A radiomics nomogram for prediction of overall survival in hepatocellular carcinoma after hepatectomy

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Research

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A radiomics nomogram for prediction of overall survival in hepatocellular carcinoma after hepatectomy

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Abstract

Background Hepatocellular carcinoma (HCC) is associated with dismal prognosis, and prediction of the prognosis of HCC can assist the therapeutic decisions. More and more studies showed that the texture parameters of images can reflect the heterogeneity of the tumor, and may have the potential to predict the prognosis of patients with HCC after surgical resection. The aim of the study was to investigate the prognostic value of computed tomography (CT) texture parameters for patients with HCC after hepatectomy, and try to develop a radiomics nomograms by combining clinicopathological factors with radiomics signature.

Methods 544 eligible patients were enrolled in the retrospective study and randomly divided into training cohort (n=381) and validation cohort (n=163). The regions of interest (ROIs) of tumor is delineated, then the corresponding texture parameters are extracted. The texture parameters were selected by using the least absolute shrinkage and selection operator (LASSO) Cox model in training cohort, and the radiomics score (Rad-score) was generated. According to the cut-off value of the Rad-score calculated by the receiver operating characteristic (ROC) curve, the patients were divided into high-risk group and low-risk group. The prognosis of the two groups was compared and validated in the validation cohort. Univariate and multivariable analyses by COX proportional hazard regression model were used to select the prognostic factors of overall survival (OS). The radiomics nomogram for OS were established based on the radiomics signature and clinicopathological factors. The Concordance index (C-index), calibration plot and decision curve analysis (DCA) were used to evaluate the performance of the radiomics nomogram.

Result 7 texture parameters associated with OS were selected in the training, and the radiomics signature was formulated based on the texture parameters. The patients were divided into high-risk group and low-risk group by the cut-off values of the Rad-score of OS. The 1-, 3- and 5-year OS rate was 71.0%, 45.5% and 35.5% in the high-risk group, respectively, and 91.7%, 82.1% and 78.7%, in the low-risk group, respectively, with significant difference ($P < 0.001$). COX regression model found that Rad-score was an independent prognostic factor of OS. In addition, the radiomics nomogram was developed based on five variables: α-fetoprotein (AFP), platelet lymphocyte ratio (PLR), largest tumor size, microvascular invasion (MVI) and Rad-score. The nomograms displayed good accuracy in predicting OS (C-index=0.747) in the training cohort and was confirmed in the validation cohort (C-index=0.777). The calibration plots also showed an excellent agreement between the actual and predicted survival probabilities. The DAC indicated that the radiomics nomogram showed better clinical usefulness than the clinicopathologic nomogram.

Conclusion The radiomics signature is potential biomarkers of the prognosis of HCC after hepatectomy. Radiomics nomogram that integrated radiomics signature can provide more accurate estimate of OS for patients with HCC after hepatectomy.

Keywords: CT texture analysis; hepatocellular carcinoma; overall survival; prediction; nomogram

1. Background

HCC is the fifth most common malignancy and ranks as the third most common cause of cancer-related death globally. [1,2] Surgical resection is the preferred treatment option for people with HCC.[3] However, the long-term prognosis of patients with hepatocellular carcinoma after resection is dismal with 5-year survival rate of 25-55% and 5-year recurrence rate of 60-100% . [4-7] The prognosis of HCC is influenced by numerous factors, and thus early prediction of the prognosis is of great significance for the long-term management and effective treatment. At present, Barcelona Clinic Liver Cancer (BCLC) is a worldwide recognized staging system for HCC, which is widely used tool to guide the prognostic prediction and treatment decisions. [3] Despite this, BCLC classification is still controversial and shows limited predictive power.[8-10] Therefore, it is worth exploring more reliable and pragmatic methods to evaluate the prognosis of HCC.

