Catholic University of the Sacred Heart, Foundation A. Gemelli Hospital, Rome, Italy, 00136*
[g] *Department of Hepatobiliary and Pancreatic Surgery and Liver Transplantation Unit. A.O.U. S. Martino [S. Martino University Hospital], Genoa, Italy, 16132*
[h] *Department of Medicine, Università Degli Studi Di Udine [University of Udine], Udine, Italy, 33100*
[i] *Liver Transplant Unit, Department of Surgical Science, University and Hospital Trust of Verona. Azienda Ospedaliera Verona, Verona, Italy, 37129*
[j] *Hepatobiliary and Transplant Unit, AOU Sant'Orsola IRCCS [Sant'Orsola University Research Hospital], Department of Medical and Surgical Sciences, University of Bologna, Italy, 40138*
[k] *Hepatobiliary Surgery and Liver Transplantation Unit, University of Padua, Padua, Italy, 35135*
[l] *Department of Organ Failure and Transplantation. Ospedale Papa Giovanni XXIII [Papa Giovanni XXIII Hospital] Bergamo, University of Milano-Bicocca, Milan, Italy, 24127*
[m] *Division of General Surgery & Abdominal Transplantation, ASST Grande Ospedale Metropolitano Niguarda [Niguarda Metropolitan Hospital], University of Milano-Bicocca, Milan, Italy, 20161*
[n] *Hepatobiliary Surgery and Liver Transplantation, AOU Pisana [Pisana University Hospital], Pisa, Italy, 56124*
[o] *Hepato-Pancreato-Biliary Surgery and Liver Transplantation Unit, Azienda Ospedaliera Policlinico [General Hospital], University of Modena and Reggio Emilia, Modena, Italy, 41125*
[p] *Division of General Surgery and Liver Transplantation. Azienda Ospedaliera San Camillo Forlanini [San Camillo Forlanini Hospital], Rome, Italy, 00152*
[q] *Department for the Treatment and Study of Abdominal Diseases and Abdominal Transplantation, IRCCS-ISMETT (Istituto di Ricovero e Cura a Carattere Scientifico—Istituto Mediterraneoper i Trapianti e Terapie ad alta specializzazione [Research Hospital – Highly-specialized Mediterranean Institute for Transplants and Therapies]), UPMC (University of Pittsburgh Medical Center), Palermo, Italy*
[r] *Department of Surgery and Medical and Surgical Specialties, University of Catania, Catania, Italy, 90127*
[s] *General Surgery and Liver transplantation Unit, University of Bari, Bari, Italy, 70121*
[t] *HPB Surgery and Liver Transplantation Unit, Department of Oncology, University of Milan and Department of Surgery, Fondazione IRCCS [Research Hospital Foundation], Istituto Nazionale Tumori [National Cancer Institute], IRCCS, Milan, 20133, Italy*
[u] *Liver Transplant Center, General Surgery 2 U, University of Turin, AOU Città della Salute e della Scienza di Torino, Turin, Italy, 10126*
[v] *Division of General Surgery and Liver Transplantation, Ospedale Maggiore Policlinico, University of Milan, Milan, Italy, 20122*
[w] *General Surgery and Organ Transplantation, Sapienza University of Rome, Umberto I Polyclinic of Rome, Rome, Italy, 00185*
[x] *Department of Specialized Surgery, Division of Hepato-Pancreato-Biliary Surgery and of Liver and Kidney Transplantation, Bambino Gesù Children's Hospital, IRCCS [Research Hospital], Rome, Italy, 00165*
[y] *Unit of Hepatobiliary Surgery and Liver Transplant Center, Department of Gastroenterology and Transplantation, "A. Cardarelli" Hospital, Naples, Italy, 80131*
[z] *Hepatobiliary and Abdominal Transplantation Surgery, Department of Experimental and Clinical Medicine, Polytechnic University of Marche, AOU Ospedali Riuniti [Joint Hospitals], Ancona, Italy, 60126*
[aa] *Department of Surgery, General and Hepatic Transplantation Surgery Unit, A.O.B. Brotzu, Cagliari, Italy, 09047*

* Corresponding author at: Department of Surgical Sciences, University of Rome Tor Vergata, Hepatobiliary and Transplantation Unit, Policlinico Tor Vergata, Rome, Italy, 00133.
*E-mail address:* roberta.angelico@uniroma2.it (R. Angelico).

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ABSTRACT

*Background:* The challenge of transplant waiting-lists is to provide organs for all candidates while maintaining efficiency and equity.
*Aims:* We investigated the probability of being transplanted or of waiting-list dropout in Italy.
*Methods:* Data from 12,749 adult patients waitlisted for primary liver-transplantation from January 2012 to December 2022 were collected from the National Transplant-Registry.The cohort was divided into Eras:1 (2012–2014);2 (2015–2018);and 3 (2019–2022).
*Results:* The one-year probability of undergoing transplant increased (67.6 % in Era 1*vs*73.8 % in Era 3,$p < 0001$) with a complementary 46 % decrease in waiting-list failures. Patients with hepatocellular-carcinoma were transplanted more often than cirrhotics[at model for end-stage liver-disease (MELD)-15:HR = 1.28,95 %CI:1.21–1.35;at MELD-25:HR = 1.04,95 %CI:0.92–1.19) and those with other indications (at MELD-15:HR = 1.27,95 %CI:1.11–1.46) across all eras. Candidates with Hepatitis-B-virus (HBV)related disease had a greater probability of transplant than those with Hepatitis-C virus-related (HR = 1.13,95 %CI:1.07–1.20), alcohol-related (HR = 1.13,95 %CI:1.05–1.21), and metabolic-related (HR = 1.18,95 %CI:1.09–1.28)disease. Waiting-list failures increased by 27 % every 5 MELD-points and by 14 % for every 5-year increase in recipient-age and decreased by 10 % with each 10-cm increase in stature. Blood-group O patients showed the highest probability of waiting-list failure (HR = 1.28,95 %CI:1.15–1.43).
*Conclusions:* Liver-transplantation waiting-list success-rates have significantly improved in Italy, with patients with hepatocellular-carcinoma and/or HBV-related diseases being favored. High MELD-score, old-age, short-stature, and blood-group O were significant risk-factors for waiting-list failure. Efforts to improve organ-allocation and prioritization-policies are underway.



