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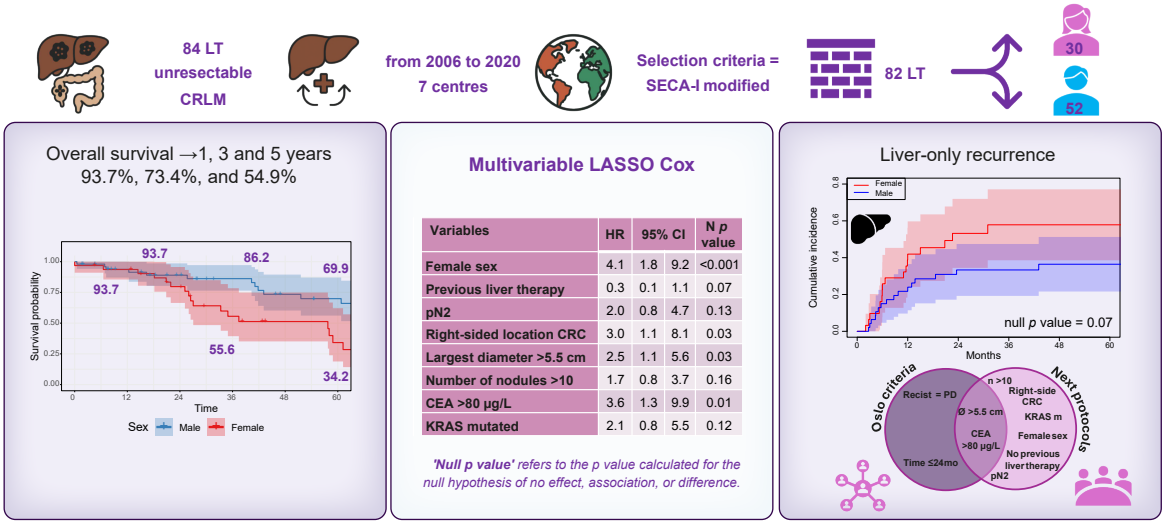
Graphical abstract



Highlights:

- First multivariable survival analysis of LT for CRLMs.
- Higher mortality in female patients aligns with a potential relationship between sex and outcomes, which requires further exploration.
- Post LT recurrence is more likely in the liver for women, but only in the lungs for men.
- The prognostic strength of some variables used in clinical practice is not confirmed.
- Future prognostic models should prioritise improved discrimination and calibration in relation to the defined endpoint.

Impact and implications:

This multicentre retrospective study analysed survival outcomes in 82 patients undergoing liver transplantation for colorectal liver metastases across seven US and European centres. Several factors, including female sex, high carcinoembryonic antigen levels, right-sided colorectal cancer, larger tumours, KRAS mutation, pN2-positive CRC, number of nodules, and no prior liver therapy, were linked to poorer outcomes. The study questions current prognostic models and selection criteria, emphasizing the need for more accurate tools to guide decision-making in patients with colorectal liver metastases.

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Research article

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Sex-based differences in survival after liver transplantation for colorectal cancer liver metastases: A multivariable analysis

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Background & aims: Liver transplantation (LT) for colorectal liver metastases (CRLMs) is attracting increasing interest, especially after publication of the TransMet trial. However, multivariable survival analyses are lacking. Here, we performed such an analysis in a multicentre cohort.

Methods: We conducted a retrospective multicentre study of 82 patients with CRLMs undergoing LT (from 2006 to 2020) across seven US and European centres, using multivariable Cox, competing-risk models, and extensive sensitivity analyses.

Results: Overall survival rates after 1, 3, and 5 years were 93.7%, 73.4%, and 54.9%, respectively. The findings align with an association between higher risk and the female sex (estimated hazard ratio (HR) 4.1, 95% CI: 1.8–9.2), and the following variables: carcinoembryonic antigen >80 μg/L, right-located colorectal cancer (CRC), largest diameter >5.5 cm, KRAS mutation, and absence of previous liver therapy. Other possible associations with higher uncertainty were pN2-positive CRC and the number of nodules (>10). Variables such as progressive disease after pretransplant chemotherapy and time from primary CRC surgery to LT of ≤24 months, exhibited weaker, less consistent associations.

Conclusions: This first multivariable survival analysis of LT for CRLM suggests that female sex is associated with worse outcomes, whereas the prognostic strength of the model currently used in clinical practice is not confirmed. Our findings challenge current selection criteria, highlighting the need for improved prognostic models with better discrimination and calibration.

Introduction

Liver transplantation (LT) offers a potentially curative treatment for highly selected patients with unresectable colorectal liver metastases (CRLMs).[1] Despite growing interest, evidenced by >1,700 publications on CRLMs and LT (PubMed search, June 2024),[2] fewer than 200 actual transplant cases have been documented worldwide. This limited clinical experience likely explains the absence of robust multivariable survival analyses in this field.

Currently, the Oslo criteria[3,4] are the most widely used selection guidelines for LT in CRLMs, although they are based only on univariable survival analyses. These criteria include a disease-free interval of >2 years after primary tumour resection, no progressive disease (PD) after pretransplant chemotherapy, a maximum tumour diameter of <5.5 cm, and a carcinoembryonic antigen (CEA) level <80 μg/L at the time of LT.[3] Despite their limitations, these criteria have been effective in guiding patient selection.[4]

More recently, additional tumour biology-related predictors of post-transplant outcomes have been identified, including low metabolic tumour volume (MTV) on positron emission tomography (PET)/computed tomography (CT) (<70 cm^3),[5,6] left-sided primary colorectal cancer (CRC), and its histological differentiation.[7,8]

Conversely, several prognostic factors, such as the number of positive lymph nodes, previous surgical liver treatments (resection or ablation), and biological sex, remain underexplored. For example, preclinical studies suggest that female sex hormones increase the hepatic tropism of CRC cells.[9] Given the complexity and interplay of known and unknown variables influencing post-transplant outcomes, there is a pressing need for multicentre studies with robust multivariable

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analyses.[1,10] This urgency was heightened by the TransMet trial[11] results, which, despite excellent per-protocol outcomes, showed reduced benefit in intention-to-treat analyses. This discrepancy could reflect 'biological selection', where patients with aggressive tumours are excluded because of disease progression during wait times. The trial underscores the need for validated, rigorous selection criteria to optimise graft allocation and patient outcomes. To address this gap, we conducted the first exploratory multivariable survival analysis of patients undergoing LT for CRLM using a multicentre dataset. Our goal was to identify patterns of risk association to support the refinement of prognostic criteria, enabling better candidate selection, avoiding exclusion of patients with potentially curable disease, and ensuring judicious use of scarce liver grafts.