The previous imaging studies were based on the size, shape, density and enhancement of tumors, [11]which did not quantify the information of the images and were easily affected by the subjective factors of the radiologists. Radiomics is a new emerging field, which can extract high-dimensional information from medical images. Texture analysis (TA), an image post-processing technique, can evaluate the potential heterogeneity of the lesions using a large set of quantitative features.[12-14] Emerging studies showed that texture features have the potential to differentiate tumor types, monitor therapeutic response, identify the regional lymph node metastasis of malignant tumors and predict the prognosis. [15,16] Furthermore, radiomics features are closely associated with gene expression, gene mutation and epigenetic alterations, which can reflect proliferation, invasion, metastasis and drug resistance of the tumors. [17] In the future, the accurate and quantitative imaging information by automatic identification with artificial intelligence in combination with clinical data can help doctors evaluate the patient survival. It plays an important role in clinical decision making, treatment planning and postoperative long-term follow-up, and provide new opportunities for individual precise treatment.

The underlying correlation of radiomics features, pathology and survival is not clear, and relatively few studies have addressed the efficacy of TA in prognostic prediction. The intratumor heterogeneity can reflect the biological characteristics, which may be of prognostic significance. The purpose of this study is to explore the prognostic value of preoperative CT texture parameters for patients underwent radical hepatectomy. In addition, a prognostic nomogram is proposed on the basis of texture parameters to provide useful references for precision medicine.

2.Materials and methods

2.1Patients

A total of 544 consecutive patients with HCC underwent hepatectomy in the Department of Liver Surgery at West China Hospital between January 2013 and December 2016 were enrolled according to the criteria for inclusion: (1) patients who underwent an initial radical hepatectomy with pathologically confirmed HCC; (2) Child-Pugh A or B liver function;(3) no preoperative treatments such as radiofrequency ablation, transcatheter arterial chemoembolization (TACE) and chemotherapy; and(4) preoperative contrast-enhanced CT within 4 weeks. The exclusion criteria were as follows: (1) The CT images failed to meet the requirements; (2) benign or mixed types of liver tumor; (3) simultaneously underwent hepatectomy and radiofrequency ablation; (4) receipt of liver transplantation during the course

of disease; (5) incomplete clinical or follow-up data. We randomly divided the eligible patients into 2 groups at a ratio of 7:3, the training cohort (n=381) and the validation cohort (n=163). The study was approved by the Committee of Ethics in West China Hospital of Sichuan University. The clinicopathologic variables were collected, including patient demographics, laboratory data, tumor characteristics, surgical outcomes, postoperative pathological data.

2.2Patient follow-up and surveillance

All patients were followed up by telephone or outpatient at the first month after surgery and then every 3 months thereafter until November 2019. The routine examinations including serum AFP levels, routine blood tests, serum biochemistry, HBV-DNA, abdominal ultrasonography, contrast-enhanced CT/MRI was performed at each of these follow-up visits. OS was calculated as the period from the time of surgery to the time of either death or last follow-up.

2.3image acquisition and imaging texture analysis

The target images were retrieved from the Picture Archiving and Communication System in Digital Imaging and Communications in Medicine (DICOM) format and transferred to Mazda software (version 4.6) for further TA. All manual segmentations were performed by an abdominal radiologist with 5 years of experience and verified by a senior radiologist with 20 years of experience. The regions of interest (ROIs) delineated the largest cross-sectional area of the tumors on the preoperative portal venous phase images. Based on the segmented tumor(s), 269 texture features reflecting tumor heterogeneity were extracted, including 5 categories: (1) histogram features; (2) co-occurrence matrix; (3) run-length matrix; (4) autoregressive model; (5) wavelet transform.

2.3 feature selection and radiomics signature building

We used the LASSO Cox regression model to select the features most associated with the survival status in the training cohort, with 10-fold cross validation utilized to reduce overfitting.[18] The LASSO is a data analysis method that can shrinks the coefficients of survival-unrelated variables to zero and the features with non-zero coefficient were selected.[19] The radiomics signature was built via a linear combination of selected features multiplied by their corresponding non-zero coefficients. Then, the Rad-score was calculated for each patient.

2.4 Model construction and evaluation

The patients were stratified into high-risk or low-risk groups according to the threshold of the Rad-score calculated by using ROC curve analysis. The difference between the survival curves of the high-risk and low-risk groups was assessed in the training cohort and then validated in the validation cohort. Univariate and multivariate COX regression analyses were performed in the training cohort to determine the potential independent risk factors. Then the radiomics nomogram integrating the radiomics signature and the independent clinicopathological risk factors according to the result of multivariate analysis was constructed to predict postoperative survival status. The discrimination ability of the nomogram was evaluated by the C-index. The calibration performance was measured by the calibration curve, which described the agreement between the predicted and observed survival probability. The clinical value of the nomogram was assessed by DCA[20] in the entire cohort, which generated by calculating the net benefits at different threshold probabilities.

