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A Pre-TACE Radiomics Model to Predict HCC Progression and Recurrence in Liver Transplantation: A Pilot Study on a Novel Biomarker

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Background. Despite transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC), a significant number of patients will develop progression on the liver transplant (LT) waiting list or disease recurrence post-LT. We sought to evaluate the feasibility of a pre-TACE radiomics model, an imaging-based tool to predict these adverse outcomes. **Methods.** We analyzed the pre-TACE computed tomography images of patients waiting for a LT. The primary endpoint was a combined event that included waitlist dropout for tumor progression or tumor recurrence post-LT. The radiomic features were extracted from the largest HCC volume from the arterial and portal venous phase. A third set of features was created, combining the features from these 2 contrast phases. We applied a least absolute shrinkage and selection operator feature selection method and a support vector machine classifier. Three prognostic models were built using each feature set. The models' performance was compared using 5-fold cross-validated area under the receiver operating characteristic curves. **Results**. Eighty-eight patients were included, of whom 33 experienced the combined event (37.5%). The median time to dropout was 5.6 mo (interquartile range: 3.6–9.3), and the median time for post-LT recurrence was 19.2 mo (interquartile range: 6.1–34.0). Twenty-four patients (27.3%) dropped out and 64 (72.7%) patients were transplanted. Of these, 14 (21.9%) had recurrence post-LT. Model performance yielded a mean area under the receiver operating characteristic curves of 0.70 (±0.07), 0.87 (±0.06), and 0.81 (±0.06) for the arterial, venous, and the combined models, respectively. **Conclusions.** A pre-TACE radiomics model for HCC patients undergoing LT may be a useful tool for outcome prediction. Further external model validation with a larger sample size is required.

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INTRODUCTION

Liver transplantation (LT) represents the best treatment option in carefully selected patients with hepatocellular carcinoma (HCC) given that it offers tumor removal with the widest possible margin and therein also achieving the elimination of the pro-carcinogenic liver microenvironment.[1-4] To avoid tumor progression and dropout from the waiting list, locoregional therapies such as transarterial chemoembolization (TACE) can be used as a bridge to LT. Using risk-score based strategies for patient selection and performing TACE as the primary bridging therapy, the dropout rates from the waitlist remain as high as 12–30%.[5,6] Adverse outcomes such as dropout and tumor recurrence post-transplant portend a dismal prognosis for HCC patients with a median survival of 1.0–3.3 and 3.8–20.2 mo, respectively.[7-10] Both long-term patient survival and waitlist mortality represent common quality indicators of transplant programs that influence both the regional transplant allocation but also patient selection.[11] Improvements in the prognostic scores for a selection of the most appropriate LT candidates are a priority in LT centers worldwide.

Aiming to reflect tumor biology, morphologic criteria such as tumor size and rate of growth have long remained the most important benchmarks for LT patient selection (ie, Milan criteria). However, these criteria are insufficient to predict a tumor's biologic behavior and aggressiveness and underestimate tumor capacity for progression and recurrence.[12] Therefore, other additional serum surveillance tests such as alpha-fetoprotein (AFP), inflammatory biomarkers, and des-gamma-carboxy prothrombin have been used.[13]

Radiomics is in an emerging field of imaging research, aiming to extract high-dimensional data from clinical images.[14] Quantitative radiomic features have shown possible prognostic value in HCC for tumor recurrence,[15] microvascular invasion,[16] and survival.[17,18] Furthermore, there is a growing body of evidence supporting the capacity of radiomics to capture the genetic landscape of HCC[19] and predict treatment response, for example, doxorubicin chemoresistance in TACE.[20,21] Therefore, radiomics has the potential to become an additional HCC imaging biomarker with the capability to reflect the tumor biologic behavior and provide prognostic information related to LT outcomes. Nonetheless, there is a lack of data on how best radiomics can be applied to HCC and ultimately incorporated in prediction models, particularly for patients receiving bridging therapy while awaiting a LT.

To move beyond a sole reliance on size and number criteria to decide on transplant eligibility for patients with HCC, innovative biomarkers are in urgent need. We sought to evaluate the feasibility of using pretreatment tumoral radiomic features in patients undergoing TACE as a bridge to LT for the prediction of pre-LT tumor progression and post-LT recurrence.

MATERIALS AND METHODS

This study was approved by our institutional Research Ethics Board (REB #16-6105), and a waiver of informed consent was obtained. This study complies with the STROBE statement for retrospective studies.[22]

Study Population

We assessed adults (≥18 y) listed for LT between July 12, 2005 and August 19, 2016 at the University Health Network, University of Toronto, Canada. Patients were followed until May 30, 2019. All patients were listed for LT as a treatment for HCC according to a previously established multidisciplinary protocol.[23] The diagnosis of HCC was made according to international guidelines.[24] The listing criteria for LT in HCC patients have evolved at our institution, similar to many other North American centers.[25] In 2004, the extended Toronto criteria were applied to prospective LT patients beyond the Milan criteria.[25] Thus, since that time, patients were eligible for transplant listing if (1) their tumors were within the Milan criteria or (2) the tumors fulfilled the extended Toronto criteria.[25] The extended Toronto criteria are outlined elsewhere, but briefly include tumors confined to the liver, the absence of radiologic venous or biliary tumor thrombus, no cancer-related symptoms, and an obligatory percutaneous biopsy not demonstrating poor tumor differentiation.[2]

Only patients that underwent TACE as a bridge to LT and had a contrast-enhanced CT scan with at least an arterial and portal venous phase were included. Patients were excluded if the outcome information was unavailable or incomplete. Moreover, patients who received no bridging therapy, received bridging therapy other than TACE, or had poor quality or missing imaging were excluded. A flow diagram of inclusion and exclusion criteria is depicted in Figure 1.

