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ORIGINAL SCIENTIFIC REPORT

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Preoperative identification of early extrahepatic recurrence after hepatectomy for colorectal liver metastases: A machine learning approach

Jun Kawashima[1,2] | Yutaka Endo[3] | Selamawit Woldesenbet[1] | Odysseas P. Chatzipanagiotou[1] | Diamantis I. Tsilimigras[1] | Giovanni Catalano[1,4] | Muhammad Muntazir Mehdi Khan[1] | Zayed Rashid[1] | Mujtaba Khalil[1] | Abdullah Altaf[1] | Muhammad Musaab Munir[1] | Alfredo Guglielmi[4] | Andrea Ruzzenente[4] | Luca Aldrighetti[5] | Sorin Alexandrescu[6] | Minoru Kitago[7] | George Poultsides[8] | Kazunari Sasaki[8] | Federico Aucejo[9] | Itaru Endo[2] | Timothy M. Pawlik[1]

[1]Department of Surgery, The Ohio State University Wexner Medical Center and James Comprehensive Cancer Center, Columbus, Ohio, USA

[2]Department of Gastroenterological Surgery, Yokohama City University School of Medicine, Yokohama, Japan

[3]Department of Surgery, University of Rochester, Rochester, New York, USA

[4]Department of Surgery, University of Verona, Verona, Italy

[5]Department of Surgery, Ospedale San Raffaele, Milan, Italy

[6]Department of Surgery, Fundeni Clinical Institute, Bucharest, Romania

[7]Department of Surgery, Keio University, Tokyo, Japan

[8]Department of Surgery, Stanford University, Stanford, California, USA

[9]Department of General Surgery, Cleveland Clinic Foundation, Cleveland, Ohio, USA

Correspondence

Timothy M. Pawlik, Department of Surgery, The Urban Meyer III and Shelley Meyer Chair for Cancer Research, The Ohio State University, Wexner Medical Center, 395 W. 12th Ave., Suite 670, Columbus, OH, USA.
Email: Tim.Pawlik@osumc.edu

Abstract

Background: Machine learning (ML) may provide novel insights into data patterns and improve model prediction accuracy. The current study sought to develop and validate an ML model to predict early extra-hepatic recurrence (EEHR) among patients undergoing resection of colorectal liver metastasis (CRLM).

Methods: Patients with CRLM who underwent curative-intent resection between 2000 and 2020 were identified from an international multi-institutional database. An eXtreme gradient boosting (XGBoost) model was developed to estimate the risk of EEHR, defined as extrahepatic recurrence within 12 months after hepatectomy, using clinicopathological factors. The relative importance of factors was determined using Shapley additive explanations (SHAP) values.

Results: Among 1410 patients undergoing curative-intent resection, 131 (9.3%) patients experienced EEHR. Median OS among patients with and without EEHR was 35.4 months (interquartile range [IQR] 29.9–46.7) versus 120.5 months (IQR 97.2–134.0), respectively ($p < 0.001$). The ML predictive model had c-index values of 0.77 (95% CI, 0.72–0.81) and 0.77 (95% CI, 0.73–0.80) in the entire dataset and the validation data set with bootstrapping resamples, respectively. The SHAP algorithm demonstrated that T and N primary tumor categories, as well as tumor burden score were the three most important predictors of EEHR. An easy-to-use risk calculator for EEHR was developed and made available online at: https://junkawashima.shinyapps.io/EEHR/.

Conclusions: An easy-to-use online calculator was developed using ML to help clinicians predict the chance of EEHR after curative-intent resection for

CRLM. This tool may help clinicians in decision-making related to treatment strategies for patients with CRLM.

KEYWORDS
colorectal liver metastasis, early recurrence, extrahepatic recurrence, machine learning, online calculator, predictive model

1 | INTRODUCTION

Over the last 2 decades, the indications for surgical treatment of advanced colorectal liver metastases (CRLM) have expanded.[1] In light of these expanded indications, individuals who undergo curative-intent hepatectomy for advanced CRLM can be at higher risk of recurrence, with some estimates as high as 50%–70%.[2] The National Comprehensive Cancer Network guideline recommends several treatment options for recurrent CRLM including re-resection, local therapy, and systemic chemotherapy.[3] Among these treatment options, repeat hepatectomy remains a safe treatment approach that can improve long-term outcomes.[4] However, patients with recurrent extrahepatic recurrences (EHR) are often not considered eligible for repeat surgical treatment given the presumed negative prognosis.[5,6] In fact, a subset of patients who undergo hepatectomy for CRLM will experience early EHR (EEHR), suggesting they likely had undetected systemic disease at the time of hepatectomy.[6–11] Given the efficacy of chemotherapy to extend OS for advanced CRC, some investigators have questioned whether initial surgical treatment of CRLM is warranted for patients at high risk of EEHR.[6] Although several studies have examined risk factors associated with early recurrence (ER) following hepatectomy, risk factors for EEHR after CRLM resection have received less attention and are still unclear.[6,9,12] To our knowledge, there is no preoperative tool to predict EEHR risk among patients undergoing curative-intent resection for CRLM.