## 1. Introduction

Liver transplantation (LT) is currently the only cure for many end-stage liver diseases [1]. Despite advances in organ-donation and allocation, the resource in most countries is insufficient to promptly provide an organ for all candidates [2]. Organ-shortage has forced clinicians to develop ever more complex systems to impartially guide the allocation process. Most national organ allocation authorities have adopted the model for end-stage liver disease (MELD) score as the basis for organ allocation. MELD has proven itself to be a formidable and simple tool to evaluate the severity of cirrhotic patients [3], yet showed several limitations when applied to other LT indications [4]. For instance, while LT is an extraordinary (and sometimes the only) option for primary liver tumors, especially hepatocellular carcinoma (HCC), the complexity of this diagnosis is not captured by MELD. Likewise, estimating the clinical severity and prognosis of other non-cirrhotic LT indications is a difficult task, which needs more than the simple measurement that the MELD score provides [5]. Hence, delivering a fair process in terms of efficiency, equity, and utility in organ allocation remains one of the most significant clinical and ethical challenge in LT. This is documented by the yearly publication of data in the United States [6] and constant modifications and additions that are provided to many allocation systems worldwide in response to detected waiting list inequities [7–9]. Ultimately, all systems are different and influenced by the local epidemiological reality, they all need rules that necessitate frequent internal assessment, and all can benefit much in learning from the experience of their extra-national counterparts. Italy has seen an evolution in the etiologies underlying liver disease requiring transplantation, and an evaluation of whether the system has been correctly satisfying patient needs was warranted [10]. The study investigates the changes in waiting-list (WL) outcomes that have occurred over time in the last 11 years in Italy and the factors playing a role in directing patients toward success or failure.

### 1.1. Liver allocation policy in Italy

The Italian National Transplantation centre (CNT) sets national allocation-rules for organ allocation that are constantly updated, with the intent to guarantee the best chances for a timely and successful LT for every patient on the waiting list. The country has 22 LT centres located in 13 regions, grouped into two macro-areas (north and south), all controlled by the CNT network. Since the CNT's establishment (1999), liver allocation policies have seen three significant changes: 1) in 2013, when CNT took over the governance and the management of the national organ allocation programs (previously delegated to the regions); 2) in 2015, when a mandatory split liver policy was introduced for all donors aged between 18 and 50 years [11]; 3) in 2019, with the introduction of the Italian Score for Organ Allocation (ISO score) [12]. Therefore, liver grafts are currently shared according to the following principles: 1) nationwide, for (a) UNOS (United Network for Organ Sharing) status one patients, and (b) pediatric candidates; 2) macro-areas for adult LT candidates with MELD-sodium ≥29; 3) regionally for adult patients with MELD-sodium <29 and based on ISO score.

## 2. Materials and methods

### 2.1. Study design and population

This is a retrospective, multicenter, national-registry study investigating the extent of LT-WL success and the predictors of WL outcomes over time. The study included patients registered on the Italian national LT-WL between January 1, 2012 and December 31, 2022. Patients were identified retrospectively from the prospectively maintained transplant information system (TIS) database developed by CNT, collecting data from 22 Italian Transplant-Centers. WL outcomes were compared between different eras, where the intervals were chosen considering two relevant events: in the year 2012, the implementation of the TIS database, and in the year 2015, the availability of direct-acting antivirals (DAAs) against HCV. The study cohort was, therefore, arbitrarily grouped into three eras based on the date of entry in the WL as follows: Era 1: from 2012 to 2014; Era 2: from 2015 to 2018; and Era 3: from 2019 to 2022. The study was approved by the promoting center's independent ethics-committee *(Policlinico Tor Vergata; n: 256.20)* and was conducted in accordance with the declaration of Helsinki and Istanbul.

### 2.2. Outcome measures

Within the framework of a competing-risk analysis, the three co-primary outcomes of the study were: 1) likelihood of LT; 2) likelihood of waiting-list failure (WLF); and 3) WL dropout for clinical improvement. Outcome measures were analyzed and compared between and within each era. WLF was defined as either patient death, or WL dropout due to worsening clinical conditions; WL dropout for clinical improvement was considered when clearly stated in the TIS, or when the MELD score of cirrhotic patients decreased below 15.

### 2.3. Patients, inclusion and exclusion criteria

The study cohort included all adult patients on the WL for cadaveric LT in Italy during the study era without incomplete, uncertain or missing data regarding WL outcomes. Exclusion criteria were: i) patients under 18 years of age; ii) patients on the waiting list due to acute or acute on chronic liver failure; iii) combined transplantation; iv) re-transplantation; and v) living-donor LT. Patients who dropped from the list ($n$ = 105; 0.82 %) or were suspended ($n$ = 19; 0.15 %) for unknown reasons were also excluded from the analysis.

### 2.4. Database and data handling

The TIS database is based on an XML protocol (Simple Object Access Protocol, SOAP) and includes comprehensive clinical records of LT candidates and organ donors. Data were collected from the TIS database and categorized following accurate review of any possible conflicting information. For the purpose of this study, the indications for waiting list inclusion fell within three categories: 1) cirrhosis; 2) HCC; and 3) "other indications". Patients on the waiting list for HCC were identified by cross-matching all available records: whenever the term "HCC" was present in the database, HCC was considered the primary indication for waiting list inclusion. The category "other indications" included non-HCC malignancies, MELD exceptions and others (Table S1).

