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Short Report

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Short Report

Validation of the Liver Transplant Risk Score in Europe

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Introduction

A simple clinical instrument is needed to assist clinicians in the risk stratification of patients referred for liver transplantation during the very first phases of evaluation[1]. The authors developed the Liver Transplant Risk Score (LTRS) with the assistance of machine-learning techniques to predict the short- and long-term outcomes of patients undergoing liver transplantation. The LTRS includes recipient age, BMI, native Model for End-Stage Liver Disease (MELD) score calculated at the time of listing, need for dialysis, and history of diabetes. The LTRS has been validated in patients undergoing transplantation in the USA[2], but has never been tested in patients transplanted in other countries. The primary aim of this study was to assess the performance of the LTRS in adult patients who underwent a first-time liver transplantation in Europe.

Methods

Selected parameters of adult recipients (aged at least 18 years) who underwent a first-time liver transplantation between 1 January 2002 and 31 December 2013 in Europe were analysed retrospectively (*Fig. S1*). Follow-up was completed on 31 December 2018. All parameters were extracted from the European Liver Transplant Registry. Exclusion criteria were: incompatibility between donors' and their recipients' blood types, and the use of partial grafts or grafts from cardiac death donors, or simultaneous multivisceral transplants. Patients with primary or secondary hepatic malignancies were also excluded, except for those with hepatocellular carcinoma.

Outcomes, data collection, and definitions

The main outcome was patient death. The LTRS was measured for each liver transplantation recipient at the time of listing. The number of points associated with each variable of the LTRS is summarized in *Fig. 1d*. The European Liver Transplant Registry does not collect data on recipients' history of diabetes. In this study, therefore, calculation of the LTRS was based only on recipients' age, native MELD score at the time of listing, BMI, and need for dialysis.

Statistical analysis

Continuous variables are reported as mean(s.d.) values, except that median (i.q.r) was used for data without a normal distribution. Categorical variables are reported using frequencies and percentages. Comparisons were performed using Student's *t* test, ANOVA, χ^2 or Fisher's exact test, Kruskal–Wallis test, and Kaplan–Meier methods for survival. Patient survival was defined as the time between the date of transplantation and date of death. Censoring was used for patients who underwent