We recorded patients' demographics, body mass index (BMI), etiology of liver disease, model for end-stage liver disease score at listing and immediately before transplant, AFP levels, tumor burden, bridging therapy, location of recurrence, and treatment of recurrence. Tumor burden was assessed before LT and on the pathologic specimen. Milan criteria were defined according to criteria by Mazzaferro et al.[3] Tumor differentiation was defined according to the modified Edmondson criteria.[26]

Waitlist Surveillance and Posttransplant Follow-up

On the waitlist, surveillance is performed with contrast-enhanced CT of the liver and chest and laboratory blood work in 3-mo intervals. Following LT, patients are followed using contrast-enhanced CT of the chest and abdomen or ultrasound in 3-mo intervals for the first 2 y, 6-mo intervals for 2 y, and yearly after that. If a recurrence is suspected, additional imaging investigation is performed, including contrast-enhanced CT, contrast-enhanced ultrasound, or MRI.[27] A biopsy is performed if imaging is inconclusive. Overall survival is calculated from the day of LT to the day of death or last known contact. The time to recurrence is calculated from the day of LT to the first imaging study confirming tumor recurrence.

Outcome Measures

The study's primary endpoint was a combined event that included dropout from the waitlist or tumor recurrence after LT. In our clinical setting, the number of patient dropouts from the waiting list and tumor recurrences after LT were low. A combined event ensures a sufficient number of events, which is necessary for the development of robust prediction models, particularly in the presence of a large number of predictor variables. The definition of dropout constituted withdrawal from the waitlist due to tumor progression other than LT. Any patient that dropped out for reasons other than tumor progression (ie, patient refused LT) were therefore excluded from the subsequent radiomics model.

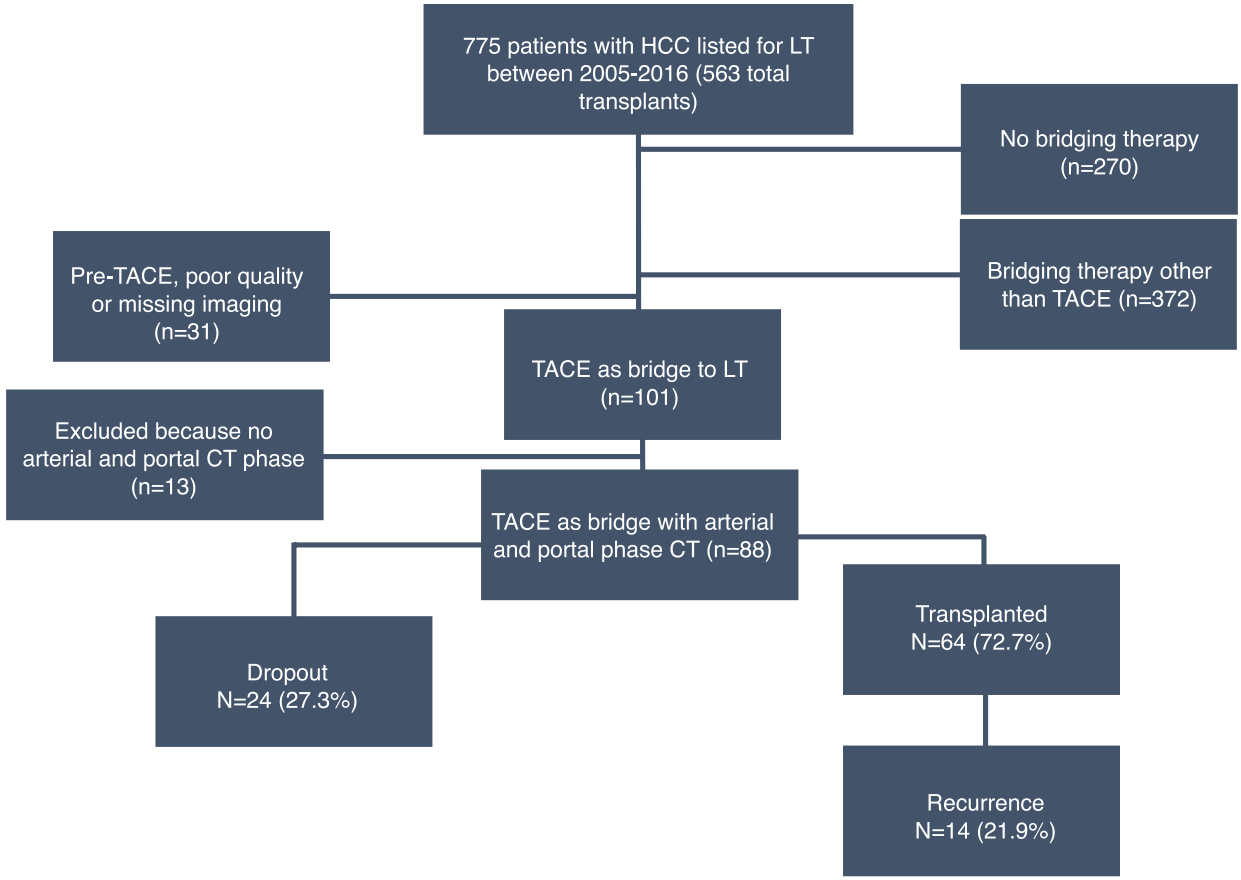

FIGURE 1. Study flowchart. CT, computed tomography; HCC, hepatocellular carcinoma; LT, liver transplantation; TACE, transarterial chemoembolization.