To date, most predictive models have utilized conventional statistical techniques and have not included novel machine learning (ML) methods, which are more adept at analyzing intricate, high-dimensional datasets.[13] The use of ML to incorporate preoperative data may provide novel insights into comprehending intricate data patterns and improve model prediction accuracy.[14] Therefore, the aim of this study was to develop and validate an ML model (i.e., eXtreme gradient boosting [XGBoost] algorithm) to predict EEHR based on factors known before surgery using a large international multi-institutional database. Furthermore, to facilitate the clinical applicability of the model, we sought to provide an easy-to-use online calculator to predict the risk of EEHR.

2 | METHODS

2.1 | Study population and data collection

Patients treated with curative-intent hepatectomy for CRLM between 2000 and 2020 were identified from an international multi-institutional database Supplemental Table S1.[15] The study was approved by the institutional review board in each participating institution. Data were collected on age, sex, Charlson comorbidity index (CCI), year of surgery, primary tumor location, T and N category based on the 8th version of AJCC staging system.[16] Information on KRAS and BRAF mutational status, timing of CRLM manifestation (i.e., synchronous, metachronous), disease-free interval (DFI), carcinoembryonic antigen (CEA) levels at the time of CRLM diagnosis, receipt of neoadjuvant chemotherapy (NAC), tumor burden score (TBS), the extent of hepatectomy, margin status, severe complications after hepatectomy, and adjuvant chemotherapy after hepatectomy was also collected (Supplemental Table S2).[4,17–20] EEHR was defined as extrahepatic recurrence after hepatectomy within less than 12 months.[21–24]

2.2 | Statistical analysis

Descriptive statistics were presented as median values (interquartile range [IQR]) and frequency (%) for continuous and categorical variables, respectively. Continuous variables were compared using the Mann–Whitney U or Kruskal–Wallis test, as appropriate. Categorical variables were compared with the χ^2 test or Fisher's exact test. Multiple imputations with chain equation procedures were utilized to handle missing values.[25] Survival was assessed using Kaplan-Meier curves and log-rank tests. Statistical significance was determined at $\alpha = 0.05$.

XGBoost-algorithm-powered survival model was developed to predict EEHR.[26] XGBoost, an advanced gradient-boosting framework, builds an ensemble of decision trees to enhance predictive accuracy.[27] Candidate variables were selected based on the previous literature, including primary tumor location, T and

N categories, KRAS status, DFI, CEA levels, administration of NAC, and TBS—all of which can be discerned in the preoperative period.[6,17,28–31] To reduce overfitting, a 10-fold cross-validation was employed on the entire cohort.[32] The process involved dividing the entire dataset randomly into 10 equal parts. For each iteration, 9 of these parts were used as the training cohort to build the model, while the remaining part served as the validation cohort to assess the model's performance. This procedure was repeated 10 times, ensuring that each part of the data was used as a validation cohort exactly once. Furthermore, after the model was developed using 10-fold cross-validation, internal validation through bootstrapping was performed. This process involved generating 5000 resampled datasets from the entire cohort and evaluating the model's performance across these resampled datasets. Shapley additive explanations (SHAP) values were used to interpret the relative weight of the different factors in the predictive model.[33] Subsequently, patients were stratified into low-, intermediate-, or high-risk for EEHR using the X-tile program.[34] An easy-to-use web application to calculate EEHR risk was made freely available.

Additional multivariable Cox proportional hazards analysis was performed to assess the association of the aforementioned factors with EEHR. The beta-coefficients of the risk factors significant on multivariate analysis ($p < 0.05$) were used to construct a risk score based on weighting of the composite factors. The proposed XGBoost-based predictive model and conventional predictive model developed by the multivariable Cox proportional hazards regression model were compared with a previous model including seven parameters (i.e., primary tumor location, AJCC T and N category, BRAF and KRAS status, tumor size, and tumor number).[6] Model discrimination was estimated using the area under the time-dependent receiver operating characteristic curve (time-dependent AUC) at 12 months following hepatectomy. Furthermore, to account for any possible period effect, additional sensitivity analyses were performed among patients who underwent liver resection only between 2011 and 2020. All statistical analyses were performed using R version 4.2.0 (R Project for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Patient characteristics

Among 1410 patients included in the analytic cohort, median patient age was 64.6 years (IQR 56.0–72.0), 858 (60.9%) patients were male, and median CCI was 7.0 (IQR 7.0–8.0) (Table 1). Overall, 559 (39.6%) patients had a left-sided colon cancer primary tumor with T2/3 ($n = 1007$, 71.4%) and N2 ($n = 715$, 50.7%) disease; a subset of patients ($n = 219$, 15.5%) had mutated KRAS status. Roughly one-half of the patients ($n = 747$, 53.0%) presented synchronous liver metastasis with a median CEA level of 10.5 ng/mL (IQR, 4.0–40.7) and a median TBS of 4.9 (IQR 3.3–6.9). Use of systemic chemotherapy was common in both the neoadjuvant ($n = 855$, 60.6%) and adjuvant ($n = 1,034$, 73.3%) settings (Table 1).