Patients and methods

Study population

This multicentre retrospective study enrolled all consecutive patients with unresectable CRLM undergoing LT from January 2006 to December 2020 across two US and five European centres.

In all centres, LT was indicated for unresectable liver-only metastases. The non-resectability of CRLM was always determined by a multidisciplinary team comprising at least one of the following: a hepatobiliary surgeon, a transplant surgeon, a hepatologist, a radiologist, and an oncologist.

Only patients meeting the SECA-I study[3] criteria were included in this study to minimise selection bias and the centre effect. Thus, the following criteria were considered absolute exclusion criteria: Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score >1; lack of radical excision of the primary CRC; <6 weeks of pretransplant chemotherapy; and presence of extrahepatic disease. Further exclusion criteria included age ≥72 years (increased from 60 years in the original trial for consistency with subsequent trials), weight loss exceeding 10%, standard contraindications for LT,[12] and concurrent other malignancies. Both deceased and living donor liver transplants (LDLTs) were eligible for the study. Each patient received at least 6 weeks of chemotherapy, which was the standard of care based on each patient's stage and previous lines of therapy, if any. The specific criteria used by each participating centre (within the broad range of SECA-I criteria) are described in Table S1.

Before LT, all patients underwent radiological staging with either CT or magnetic resonance imaging (MRI), depending on centre protocols. A PET/CT scan was performed for each patient to exclude extrahepatic disease. However, PET values were not included in the analysis because of potential variability in calculation methods and the lack of standardised metabolic tumour volume (MTV) measurements before 2018.[5]

Each patient underwent a perioperative staging laparotomy, including frozen-section analysis of hepatic ligament lymph nodes. LT proceeded per institutional protocol only if no extrahepatic malignancy was detected.

The study adhered to the ethical guidelines of the 2013 revised Declaration of Helsinki. Each patient underwent LT for unresectable CRLM solely as part of a non-randomised controlled trial approved by the ethics committee of each sponsoring centre participating in this observational cohort. Before inclusion, each patient provided written informed consent for every procedure performed in the hospital and for the use of data for research and publication purposes. All procedures were carried out following the Declaration of Istanbul. No individual received compensation or was offered any incentive for participating in this study.

The parameters included in the current analysis were as follows: demographics (age, sex); BMI; Oslo centre; primary tumour-related factors (location of the primary tumour, positive lymph nodes at pathology [pN+, pN1, pN2]); KRAS status; time from primary CRC resection and LT; previous liver therapy (resection or ablation) before LT; liver metastases variables (PD after pretransplant systemic therapy according to response evaluation criteria in solid tumours [RECIST 1.1]:[13] number of lesions; size of the largest lesion from the last available radiology; last CEA level); LDLT; and follow-up parameters (recurrence site and patient status). Positive lymph nodes (*i.e.* at least one positive lymph node) in the pathological report of primary tumour resection (pN+) were categorised into pN1 (one to three positive lymph nodes) and pN2 (four to nine positive lymph nodes). According to the chosen analysis, these three categories (pN+, pN1, and pN2) were tested separately to observe the most influential one (File S1, Supplementary data). Synchronous CRLMs were not considered given that each group had only four cases of metachronous CRLMs.

It was decided to include only radiological measures of liver lesions to identify potential predictors of post-LT outcomes, focusing exclusively on the variables available in the preoperative outpatient setting. Finally, patients with a BMI >25 kg/m^2 were considered overweight.

Statistical analysis

The fundamental assumptions of all statistical models are discussed in the main text and Files S1 and S2, following established evaluation standards.[14,15] Categorical variables are presented as frequencies (%), whereas continuous variables are shown as medians with IQRs. Differences between groups were assessed using a two-tailed Welch *t* test or Mann-Whitney *U* test for continuous variables, and Pearson's Chi-square or Fisher's exact test for categorical variables, as appropriate. Effect sizes were calculated using Cohen's d and Mann–Whitney $z/(n_1+n_2)^{1/2}$ for continuous variables, and Cohen's w for categorical variables, to estimate statistical (non-clinical) relevance. The entry 'standardised size difference' (last column of Table 1) refers to Cohen's d and Mann–Whitney $z/(n1+n2)^{1/2}$ for continuous variables and Cohen's w for categorical variables: low values (<0.3) corroborate high group similarity at the statistical (but not necessarily clinical) level.

The primary endpoint was overall survival (OS), defined from the date of LT to death or the last follow-up (July 2022), with follow-up durations expressed as medians (IQR). OS was analysed using Kaplan–Meier curves and compared via the log-rank test under the null hypothesis of no difference. The term 'null *p*' refers to the *p* value calculated for the null hypothesis of no effect, association, or difference.

To assess covariate effects, Cox regression models were constructed hierarchically across four domains: (1) tumour biology and response to therapy; (2) metastatic and biomarker characteristics; (3) technical-logistical factors; and (4) patient-related clinical features. Model selection was guided by the

Table 1. Demographical and clinical characteristics of enrolled patients.

Variables	Study group (n = 82); median (IQR) no. (%)	Males (n = 50); median (IQR) no. (%)	Females (n = 32); median (IQR) no. (%)	Null *p* value (male *vs.* female)	Standardised size difference (male *vs.* female)
Age	54 (47–59)	54 (48–60)	54 (45–59)	0.63	0.11
Age >55 years	39 (48)	24 (48)	15 (47)	0.90	<0.01
Oslo centre	54 (66)	30 (60)	24 (75)	0.16	0.22
Living donor	12 (15)	7 (14)	5 (16)	0.84	0.05
Previous liver therapy	21 (26)	11 (22)	10 (32)	0.44	0.21
BMI >25 kg/m^2	48 (59)	30 (60)	18 (56)	0.74	0.01
pN1	37 (45)	21 (42)	16 (50)	0.43	0.06
pN2	22 (27)	14 (28)	8 (25)	0.97	<0.01
Synchronous CRLM	74 (90)	46 (92)	28 (88)	0.71	0.03
Right-sided CRC	16 (20)	9 (18)	7 (22)	0.67	0.02
Time from CRC surgery to LT ≤24 months	50 (61)	29 (58)	21 (66)	0.49	0.05
Progressive disease	16 (20)	8 (16)	8 (25)	0.32	0.11
CEA >80 μg/L	16 (20)	11 (22)	5 (16)	0.48	0.06
No. of nodules	10 (5–14)	10 (7–14)	8 (4–15)	0.47	0.04
>10 nodules	27 (33)	17 (34)	10 (31)	0.80	<0.01
Diameter (cm)	4 (3–7)	4 (3–7)	4 (2–8)	0.67	<0.01
Diameter >5.5 cm	29 (35)	16 (32)	13 (41)	0.43	0.07
KRAS mutated	20 (25)	12 (24)	8 (25)	0.87	<0.01