Primary underlying disease-etiologies were categorized as follows: 1) HCV-related; 2) HBV-related; 3) alcohol-related; 4) metabolic-related; 5) others. Concerning HCV- and HBV-related etiologies, LT candidates were categorized after cross-matching the information on disease-etiology with the presence of one or more virological blood markers (HBV-DNA, HCV-RNA, HBsAg, HBsAb, HBcAb, HCV-Ab). In the case of multifactorial etiologies, HCV infection was considered the leading underlying disease etiology. In the absence of HBV DNA and HBsAg and in concomitance with alcoholic or metabolic disease, these were considered to be primary underlying etiologies, in hierarchical order, irrespective of the presence of HBcAb. Metabolic-related etiology was considered to be primary underlying disease whenever the terms NASH, NAFLD, or MAFLD were recorded in the TIS, or when the term cryptogenic or the lack of any known etiology were associated with the presence of one or more of the following: i) BMI >30; ii) diagnosis of metabolic syndrome; iii) diabetes mellitus; iv) any kind of dyslipidemia.

### 2.5. Statistical analysis

Continuous variables were summarized by median, first and third quartiles, while categorical variables were described by absolute frequencies and percentages. For competing risk analyses three main endpoints were considered: probability of undergoing LT, WLF, or WL dropout due to clinical improvement. In the marginal analysis, cumulative incidence functions (CIF) were used to investigate the three possible outcomes, and stratified curves were compared by Gray's test. In the multivariate analysis, the cumulative incidence of the three events was modelled using the Fine & Gray model [13]. The following covariates, taken at the time of listing, were considered: indication and era for waiting list inclusion, disease etiology, calculated MELD score, age, gender, nationality, BMI, height, and ABO blood type. Variables were selected on the basis of non-automated backward selection, taking correlation structure among covariates and clinical interpretation of their effects into account. We explored possible two-way interactions following a clinically-driven approach. Special attention was paid to interactions to assess possible changes in covariate effects across the three different eras. For hypothetical sets of individual covariates, the predictive cumulative incidences of LT at one year were computed based on estimates of the corresponding cumulative subdistribution hazards. The log transformation was used to compute confidence intervals. Analyses were conducted using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA) and R, version 4.2 (The R Foundation for Statistical Computing).

## 3. Results

Out of 16,404 patients who were included on the LT waiting list from January 1, 2012 to December 31, 2022, 12,749 [median age:57 (IQR 51–62) years;males:9651,75.7 %] met the inclusion criteria and were enrolled in the study cohort. Demographic characteristics are summarized in Table S2. Overall, 10,152 patients (79.6 %) underwent LT, 1659 (13.0 %) experienced WLF and 304 (2.4 %) dropped out from the waiting list due to clinical improvement. As of February 28, 2023, 634 patients (5.0 %) were still on the WL, 91.5 % of whom were listed in Era 3.

### 3.1. Probability of undergoing liver transplantation

The overall cumulative probability of undergoing LT at four years was 81.6 % (CI:80.9 %–82.3 %). The median waiting list time for transplanted patients was 3.8 (IQR:1.0–15.0) months. The estimated likelihood to undergo LT at 6 and 12 months was 56.4 % and 67.6 %, respectively, in Era 1, 61.2 % and 73.7 % in Era 2, and 60.7 % and 73.8 % in Era 3 ($p < 0.0001$) (Figure S1A).

In the univariate marginal analysis, patients on the waiting list for HCC (Fig. 1A-1C) and those with HBV-related etiology (Fig. 2A-2C) showed a higher probability of being transplanted across all three eras.

Patients with HBV have a higher likelihood of being transplanted *vs* all other aetiologies ($p < 0.0001$) even when considering only patients with cirrhotic as LT indication (Figures S2). Among HBV candidates, the probability of being transplanted for HCC increased in the last two eras compared to the first, while for cirrhosis, it remained stable over time (Figure S3A, S3B, S3C, S4). On the contrary, autoimmune etiology which were listed for cirrhosis in most cases (n:748/784; 95.4 %) showed the same probability of being transplanted across all eras ($p = 0.7530$).

Short stature candidates (height<165 cm) (Figures S5A,S5B,S5C), blood group O (Figures S6A,S6B,S6C) and female gender (Era 1,$p = 0.0032$;Era 2 and Era 3,$p < 0.0001$) showed a lower probability of being transplanted. Patients with BMI <23 (1st quartile) and age<51 years showed a reduced probability of undergoing LT in Eras 2–3 ($p = 0.0002$;$p = 0.0124$) and in Era 3 ($p = 0.0009$), respectively. Among cirrhotic patients, those with MELD>21 (3rd quartile) had significantly higher access to LT across all three eras (Figures S7A,7B,7C). The impact of MELD was much lower for patients with HCC, being significant only in Era 3 ($p = 0.0002$), and it was irrelevant for "other indications".