2.2Statistical analysis

Statistical analysis was performed with SPSS version 22.0 software (Chicago, IL, USA)

and R software (version 3.5.1 ;**http://www.R-project.org**). Continuous variables were presented as mean ± standard deviation for normally distributed variables or median (interquartile range) for non-normally distributed variables. Differences between the two groups were compared using *t*-test or Mann-Whitney *U* test. Meanwhile, categorical variables were expressed by frequency (percentage) and assessed by Pearson's chi-square test or Fisher exact test. ROC curve analysis was used to determine the optimal cutoff values base on the maximum Youden index. Survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. The Cox regression analysis was used for both univariate and multivariate analyses. Variables with *P*-values < 0.10 in univariable analysis were introduced into the multivariate COX proportional hazards model to further determine the independent prognostic factors with a backward stepwise selection. The LASSO Cox regression model analysis was based on the glmnet package. The nomogram and calibration curve were established using rms package, while DCA was performed using the dca.R package. The predictive performance of the nomograms was evaluated by the C-index. A *P* value< 0.05 was considered statistically significant.

3.Results

3.1 Patient demographics and clinicopathological characteristics

544 patients who met the inclusion and exclusion criteria were retrospectively analyzed in the study. The comparison of clinicopathological characteristics between the training cohort (n=381) and validation cohort (n=163) are shown in Table 1. The median follow-up time was 28.8 months (15.1-40.5 months) in training cohort and 27.2 (16.9-39.5) months in validation cohort. No significant differences in baseline characteristics were noted between the two groups ($P > 0.05$), suggesting similarity in the cohorts.

3.2 construction and validation of radiomics signature

We evaluated the ROIs of the hepatic tumors from preoperative CT images and extracted a total of 269 texture features. Then, the LASSO Cox regression model was used to select the most significant features for survival prediction (Fig.1). When the minimum lambda was 0.03427317, seven potential predictors of OS-related features with non-zero coefficients were screened out in the training cohort. A radiomics signature was constructed with selected features and their respective weights. The Rad-score for each patient can be calculated using the following formula: Rad-score = S(0,1)Correlat *0.02621384+S(0,3)Correlat*0.03557228+ Horzl_GLevNonU*0.31206038+45dgr_RLNonUni*0.02432387+45dgr_GLevNonU*0.0355 6648+Sigma*(-0.06838016)+WavEnLH_s-4*0.03722060). According to the optimum cut-off Rad-score based on the maximum Youden index in the training cohort, all patients were classified into high-risk group (Rad-score≥ -0.559) and low-risk group (Rad-score < -0.559). The OS was compared between the two groups using Kaplan-Meier analysis (Fig.2) in both training and validation cohorts. The 1, 3 and 5-year OS of the low-risk group was 91.7%, 82.1% and 78.7%, which were significantly higher than those of the high-risk group in training cohort (71.0%, 45.5% and 35.5%, P < 0.001).The performance of the radiomics signature was confirmed by testing in the validation cohort, with significant difference at 1, 3 and 5-year OS between the high-risk and low-risk groups (72.3%, 40.9%, 36.8% vs. 93.8%, 83.4%, 81.0%, P < 0.001). We observed that patients with lower Rad-scores generally had better OS.

In order to further evaluate the association between the radiomics signature and clinicopathological features, the clinicopathological data of high-risk group and low-risk group

were compared (Table 2). In the training cohort, there was no significant difference between the low-risk and high-risk groups with regard to age, sex, BMI, HBsAg, HBV-DNA, liver cirrhosis, Child-Pugh classification, previous abdominal surgery, comorbidities, CEA, CA19-9, TBIL, DBIL, ALT, Albumin, NLR, ASA grade, tumor number, hepatectomy, differentiation. However, high-risk group was positively associated with higher AFP (P=0.007), higher AST ($P < 0.001$), higher PLR ($P = 0.001$), larger tumor size ($P < 0.001$), more hemorrhage ($P < 0.001$), more intraoperative transfusion ($P = 0.019$), presence of MVI ($P = 0.003$), incomplete tumor capsule ($P < 0.001$) and higher Rad-score ($P < 0.001$). A significant difference was evident between the Rad-scores of the two groups in the training cohort (-0.1[-0.3~0.5] vs-0.8[-1.0~-0.7]; $P < 0.001$).