CT Protocol

All patients underwent the standard institutional multiphase contrast-enhanced CT of the liver performed at our institution or at the referring institution.[28] The tomography slice thickness was 2–5 mm, and detector rows ranged from 64 to 256. According to our standardized institutional protocol for contrasted imaging studies, contrast media is injected into the antecubital vein with an injection velocity of 5–7 mL/s. The arterial and portal venous phases acquisitions are performed with 15-s and 60-s delays, respectively. Delayed images were acquired after 180 s.

Image Segmentation and CT Analysis

One radiologist (E.S.) manually contoured the HCC volume of interest in the arterial and portal phases. A radiologist with >20 y of experience in abdominal radiology (M.H.) confirmed the contours. The lesion selected for contouring was the one with the highest LI-RADS[29] score. In the case of 2 differentially sized lesions with similar LI-RADS score, the largest lesion was selected for analysis. The tumor boundaries were defined by the tumor enhancement in the arterial and portal phases. When tumor boundaries were unclear, the arterial phase was used as a reference. A commercially available software (v3.4.3; Mint Medical GmbH, Heidelberg, Germany) was used for segmentation.

Feature Extraction and Feature Reduction

Radiomic features were extracted using the PyRadiomics library (v.2.2.0).[30] PyRadiomics features followed the Imaging Biomarker Standardization Initiative.[31] The definition of extracted features are available online (pyradiomics.readthedocs.io). The classification and description of radiomic classes and features is shown in Table S1 (**SDC**, http://links.lww.com/TP/C96). For feature selection, zero or very low variance (<0.05) features and highly correlated features (correlation coefficients > 0.8) were removed. Z-score normalization (standardization) was conducted. Afterward, 3 feature banks were constructed: arterial, portal, and arterial plus portal (combined) banks. Least absolute shrinkage and selection operator (LASSO) was used for feature selection and the best tuning parameter λ which is the penalty coefficient is selected by 5-fold cross-validation. Trace plots of coefficients fit by LASSO and selected features after performing feature selection (λ = 0.02) for 3 feature banks are shown in Figure S1 (**SDC**, http://links.lww.com/TP/C96). A total of 26, 27, and 38 features were selected from the arterial, portal, and combined feature banks, respectively. Clinical variables were not incorporated into the model to allow an evaluation of radiomic features in isolation.

Coefficients correspond to the weights assigned to the features, based on their importance. Variable importance plots indicate that "wavelet-LHH_gldm_LargeDepdendenceLowGrayLevelEmphasis" is the most influential variable in the arterial and combined model. Most influential variables for the portal phase model were: "wavelet-LLH_glszm_LargeAreaLowGrayLevelEmphasis," "wavelet-LHH_gldm_LargeDepdendenceLowGrayLevelEmphasis," and "wavelet-HHH_gldm_LargeDependenceLowGrayLevel Emphasis" (**Figure 1, SDC**, http://links.lww.com/TP/C96).

Predictive Model

Several machine learning algorithms for the classification such as logistic regression, random forest, gradient boosting decision tree were attempted. The performance of the remaining classifiers with the various contrast phase was all below 0.7. The best accuracy was achieved with the LASSO based support vector machine (SVM) classifier, which was selected for this reason. The SVM algorithm was used to generate the 3 prognostic models with different Kernel, C, and Gamma hyperparameters. The effect was assessed of the parameters gamma and C of the radial basis function kernel SVM in model development. Kernel, C, and gamma hyperparameters are described in Table S2 (**SDC**, http://links.lww.com/TP/C96). The prediction was for the occurrence of the outcome event at any time during the follow-up period.

Statistical Analysis

The time to dropout was computed from the entrance of the patient to the LT waiting list to dropout from the waitlist, and time to recurrence was calculated from LT to HCC recurrence noted on the post-LT imaging surveillance. The combined event was treated as a binary variable in the radiomics model. Using exploratory univariate Cox proportional hazards models and log-rank tests with multiple testing correction (false discovery rate), we found that single radiomic features used in isolation provided no significant prognostic value. As a result, we evaluated the prognostic performance of models incorporating a set of radiomic features using the average value of the 5-fold cross-validated area under the receiver operating characteristic curves (AUC) for the prediction of the combined event (either dropout from the waitlist because of tumor progression, or HCC recurrence in the post-LT imaging surveillance). The AUC was used to evaluate the radiomics model discriminatory ability. Additional diagnostic performance measures, including sensitivity and specificity, were calculated for model thresholds corresponding to the maximum Youden index.[32] Continuous variables with normal and non-normal distribution are presented as mean with SD and median with interquartile range (IQR), respectively. All 2-sided $P < 0.05$ were considered significant. Statistical analyses were performed using R (version 3.5.3) (The R foundation for statistical computing, Vienna, Austria).[33]