3.2 | Characteristics and survival of patients with EEHR

Overall, 631 (44.8%) patients experienced a recurrence following hepatic resection of CRLM, whereas 779 (55.2%) did not. Among the 631 patients who recurred, the recurrence was classified as an EEHR in 131 (20.7%) individuals (Table 1). After a median follow-up of 30.7 months (IQR 15.1–56.1), median and 5-year OS among patients with and without EEHR was 35.4 months (IQR 29.9–46.7) and 28.5% versus 120.5 months (IQR 97.2–134.0) and 70.9%, respectively (log-rank, $p < 0.001$) (Figure 1). Patients with EEHR were more likely to experience multi-site recurrence compared with patients who had late or other patterns of recurrence ($n = 85$, 64.9% vs. $n = 89$, 17.8%; $p < 0.001$). Initial recurrence patterns among patients with EEHR after hepatectomy for CRLM included lung-only recurrence in 18 (13.7%) patients and other single sites in 28 (21.4%) patients (Supplemental Table S3).

3.3 | Development and validation of the predictive model of EEHR

Based on factors available in the preoperative setting, a model to predict EEHR was developed using XGBoost statistical approach. The contributions of the different variables to predict EEHR following the resection of CRLM are presented in Figure 2. It is worth noting that the top contributors were primary tumor T and N categories, with T3/T4 diseases and N2 disease having the strongest influence on risk of EEHR (Figure 3). TBS was the third most important preoperative determinant of EEHR risk based on SHAP values (Figure 4). Patients who underwent upfront surgery tended to have lower TBS, whereas individuals treated with NAC tended to have higher TBS. The discriminative accuracy of the preoperative model based on these factors was very good in both the derivative (C index: 0.77; 95% CI, 0.72–0.80) and validation (C index: 0.77; 95% CI, 0.73–0.80) cohorts.

TABLE 1 Clinicopathological characteristics of the analytic cohort.

Characteristics	All patients $n = 1410$	Non EEHR $n = 1279$ (90.7%)	EEHR $n = 131$ (9.3%)	p value
Age, y, median (IQR)	64.6 (56.0–72.0)	65.0 (56.0–72.1)	59.0 (51.0–67.0)	<0.001
Sex, male, *n* (%)	858 (60.9)	774 (60.5)	84 (64.1)	0.48
CCI	7.0 (7.0–8.0)	7.0 (7.0–8.0)	7.0 (7.0–8.0)	0.38
Year of surgery, *n* (%)				0.88
2000–2010	412 (29.2)	375 (29.3)	37 (28.2)	
2011–2020	998 (70.8)	904 (70.7)	94 (71.8)	
Location of primary tumor, *n* (%)				<0.01
Right-sided colon	489 (34.7)	458 (35.8)	31 (23.7)	
Left-sided colon	559 (39.6)	507 (39.6)	52 (39.7)	
Rectum	362 (25.7)	314 (24.6)	48 (36.6)	
T category of primary tumor, *n* (%)				<0.001
T1/2	481 (34.1)	467 (36.5)	14 (10.7)	
T3/4	929 (65.9)	812 (63.5)	117 (89.3)	
N category of primary tumor, *n* (%)				<0.001
N0	303 (21.5)	271 (21.2)	32 (24.4)	
N1	715 (50.7)	671 (52.5)	44 (33.6)	
N2	392 (27.8)	337 (26.3)	55 (42.0)	
KRAS, *n* (%)				<0.001
Wild	488 (34.6)	468 (36.6)	20 (15.3)	
Mutated	219 (15.5)	196 (15.3)	23 (17.6)	
Unknown	703 (49.9)	615 (48.1)	88 (67.2)	
BRAF, *n* (%)				0.19
Wild	217 (15.4)	204 (15.9)	13 (9.9)	
Mutated	40 (2.8)	36 (2.8)	4 (3.1)	
Unknown	1153 (81.8)	1039 (81.2)	114 (87.0)	
Synchronous liver metastases, *n* (%)	747 (53.0)	667 (52.2)	80 (61.1)	0.06
DFI, *n* (%)				<0.001
<12 months	919 (65.2)	813 (63.6)	106 (80.9)	
≥12 months	491 (34.8)	466 (36.4)	25 (19.1)	
CEA, *n* (%)				0.04
≤100 ng/mL	698 (49.5)	635 (49.6)	63 (48.1)	
>100 ng/mL	121 (8.6)	102 (8.0)	19 (14.5)	
Unknown	591 (41.9)	542 (42.4)	49 (37.4)	
Neoadjuvant chemotherapy, *n* (%)	855 (60.6)	796 (62.2)	59 (45.0)	<0.001
TBS, median (IQR)	4.9 (3.3–6.9)	5.0 (3.3–7.0)	4.4 (3.2–6.1)	0.23
The extent of hepatectomy, *n* (%)				0.57
Minor	537 (69.9)	447 (69.8)	90 (70.3)	
Major	231 (30.1)	193 (30.2)	38 (29.7)	
Margin status, *n* (%)				0.04
$R = 0$	1229 (87.2)	1123 (87.8)	106 (80.9)	

(Continues)

TABLE 1 (Continued)

Characteristics	All patients *n* = 1410	Non EEHR *n* = 1279 (90.7%)	EEHR *n* = 131 (9.3%)	*p* value
R = 1	181 (12.8)	156 (12.2)	25 (19.1)	
Severe complications, *n* (%)	1248 (88.5)	1135 (88.7)	113 (86.3)	0.48
Adjuvant chemotherapy, *n* (%)	1034 (73.3)	953 (74.5)	81 (61.8)	<0.01

Abbreviations: CCI, Charlson Comorbidity Index; CEA, Carcinoembryonic antigen; DFI, Disease-free interval; EEHR, Early extrahepatic recurrence; TBS, Tumor burden score.