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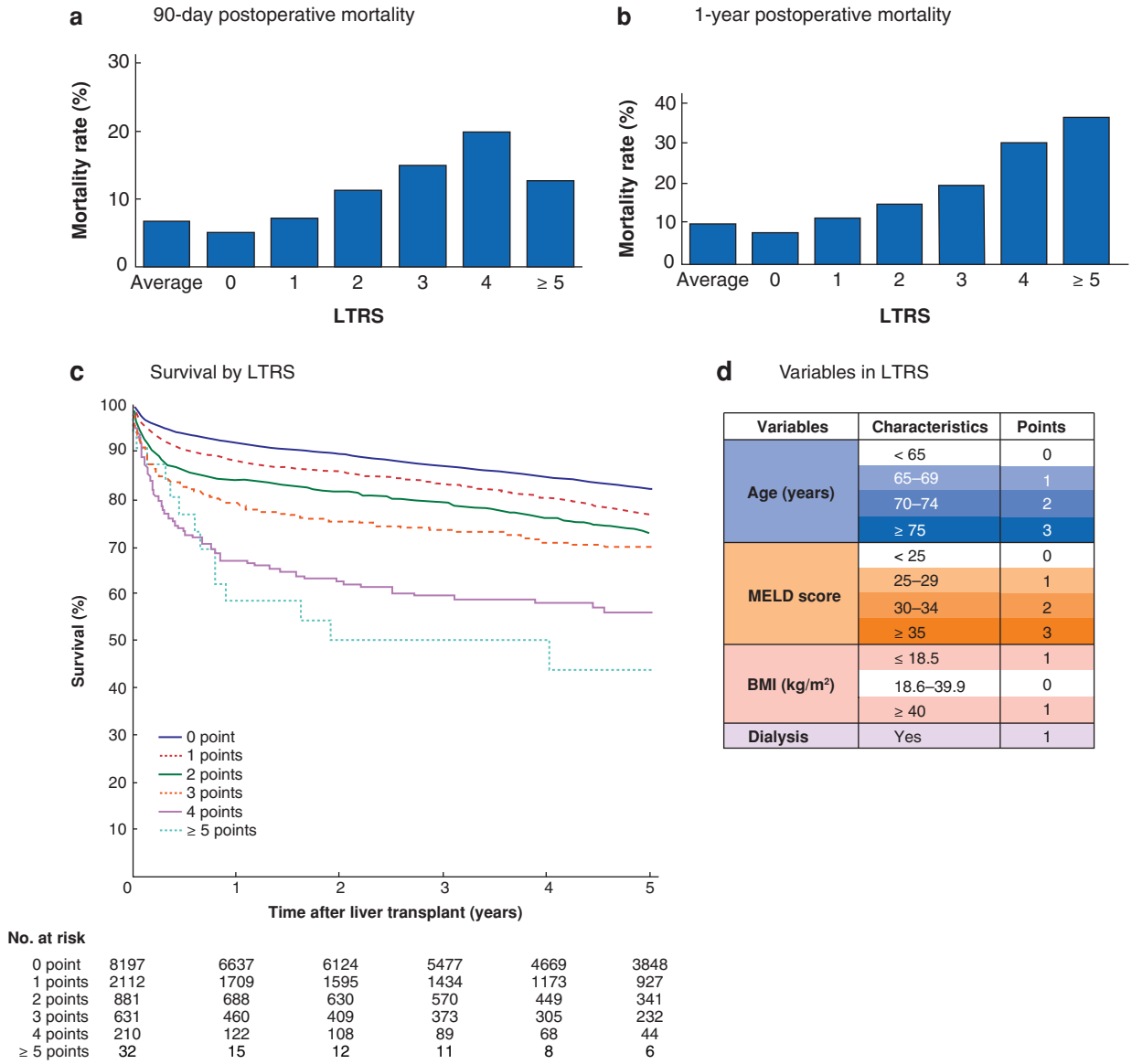

Variables	Characteristics	Points
Age (years)	< 65	0
	65–69	1
	70–74	2
	≥ 75	3
MELD score	< 25	0
	25–29	1
	30–34	2
	≥ 35	3
BMI (kg/m²)	≤ 18.5	1
	18.6–39.9	0
	≥ 40	1
Dialysis	Yes	1

Fig. 1 Ninety-day and 1-year mortality rates, and survival stratified by Liver Transplant Risk Score, and risk score components

a Ninety-day mortality rate stratified by Liver Transplant Risk Score (LTRS). For each point on the LTRS, 90-day mortality increased on average by 1.5 per cent (Spearman's correlation coefficient $\rho = 0.64$; $P < 0.001$). **b** One-year mortality rate stratified by LTRS. For each additional point on the LTRS, 1-year mortality increased on average by 6 per cent (Spearman's correlation coefficient $\rho = 0.95$; $P < 0.001$). **c** Kaplan–Meier 5-year survival functions for deceased donor liver transplant recipients who underwent surgery in Europe and stratified by LTRS. For every additional point on the LTRS, the 5-year survival rate decreased on average by 7 per cent ($P < 0.001$). $P < 0.050$ for all pairwise comparisons, except $P = 0.57$ (score 2 *versus* 3) and $P = 0.313$ (score 4 *versus* 5) (log rank test). **d** Variables included in the LTRS and respective points. The original LTRS included recipient age, BMI, history of diabetes, need for dialysis, and Model for End-Stage Liver Disease (MELD) score. Because the European Liver Transplant Registry does not collect data on diabetes, this parameter was not one of the variables used to calculate LTRS in the present study.

retransplantation, those who were lost to follow-up, or for patients who were alive at the end of the study. The Cox proportional hazards model was used to calculate the adjusted HR stratified by the number of points on the LTRS. For regression analyses, sex and primary indication for liver transplantation were included in the model, and patients with an LTRS score of 0 represented the reference group.

C-statistics[3] and corresponding areas under the curve with 95 per cent confidence intervals were used to assess the performance of the model for 90-day and 1-year mortality. Statistical tests were done with Bonferroni-corrected P values when appropriate. Two-tailed $P < 0.050$ was considered statistically significant.