Two-tailed Welch *t* test and Mann-Whitney *U* test were used to compare continuous variables; two-tailed Pearson's Chi-square test and Fisher's exact test were used to compare categorical variables. The 'Standardised size difference' column refers to Cohen's d and Mann-Whitney $z/(n_1+n_2)^{1/2}$ for continuous variables and Cohen's w for categorical variables: low values (<0.3) corroborate high group similarity at the statistical (but not necessarily clinical) level. Given a markedly asymmetric distribution, synchronous CRLM was not included in the main analysis. CEA, carcinoembryonic antigen; CRC, colorectal cancer; CRLM, colorectal liver metastases; pN1, metastasis in one to three regional lymph nodes after colorectal surgery; pN2, metastasis in four to nine regional lymph nodes after colorectal surgery.

corrected Akaike information criterion (AICc) and least absolute shrinkage and selection operator (LASSO), using 10-fold cross-validation. The final multivariable model was selected following sensitivity analyses (detailed in File S2).

Dichotomisation of continuous variables was based on thresholds reported in the literature, except for age. Given that age as a continuous covariate was not associated with risk of death or recurrence (Files S1 and S2), we dichotomised it at 55 years, close to the cohort median.

Stratified Kaplan–Meier survival curves were used to illustrate interaction effects. By stratifying curves based on levels of interacting variables, we examined whether the influence of one variable on survival was modified by another. In addition, a sex-based stratified analysis was conducted.

Considering literature suggesting that post-transplant prognosis is influenced by the site of recurrence, we incorporated recurrence patterns as exploratory endpoints. We used a time-varying Cox model to evaluate the impact of recurrence type (liver, lung, or no recurrence) on OS. Follow-up was divided into two periods for patients with recurrence: from LT to diagnosis of recurrence; and from recurrence to death or last follow-up. The recurrence type was included as a time-dependent covariate, altering its value upon diagnosis.

Conventional disease-free survival (DFS) and cause-specific Cox analyses were used to investigate predictors of tumour recurrence.[16] DFS was defined as the period from LT to recurrence or death, whichever occurred first, with censoring at the last follow-up (July 2022). Variables with a null p <0.20 in univariable analyses were included in the multivariable DFS model.

In cause-specific analyses, competing events were defined as lung-only recurrence, liver-involved recurrence, extrahepatic non-lung-only recurrence, and death without recurrence. In cases of extrahepatic non-lung-only recurrence, lung involvement was possible as part of multisite progression. Fine & Gray competing-risk models were also explored as a supplementary analysis (Files S2 and S3).

Missing covariate data were present in <10% of patients and were handled via multiple imputation (details in File S1).[17] The strength of observed associations was assessed using p values and 95% CIs.[18,19] p values close to 1 indicate strong compatibility with the null hypothesis, while those close to 0 indicate lower compatibility. Following recent methodological recommendations, we used an unconditional interpretation of p values, allowing for nuanced assessment across plausible hypotheses, including limitations.[20,21] Additional quantification of p value information was carried out using the s-value metric (File S1). All analyses were conducted using R (RStudio 4.2.3, RStudio, Inc., Boston, MA, USA) and STATA (Stata/SE 18.0, StataCorp LLC, College Station, TX, USA).

Results

Patients' characteristics

This study population comprised 84 patients who underwent LT for unresectable CRLMs between January 2006 and December 2020. One patient was excluded because of a weight loss exceeding 10%, and another had an ECOG PS >1. Ultimately, 82 patients were included in the analysis.

Most of the patients were men (61%), with a median age of 54 (IQR 47–59). Table 1 presents the characteristics of the enrolled patients.

Twelve patients (14.6%) received an LDLT, with most (66%) undergoing transplants in Oslo. Most patients were overweight (59%), had positive lymph nodes (72%) in the primary tumour specimen, and underwent LT within 24 months (61%) of primary tumour resection. A minority of enrolled patients (20%) had a right-sided primary tumour, experienced PD after systemic therapy (20%), and had a pretransplant CEA level >80 μg/L (20%). In addition, a considerable proportion of patients had >10 liver nodules (33%), a diameter of the largest nodule >5.5 cm (35%), and presented with a KRAS mutation (25%). The distributions of these variables in male and female

patients were similar, which aligns with the low value of standardised mean differences (Table 1).

Overall survival analysis of the study population

In the whole population, the median follow-up for survivors was 70.0 months (IQR 26.4–91.0), median OS was 72.7 months (IQR 34.9–not reached), and OS after 1, 3, and 5 years was 93.7% (95% CI: 87.8–99.6%), 73.4% (95% CI: 62.7–84.1%), and 54.9% (95% CI: 41.7–68.1%), respectively. Thirty-three deaths were recorded during the follow-up period, and only two deaths (6.1%) occurred in patients without tumour recurrence. Thus, OS analysis in this setting almost coincided with a cancer-related death analysis.

The multivariable analysis agreed with an association between higher risk and the following variables (Table 2): female sex; CEA >80 μg/L; right-sided CRC; largest diameter >5.5 cm; absence of previous liver therapy; KRAS mutation; pN2; and number of nodules >10. We observed a high degree of concordance between the hierarchical and LASSO models. The most evident divergences in Kaplan–Meier survival curves were observed for right-sided CRC, CEA >80 μg/L, and KRAS mutation, all displaying an early separation (File S3). Additional variables associated with later divergence included pN2 status (separation at 6 months), largest diameter >5.5 cm, PD, female sex, and absence of prior liver therapy (separation at 12–18 months). A more modest divergence was noted for time from CRC surgery to LT ≤24 months (separation at 6 months). We also noted a more uncertain separation at 30 months for the variable Oslo, which is compatible with the hypothesis that the centre handles more severe cases; at 24 months up to 60 patients with >10 nodules, and around 12 months for the older group, which, surprisingly, showed a lower frequency of events. Such findings should be interpreted cautiously, because these curves do not account for confounding factors.