RESULTS

Study Population and Pathology

A total of 88 patients met the criteria for inclusion (Figure 1). Most patients were male 68/88 (77.3%) with a median age of 59 y (IQR: 54–64) and a median BMI of 26.5 (IQR: 24.2–30.4). The etiology of the underlying liver disease was predominantly hepatitis C virus cirrhosis (n = 37 [42.0%]), followed by hepatitis B virus cirrhosis (n = 25 [28.4%]). At listing, the median model for end-stage liver disease was 8 (IQR: 7–10), median AFP was 12.5 (5–110), and tumor median tumor size was 3.8 cm (IQR: 2.5–5.5). Before the transplant, 26 (29.5%) patients had single tumor and 48 patients (54.5%) were within Milan criteria. Most tumors were moderately differentiated (n = 51 [79.7%]) and 22 (34.4%) were within Milan criteria on pathology. Most patients had viable tumors at explant (n = 55 [85.9%]). Microvascular and macrovascular invasion was present on pathology examination of the explanted livers in 19 (29.7%) and 4 (6.3%) of patients, respectively (Table 1).

TABLE 1.

Patients demographic and clinicopathologic characteristics by groups

Preoperative characteristics	Overall (n = 88)
Sex, male (%)	68 (77.3)
Age (y), median (IQR)	59 (54–64)
BMI (kg/m^2), median (IQR)	26.5 (24.2–30.4)
Etiology, n (%)	
HCV	37 (42.0)
HBV	25 (28.4)
ETOH	9 (10.2)
NASH	8 (9.1)
Other	9 (10.2)
MELD at listing, median (IQR)	8 (7–10)
AFP at listing (ng/mL), median (IQR)	12.5 (5–110)
Tumor size at listing (cm), median (IQR)	3.8 (2.5–5.5)
Tumor number at listing, median (IQR)	2 (1–3)
Milan in at listing, n (%)	37 (42.0)
Neutrophil-Lymphocyte ratio pretransplant, median (IQR)	2.8 (1.8–4.0)
Tumor size pretransplant (cm), median (IQR)	2.3 (0.6–4.6)
Number of BT procedures, n (%)	
1	43 (48.9)
2	30 (34.1)
3	13 (14.8)
4	2 (2.3)
Dropout, n (%)	24 (27.3)
Explant pathology characteristics	
Tumor size at pathology (cm), median (IQR)	3.6 (2.0–5.4)
Number of tumors at pathology, median (IQR)	2 (1–6)
Milan in at pathology, n (%)	22 (34.4)
Tumor differentiation, n (%)	
Well differentiated	2 (3.1)
Mod differentiated	51 (79.7)
Poor differentiated	2 (3.1)
Not assessed	9 (14.1)
Percentage of viable tumor, n (%)	55 (85.9)
Presence of mVI at pathology, n (%)	19 (29.7)
Presence of MVI at pathology, n (%)	4 (6.3)
Tumor recurrence, n (%)	14 (21.9)
Follow-up time (mo), median (IQR)	44.4 (20.7–86.6)

AFP, alpha-fetoprotein; BMI, body mass index; BT, bridging therapy; CIT, cold ischemia time; ETOH, alcoholic cirrhosis; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; MELD, model for end-stage liver disease score; mVI, microvascular invasion; MVI, macrovascular invasion; NASH, nonalcoholic steatohepatitis.

Combined Event and Outcomes

The group experienced 33 combined events (37.5%). Twenty-four patients (27.3%) dropped out from the waitlist with a median time of 5.6 mo (IQR: 3.7–9.2). Five patients in the dropout group did not experience tumor progression and were therefore not included in the combined event group (n = 1 too sick, n = 3 refused LT, n = 1 death). Causes for all dropouts were tumor progression in 19 cases (79.2%). Sixty-four (72.7%) patients underwent

TABLE 2.

Summary of model performance in each phase

Model	Arterial model	Portal model	Combined model (arterial and portal)
Number of features after LASSO	26	27	38
Hyperparameters			
Kernel	RBF	RBF	RBF
C	9	50	20
Gamma	0.001	0.0025	0.002
Mean AUC (±SD)	0.70 (±0.07)	0.87 (±0.06)	0.81 (±0.06)

AUC, area under the curve; C, Constant C; LASSO, least absolute shrinkage and selection operator; RBF, radial basis function.

LT. Of the patients that underwent LT, 14 (21.9%) developed tumor recurrence with a median time to recurrence of 19.2 mo (IQR: 6.1–34.0); Figure S2 (**SDC**, http://links.lww.com/TP/C96).

Radiomics Model Performance

A total of 1441 radiomic features were extracted using the PyRadiomics library. These features were used in a univariate Cox proportional regression model but yielded no identification of statistically significant prognostic features. This was repeated with data split into various ratios of training and test sets (70/30, 50/50), which also did not yield any significant features, even despite the application of multiple testing correct (false discovery rate). In contrast, using the SVM algorithm for the generation of prognostic models, the mean AUC (±SD) for predicting the combined outcome was 0.70 (±0.07), 0.87 (±0.06), and 0.81 (±0.06) for the arterial, portal, and combined models, respectively (Table 2 and Figure 2). We selected the portal phase-based model for further analysis due to its superior performance. The mean sensitivity and mean specificity across the 5 folds are 0.824 and 0.816 using the optimal cutoff point in each fold. Within a clinical context, a sensitivity of 82.4% refers to the probability of being correctly identified as