Fig.1 Radiomics feature selection using the LASSO Cox regression model. **a** Tuning parameter (λ) was selected in the LASSO model via 10-fold cross-validation based on minimum criteria. **b** The coefficients of the 269 radiomics features were examined and 7 features with nonzero coefficients were selected to build the radiomics signature.

Fig.2 Kaplan-Meier survival analysis for the patients in the high- and low-risk groups in the training cohorts (a) and validation cohort (b).

3.3 development and validation of radiomics nomogram

The results of the univariate analysis based on the validation cohort are displayed in Table 3. According to the univariate analysis, HBsAg, HBV-DNA, AFP, NLR, PLR, largest tumor size, hemorrhage, intraoperative transfusion, differentiation, MVI, capsule and Rad-score were potential risk factors for OS. However, the result of multivariate analysis suggested that only AFP (HR 1.566; CI 1.101-2.226; p=0.013), PLR (HR 1.004; CI 1.001-1.007; p=0.010), largest tumor size (HR 1.084; CI 1.027-1.145; p=0.003), MVI (HR 2.509; CI 1.751-3.594; $p<$ 0.001) and Rad-score (HR 1.398; CI 1.188-1.646; $p<0.001$) were independently associated with unfavorable postoperative survival. The radiomics nomogram was constructed with the 5 independent risk predictors identified above to predict the personalized survival status, while the clinicopathologic nomogram incorporated only the independent clinicopathological risk factors. The C-index of clinicopathologic nomogram is 0.726 (95% CI 0.705-0.748) in the training cohort and 0.720 (95% CI 0.686-0.755) in the validation cohort. The radiomics nomogram yielded a C-index of 0.747 (95% CI, 0.727-0.768) in the training cohort, and a C-index of 0.777 (95% CI, 0.748–0.806) in the validation cohort. The radiomics nomogram showed improved discrimination performance when it integrated the radiomics signature into clinicopathologic nomogram (P=0.002 in the training cohort, p<0.001 in the validation cohort). (Table 4) The radiomics nomogram and corresponding calibration curve were presented in Fig. 3. The calibration curve demonstrated satisfying consistency between nomogram-predicted survival and actual observation in the training and validation cohort.

Fig.3 The radiomics nomogram for the prediction of survival status(a). The calibration curves of the radiomics nomogram in the training cohorts (b) and validation cohort (c).

Clinical utility

The DCA of the radiomics and clinicopathologic nomogram are presented in Fig.4. The DCA demonstrated that the radiomics nomogram provided higher net benefit than the clinicopathologic nomogram on survival prediction in patients with HCC.

Fig.4 Decision curve analysis for the radiomics and clinicopathologic nomogram in the entire cohort(n=544). The y-axis represents the net benefit, and the x-axis represents the threshold probability. The black line represents the assumption that no patients had long-term overall survival (OS). The grey line represents the assumption that all patients had long-term OS. The decision curves indicated that radiomics nomogram (red line) showed better clinical utility than clinicopathologic nomogram (blue line).

4.Dicussion

Surgical resection remains the mainstay curative treatment for people with HCC, but the prognosis varies from people to people. Prediction of survival status in patients with HCC after operation is important for clinical decision-making. Among numerous prognostic factors, tumor heterogeneity is one of the most important contributions, which may relate to different natural history, environmental susceptibility and individual genetic tendency.[21] Intra-tumoral heterogeneity can reveal tumor growth, metastatic potential and response to treatment, which may be a potential prognostic predictor of disease outcome[22]. However, previous studies were mainly based on clinicopathological factors,[23,24] and seldom involved imaging information, or only included a small number of subjective imaging parameters.[25,26] What' more, a large amount of tumor information hiding behind the imaging is ignored. Radiomics can capture the potential heterogeneity of the lesions using a large number of quantitative image features, which may be a valuable supplement to the existing predictors.