The median follow-up for survivors was 70.0 months (IQR 29.5–91.0) for women and 68 (IQR 23.3–88.3) for men. OS after 1, 3, and 5 years was 93.7%, 55.6%, and 34.2%, respectively in the female population, compared with 93.7%, 86.2%, and 69.9%, respectively in the male population (Fig. 1), although there were similar baseline characteristics (Table 1).

Table 2. Multivariable survival analysis of enrolled patients.

	LASSO Cox			
Variable	**HR**		**95% CI**	**Null *p* value**
Female sex	4.1	1.8	9.2	<0.001
Age >55 years	–	–	–	–
Oslo centre	–	–	–	–
Living donor	–	–	–	–
Previous liver therapy	0.3	0.1	1.1	0.07
BMI >25 kg/m^2	–	–	–	–
pN2	2.0	0.8	4.7	0.13
Right-sided CRC	3.0	1.1	8.1	0.03
Time ≤24 months	–	–	–	–
Progressive disease	–	–	–	–
Largest diameter >5.5 cm	2.5	1.1	5.6	0.03
No. of nodules >10	1.7	0.8	3.7	0.16
CEA >80 μg/L	3.6	1.3	9.9	0.01
KRAS mutated	2.1	0.8	5.5	0.12

Interval estimates and p-values are from the LASSO Cox model (Wald Z-test). Concordance = 0.836 (SE = 0.034), Likelihood ratio test p <0.001, Wald test p <0.001, Score (log-rank) test p <0.001. The coherence with the hierarchical model was strong (File S2). CEA, carcinoembryonic antigen; CRC, colorectal cancer; CRLM, colorectal metastasis; HR, hazard ratio; LASSO, least absolute shrinkage and selection operator; pN2, metastasis in four or more regional lymph nodes after colorectal surgery.

Given the potential association between sex and two factors, such as the diameter of the largest nodule (Fig. 2A,B) and the KRAS mutation (Fig. 2C,D), we performed a stratified survival analysis according to sex. Table 3 shows the results of univariable Cox survival analyses in men and women.

The original research intent was to perform a Cox multivariable survival analysis by sex. However, we encountered substantial violations of the basic assumptions (severe sparse-data bias), which might signal the need for larger sample sizes.

Univariable analysis agreed with an inverse association between risk and previous liver therapy, and a direct association between risk and right-sided CRC and CEA >80 μg/L in both sexes (Table 3). In women, the results were also

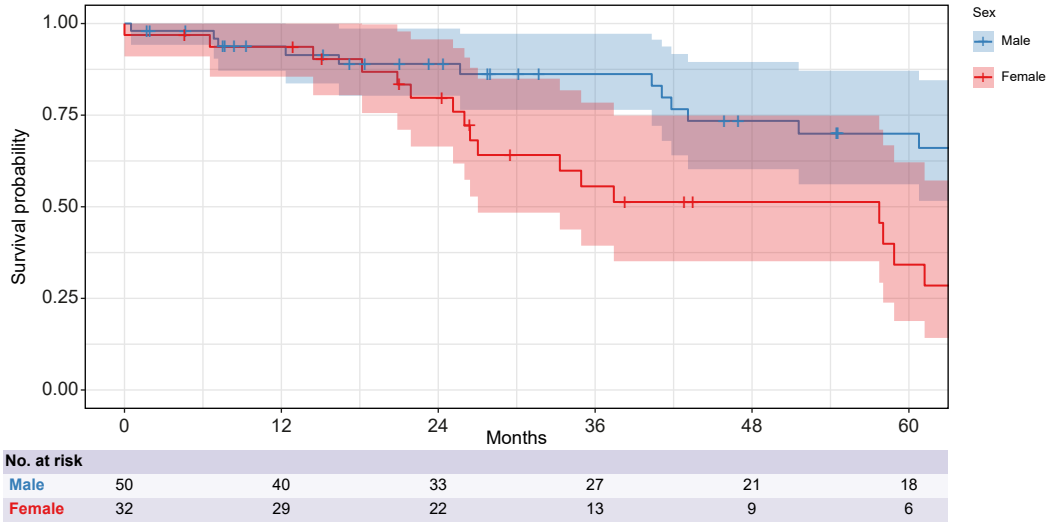


Fig. 1. Overall survival curves of men *vs.* women. Compatibility with the null hypothesis: p = 0.03 (Kaplan–Meier compared with the log-rank test for the null hypothesis of no difference). Shaded areas represent 95% CIs.