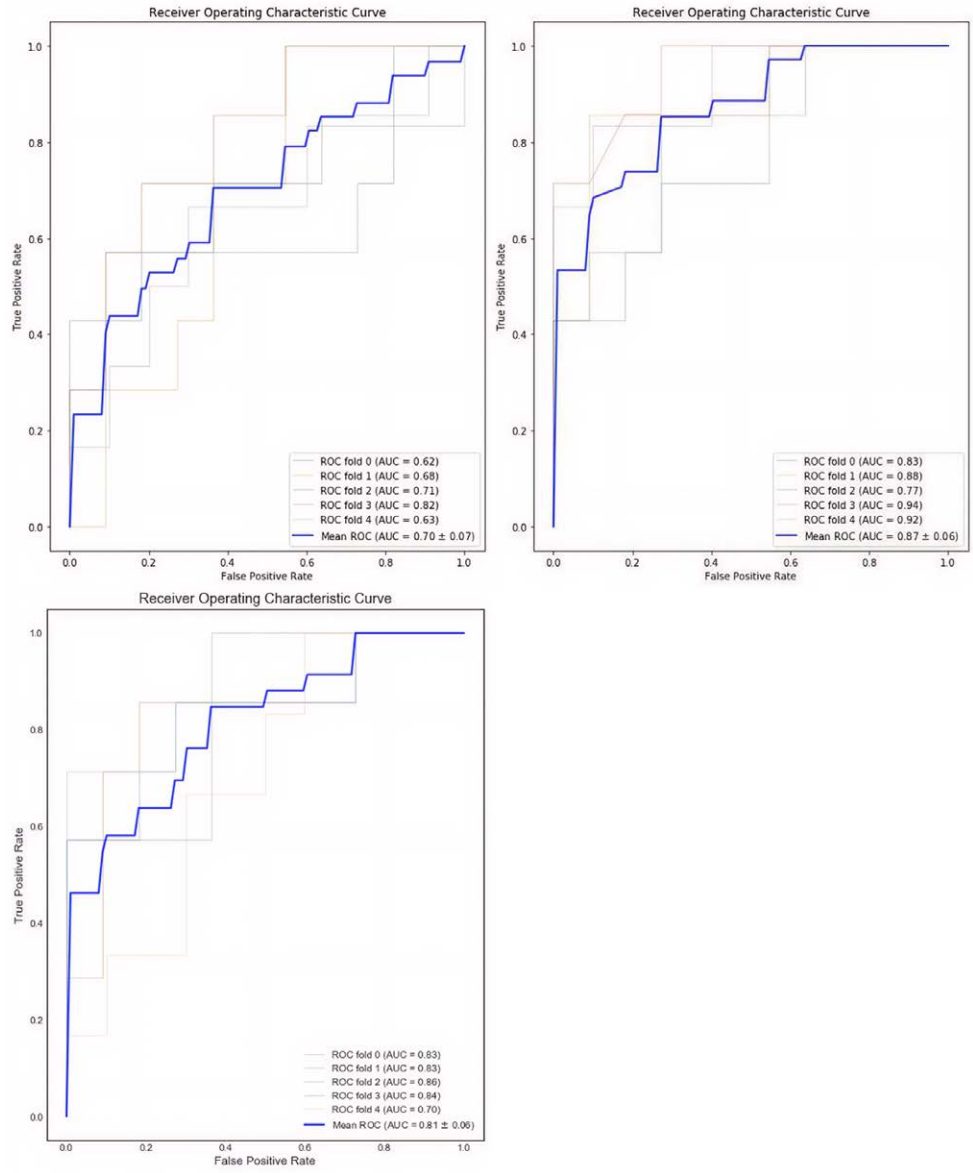

FIGURE 2. ROC curves and AUCs for 3 models: arterial phase (upper left), portal phase (upper right), and combined (bottom left). The 5-fold cross-validated AUC and mean AUC are shown for each model. AUC, area under the curve; ROC, receiver operating characteristic.