In the multivariate analysis, all the findings from the univariate marginal analyses were confirmed, except for the role of recipient BMI (Table 1). More specifically, blood group markedly influenced the chances of LT, with AB blood type patients being fa-

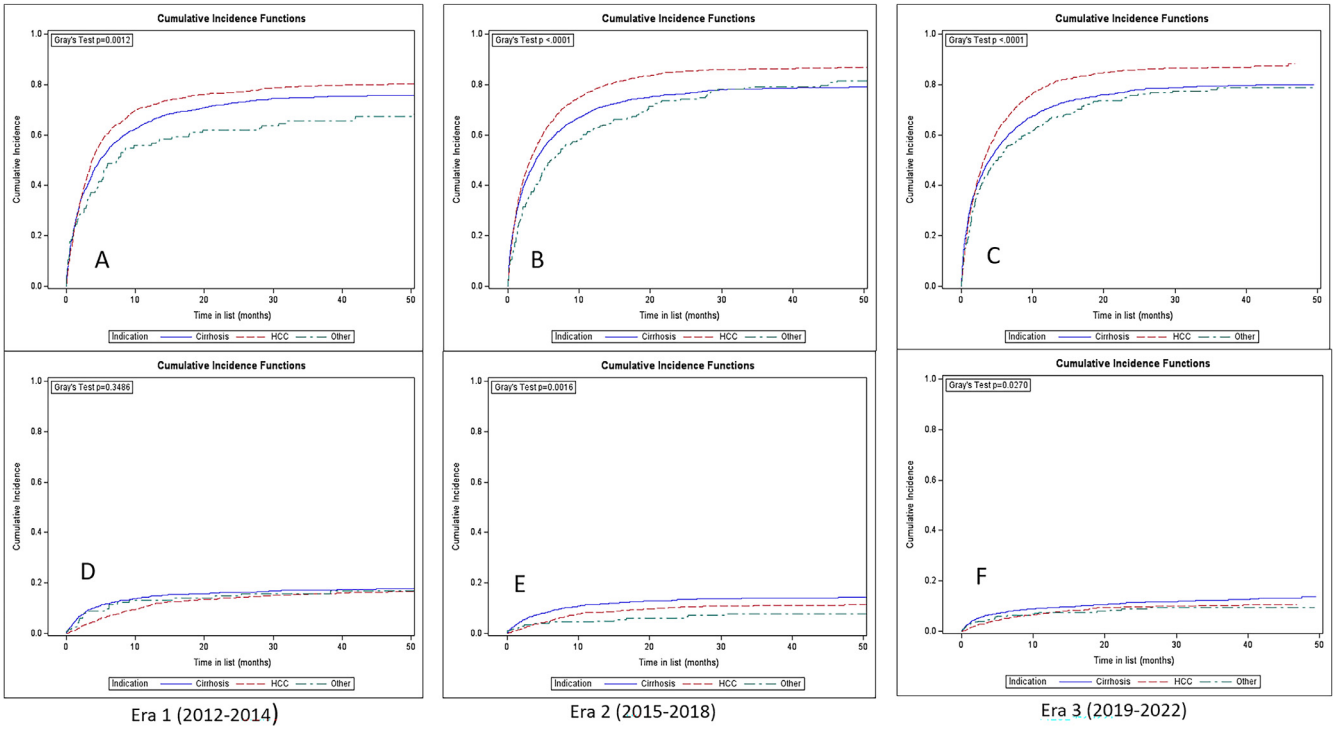


**Fig. 1.** Cumulative incidence functions for liver transplantation rate (A-B-C) and waiting list failure (D-E-F) according to indication in Era 1 (A-D), Era 2 (B-E) and Era 3 (C-F).

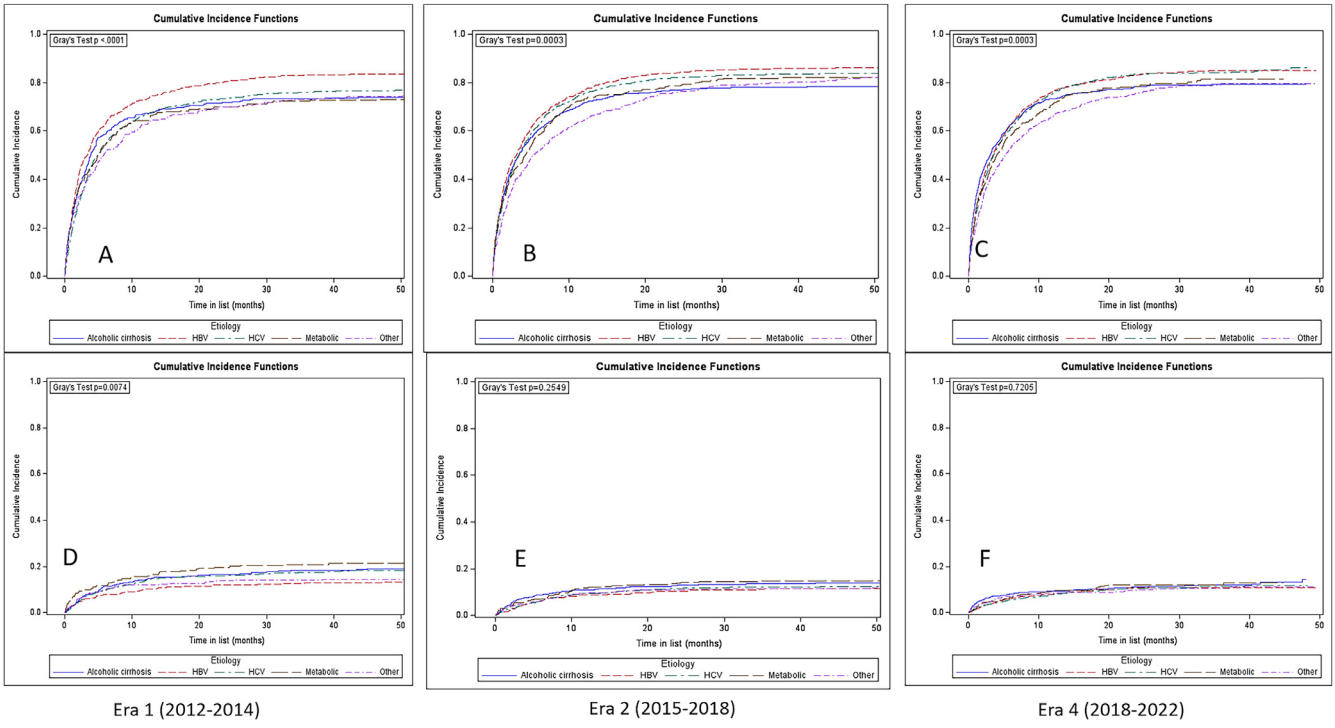


**Fig. 2.** Cumulative incidence functions for liver transplantation rate (A-B-C) and waiting list failure (D-E-F) according to etiology in Era 1 (A-D), Era 2 (B-E) and Era 3 (C-F).