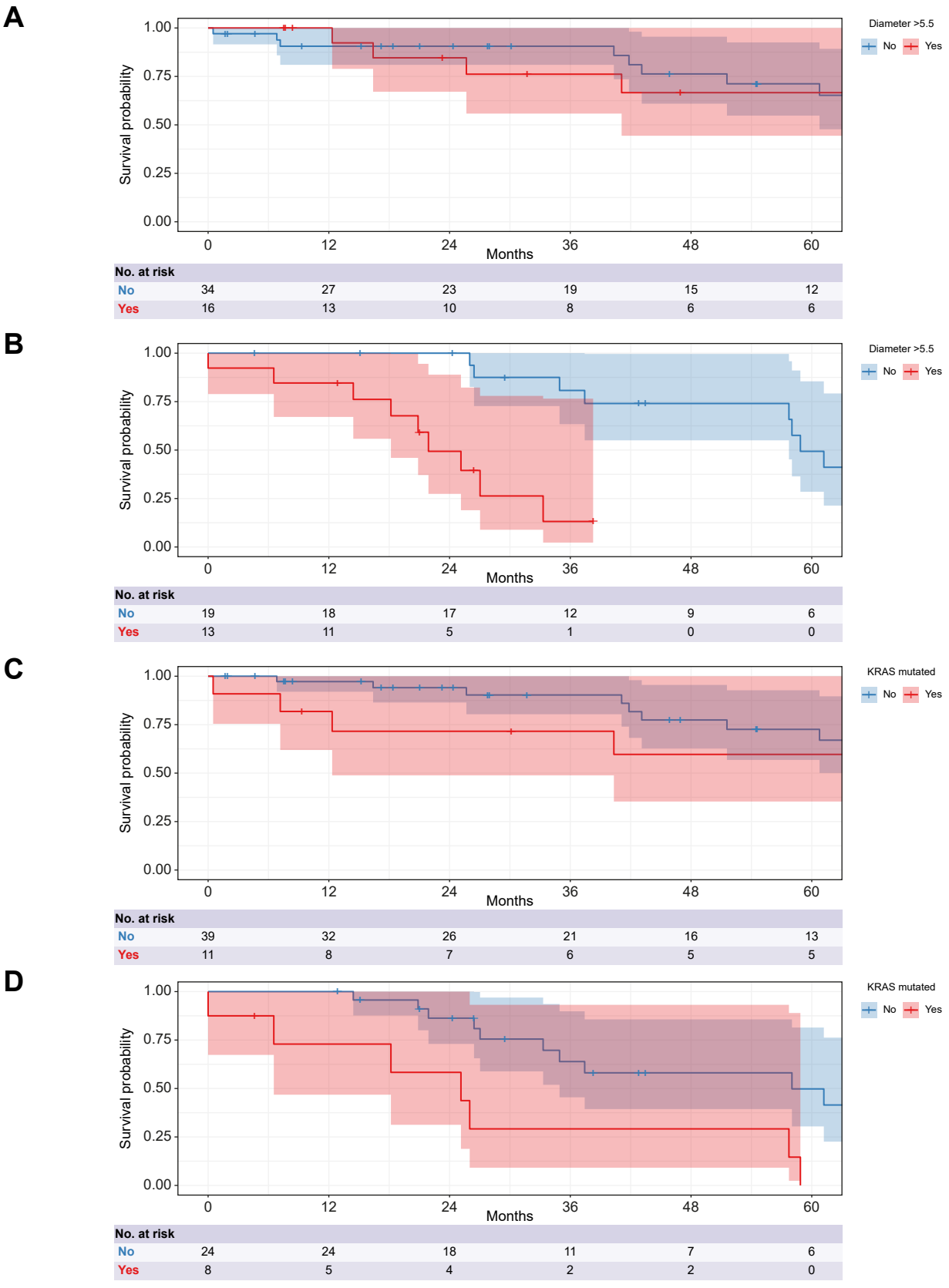


Fig. 2. Overall survival curves according to the diameter of the largest nodule and KRAS mutation. (A) Diameter of the largest nodule in men. Compatibility with the null hypothesis: p = 0.44 (Kaplan–Meier compared with the log-rank test for the null hypothesis of no difference). (B) Diameter of the largest nodule in women. Compatibility with the null hypothesis: p <0.001 (Kaplan–Meier compared with the log-rank test for the null hypothesis of no difference); (C) KRAS mutation in men. Compatibility with the null hypothesis: p = 0.35 (Kaplan–Meier compared with the log-rank test for the null hypothesis of no difference); (D) KRAS mutation in women. Compatibility with the null hypothesis: p = 0.03 (Kaplan–Meier compared with the log-rank test for the null hypothesis of no difference). Shaded areas represent 95% CIs.

Table 3. Univariable survival analysis stratified by sex.

	Proportional hazards Cox			
Variables	**HR**		**95% CI**	**Null *p* value**
Males				
Age >55 years	0.8	0.3	2.2	0.72
Oslo centre	3.9	0.5	31	0.19
Living donor*	–	–	–	–
Previous liver therapy	0.2	0.0	1.8	0.17
BMI >25 kg/m^2	1.1	0.4	3.2	0.84
pN2	3.0	1.1	8.0	0.03
Right-sided CRC	7.2	2.4	21	0.004
Time ≤24 months	1.2	0.4	3.4	0.71
Progressive disease	1.0	0.3	3.6	0.99
Largest diameter >5.5 cm	1.5	0.5	4.3	0.44
No. of nodules >10	1.1	0.4	3.1	0.81
CEA >80 μg/L	3.9	1.4	11	0.01
KRAS mutated	1.7	0.6	4.7	0.34
Females				
Age >55 years	0.4	0.2	1.1	0.07
Oslo centre	0.4	0.1	1.5	0.18
Living donor	2.1	0.4	10	0.35
Previous liver therapy	0.4	0.1	1.3	0.12
BMI >25 kg/m^2	0.8	0.3	2.2	0.70
pN2	1.5	0.5	4.2	0.47
Right-sided CRC	5.0	1.6	16	0.007
Time ≤24 months	2.6	0.8	9.1	0.13
Progressive disease	4.1	1.4	13	0.01
Largest diameter >5.5 cm	8.7	2.5	30	0.001
No. of nodules >10	1.6	0.6	4.1	0.38
CEA >80 μg/L	13	3.8	48	<0.001
KRAS mutated	4.0	1.5	11	0.006

Interval estimates and p-values are from the proportional hazards Cox model (Wald Z-test). CEA, carcinoembryonic antigen; CRC, colorectal cancer; CRLM, colorectal metastasis; HR, hazard ratio; pN2, colorectal cancer with metastasis in four or more regional lymph nodes after colorectal surgery.
*Not evaluable because of the absence of events in this group (*i.e.* seven patients, zero deaths).

consistent with a stronger direct association between risk and PD, largest diameter >5.5 cm, and KRAS mutations, and an inverse association between risk and age >55. Inspection of the Kaplan–Meier curves revealed a pattern consistent with the univariable analysis, although the latter remained susceptible to confounding (File S3). This corroborates the sex-related differences highlighted in the previous multivariable analysis.

Role of recurrence site on survival and its interaction with female sex

Sixty-two patients (75.6%) developed post-LT tumour recurrence after a median time of 12 months (IQR 5.2–23.6). The lungs were the only organ involved in 23 patients with recurrence (37.1%). The liver was the only organ involved in six patients (9.7%), whereas in 27 (43.5%), multiple organs, including the liver, were involved. Two patients had single bone and lymph node metastases (3.2%), and four patients had numerous metastases not involving the liver (lung and bone, lung and brain, multisite involving lung, multisite not involving lung; 6.5%). In summary, 20 patients had no recurrence, 33 had recurrences involving the liver, and 29 showed non-liver recurrences (23 lung-only recurrences and six extrahepatic-non-lung-only recurrences).

OS after 1, 3, and 5 years was 90.0%, 90.0%, and 90.0%, respectively, for patients without recurrence, 100.0%, 86.3%, and 60.1%, respectively, for patients with lung-only recurrences, and 90.9%, 58.8%, and 37.2%, respectively, for patients with liver recurrences (Fig. 3).