Medical imaging plays an important role in preoperative diagnosis, choice of therapy, therapeutic effect evaluation and surveillance of diseases. However, the interpretation of medical imaging was often based on the physicians' personal expertise and experience, which was subjective and qualitative. Radiomics can analyze the texture parameters extracted by computer and allow the quantitative assessment of the pixel differences of imaging to provide more comprehensive information of tumors that may not be detected by the human eye. And the temporal and spatial heterogeneity of the tumor can be evaluated by entire tumor analysis instead of limited biopsy samples. Medical imaging analysis can reveal the tumor biological process and microenvironment characteristics and may assist in therapeutic decision-making. However, few studies focused on prognosis prediction in patients with HCC. Therefore, this study aimed to develop a radiomics signature to predict the prognosis of patients with HCC after surgical resection based on selected radiomics features. Moreover, a nomogram was constructed based on the independent risk factors, allowing for more precise prognostication, better clinical management and more appropriate adjuvant therapy. This study introduced a noninvasive, low cost and reproducible method to predict the outcomes in patients with resectable HCC, which of great significance for personalized medicine.

Malignant tumor is composed of heterogeneous cells and their surrounding microenvironment, and the intra-tumor heterogeneity is associated with tumor angiogenesis and biological behavior，which could be assessed through imaging traits. And the potential clinical applicability of radiomics has been explored. Huang et al.[27] developed a radiomics nomogram，

which exhibited favorable accuracy for preoperative prediction of lymph node metastasis in patients with colorectal cancer. Wu et al.[28] developed a radiomics nomogram for preoperative prediction of lymph node metastasis in bladder cancer, found that CT texture parameters were independent predictors of response to chemotherapy. Ahn et al. [29] demonstrated lower skewness in the 2D analysis and narrower SD in the 3D analysis were useful predictors to chemotherapy response in colon cancer liver metastasis. In addition, the radiomics signature could be used to predict preoperative individualized MVI status and the early recurrence of HCC. [30,31] The previous studies showed that the radiomics features correlate with genomics and proteomics, through capturing the tumor phenotypes, which are associated with underlying gene expression patterns of cancer and may help reflect cellular proliferation, liver synthetic function and patient prognosis. [32-35]Segal et al. [32]reported that the variation of all 116 genes modules can be reconstructed from 28 imaging traits. However, more studies are needed to confirm the potential association between radiophenotype and gene expression for a limited number of literatures. [36,37]

In our study, 5 optimal features were chosen from 269 radiomics features of portal venous phases via the LASSO method to build a radiomics signature and the patients were divided into high-risk group and low-risk group according to the threshold of the Rad-score. The results indicated that patients with higher Rad-scores were associated with worse OS than lower Rad-scores. In multivariate analysis, the radiomics signature was further proved to be an independent predictor of OS. The study provides a method for prognosis-related high dimensional data selection. LASSO is penalized regression approach through selecting covariates with non-zero coefficient to among numerous covariates to avoid overfitting, thus improving the prediction efficiency. [38]Those radiomic features provided a quantitative description of the position, intensity and inter-relationship of the pixels [12,39] to reveal tumor phenotypic differences and evaluate the intra-tumor heterogeneity, which is related to tumor proliferation, hypoxia, angiogenesis and necrosis. Increased homogeneity in colorectal cancer was related with a poor prognosis, while increased heterogeneity in oesophageal cancer and gastric cancer was associated with a poor prognosis.[40-43] Entropy and uniformity are common texture parameters, and higher entropy and lower uniformity reflected increased tumor heterogeneity. [44] However, a large number of texture parameters concerning with tumor aggressiveness have not been well studied.

The present study showed that AFP, PLR, the largest tumor size, MVI and radiomics signature were the independent risk factors for OS. In agreement with the previous study, these clinicopathologic factors are known effective predictors of the clinical outcome.[45-48]It also has been noted that the inflammation marker was related to HCC aggressiveness and PLR was included in the final model in our study.[49] However, the tumor number and the differentiation of the tumor were not associated with survival status in our study. The possible reasons are limited cases of multifocal lesions and short follow-up time in the present study. Furthermore, in the subgroup analysis, the high-risk group tended to show higher AFP, higher AST, higher PLR, larger tumor size, more hemorrhage, more intraoperative transfusion, presence of MVI and incomplete tumor capsule, which are proven prognostic indicators of HCC, [23,24,50,51]indicating the potential association between the radiomics signature and clinicopathologic factors. In this light, texture parameters are linked to clinicopathologic factors, which could assist clinicians in prognostic evaluation.