vored and group O being disfavored. A significant and interesting effect of stature on gender was also evident: females appear to be at significant disadvantage only at 160 cm of stature or less. Table 2 illustrates the likelihood to be transplanted in relation to a variety of hypothetical changing clinical scenarios. For example, a patient with blood group O, HCV-related cirrhosis, and MELD 25 showed a 19 % lower probability of undergoing LT compared to a patient with blood group AB and the same LT indication. An even greater disadvantage was also evident between a young group O patient with HCV-related-cirrhosis and high MELD score and an older Group A patient with HBV-related HCC.

With regards to the role of stature, every 10 cm of height was associated with an almost 6 % increased chance of being transplanted. HBV-related etiology was associated with a greater probability of LT compared to HCV-, alcohol- and metabolic-associated etiologies. Increasing recipient age was also associated with a

**Table 1**
Multivariate analysis for the identification of factors predicting the probability of liver transplantation in patients on the waiting list between January 2012 and December 2022 in Italy (number of observations used 11,820).

| Variable | Contrast | Hazard Ratio | 95 % Confidence Interval | Wald statistic | *p*-value |
|---|---|---|---|---|---|
| **ABO blood type** | | | | 257.58 | **<0.0001** |
| | O *vs* A | 0.76 | (0.73, 0.80) | | |
| | AB *vs* A | 1.49 | (1.35, 1.64) | | |
| | B *vs* A | 0.85 | (0.80, 0.91) | | |
| **Etiology** | | | | 24.30 | **<0.0001** |
| | HBV *vs* HCV | 1.13 | (1.07, 1.20) | | |
| | HBV *vs* Metabolic | 1.18 | (1.09, 1.28) | | |
| | HBV *vs* Other | 1.13 | (1.03, 1.24) | | |
| | HBV *vs* Alcoholic | 1.14 | (1.06, 1.22) | | |
| **Stature** | | | | 12.82 | **0.0003** |
| **Sex** | | | | 7.14 | **0.0076** |
| **Stature*Sex** | | | | 6.63 | **0.0100** |
| | Females *vs* Males at stature 160 cm | 0.91 | (0.84, 0.97) | | |
| | Females *vs* Males at stature 165 cm | 0.95 | (0.89, 1.01) | | |
| | Females *vs* Males at stature 170 cm | 0.99 | (0.92, 1.07) | | |
| | Females *vs* Males at stature 175 cm | 1.04 | (0.87, 1.06) | | |
| | x 10 cm of stature in Females | 1.12 | (1.05, 1.20) | | |
| | x 10 cm of stature in Males | 1.02 | (0.99, 1.06) | | |
| **Era** | | | | 5.86 | **0.0535** |
| **Age at listing** | | | | 5.40 | **0.0201** |
| **Era*Age at listing** | | | | 11.23 | **0.0036** |
| | x 5 years of age at Era 3 | 1.02 | (1.00, 1.04) | | |
| | Era 2 *vs* Era 1 at median age of 57 years | 1.21 | (1.14, 1.28) | | |
| | Era 3 *vs* Era 1 at median age of 57 years | 1.22 | (1.15, 1.29) | | |
| **Indication** | | | | 58.02 | **<0.0001** |
| **MELD** | | | | 0.29 | **0.5928** |
| **Indication*MELD** | | | | 19.52 | **<0.0001** |
| | x 5 units of MELD in HCC | 1.04 | (1.00, 1.08) | | |
| | x 5 units of MELD in cirrhosis | 1.15 | (1.11, 1.19) | | |
| | HCC *vs* Cirrhosis at Meld 15 | 1.27 | (1.20, 1.34) | | |
| | HCC *vs* Other at Meld 15 | 1.27 | (1.11, 1.45) | | |
| | HCC *vs* Cirrhosis at Meld 25 | 1.03 | (0.91, 1.18) | | |
| | HCC *vs* Other at Meld 25 | 1.31 | (1.00, 1.70) | | |

MELD: model for end-stage liver disease; HCC: hepatocellular carcinoma; HBV: hepatitis B Virus; HCV: Hepatitis C virus;.

**Table 2**
Hypothetical clinical scenarios showing the impact of different levels of the most significant factors to predict the probability of undergoing liver transplantation within 1 year of listing.

| Indication | Etiology | Age | ABO Blood group | Stature | MELD | Estimated probability of LT at 1 year | 95 % CI |
|---|---|---|---|---|---|---|---|
| HCC | HBV | 57 | AB | 175 | 10 | 0.94 | (0.92, 0.95) |
| HCC | HBV | 57 | AB | 160 | 10 | 0.92 | (0.90, 0.94) |
| Cirrhosis | HCV | 57 | AB | 175 | 25 | 0.93 | (0.90, 0.95) |
| Cirrhosis | HCV | 57 | O | 175 | 25 | 0.74 | (0.71, 0.77) |
| Cirrhosis | HCV | 40 | O | 175 | 25 | 0.71 | (0.68, 0.75) |
| HCC | HCV | 62 | A | 175 | 10 | 0.81 | (0.80, 0.83) |
| Cirrhosis | Alcoholic | 51 | A | 160 | 15 | 0.70 | (0.67, 0.72) |
| Cirrhosis | Alcoholic | 62 | O | 175 | 25 | 0.75 | (0.72, 0.78) |
| HCC | MAFLD | 62 | B | 175 | 10 | 0.75 | (0.72, 0.78) |
| Cirrhosis | MAFLD | 51 | B | 165 | 15 | 0.63 | (0.60, 0.67) |

MELD: model for end-stage liver disease; HCC: hepatocellular carcinoma; HBV: hepatitis B Virus; HCV: Hepatitis C virus; MAFLD: metabolic-associated fatty liver disease.