We conducted a conventional DFS survival analysis, which showed no clear association with female sex. However, KRAS mutation and CEA >80 μg/L consistently correlated with poorer DFS (Table S9).

Next, we analysed liver and lung-only recurrence risks (Table 4). In the liver recurrence model, higher risk was linked to pN2-positive lymph nodes, >10 nodules, KRAS mutation, and female sex. Right-sided primary tumour, CEA >80 μg/L, and PD also indicated increased risk, although with statistical uncertainty. In the lung recurrence model, KRAS mutation, CEA >80 μg/L, and largest diameter >5.5 cm were significant risk factors. Notably, some variables, including female sex, appeared inversely related to lung-only recurrence risk, suggesting sex-specific patterns, namely higher liver recurrence in women, but lower lung-only recurrence (Fig. 4 and Table 4).

Table S8 details post-LT treatments by sex and recurrence type. Treatment strategy was driven by recurrence location, not biological sex, and no substantial sex-based differences in treatment were observed despite differences in recurrence patterns.

Discussion

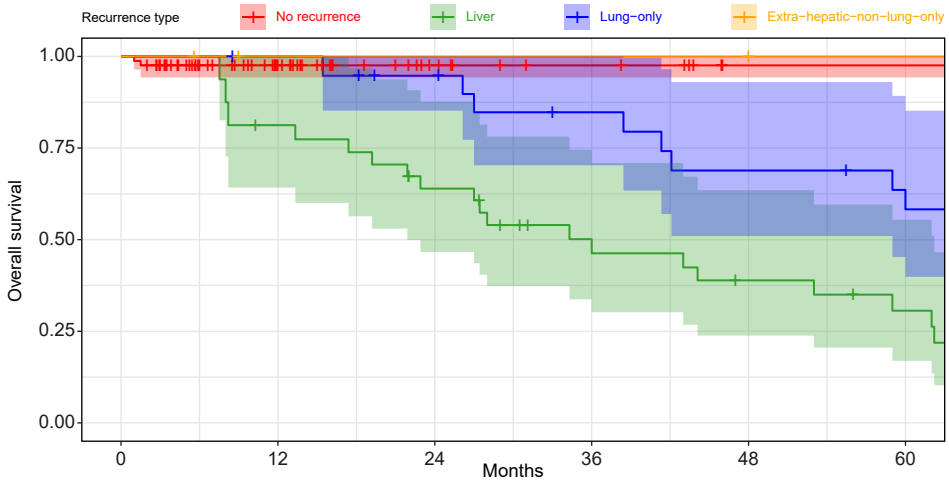
To our knowledge, this study includes the largest cohort of patients with CRLM undergoing LT published to date. It is also the first to conduct a multivariable survival analysis aimed at identifying independent aetiological predictors of post-transplant outcomes. Given the increasing interest in LT for CRLMs, especially following the publication of the TransMet trial,[11] our findings are of considerable clinical and scientific relevance.

Here, we reported the number and size of nodules based on the last available radiological assessment before LT. Although our cohort appears to differ from that of the TransMet trial, particularly in terms of the initial tumour burden, these differences can be largely explained by methodological distinctions. The TransMet trial presented imaging characteristics at the time of diagnosis or randomisation, whereas we focused on imaging immediately before LT. Moreover, the trial used a central radiological review, likely resulting in more accurate nodule characterisation.

Our results confirm the excellent OS associated with LT for CRLMs. The 5-year OS rate in our cohort was 55%, closely matching the 54% reported in the UNOS database.[22] Although this is somewhat lower than survival for traditional LT indications,[23] it compares favourably with other accepted indications, such as LT in patients >70 years of age, those with obesity, combined organ transplantation, or re-LT.[22]

Consistent with previous literature, our findings also highlight the weak correlation between OS and DFS, supporting the notion that DFS might not be a reliable marker of treatment efficacy in this context. The median time to recurrence was ~12 months. Thus, LT could serve to transform CRLM into a chronic disease for many patients, while offering the potential for long-term cure in a select group, particularly those who undergo successful treatment of lung metastases.[24–26]

A significant finding of this study is that two variables previously suggested as negative prognostic factors for LT in CRLM (PD and an interval of <24 months between surgery of



No. at risk						
No recurrence	82	38	16	11	5	5
Liver	0	17	19	13	10	7
Lung−only	0	12	18	15	13	12
Extra−hepatic−non−lung−only	0	2	3	2	2	1

Fig. 3. Time-varying overall survival curves according to the recurrence site. Recurrence type was considered a time-varying covariate. Compatibility with the null hypothesis: p <0.001. Lung only *vs.* no-recurrence, compatibility with the null hypothesis: p = 0.27. Liver *vs.* no recurrence, compatibility with the null hypothesis: null p = 0.03. Liver *vs.* lung only, compatibility with the null hypothesis: p = 0.05 (Kaplan–Meier compared with the log-rank test for the null hypothesis of no difference). Shaded areas represent 95% CIs.

Table 4. Multivariable cause-specific analyses (liver *vs.* lung recurrence).

	Hierarchical weighted Cox*			
Variables	**HR**		**95% CI**	**Null *p* value**
Risk of liver recurrence				
Female sex	1.8	0.9	3.8	0.11
Age >55 years	–	–	–	–
Oslo centre	–	–	–	–
Living donor	–	–	–	–
Previous liver therapy	–	–	–	–
BMI >25 kg/m^2	–	–	–	–
pN2	2.6	1.0	6.3	0.04
Right-sided CRC	2.0	0.7	5.3	0.18
Time ≤24 months	–	–	–	–
Progressive disease	1.7	0.7	3.9	0.24
Largest diameter >5.5 cm	0.7	0.3	1.6	0.46
No. of nodules >10	2.0	1.0	4.2	0.06
CEA >80 μg/L	2.0	0.7	6.0	0.22
KRAS mutated	2.1	0.9	5.2	0.11
Risk of lung recurrence				
Female sex	0.4	0.1	1.4	0.16
Age >55 years	0.6	0.3	1.6	0.36
Oslo	–	–	–	–
Living donor	–	–	–	–
Previous liver therapy	–	–	–	–
BMI >25 kg/m^2	–	–	–	–
pN2	1.3	0.4	4.2	0.6
Right location CRC	0.6	0.2	2.0	0.38
Time ≤24 months	–	–	–	–
Progressive disease	1.5	0.5	4.7	0.51
Largest diameter >5.5 cm	2.1	0.8	5.3	0.13
No. of nodules >10	1.3	0.5	3.2	0.54
CEA >80 μg/L	4.2	1.4	13	0.01
KRAS mutated	7.0	2.7	18	<0.001

Interval estimates and p-values are from the weighted Cox model (Wald Z-test). CEA, carcinoembryonic antigen; CRC, colorectal cancer; CRLM, colorectal metastasis; HR, hazard ratio; pN2, colorectal cancer with metastasis in four or more regional lymph nodes after colorectal surgery.