We established a combined nomogram incorporating clinicopathologic factors and radiomics signature for prognostic prediction at individual level. The results indicated that the radiomics nomogram showed improved predictive accuracy than the clinicopathologic nomogram, thereby indicating that the radiomics signature can provide additional prognostic and biologic information, which was consistent with the previous studies. Meng et al.[52] performed a study in 108 consecutive patients with locally advanced rectal cancer, and the results implied that the combined model (C-index=0.788) possessed improved predictive ability for 3-year disease free survival than the radiomic (C-index=0.767) and clinicoradiologic model (C-index=0.644). Li et al.[53] explored the prognostic value of radiomics in 181 patients with gastric cancer following curative resection，which revealed that radiomics nomogram (C-index=0.82) showed better predictive ability than clinical nomogram（C-index= 0.71）or radiomics signature（C-index= 0.74）. Based on the results of our study, the aggressive precautions can be taken in patients with predicted poor prognoses, thus facilitating the effective therapeutic management and reduced risk of recurrence.

The limitations of this study are as follows: (1) this study is a retrospective single-center study with small sample size, and the results of the study are limited. In addition, the model was only verified internally and lacked the external validation. (2) Contrast-enhanced CT is used in our study, while contrast-enhanced MRI can capture more microstructure characteristics of tumor and may provide more comprehensive information of tumor heterogeneity.[54](3) In our study, only the largest cross-section of a lesion in portal phase was analyzed, while the whole tumor analysis in both arterial and portal phase may improve the efficiency of survival prediction in people with HCC. (4) Although the ROIs were derived through manual segmentation by two radiologists, the subjective bias could not be completely eliminated. Therefore, further study is warranted to confirm our results.

In conclusion, the radiomics signature provided a quantitative method for assessment of survival status in patients with HCC after hepatectomy. The patients with high Rad-scores may experience higher risk of recurrence and metastasis. What's more, the radiomics nomogram integrating clinicopathological factors and radiomics signature may serve as an effective tool to guide the individualized management and tailored follow-up. In the future, multicenter prospective studies are needed to further investigate the potential value of radiomics signature in clinical practice.

Declarations

Ethics approval and consent to participate

The study was approved by the Committee of Ethics in West China Hospital of Sichuan University. Informed consent was obtained from each individual for the study.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

(I) Conception and design: Weixia Chen, Yonggang Wei, Bo Li, Lu Zheng; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: Qinqin Liu, Jing Li, Fei Liu, Weilin Yang, Jingjing Ding; (V) Data analysis and interpretation: Qinqin Liu, Jing Li, Fei Liu, Weilin Yang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abbreviations

HCC: Hepatocellular carcinoma

CT: computed tomography

LASSO: least absolute shrinkage and selection operator

OS: overall survival

ROIs: regions of interest

ROC: receiver operating characteristic

C-index: concordance index

DCA: decision curve analysis

BCLC: Barcelona Clinic Liver Cancer

TA: texture analysis

TACE: transcatheter arterial chemoembolization

AFP: α-fetoprotein
PLR: platelet lymphocyte ratio
MVI: microvascular invasion
DICOM: Digital Imaging and Communications in Medicine
Rad-score: radiomics score
ASA: American Society of Anesthesiologists
BMI: body mass index
ALT: alanine transaminase
AST: aspartate aminotransferase
NLR: neutrophil-to-lymphocyte ratio