All statistical analyses were done using SPSS® for Windows version 26 (IBM Corporation, Armonk, NY, USA).

Results

The demographic and clinical characteristics of 12 063 liver transplantation recipients are summarized in *Table 1*.

Ninety-day mortality

There was a linear correlation between 90-day mortality and LTRS (Spearman's correlation coefficient (ρ) = 0.64; $P < 0.001$) (*Fig. 1a*). The 90-day mortality rate was 5.6 per cent for low-risk recipients (LTRS 0–1), 12.9 per cent for intermediate-risk

Table 1 Sociodemographic and clinical characteristics of adult patients who underwent first-time deceased donor liver transplant in Europe between 1 January 2002 and 31 December 2013

	All patients (*n* = 12 063)	Patients who died within 90 days (*n* = 815)	Patients who survived beyond 90 days (*n* = 11 248)	P†
Age (years), mean(s.d.)	51.4 (11.0)	53.2 (10.1)	51.3 (11.1)	<0.01
< 65	11 108 (92.1)	728 (89.3)	10 380 (92.3)	<0.01
65–69	839 (7.0)	79 (9.7)	760 (6.8)	<0.01
70–74	111 (0.9)	8 (1.0)	103 (0.9)	0.891
≥ 75	5 (0.0)	0 (0)	5 (0.0)	0.334
Sex ratio (F : M)	4220 : 7843	281 : 534	3939 : 7309	0.756
MELD score, mean(s.d.)	18.7 (8.0)	21.9 (9.4)	18.55 (7.9)	<0.01
< 15	4399 (36.5)	227 (27.9)	4172 (37.1)	<0.01
15–20	3660 (30.3)	197 (24.2)	3463 (30.8)	<0.01
21–25	1771 (7.8)	111 (13.6)	1660 (14.8)	0.344
26–30	963 (7.8)	103 (12.6)	833 (7.4)	<0.01
> 30	1297 (10.8)	177 (21.7)	1120 (10.0)	<0.01
Need for dialysis before transplantation	426 (3.5)	78 (9.6)	348 (3.1)	<0.01
BMI (kg/m^2), mean(s.d.)*	25 934 (4.8)	26.2 (5.4)	25.9 (4.8)	<0.01
Normal weight (BMI 18.5–24.9)	5306 (44.0)	350 (42.9)	4956 (44.1)	0.533
Underweight (BMI <18.5)	384 (3.2)	32 (3.9)	352 (3.1)	0.217
Overweight (BMI 25.0–29.9)	4122 (34.2)	262 (32.1)	3860 (34.3)	0.202
Class I obesity (BMI 30.0–34.9)	1646 (13.6)	114 (14.0)	1532 (13.6)	0.768
Class II obesity (BMI 35.0–39.9)	483 (4.0)	39 (4.8)	444 (3.9)	0.239
Class III obesity (BMI 40.0–44.9)	92 (0.8)	16 (2.0)	76 (0.7)	<0.01
Class III obesity (BMI ≥ 45)	30 (0.2)	2 (0.2)	28 (0.2)	0.986
LTRS, mean(s.d.)	0.6 (0.9)	1.02 (1.3)	0.53 (1.0)	<0.01
0	8197 (68.0)	419 (51.4)	7778 (69.2)	<0.01
1	2112 (17.5)	155 (19.0)	1957 (17.4)	0.24
2	881 (7.3)	100 (12.3)	781 (6.9)	<0.01
3	631 (5.2)	95 (11.7)	536 (4.8)	<0.01
4	210 (1.7)	42 (5.2)	168 (1.5)	<0.01
≥ 5	32 (0.3)	4 (0.5)	28 (0.2)	0.192
Primary indication for liver transplant				
Hepatitis C virus	1432 (11.9)	118 (14.4)	1314 (11.7)	<0.01
Primary biliary cirrhosis	821 (6.8)	32 (3.9)	789 (7.0)	<0.01
Primary sclerosing cirrhosis	1112 (9.2)	49 (6.0)	1063 (9.4)	<0.01
Non-alcoholic steatohepatitis	212 (1.7)	10 (1.2)	202 (1.8)	0.232
Alcoholic cirrhosis	3644 (30.2)	265 (32.5)	3379 (30.0)	0.131
Other causes	4751 (39.3)	333 (40.8)	4418 (39.2)	0.379
Unknown	91	8	83	0.436