*The hierarchical model was realised by dividing the variables into four categories of importance, as shown in Files S2 and S3.

the primary tumour and LT [Oslo criteria[3]]) did not show strong independent associations in our multivariable analysis. High statistical uncertainty and relatively weak risk estimates compared with other variables limited their significance. By contrast, several other factors emerged as more consistent predictors of poorer post-LT outcomes: CEA levels >80 μg/L, right-sided primary tumour, largest nodule diameter >5.5 cm, KRAS mutation, presence of four to nine positive lymph nodes, and >10 liver metastases (Table 2). These findings align with established knowledge of tumour biology and support the continued evaluation of these variables in refining prognostic models.

Despite their clinical utility, such categorical thresholds should not be applied rigidly. For example, a nodule diameter of 5.49 cm *vs.* 5.51 cm should not lead to categorically different clinical decisions. Similarly, BMI >25 kg/m^2 might have prognostic relevance according to our hierarchical model (File S2), warranting further exploration.

Given that many patients do not fully meet existing LT criteria, a better understanding of the individual predictive value of each factor is essential. Notably, previous liver-directed therapies appeared to have a potential protective effect, whereas treating the interval from primary surgery to LT as a continuous variable could enhance prognostic accuracy, an area requiring further research. By contrast, CEA was more reliably analysed as a categorical variable because of its skewed distribution and outliers.

Another unexpected observation was the potential prognostic impact of female sex, especially when combined with KRAS mutation and the largest nodule diameter >5.5 cm (Fig. 2 and Table 3). This suggests that women experience worse outcomes under certain biological conditions, possibly requiring sex-specific selection strategies for LT. However, this finding might reflect statistical fluctuation resulting from limited external

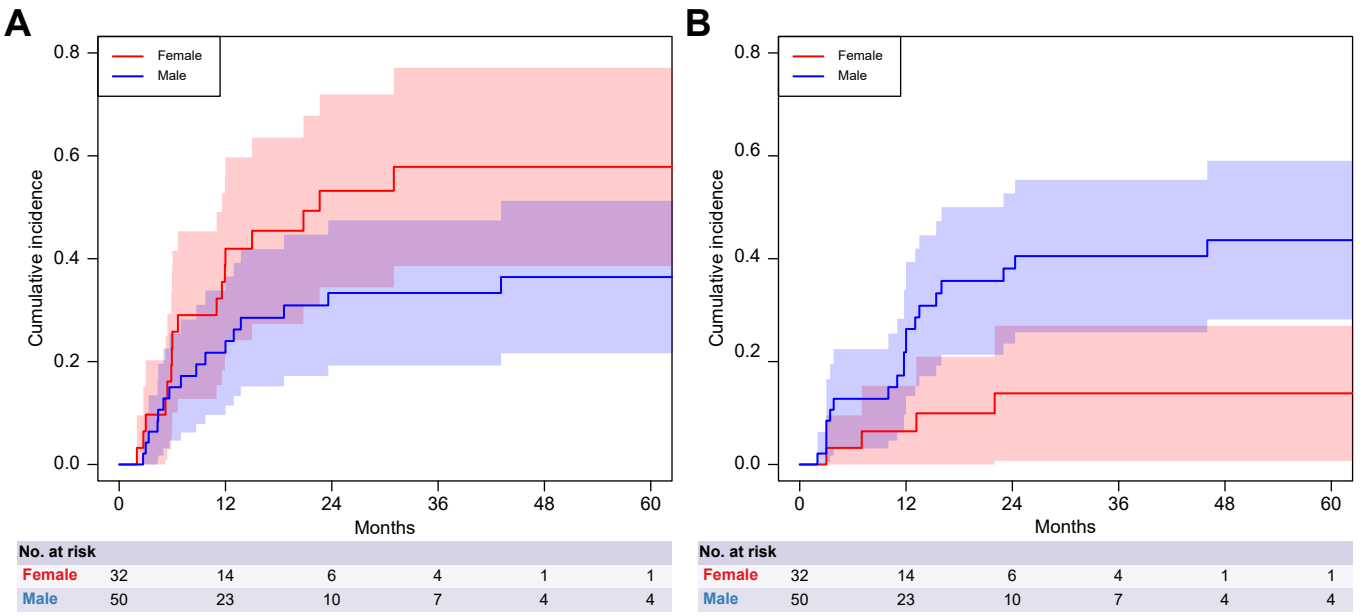


Fig. 4. Cumulative incidence of liver and lung-only recurrences according to sex, accounting for competing risks. (A) Cumulative incidence of liver-only recurrence in men *vs.* women. (B) Cumulative incidence of lung-only recurrence in men *vs.* women. At 60 months, the cumulative incidence of liver recurrence was 58% in women and 36% in men (Gray's test null $p = 0.07$), and the cumulative incidence of lung-only recurrence was 14% in women and 44% in men (Gray's test null $p = 0.01$). Shaded areas represent 95% CIs.

validity. It underscores the need for future research to investigate potential oncogenetic and epidemiological mechanisms before implementing changes in clinical practice. Here, we outline several such hypotheses to be explored in subsequent studies.

Sex-related differences in CRC and its CRLM might result from both biological (sexual dimorphism) and non-biological (sociobehavioural) factors. Globally, women show a lower age-standardised incidence and mortality from CRC compared with males, who also have a higher cumulative risk.[27] CRC incidence increases with age, particularly after 50, although recent years have seen a relative rise in younger adults (20–40 years), despite their smaller absolute numbers.[28] Sex hormones significantly influence CRC initiation and progression, with effects that vary by age. Premenopausal women generally have better survival rates compared with age-matched men,[29] whereas women over 65 often have poorer outcomes, potentially because of later-stage diagnosis or more aggressive tumour biology.[30–32]

Women also present more frequently with right-sided tumours and BRAF mutations, both associated with a worse prognosis.[33] Sexual dimorphism affects tumour pathways, including Wnt/β-catenin signalling, hypoxia response, ion channel expression, and X-linked genes.[34] Sex-based differences have also been observed in treatment response, such as with circadian chemotherapy and anti-tumour immunity.[35,36] However, consistent sex-specific survival differences following liver resection for CRLM have not been consistently reported and are not evident in registries such as the LiverMet Survey.[37]

This study was not designed to uncover the mechanisms behind sex differences in post-LT outcomes, but does offer potential insights (Fig. 4). Women experienced liver recurrence more often than men, a pattern associated with worse prognosis compared with no-liver recurrence (Fig. 3). This might also explain why large metastasis size had a more negative impact in women.