References

1. El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology 2007;132:2557-2576.
2. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011;61:69-90.
3. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol 2012;56:908-943.
4. Earl TM, Chapman WC. Hepatocellular carcinoma: resection versus transplantation. Semin Liver Dis 2013;33:282-292.
5. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg 2002;235:373-382.
6. Shah SA, Cleary SP, Wei AC, et al. Recurrence after liver resection for hepatocellular carcinoma: risk factors, treatment, and outcomes. Surg 2007;141:330-339.
7. Lacaze L, Scotte M. Surgical treatment of intra hepatic recurrence of hepatocellular carcinoma. World J hepato 2015;7:1755-1760.
8. Vitale A, Burra P, Frigo AC, et al. Survival benefit of liver resection for patients with hepatocellular carcinoma across different Barcelona Clinic Liver Cancer stages: a multicentre study. J Hepatol 2015;62:617-624.
9. Bolondi L, Burroughs A, Dufour JF, et al. Heterogeneity of patients with intermediate (BCLC B) Hepatocellular Carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis 2012;32:348-359.
10. Huitzil-Melendez FD, Capanu M, O'Reilly EM, et al. Advanced hepatocellular carcinoma: which staging systems best predict prognosis? J Clin Oncol 2010;28:2889-2895.
11. Roberts LR, Sirlin CB, Zaiem F, et al. Imaging for the diagnosis of hepatocellular carcinoma: A systematic review and meta-analysis. Hepatol 2018;67:401-421.
12. Castellano G, Bonilha L, Li LM, Cendes F. Texture analysis of medical images. Clin Radiol 2004;59:1061-1069.
13. Lubner MG, Smith AD, Sandrasegaran K, Sahani DV, Pickhardt PJ. CT Texture Analysis: Definitions, Applications, Biologic Correlates, and Challenges. Radiographics 2017;37:1483-1503.

14. Gillies RJ, Kinahan PE, Hricak H. Radiomics: Images Are More than Pictures, They Are Data. Radiology 2016;278:563-577.
15. Miles KA, Ganeshan B, Griffiths MR, Young RC, Chatwin CR. Colorectal cancer: texture analysis of portal phase hepatic CT images as a potential marker of survival. Radiology 2009;250:444-452.
16. Ba-Ssalamah A, Muin D, Schernthaner R, et al. Texture-based classification of different gastric tumors at contrast-enhanced CT. Eur J Radiol 2013;82:e537-543.
17. Simpson AL, Adams LB, Allen PJ, et al. Texture analysis of preoperative CT images for prediction of postoperative hepatic insufficiency: a preliminary study. J Am Coll Surg. 2015;220:339-346.
18. Sauerbrei W, Royston P, Binder H. Selection of important variables and determination of functional form for continuous predictors in multivariable model building. Stat Med 2007;26:5512-5528.
19. Vasquez MM, Hu C, Roe DJ, Chen Z, Halonen M, Guerra S. Least absolute shrinkage and selection operator type methods for the identification of serum biomarkers of overweight and obesity: simulation and application. BMC Med Res Methodol 2016;16:154.
20. Vickers AJ, Elkin EB. Decision curve analysis: a novel method for evaluating prediction models. Med Decis Making 2006;26:565-574.
21. Li L, Wang H. Heterogeneity of liver cancer and personalized therapy. Cancer lett 2016;379:191-197.
22. Hlady RA, Robertson KD. Genetic and Epigenetic Heterogeneity in Normal Liver Homeostasis and Its Implications for Liver Disease and Hepatocellular Cancer. Semin Liver dis. 2018;38:41-50.
23. Wan G, Gao F, Chen J, et al. Nomogram prediction of individual prognosis of patients with hepatocellular carcinoma. BMC cancer. 2017;17:91.
24. Zhang W, Tan Y, Jiang L, et al. Prognostic nomogram for patients with non-B non-C hepatocellular carcinoma after curative liver resection. Int J Surg 2017;44:160-165.
25. Han JH, Kim DG, Na GH, et al. Evaluation of prognostic factors on recurrence after curative resections for hepatocellular carcinoma. World J Gastroentero 2014;20:17132-17140.
26. Hayano K, Yoshida H, Zhu AX, Sahani DV. Fractal analysis of contrast-enhanced CT images to predict survival of patients with hepatocellular carcinoma treated with sunitinib. Digest Dis Sci 2014;59:1996-2003.
27. Huang YQ, Liang CH, He L, et al. Development and Validation of a Radiomics Nomogram for Preoperative Prediction of Lymph Node Metastasis in Colorectal Cancer. J Clin Oncol 2016;34:2157-2164.
28. Wu S, Zheng J, Li Y, et al. A Radiomics Nomogram for the Preoperative Prediction of Lymph Node Metastasis in Bladder Cancer. Clin cancer res 2017;23:6904-6911.
29. Ahn SJ, Kim JH, Park SJ, Han JK. Prediction of the therapeutic response after FOLFOX and FOLFIRI treatment for patients with liver metastasis from colorectal cancer using computerized CT texture analysis. Eur J radiol 2016;85:1867-1874.
30. Peng J, Zhang J, Zhang Q, Xu Y, Zhou J, Liu L. A radiomics nomogram for preoperative prediction of microvascular invasion risk in hepatitis B virus-related hepatocellular