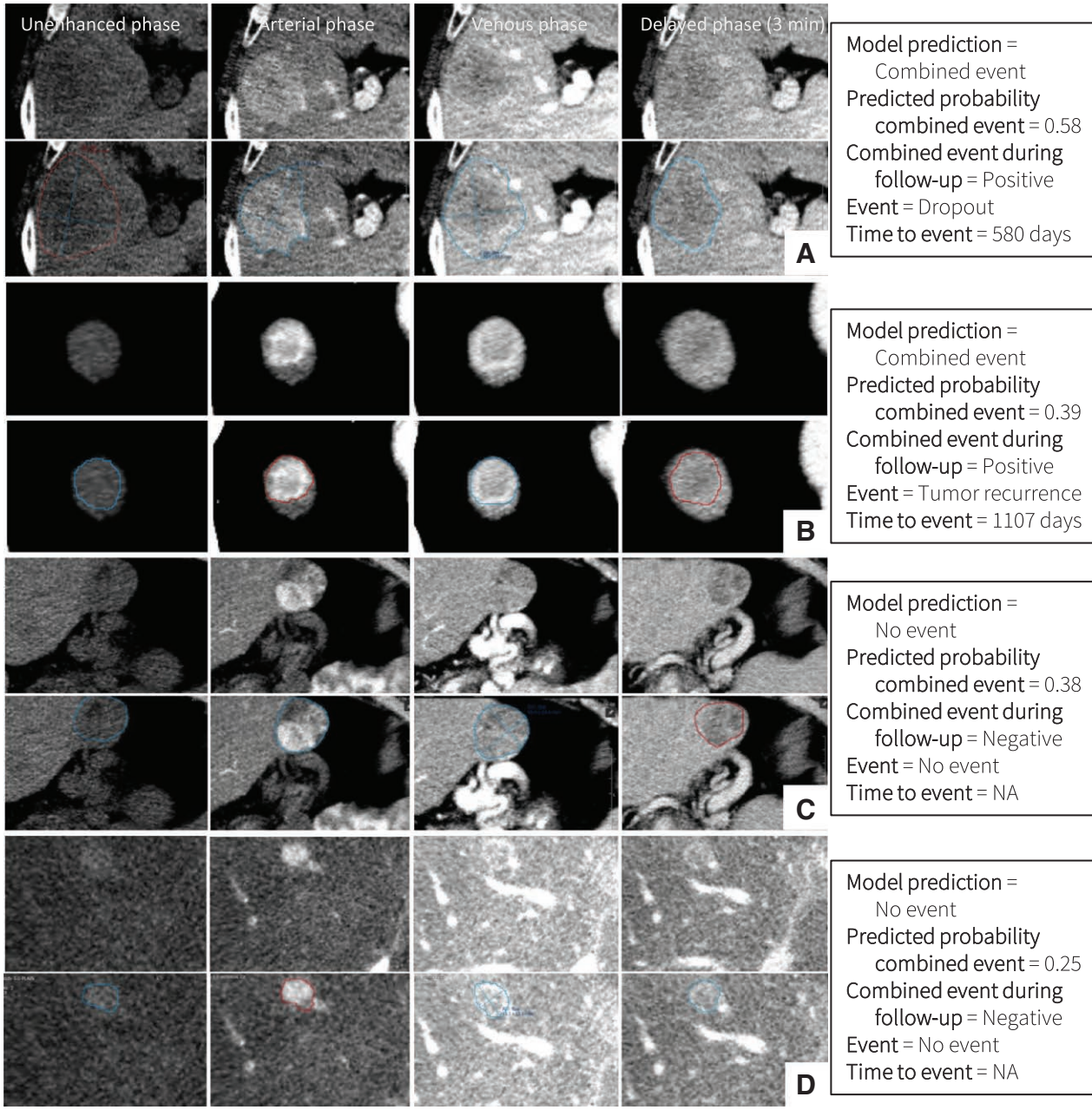

FIGURE 3. Representative images of pre-TACE contoured tumors and its radiomic predictions using the portal-based model. Model predicts the combined event for the cases (A) and (B) and no combined event for the cases (C) and (D). Cases had similar tumor sizes: 37 × 33 mm (A), 25 × 23 mm (B), 38 × 37 (C) and 25 × 23 (D). TACE, transarterial chemoembolization.

experiencing the combined event based on the model's prediction. The 81.6% specificity represents the probability of being correctly identified as not experiencing the combined event based on the radiomic features. The corresponding mean Youden Index is 0.64. Two examples of patients with model predictions are shown in Figure 3. An outline of the clinical workflow, image segmentation, feature extraction, and model building is shown in Figure 4.

DISCUSSION

This pilot study demonstrates that a pre-TACE radiomics model is feasible for use in the development of a future prognostic model for HCC progression and recurrence in patients undergoing LT. We concluded that the model based on portal features had a higher performance compared with the arterial-based and the combined models. This finding suggests that HCC features obtained from the portal phase may play an essential role in pre- and post-transplant outcomes.

As newer selection criteria for LT for patients with HCC grow increasingly complex and are based on a multitude of factors including clinical, pathologic, laboratory, and imaging variables, accurate outcomes prediction models that can offer decision-making support are needed. Imaging represents a cornerstone in both HCC diagnosis and treatment decision-making making it an ideal platform in the development of such prediction models. The use of radiomics has demonstrated the potential for predicting microvascular invasion and clinical outcomes in HCC patients