**Table 3**
Multivariable analysis of risk factors predicting waiting list failure in patients on the waiting list for liver transplantation in Italy between January 2012 and December 2022 (number of observations used 12,480).

| Variable | Contrast | Hazard Ratio | 95 % Confidence Interval | Wald statistic | *p*-value |
|---|---|---|---|---|---|
| **ABO blood type** | | | | 45.75 | **<0.0001** |
| | O *vs* A | 1.28 | (1.15, 1.43) | | |
| | AB *vs* A | 0.49 | (0.35, 0.69) | | |
| | B *vs* A | 1.19 | (1.03, 1.39) | | |
| **Stature** | x 10 cm | 0.90 | (0.85, 0.96) | 11.49 | **0.0007** |
| **Era** | | | | 92.42 | **<0.0001** |
| | Era 2 vs Era 1 | 0.69 | (0.62, 0.78) | | |
| | Era 3 vs Era 1 | 0.54 | (0.48, 0.62) | | |
| **Age at listing** | x 5 years | 1.14 | (1.11, 1.72) | 77.15 | **<0.0001** |
| **MELD** | x 5 units | 1.27 | (1.23, 1.32) | 200.62 | **<0.0001** |

MELD: model for end-stage liver disease;.

greater chance of LT in Era 3 (2 % increase for every 5 years of age). Finally, higher MELD scores were confirmed to increase the chance of undergoing LT in patients with cirrhosis but not in those with HCC. Cirrhotic patients had a 15 % (95 %CI:1.11–1.18) increase in LT probability every 5 MELD points. Conversely, patients with HCC had a higher LT probability compared to cirrhotic patients with low MELD scores (HR:1.28;95 %CI:1.21–1.35) and patients with other indications (HR:1.27; 95 %CI:1.11–1.46). However, the advantage of HCC *vs* cirrhosis decreased as MELD increased, with an estimated HR of 1.04 (95 %CI:0.92–1.19) at MELD 25.

### 3.2. Probability of waiting list failure

WLF occurred in 17.8 % ($n = 562$), 12.9 % ($n = 601$) and 10.1 % ($n = 496$) of patients in Era 1, Era 2, and Era 3, respectively. Unadjusted WLF significantly differed among the three eras, with a significant decrease in WLF recorded in Era 3 (Figure S1B).

The univariate marginal analysis found that patients with higher MELD scores were at greater risk of WLF ($p < 0.0001$ in all eras). Cirrhotic patients were at greater risk of WLF compared to those with HCC and "other" indications (Fig. 1D-1F), but only in Eras 2 and 3, while there were no differences between disease etiologies (Fig. 2D-2F). AB group and younger patients were less exposed to the risk of WLF across all eras. WLF rate significantly increased in Eras 2 and 3, as the patients' stature decreased ($p = 0.0045$ in Era 2;$p = 0.0437$ in Era 3).

In the multivariate analysis (Table 3), patients on the waiting list showed a 31 % lower risk of WLF (95 %CI:0.62–0.78) in Era 2 and 46 % (95 %CI:0.48–0.62) in Era 3 compared to Era 1. MELD and age exerted a linear effect, with a 27 % increase in WLF hazard for every 5 MELD points and 14 % for every five years of increasing age. AB blood type had a remarkable effect on WLF: taking patients with blood group A as a reference level, those with groups O and AB showed the highest and lowest probability of WLF[estimated HR=1.28 (95 %CI:1.15–1.43) and 0.49 (95 %CI:0.35–0.69), respectively]. The hazard of WLF was reduced by 10 % (95 %CI:0.85–0.96) with stature increases of 10 cm.

### 3.3. Probability of waiting list dropout due to clinical improvement

The overall dropout due to clinical improvement was 4.0 % ($n = 125$), 2.8 % ($n = 128$) and 1.0 % ($n = 51$) of patients in Era 1, Era 2, and Era 3, respectively. The one-year probability of WL dropout due to clinical improvement was 0.8 %, 0.7 % and 0.4 % in the three eras, respectively ($p = 0.0015$). Patients with HCC and cirrhotic patients with high MELD scores showed the lowest probability of being suspended from the WL due to clinical improvement across all eras, while female recipients with alcohol- or metabolic-related cirrhosis showed the highest (Table S3).

## 4. Discussion

This study reports for the first time the success rate of the Italian national WL for liver transplantation over the last decade. The study showed a significant increase in waiting list success over time, expressed as a rising probability of undergoing LT, and a complementary decrease in WLF and dropouts for clinical improvement.