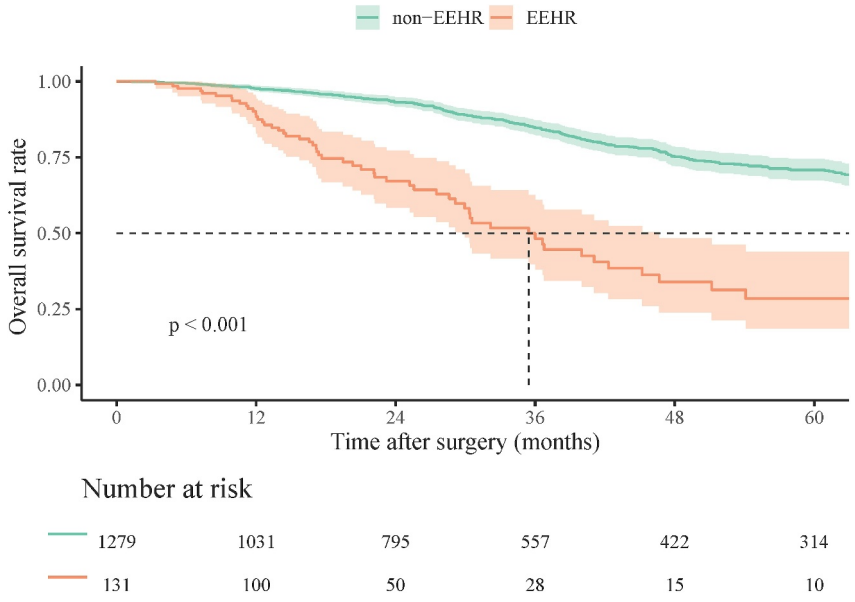

FIGURE 1 Kaplan–Meier curves demonstrating the differences in overall survival between patients with and without early extrahepatic recurrence (early extra-hepatic recurrence). [Colour figure can be viewed at wileyonlinelibrary.com]

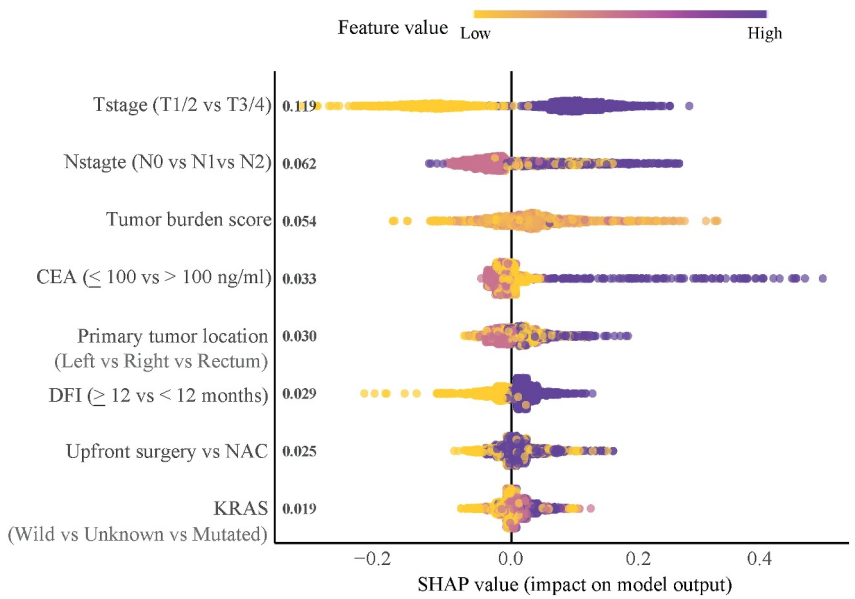

FIGURE 2 Shapley additive explanation (SHAP) summary. [Colour figure can be viewed at wileyonlinelibrary.com]