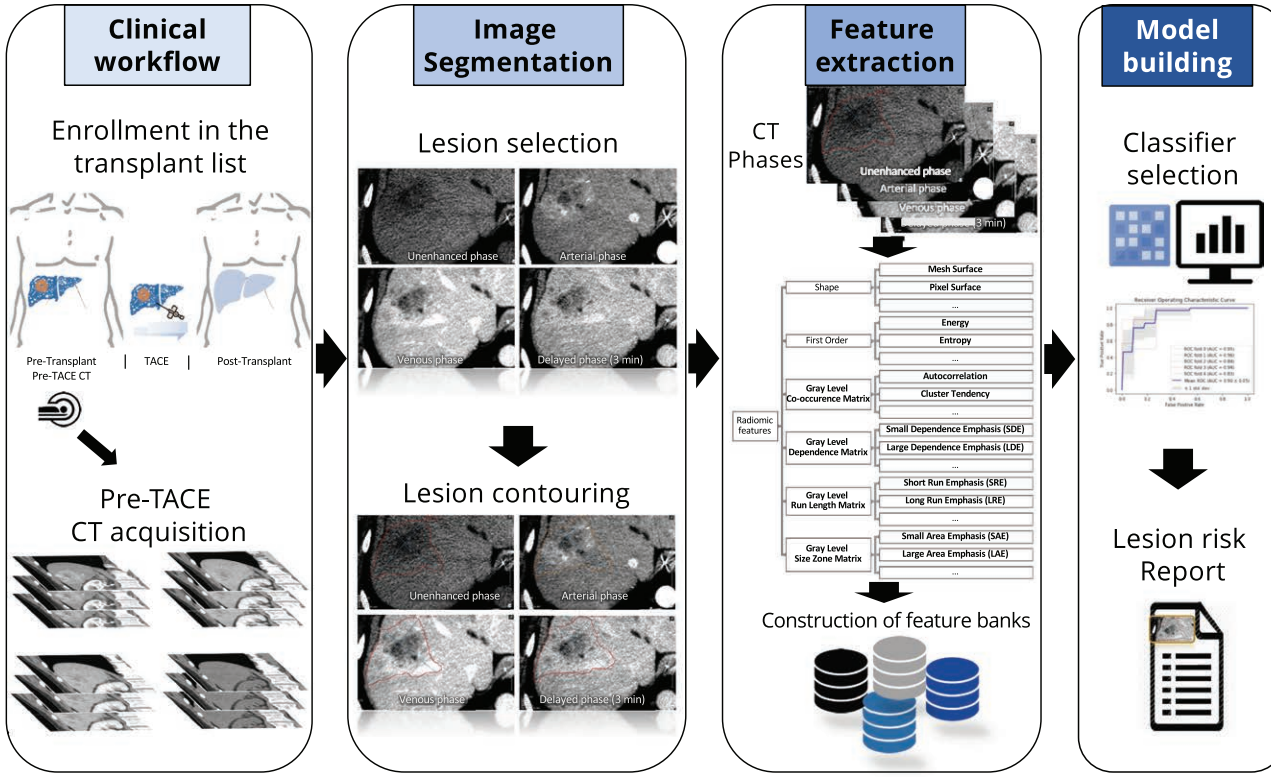

FIGURE 4. Radiomics workflow. CT, computed tomography; TACE, transarterial chemoembolization.

undergoing liver resection.[34–36] There is, however, a lack of data using radiomics in predicting HCC outcomes in an LT population.[37] To the best of our knowledge, there are no studies specifically evaluating receipt of TACE on the LT waitlist using radiomics, especially in a Western HCC cohort. Though it may be conceivable that a pre-TACE HCC radiomics signature may be associated with a higher risk of recurrence post-LT, it is also possible that this signature may also influence the risk of progression after TACE, which might affect by itself the risk of tumor recurrence. Abajian et al[38] used an artificial intelligence framework, including MRI and clinical data, to develop a model that was able to predict a patient's response to TACE. Furthermore, an improved understanding of the patient's expected TACE response may help to tailor the therapeutic strategies to maximize its benefit. In another study, Xu et al[34] assessed the integration of clinical and radiomics in the development of a computation approach to predict microvascular invasion and clinical outcomes in 495 patients with HCC after liver resection. Their radiographic-radiomic model for absence and presence of microvascular invasion showed a median progression-free survival of 49.5 versus 12.9 mo and a median overall survival of 76.3 versus 47.3 mo.[34] They concluded that such a computational approach demonstrated good performance for microvascular invasion and clinical outcomes prediction.[34] However, the group found that radiomics with current CT imaging analysis protocol did not offer a statistically significant added benefit to radiographic scores.[34] Guo et al[37] evaluated whether radiomics could predict outcomes such as recurrence after LT for HCC. The groups included a training set of 93 patients and a validation dataset of 40 patients and found that an optimal prediction model was obtained when radiomics features and clinical parameters were combined.[37] The model had a predictive performance for recurrence-free survival with a C-index of 0.79 (95% confidence interval, 0.67-0.90) and 0.79 (95% confidence interval, 0.62-0.96) in the training and validation datasets, respectively.[37] In contrast to our study, the group by Guo et al included a Chinese patient cohort, with predominantly HBV-related HCC, and without any pre-LT locoregional therapy receipt. As many patients receive locoregional therapy such as TACE or RFA, considering these bridging therapies becomes essential not only to improve understanding of tumor biology,[39] but also which patients may be more likely to respond to a particular bridging therapy. This information can help to define individualized treatment protocols.[40]

Though the use of radiomics appears feasible for outcomes prognostication in HCC, the best way to incorporate this technology remains to be fully elucidated. Further large-scale investigations with continued methodologic refinements are thus warranted. This exploratory analysis has highlighted several aspects that should be addressed in future studies using radiomics. For instance, as many patients listed for LT for HCC have >1 tumor, some, if not all, undergo bridging therapy. Though this study evaluated pretreatment tumoral radiomic features in a cohort of HCC patients undergoing TACE as a bridge to LT, patients may receive various forms of ablative therapies, which should ideally be considered together. This pilot study evaluated a highly confined patient population, specifically patients listed for LT for HCC with TACE bridging therapy, which minimizes the influence of other confounding variables with potential for the introduction of noise into the data. As more data for radiomics in HCC accumulates,

comparisons between methods should be sought, encompassing the whole spectrum of patients with HCC, and not only patients selected for 1 treatment, for an improved global understanding of HCC. The LT platform offers the benefit of providing the largest amount of tumor and surrounding liver for not only radiomic analyses but also genomic studies. Such findings can subsequently potentially be extrapolated to other areas of HCC treatment, such as for patients who receive locoregional therapy with, for instance, radiofrequency ablation, and would not have a pathologic specimen available for examination. Moreover, in the case of multiple lesions in our study, the largest lesion with the highest LI-RADS score was used for the radiomics analysis, and the model did not account for multiple tumors. A fully automatic liver segmentation can potentially overcome this methodologic issue using a convolutional neural network, which will be able to take into account the entire hepatic tumor burden. Furthermore, the event selected for prediction using radiomics in this exploratory phase was a combined event of either dropout from the waitlist or recurrence post-LT. Ideally, with a larger cohort of patients and future external validation refinements to the endpoint can be made. They may include pathologic variables such as tumor differentiation, percentage of viable tumor, and microvascular invasion.