The magnitude of these praise-worthy findings can be better understood when compared with other LT settings. For example, the one-year probability for transplantation found in this study increased from 67.6 % in 2012–2015 to 73.8 % in 2019–2022, both figures being well above the 54.4 % waiting list success-rate registered in the corresponding PTN/SRTR reports from the USA [1]. Similarly, WLF remained relatively-low, with a one-year rate that fell from 17.8 % in Era 1 to only 10.4 % in Era 3, figures which also compare favorably with contemporary data from the US LT-registry [8,9,14]. The results of this study cannot be attributed to single determinants, but rather likely represent the outcome of several interrelated-processes. Potentially-involved factors include, but are not limited to, an increase in organ-donations, as well as the more widespread use of machine-perfusion systems, which facilitated not only an increase in the use of expanded criteria donors, but also the use of donors-after-cardiac-death (DCDs). According to the data annually published by the CNT, donations in Italy increased by 33 % between 2013 and 2022, reaching a donation rate of 24.7 per million population [15]. In the same time-frame, harvested donor brain death liver grafts increased by 44 %, while DCD liver grafts grew from 0 to 114 per year [15]. In 2015, the allocation policy in Italy underwent a significant shift from an urgency-based system (*i.e.*, MELD) to a "blended-principle" model, including the concepts of transplant urgency, utility and benefit, known as the Italian Score for Organ allocation (ISO)score [16]. The ISO score uses the MELD score as a backbone prioritization tool for cirrhotic patients, while making use of a detailed rule system to categorize and rank (considering all the aforementioned principles) all other LT indications whose severity is not adequately captured by MELD (the main example of which is HCC). The new system may have been instrumental in decreasing WLF by allocating grafts to patients who were previously inappropriately ranked, as their disease severity was not captured by the MELD score alone. That said, this study was not intended to address the issue of ISO score performance, which is currently being analysed and which already features proposals for subtle integrations to balance the system. This study clearly shows that specific categories of waiting list patients had a greater probability of undergoing LT and, conversely, lower chances of WLF. Of these, the advantage gained by patients with HCC compared to those with cirrhosis is particularly striking. Notably, multivariate analysis brought to light an important, albeit intuitive, interaction between the indication for LT and the MELD

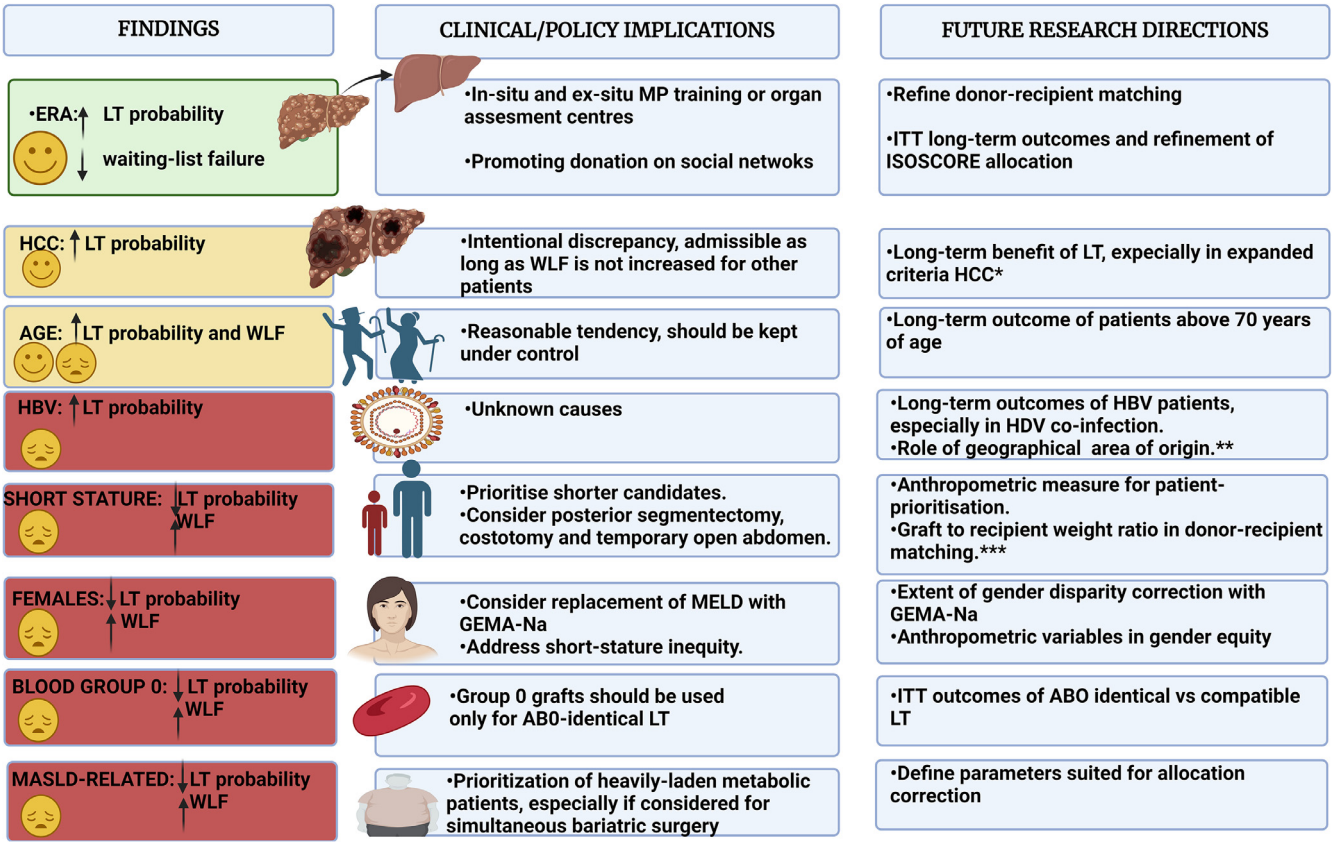


**Fig. 3.** Findings, clinical/policy implications and future research directions. LT: liver transplantation; HBV: hepatitis b virus; GEMA-Na: gender equality model for liver allocation; HCC: hepatocellular carcinoma; HDV: hepatitis-d-virus; ITT: intention-to-treat; MASLD: metabolic-associated steatotic liver disease; MELD: model for end-stage liver disease; MP: machine perfusion; WLF: waiting-list failure; *see XXL study (Mazzaferro et al. Lancet Oncology 2020); **see ECALITA study (Manzia et al. Digestive and Liver Diseases 2022);*** see Manzia et al. Updates in Surgery 2022.