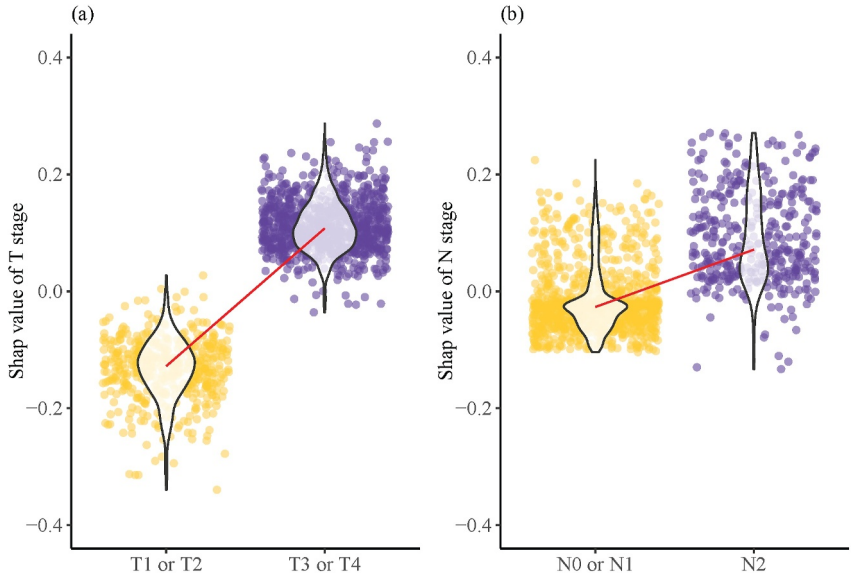

FIGURE 3 Violin plots demonstrating the relationships between Shapley additive explanation (SHAP) value and (A) T category or (B) N category. [Colour figure can be viewed at wileyonlinelibrary.com]

3.4 | Categorizing the risk groups and developing an online calculator

Based on the preoperative EEHR model, patients were categorized into three distinct risk groups using the X-tile program relative to extrahepatic RFS [EHRFS]: low-risk group (n = 642, 45.5%, 12-month EHRFS: 97.2%), intermediate-risk group (n = 622, 44.1%, 12-month EHRFS: 87.0%), and high-risk group (n = 146, 10.4%, 12-month EHRFS: 50.7%) (log-rank, $p < 0.001$) (Figure 5A). Patients were also stratified relative to OS: low-risk group (5-year OS: 83.3%), intermediate-risk group (5-year OS; 53.8%), and high-risk group (5-year OS; 29.6%) (log-rank, $p < 0.001$) (Figure 5B). To facilitate the clinical applicability of the preoperative model, a convenient online calculator to predict EEHR of CRLM patients following curative-intent surgery was constructed and made available at https://junkawashima.shinyapps.io/EEHR/ (Supplemental Figure S2).

In the Cox proportional hazards regression model, primary rectal cancer (HR 1.71, 95% CI 1.15–2.55), T3/4 stage of primary tumor (HR 4.06, 95% CI 2.31–7.14), N2 disease associated with the primary tumor (HR 1.64, 95% CI 1.05–2.56), KRAS unknown type (HR 2.80, 95% CI 1.52–5.16), KRAS mutated type (HR 2.87, 95% CI 1.71–4.82), DFI <12 months (HR 2.13, 95% CI 1.38–3.31), and CEA >100 ng/mL (HR 1.92, 95% CI 1.13–3.26) remained adverse independent preoperative predictors of EEHR (Supplemental Table S4). The beta-coefficients of these factors were utilized to develop a conventional predictive model. The conventional predictive model was evaluated with a C-index of 0.75 (95% CI, 0.71–0.79) for the entire dataset and 0.75 (95% CI, 0.72–0.78) for the validation dataset with bootstrapping resamples; the model was included to the online calculator.

It is worth noting that the predictive accuracy of the Wensink et al.'s[8] EEHR model (c-index: 0.65, 95% CI 0.61–0.70) did not perform as well as the ML model proposed in the current study (C index: 0.77; 95% CI, 0.72–0.80). In fact, the 12-month time-dependent AUC for the Wensink et al. preoperative predictive model was only 0.66 (95% CI 0.61–0.71) versus 0.81 (95% CI 0.76–0.85) for the proposed ML EEHR predictive tool and 0.77 (95% CI 0.73–0.81) for the proposed conventional EEHR predictive tool ($p < 0.001$, respectively) (Supplemental Figure S3).

A sensitivity analysis was performed to examine whether the predictive ML model had consistent discriminating power irrespective of the time period. It is worth noting that the predictive model classified patients who underwent surgery between 2011 and 2020 into 3 distinct risk groups with the results being largely unchanged (log-rank, $p < 0.001$) (Supplemental Figure S4).

4 | DISCUSSION

Following hepatectomy of CLRM, individuals who experience an intrahepatic-only recurrence may be candidates for repeat hepatectomy/ablation to improve their long-term prognosis.[4,35–39] In contrast, patients who have an EHR as a component of their recurrence pattern are less likely to be candidates for local therapy and have worse prognosis.[6–11] An ER after hepatectomy for CRLM has been associated with a particularly poor prognosis.[6,9,12] In turn, there has been interest in