Values are *n* (%) unless otherwise indicated. MELD, Model for End-Stage Liver Disease; LTRS, Liver Transplant Risk Score. *?. †? test. *Chi-Square Test was used to compare categorical variables, Student t-test was used to compare continuous variables with normal distribution and Mann-Whitney U test for nonparametric variables.

patients (LTRS 2–3), and 19.0 per cent for high-risk patients (LTRS at least 4) ($\rho = 0.99$; $P < 0.001$) (*Fig. S2*). After adjusting for the aetiology of liver disease and recipient sex, the LTRS remained an independent predictor of 90-day mortality ($P < 0.001$) (*Fig. S3*).

One-year mortality

There was a linear correlation between 1-year mortality and the LTRS ($\rho = 0.95$; $P < 0.001$) (*Fig. 1b*). The 1-year mortality rate was 9.2 per cent for low-risk recipients (LTRS 0–1), 17.9 per cent for intermediate-risk patients (LTRS 2–3), and 32.6 per cent for high-risk recipients (LTRS at least 4) ($\rho = 0.97$; $P < 0.001$) (*Fig. S4*). After adjusting for the aetiology of liver disease and recipient sex, the LTRS remained an independent predictor of 1-year mortality ($P < 0.001$) (*Fig. S5*).

Five-year survival

The 5-year survival rate was 82, 76, 72, 69, 56, and 44 per cent for patients with an LTRS of 0, 1, 2, 3, 4, and 5 or more points respectively ($P < 0.001$) (*Fig. 1c*). Cox regression analysis showed that LTRS remained an independent predictor of survival after adjusting for indications for liver transplantation and recipient sex ($P < 0.001$) (*Fig. S6*).

Discussion

The present results confirmed that the perioperative risks and long-term survival of adult European patients undergoing liver transplantation could be stratified using the LTRS. These findings were in line with the results from previous studies[1,2] of patients transplanted in the USA. Other measures commonly used for assessment of the performance of predictive models, the C-statistic and the net reclassification index, were consistent between the cohort of liver transplantation recipients who had surgery in Europe and the cohort transplanted in the USA. The C-statistic for 90-day mortality in the European cohort was 0.64 (95 per cent c.i. 0.62 to 0.66; $P < 0.001$) in comparison to 0.61 (0.59 to 0.61; $P < 0.001$) for patients transplanted in the USA[2]. The net reclassification index value was 33 per cent in the present study, compared with 35 per cent for patients transplanted in the United States, indicating that the risk classification of patients referred for liver transplantation could be improved in one-third of patients.

These findings have several implications. The early identification of high-risk patients could help the implementation of programmes to correct reversible risk factors associated with poor outcomes after liver transplantation. In addition, use of the LTRS could bring more objectivity into the way clinicians assess potential liver transplantation candidates, and provide

investigators with a simple and validated instrument to adjust for differences in risk factors among groups.

As with most predictive models, the LTRS should not be used in isolation for the selection or rejection of liver transplantation candidates. In fact, similar to other models, the LTRS showed only modest precision for the identification of patients who died immediately after surgery. Nevertheless, the authors believe that the LTRS represents an important step towards an objective and reproducible instrument that can help clinicians to identify patients who are at increased risk of perioperative death and shorter long-term survival at the time when critical decisions are made.

The LTRS has not been compared directly with other predictive models, such as the P-SOFT (preoperative survival outcomes following liver transplant)[4] or the BAR score (balance of risk scoring system)[5], and it has not been validated in recipients of living donor grafts, split livers, multiorgan transplants, or redo liver transplantation. Future studies will be necessary to assess the validity of the LTRS in such groups of patients. Finally it is very important to assess differences in the effects of graft quality on patient survival, especially for recipients with a high LTRS.

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Disclosure

The authors declare no conflict of interest.