One hypothesis involves sex-specific immunology: the female immune system tends towards greater immune tolerance, likely as an evolutionary adaptation for pregnancy.[38] Oestrogens enhance this tolerance, particularly by promoting regulatory T cell activity, which dampens anti-tumour immunity.[39] This is especially relevant in the liver, an oestrogen-sensitive organ. Preclinical studies suggest that oestrogens facilitate the development of an immunosuppressive microenvironment that favours liver metastasis growth, an effect reversible by ovariectomy or oestrogen antagonists.[9] Clinically, oestrogen receptor expression in CRC has been linked to increased tumour angiogenesis, proliferation, and migration. These mechanisms could explain why women with active oestrogen signalling are more prone to liver metastases compared with men, especially in younger age groups.[34,36,40–42] The worse prognosis of younger women aligns with this hypothesis (Table 3). Consequently, women might experience fewer lung-only recurrences, given that recurrence categories are mutually exclusive.

These findings support the hypothesis of oestrogen-mediated liver tropism in women and suggest a need for further investigation. Future research should explore the inclusion of circulating tumour cells (CTCs) and circulating tumour DNA (ctDNA) in LT candidate assessments. These biomarkers could help refine patient selection, monitor treatment response, and better understand disease behaviour.[43] In addition, expanded genetic profiling, covering mutations in RAS, RAF, P53, and hormonal receptor status, could enhance prognostic accuracy and prediction of disease progression after LT.[44]

Non-biological factors might also contribute to sex-related differences in outcomes. Studies show that female patients are less likely to undergo liver resection for CRLM.[45,46] This trend is evident in large registries, including the LiverMet Survey.[37] For example, Ljunggren *et al.*[46] reported that women

received 23% less metastatic surgery and had slightly higher post-diagnosis mortality. The cause of this disparity remains unclear. Importantly, given that survival outcomes after resection showed no significant sex-based differences, these findings might indicate preselection bias that disadvantages women. In our cohort, comprising exclusively patients with unresectable disease, such bias could have influenced who was referred for LT consideration.

It is essential to clarify that this study does not suggest excluding women from LT for CRLMs. Our findings are exploratory and require validation in larger, dedicated cohorts. Moreover, it is not appropriate to assume that data derived from predominantly male cohorts can be directly applied to women. Many clinical trials, both historical and recent, disproportionately enrol male participants,[47] introducing potential sex bias in research and treatment approaches across various specialities, including gastroenterology and hepatology.[48]

Publication bias and statistical limitations might further obscure true sex-related differences in outcomes.[49,50] Given these concerns, our study highlights the need for more inclusive research and calls attention to potential sex-specific prognostic factors in LT for CRLMs. Ultimately, our aim is to support the development of more equitable and precise patient selection strategies that consider both biological and non-biological differences, ensuring that all eligible patients, regardless of sex, have access to potentially curative therapies.

Limitations and implications

Our analysis could not differentiate between synchronous and metachronous metastases because of the strong asymmetry in the synchronous CRLM distribution variable. In addition, the lack of PET/CT data limited the depth of our analysis and might have introduced bias. The small sample size, limited understanding of biological sex- or gender-related mechanisms, and potential residual confounding prevented us from establishing any causal link between sex and LT outcomes in CRLMs. Further studies with better control of uncertainties and a focus on biological mechanisms are needed. Integrating previous knowledge into future models will improve their robustness. Sparse-data bias is a concern with small cohorts, but the alignment between penalised and non-penalised models, along with credible HR estimates, suggests this risk is limited.[15,51] Although the long study period broadens the scope, it introduces variability resulting from evolving patient selection and treatment practices. Future research should focus on more recent cohorts to enhance comparability and relevance. Despite these limitations, our cohort is larger than those informing current guidelines, highlighting the importance of sharing our findings. Future studies should refine prognostic models by improving discrimination, calibration, and variable categorisation, ideally using continuous variables where appropriate.

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Abbreviations

AICc, corrected Akaike information criterion; CEA, carcinoembryonic antigen; CRC, colorectal cancer; CRLM, colorectal cancer liver metastases; CT, computed tomography; CTCs, circulating tumour cells; ctDNA, circulating tumour DNA; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LASSO, least absolute shrinkage and selection operator; LDLT, living donor liver transplants; LT, Liver transplantation; MRI, magnetic resonance imaging; MTV, metabolic tumour volume; OS, overall survival; PD, progressive disease; PET, positron emission tomography; PS, performance status.

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Conflicts of interest

All authors have completed the Unified Competing Interest form and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have had an interest in the submitted work over the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

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

Authors' contributions

Conceptualisation and methodology: AV, JL, UC, PDL. Provision of study resources: JL, UC, MC, MS, FA, BE, LC, SI, VM, CS, RHA, KT, MH, SD, PDL. Data curation: AV, JL, IB. Formal analysis: AV, IB, AR, MAM.

Investigation: AV, JL, UC, SD, PDL. Project administration: JL, PDL. Supervision: UC, PDL. Validation: AV, AR, MAM. Visualisation: AV, JL. Writing – original draft: AV, JL. Writing – review and editing: AV, JL, UC, AR, SD, PDL. Final approval of manuscript: All authors. AV, JL, and PDL had full access to all the data in the study and verified the data. All authors had final responsibility for the decision to submit for publication. The corresponding author attests that all listed authors meet authorship criteria and that all others meeting the criteria have been included.

Data availability

Data collected for the study, including individual participant data and a data dictionary defining each field in the set, are available from the corresponding author on reasonable request, as are deidentified participant data and a data

dictionary. No additional documents will be available. Data will be available from the publication date until December 2034. Data will be shared with consultants, clinicians, and researchers with PhDs for retrospective cohort studies after approval of a proposal and a signed data access agreement. We may balance the potential benefits and risks for each request and then provide the data that can be shared.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2025.101505.

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Author names in bold designate shared co-first authorship

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