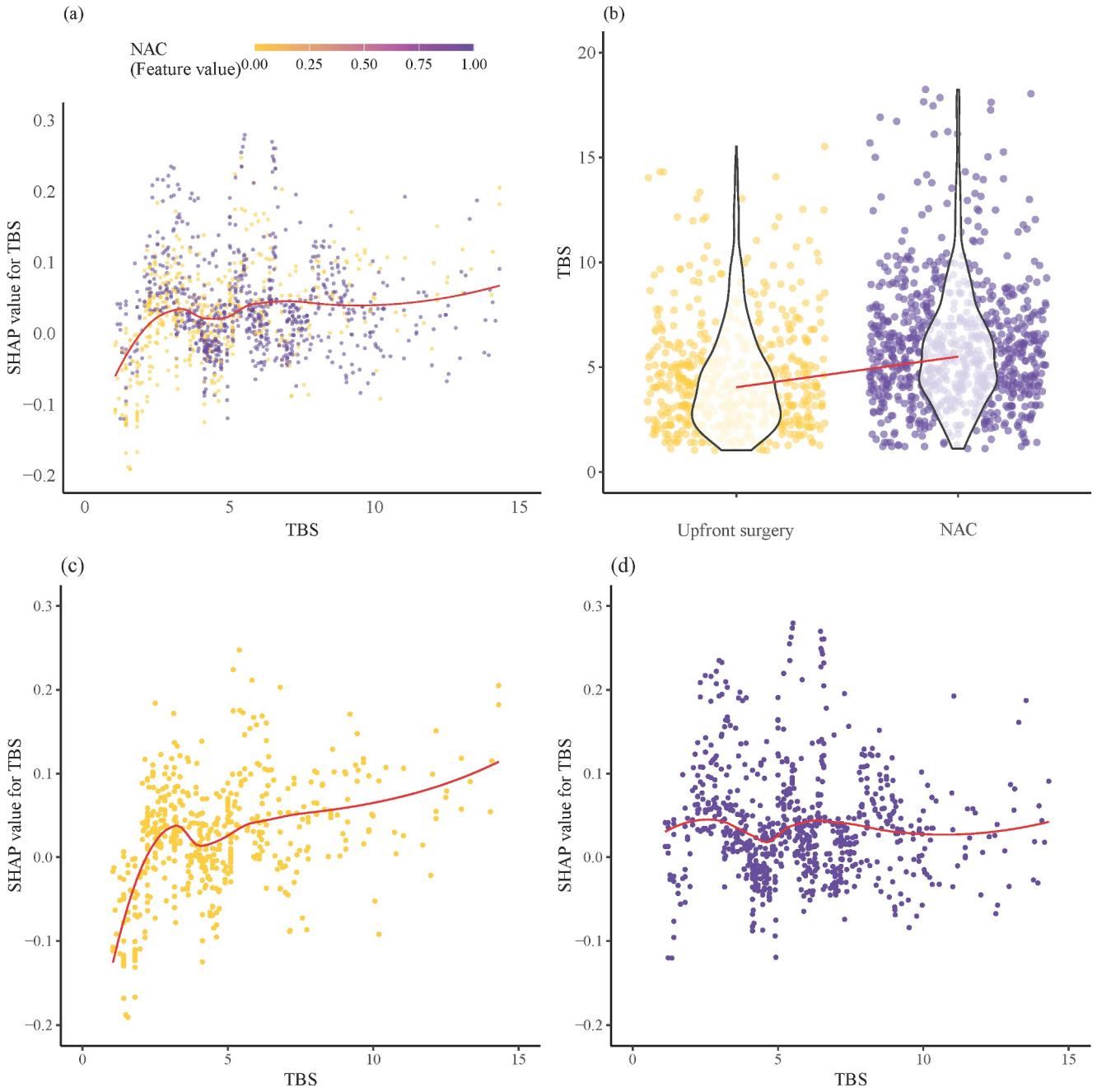

FIGURE 4 (A) Shapley additive explanation (SHAP) dependence plot showing the contribution of tumor burden score (TBS). The color represents the upfront surgery or neoadjuvant chemotherapy (NAC) for each observation. (B) Violin plots demonstrating the relationships between TBS and SHAP value. (C) SHAP dependence plot showing the contribution of TBS among patients with upfront surgery. (D) SHAP dependence plot showing the contribution of TBS among patients with NAC. [Colour figure can be viewed at wileyonlinelibrary.com]

identifying patients at highest risk of ER, as these patients may be served better by perioperative chemotherapy and/or systemic therapy alone.[6,40–42] Specifically, accurate identification of individuals at high risk of EEHR can help to risk stratify patients, as well as select patients who may benefit from systemic chemotherapy and guide surveillance. Wensink et al. had proposed a predictive model for EEHR, which used conventional Cox regression analysis.[6] The current study was important because we developed and validated a preoperative predictive model to calculate risk of EEHR using an ML approach that leveraged data from a large, international cohort of patients. Using this artificial intelligence predictive model, patients were categorized into low-risk, intermediate-risk, and high-risk groups who had an incrementally worse 12-month EHRFS (97.2%, 87.0%, 50.7%, respectively; log-rank, $p < 0.001$). Additionally, an online calculator based on