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European Colorectal Congress

28 November – 1 December 2022, St.Gallen, Switzerland

Monday, 28 November 2022

09.50
Opening and welcome
Jochen Lange, St.Gallen, CH

10.00
It is leaking! Approaches to salvaging an anastomosis
Willem Bemelman, Amsterdam, NL

10.30
Predictive and diagnostic markers of anastomotic leak
Andre D'Hoore, Leuven, BE

11.00
SATELLITE SYMPOSIUM
ETHICON

11.45
Of microbes and men – the unspoken story of anastomotic leakage
James Kinross, London, UK

12.15
LUNCH

13.45
Operative techniques to reduce anastomotic recurrence in Crohn's disease
Laura Hancock, Manchester, UK

14.15
Innovative approaches in the treatment of complex Crohn Diseases perianal fistula
Christianne Buskens, Amsterdam, NL

14.45
To divert or not to divert in Crohn surgery – technical aspects and patient factors
Pär Myrelid, Linköping, SE

15.15
COFFEE BREAK

15.45
Appendiceal neoplasia – when to opt for a minimal approach, when and how to go for a maximal treatment
Tom Cecil, Basingstoke, Hampshire, UK

16.15
SATELLITE SYMPOSIUM
Medtronic
Further,Together

17.00
Outcomes of modern induction therapies and Wait and Watch strategies, Hope or Hype
Antonino Spinelli, Milano, IT

17.30
EAES Presidential Lecture - Use of ICG in colorectal surgery: beyond bowel perfusion
Salvador Morales-Conde, Sevilla, ES

18.00
Get-Together with your colleagues
Industrial Exhibition

Tuesday, 29 November 2022

9.00
CONSULTANT'S CORNER
Michel Adamina, Winterthur, CH

10.30
COFFEE BREAK

11.00
SATELLITE SYMPOSIUM
INTUITIVE

11.45
Trends in colorectal oncology and clinical insights for the near future
Rob Glynne-Jones, London, UK

12.15
LUNCH

13.45
VIDEO SESSION

14.15
SATELLITE SYMPOSIUM
BD

15.00
COFFEE BREAK

15.30
The unsolved issue of TME: open, robotic, transanal, or laparoscopic – shining light on evidence and practice
Des Winter, Dublin, IE
Jim Khan, London, UK
Brendan Moran, Basingstoke, UK

16.30
SATELLITE SYMPOSIUM
Takeda

17.15
Lars Pahlman lecture
Søren Laurberg, Aarhus, DK

Thursday, 1 December 2022
Masterclass in Colorectal Surgery
Proctology Day

Wednesday, 30 November 2022

9.00
Advanced risk stratification in colorectal cancer – choosing wisely surgery and adjuvant therapy
Philip Quirke, Leeds, UK

09.30
Predictors for Postoperative Complications and Mortality
Ronan O'Connell, Dublin, IE

10.00
Segmental colectomy versus extended colectomy for complex cancer
Quentin Denost, Bordeaux, FR

10.30
COFFEE BREAK

11.00
Incidental cancer in polyp - completion surgery or endoscopy treatment alone?
Laura Beyer-Berjot, Marseille, FR

11.30
SATELLITE SYMPOSIUM

12.00
Less is more – pushing the boundaries of full-thickness rectal resection
Xavier Serra-Aracil, Barcelona, ES

12.30
LUNCH

14.00
Management of intestinal neuroendocrine neoplasia
Frédéric Ris, Geneva, CH

14.30
Poster Presentation & Best Poster Award
Michel Adamina, Winterthur, CH

15.00
SATELLITE SYMPOSIUM
OLYMPUS

15.45
COFFEE BREAK

16.15
Reoperative pelvic floor surgery – dealing with perineal hernia, reoperations, and complex reconstructions
Guillaume Meurette, Nantes, FR

16.45
Salvage strategies for rectal neoplasia
Roel Hompes, Amsterdam, NL

17.15
Beyond TME – technique and results of pelvic exenteration and sacrectomy
Paris Tekkis, London, UK

19.30
FESTIVE EVENING

Information & Registration **www.colorectalsurgery.eu**