score at the time of listing: at MELD 25, patients with HCC or cirrhosis had the same probability of undergoing LT or dropping-out from the list due to death or clinical worsening, while at lower MELD (namely 15), patients with HCC had a greater LT probability and lower WLF rates. On the other hand, the increase in LT probability associated with a 5-point MELD score increase was more evident among cirrhotic patients than among patients with HCC. These findings raise several considerations. First, some waiting list patients with HCC may have been favored in the allocation-process compared to cirrhotic patients simply because they were considered to be a better match for an expanded-criteria donor (ECD), the most common type of donor nowadays; second, the interaction between the indication for LT and the MELD score may simply be the result of a deliberate clinical choice of clinicians based on a perceived greater risk of waiting list dropout for patients with HCC or cirrhosis, respectively, within low or high MELD score ranges; third, as long as patients with HCC are granted a higher LT probability without affecting WLF of cirrhotic patients, this apparent inequity may not necessarily be considered to be a negative behavior, nor require amendment. Indeed, not all disparities are inherently harmful, while perfect equity may not be entirely desirable when this is at odds with transplant utility and benefit [17]. In this regard, it remains debatable whether HCC patients with predicted large and moderate transplant benefit should be permitted to maintain a small probability advantage to undergo LT, without this scenario representing an ethical issue [18].

Notably, the magnitude of success of the national liver transplantation waiting list was independently influenced by the underlying disease etiology, with patients with HBV-related disease being favored compared to other etiologies across all-three eras. There is no obvious explanation for this finding. Perhaps the mandatory use of HBsAg-positive and the preferential use of HBcAb donor grafts in HBsAg-positive recipients may be part of the explanation [19]. Otherwise, it could be argued that HBV-infected patients on the waiting list, although being generally clinically stable thanks to the universal use of nucleos (t)ide antivirals, are perceived by clinicians as being at greater risk, thus meriting prioritization and maybe capable of receiving a marginal organ. The highest probability of WLF was observed in the category of MAFLD patients. These patients are well-known to be burdened by severe comorbidities, such as heart-disease or morbid-obesity, which may limit the chance for optimal donor-recipient matching and favor performance status-related WLF [20–22]. The short-stature disadvantage is another well-known possible allocation inequity [14,23]. Given the scarcity of adequate donors, short-stature patients could benefit from a split-liver graft. The Italian split-liver policy, enforced since 2015, resulted in improved waiting times for pediatric patients, but apparently did not enhance the allocation-equity for short-stature patients [11,24]. At the same time, experience with the use of adult-to-adult split LT has so far been unsatisfactory, being unable to yield outcomes comparable to those observed with the use of whole grafts [25]. This study provides a solid argument for discussing whether short-stature should gain some priority category in a future revision of the national allocation policy, as also recently proposed in the USA [26]. Another interesting finding was the influence of gender. Since women tend to have lower creatinine levels than men, the use of MELD seems to lead the gender inequity in LT access . While the addition of extra points to women has been suggested as a possible solution [26], GEMA and GEMA-Na model showed improved discrimination between male and fe-

male and a significant reclassification benefit compared with other existing scores [26-28]. The inequity appears tightly linked to the stature as well. However, whether one variable is a surrogate of the other is unclear. In our study, men were favored only when height was 160 cm or lower, suggesting a possible effect of physical dimensions (i.e.thoracic diameters) and weight [29] rather than gender and MELD score. It is possible that an ideal correction would take into account both eGFR and physical dimensions.

As observed in the USA [9,30], the ABO blood type was another major cause of disparity in the process of organ-allocation across all-eras. Patients with blood group O, despite being the most represented in the country, were less likely to undergo LT and more likely to suffer WLF, an inequity relying uniquely on compatibility issues (i.e.ABO-compatible LT) [31,32] and on the possibility that Group 0 offer to urgency transplant [31]. Even though the CNT recommends performing ABO-identical LT, a degree of flexibility is currently left to each region. We feel that more rigorous nationwide rules, restricting the allocation of group O livers to ISO-group donations, are warranted. To summarize, Table 2 is intended to be a quick-reference tool, providing actual examples of the probability of undergoing LT at one-year from listing in relation to different hypothetical scenarios (such as changes in the candidate indication for transplant, disease etiology, age, stature, MELD and blood group). The table shows wide variations in the probability of undergoing a transplant, although even in the worst-case scenario, this remains satisfactory.

Fig. 3 summarizes the findings of this study and includes additional suggested implications and proposed future clinical, policy and research directions.

The main limitation of this study is its retrospective design. The stratification of HCC patients based on tumor size, number of nodules, alpha-fetoprotein levels and response to loco-regional treatment would have been helpful for a better understanding of our overall findings. Unfortunately, these data were largely incomplete in the database to allow meaningful analysis. A further significant limitation is the lack of center-volume analysis.

In conclusion, the success-rate of the Italian national LT waiting list has been satisfactory over the last ten years, during which time the probability of patients on the waiting list being transplanted has significantly increased, with a complementary decrease in WLF rates. Notably, patients with HCC and those with HBV-related liver disease were favored compared to all other waiting list patients. Conversely, cirrhotic patients with high MELD scores had a greater probability of dropout from the list due to clinical worsening. Although the overall findings are indicative of more precise administration of the LT waiting list in recent years, some relevant inequities remain. Efforts should therefore be directed at further improving organ allocation equity, also considering a predictable wider use of machine-perfusion, expanded-criteria donors, and DCDs.

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## Conflict of interest

The authors of this manuscript have no conflicts of interest to disclose.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2024.08.039.

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