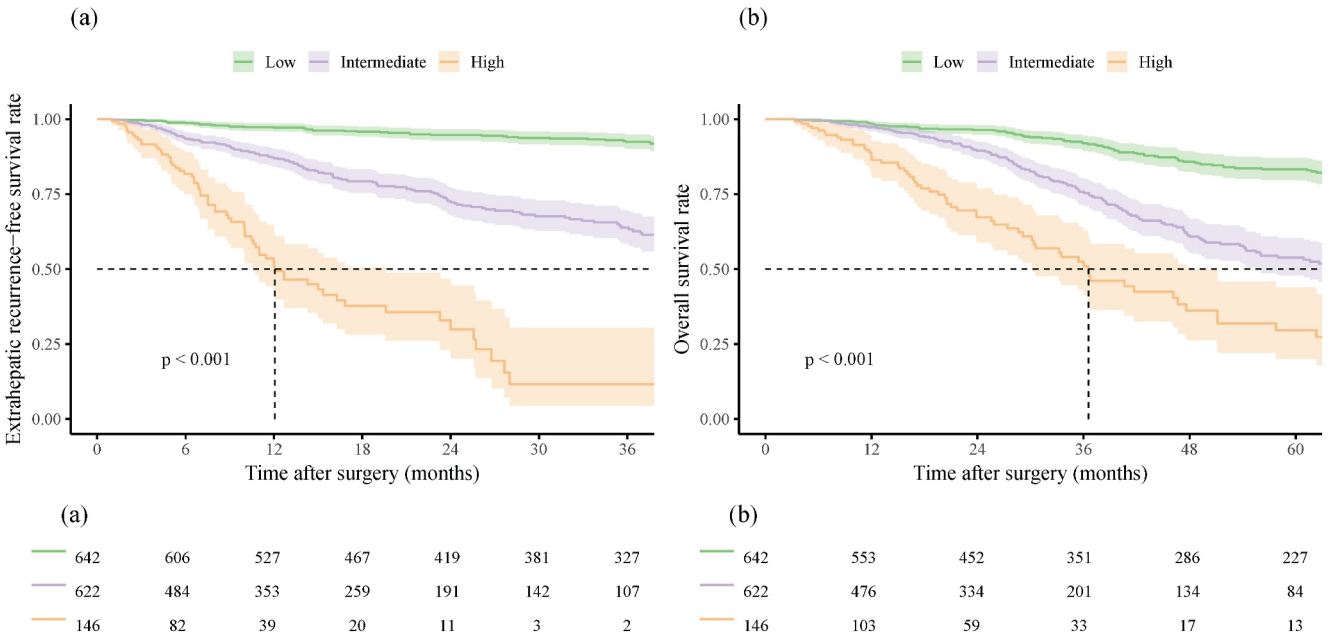

FIGURE 5 Kaplan–Meier curves demonstrating the differences in (A) recurrence-free survival and (B) overall survival curve among low-, intermediate-, and high-risk patients for early extrahepatic recurrence. [Colour figure can be viewed at wileyonlinelibrary.com]

preoperative factors was developed that physicians can easily access to individualize EEHR risk among patients undergoing CRLM resection. To the best of our knowledge, this is the first study to provide a preoperative ML predictive tool to assess the likelihood of EEHR among patients undergoing curative-intent surgery for CRLM.

It is worth noting that almost 1 in 10 patients (9.3%) who underwent curative-intent hepatectomy for CRLM experienced EHR within 12 months. This cohort of individuals had a much worse OS than patients with other recurrence patterns (Supplemental Figure S1), which was consistent with the previously published data.[6–11,43] Wensink et al. had previously reported that patients who experienced EHR had a median overall survival of 19.5 months, which was worse than the 35.4 months reported in the current study for patients with EEHR.[6] The reason for these disparate results may be related to the definition of "early" recurrence, which was within 6 months in the study by Wensink et al. versus 12 months in the current study.[6] In turn, patients who experienced a "very early" recurrence likely had even worse tumor biology. Notwithstanding these differences, the aggregate data clearly demonstrated that patients with EHR have a poor prognosis.[6–11] Interestingly, in the current study, more than 60% of patients with EEHR had multi-site recurrence (Supplemental Table S3). Patients with multi-site recurrence are less likely to be candidates for repeat resection, and have a worse prognosis than patients with intrahepatic only or lung only recurrence.[44,45] Although routine use of perioperative chemotherapy remains somewhat debated, perioperative chemotherapy has been associated with a lower risk of recurrence compared with hepatectomy alone for CRLM.[46,47] As such, patients at high risk of EEHR may benefit more from early preoperative utilization of systemic chemotherapy to assess tumor biology better. The online calculator may be beneficial as an adjunctive tool to inform the use of perioperative systemic chemotherapy, as well as intensity of postoperative surveillance among patients at high risk of EEHR.

It is worth noting that T and N categories, as well as TBS, CEA levels, and primary tumor location, were preoperative factors that significantly impacted risk of EEHR based on the ML XGBoost model. The T category of the primary tumor was among the most important preoperative factors associated with the risk of ER, as well as extrahepatic pattern of recurrence. Consistent with this finding, Vigano et al. had reported that T3 or T4 primary disease was associated with a roughly two-fold higher risk of ER, following CRLM hepatectomy.[9] In another study, Kawaguchi et al. reported that the T3 or T4 category was associated with 40% increased hazard of after resection of CRLM.[48] Interestingly, in the study by Wensink et al. that focused specifically on EEHR, T4 primary tumor status was the second most predictive factor of ER after BRAF mutation.[6] Likewise, several studies have demonstrated that lymph node metastasis was a powerful negative prognostic factor.[48–52] In the current study, primary tumor N2 disease had a higher SHAP value than N1 or N0 categories. Hokuto et al. reported that patients with CRLM who had N2 disease associated with the primary