Our portal venous phase-based model had better prognostic performance when compared with the arterial phase-based and the combined models. Conversely, previous studies have shown that arterial phase derived features may have a better performance for the prognosis of HCC tumor recurrence.[37] These portal features might capture the delayed hypo-enhancement (washout) and the tumoral capsule, which are 2 fundamental HCC portal phase characteristics. Furthermore, HCC tumors can have an atypical enhancement pattern in 43.6%[41] of patients, presenting without typical arterial hyperenhancement and early portal washout as the histologic differentiation of HCC moves towards moderate and poorly differentiated carcinomas.[41] Our portal-based model might capture these portal characteristics as well.

Predicting adverse outcomes in HCC patients in LT patients is essential for appropriate treatment selection. AFP is the most commonly used biomarker in HCC but is suboptimal in sensitivity and specificity. Multiple "omics" data (genomics, epigenomics, transcriptomics, proteomics, metabolomics, and metagenomics) has exciting potential for biomarker discovery in HCC and can be used for diagnosis, prognosis, and targeted therapy.[42] However, these technologies are still developing and are limited by requiring either blood or a tissue sample from the patient, which may not always be available. Imaging-based biomarkers can overcome these shortcomings by: (1) allow validation using historical data; (2) are noninvasive; (3) apply to all patients with HCC, even in cases where no tumor tissue is obtained for pathologic examination.

Our study had several limitations. First, we evaluated a relatively low sample size, but with a focus on a specific population of HCC patients undergoing TACE, limiting subgroup analysis (ie, according to HCC etiology, number of previous procedures, etc.). While bridging therapy is becoming more frequently used for HCC patients on the waitlist, a number of various locoregional therapies are possible. The TACE cohort in this study was selected for its homogeneity. Moreover, the stringent inclusion criteria also decreased the potential for confounding due to other locoregional therapies. Future efforts should aim to establish the utility of radiomics in predicting outcomes for waitlisted patients who remain treatment-naive until LT and patients who receive other types of locoregional therapies. Additionally, to evaluate our radiomics model's performance, we selected a combined event given our small cohort and the low number of events. This decision limited our ability to perform a fair comparison between the performance of our radiomics models and other prediction models in HCC, which have as the model outcome only 1 of the 2 possible combined events. Furthermore, our combined event was considered a dichotomous event, further limiting us as it does not take into account the time for the event's occurrence. A larger sample size with more events is likely to offer additional opportunity to evaluate both the time-to-event prediction of radiomics and its association with dropout and post-LT recurrence separately. The limitations of machine learning warrant mention, particularly the potential for prediction 'overfitting' with the potential of yielding overly optimistic estimates in training sets, with ultimately poor fit in new data sets. To overcome this, external validation is required and continuous model refinement should be pursued with larger and more diverse patient populations.[43] The CT images were obtained from >4 different CT configurations, as some patients were referred to LT from several external institutions increasing the variability in various processes specially feature extraction. Furthermore, there was no consensus on the optimal CT perfusion protocol, for example, acquisition (timing) protocol and contrast medium administration, making comparisons between different studies difficult. Several images were excluded from the analysis because of the inconsistent availability of the unenhanced and delayed imaging phases. Nonetheless, incorporating longitudinal imaging should be considered in future radiomics studies as it is possible that delta-radiomics features will yield improved prognostication and model refinement. The reason why the modified Response Evaluation Criteria in Solid Tumors[44] assessment was not incorporated in our analysis was that it has not been widely adopted at our institution, and although representing a standardized measure of response rate, it is subject to interobserver and interinstitutional variation. As such, the feasibility of the radiomics platform and imaging features was evaluated in isolation, as it has the potential for yielding stable and objective estimates for prognostication across institutions. Moreover, the utility of radiomics in MRI was not evaluated in this study as such features are less robust than those obtained from CT imaging and more affected by patient mobilization and organ movements.[45-47] Nonetheless, as MRI is becoming a more commonly used imaging modality for HCC diagnosis and surveillance, future work should aim to evaluate the utility and stability of radiomics using MRI. Regarding the method of validation, due to the pilot nature of our study, we used an internal validation cohort rather than an external validation; thus, our results might have limited generalizability. Although a large sample of radiomic features was obtained, from the full tumor volume of the largest chemo-embolized lesion, the contribution of the remaining lesions, in progression or recurrence, is still unknown. Lastly, tumor segmentation was manually

performed by 1 single reader, possibly inducing contouring variability, which makes it difficult to standardize feature extraction. We plan a further set of analyses using a larger external cohort and multiple readers to assess in a subsequent study the robustness of our current findings.

CONCLUSIONS

We demonstrate our pre-TACE radiomics model to be feasible for use as a combined predictor for pre-LT progression and post-LT recurrence in HCC patients. Notably, our portal phase-based model may have potential as an additional risk-score in patients on the transplant waitlist and might help optimize the algorithms of personalized treatment. Further biologic validation with a larger external cohort is warranted.

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