tumor were almost three-fold more likely to have an unresectable recurrence.[51] Moreover, Kato et al. demonstrated that the extent of primary tumor lymph node involvement strongly correlated with the risk of recurrent lung metastases.[52] ML identified TBS as the third most powerful factor to predict EEHR. Proposed by Sasaki et al., TBS serves as a composite score of tumor burden and has become widely adopted as an easy-to-use prognostic parameter.[18,53–55] In the current study, TBS had SHAP values that were nonlinear; specifically, among patients with an overall low TBS, the SHAP value increased as TBS increased. However, among patients with a high TBS at baseline, SHAP values did not change as TBS increased (Figure 4). It is worth noting that patients with high TBS were more likely to receive NAC likely explaining in part why higher TBS values were not associated with changes in SHAP values relative to prognosis.

The proposed XGBoost-based predictive model demonstrated very good discriminative accuracy for the entire cohort (c-index: 0.77; 95% CI, 0.72–0.80), as well as the bootstrapped resampled internal cohort (c-index: 0.77; 95% CI, 0.73–0.80). Moreover, the model stratified patients incrementally into three distinct groups relative to EERH and OS: low-risk group (12-months EHRFS: 97.2%, 5-year OS: 83.3%), intermediate-risk group (12-months EHRFS: 87.0%, 5-year OS: 53.8%), and high-risk group (12-months EHRFS: 50.7%, 5-year OS: 29.6%) (Figure 5). Recently, ML approaches have gained popularity for analyzing vast quantities of data to reveal patterns and trends that may not be readily apparent to people or identifiable by conventional statistical methods.[32] The improved performance of the XGBoost model likely derived from its decision tree architecture, which had the ability to independently capture nuanced relationships between variables.[27] Moreover, the XGBoost statistical approach may be superior to other ML techniques in terms of prediction accuracy.[33,56] For example, XGBoost-based models have been used to predict risk of cardiac surgery-associated acute kidney damage (CSA-AKI) and postoperative pancreatic fistula with high discriminatory accuracy.[27,57] In the current study, the proposed XGBoost-based predictive model outperformed the conventional model reported by Wensink et al. with respect to both c-index and time-dependent AUC, even though both models included common variables such as primary tumor location, T and N categories, tumor size, and tumor number (Supplemental Figure S3).[6]

The results of the current study should be interpreted in light of several limitations. Even though the multi-institutional nature of the database was a strength, the data may have been subject to selection biases (e.g., operative procedure and perioperative chemotherapy). Although the risk score to predict EEHR performed well in the entire cohort, as well as the bootstrapping resampled internal cohort, future studies should seek to externally validate the model. Response to preoperative therapy was not examined as a predictive risk factor. The cohort included patients who did and did not receive preoperative chemotherapy, making it difficult to evaluate the independent impact of chemotherapy response on EEHR. Additionally, due to limitations in the dataset, detailed information on the specific patterns of recurrence was not available. Although the study demonstrated that patients with EEHR generally experienced a poor prognosis, certain subgroups within the EEHR population with certain patterns of recurrence may have different prognoses. Future studies should examine recurrence patterns relative to other prognostic factors, as well as overall prognosis.

In conclusion, patients with EEHR after curative-intent surgery for CRLM had a markedly worse prognosis. An easy-to-use predictive tool based on the ML approach was made available online to predict the risk of EEHR using readily available clinicopathological variables. This online calculator may help risk stratify patients relative to EEHR risk and inform clinical decisions around perioperative treatment of patients being considered for CRLM resection.

AUTHOR CONTRIBUTIONS

Jun Kawashima: Conceptualization; data curation; formal analysis; investigation; methodology; resources; validation; visualization; writing—original draft; writing—review and editing. **Yutaka Endo**: Methodology; writing — review and editing. **Selamawit Woldesenbet**: Conceptualization; methodology; writing—review and editing. **Odysseas P. Chatzipanagiotou**: Conceptualization; methodology. **Diamantis I. Tsilimigras**: Conceptualization; methodology. **Giovanni Catalano**: Conceptualization; methodology. **Muhammad Muntazir Mehdi Khan**: Conceptualization; methodology. **Zayed Rashid**: Conceptualization; methodology. **Mujtaba Khalil**: Conceptualization; methodology. **Abdullah Altaf**: Conceptualization; methodology. **Muhammad Musaab Munir**: Conceptualization. **Alfredo Guglielmi**: Data curation. **Andrea Ruzzenente**: Data curation. **Luca Aldrighetti**: Data curation. **Sorin Alexandrescu**: Data curation. **Minoru Kitago**: Data curation. **George Poultsides**: Data curation. **Kazunari Sasaki**: Data curation. **Federico Aucejo**: Data curation. **Itaru Endo**: Data curation. **Timothy M. Pawlik**: Conceptualization; data curation; methodology; supervision; writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

ETHICS STATEMENT

The study was reviewed and approved by the Institutional Review Board and was compliant with research ethics standards.

ORCID

Muhammad Muntazir Mehdi Khan https://orcid.org/0000-0001-7196-2328
Timothy M. Pawlik https://orcid.org/0000-0002-7994-9870

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