carcinoma. Diagn Interv radiol 2018;24:121-127.
31. Zhou Y, He L, Huang Y, et al. CT-based radiomics signature: a potential biomarker for preoperative prediction of early recurrence in hepatocellular carcinoma. Abdom radiol 2017;42:1695-1704.
32. Segal E, Sirlin CB, Ooi C, et al. Decoding global gene expression programs in liver cancer by noninvasive imaging. Nat Biotechnol 2007;25:675-680.
33. Banerjee S, Wang DS, Kim HJ, et al. A computed tomography radiogenomic biomarker predicts microvascular invasion and clinical outcomes in hepatocellular carcinoma. Hepatology 2015;62:792-800.
34. Aerts HJ, Velazquez ER, Leijenaar RT, et al. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. Nat Commun 2014;5:4006.
35. Rutman AM, Kuo MD. Radiogenomics: creating a link between molecular diagnostics and diagnostic imaging. Euro J Radiol 2009;70:232-241.
36. Panth KM, Leijenaar RT, Carvalho S, et al. Is there a causal relationship between genetic changes and radiomics-based image features? An in vivo preclinical experiment with doxycycline inducible GADD34 tumor cells. Radiother Oncol 2015;116:462-466.
37. Lambin P, Rios-Velazquez E, Leijenaar R, et al. Radiomics: extracting more information from medical images using advanced feature analysis. Eur J Cancer 2012;48:441-446.
38. Kim SM, Kim Y, Jeong K, Jeong H, Kim J. Logistic LASSO regression for the diagnosis of breast cancer using clinical demographic data and the BI-RADS lexicon for ultrasonography. Ultrasonography 2018;37:36-42.
39. Chicklore S, Goh V, Siddique M, Roy A, Marsden PK, Cook GJ. Quantifying tumour heterogeneity in 18F-FDG PET/CT imaging by texture analysis. Eur J Nucl Med Mol I. 2013;40:133-140.
40. Ganeshan B, Skogen K, Pressney I, Coutroubis D, Miles K. Tumour heterogeneity in oesophageal cancer assessed by CT texture analysis: preliminary evidence of an association with tumour metabolism, stage, and survival. Clin Radiol 2012;67:157-164.
41. Ng F, Ganeshan B, Kozarski R, Miles KA, Goh V. Assessment of primary colorectal cancer heterogeneity by using whole-tumor texture analysis: contrast-enhanced CT texture as a biomarker of 5-year survival. Radiology 2013;266:177-184.
42. Yip C, Landau D, Kozarski R, et al. Primary esophageal cancer: heterogeneity as potential prognostic biomarker in patients treated with definitive chemotherapy and radiation therapy. Radiology 2014;270:141-148.
43. Giganti F, Antunes S, Salerno A, et al. Gastric cancer: texture analysis from multidetector computed tomography as a potential preoperative prognostic biomarker. Eur Radiol 2017;27:1831-1839.
44. Ganeshan B, Miles KA, Young RC, Chatwin CR. Hepatic entropy and uniformity: additional parameters that can potentially increase the effectiveness of contrast enhancement during abdominal CT. Clin Radiol 2007;62:761-768.
45. Jing YY, Liu WT, Guo SW, et al. Hepatitis B virus (HBV) receptors: Deficiency in tumor results in scant HBV infection and overexpression in peritumor leads to higher

recurrence risk. Oncotarget 2015;6:42952-42962.
46. Rodriguez-Peralvarez M, Luong TV, Andreana L, Meyer T, Dhillon AP, Burroughs AK. A systematic review of microvascular invasion in hepatocellular carcinoma: diagnostic and prognostic variability. Ann Surg Oncol 2013;20:325-339.
47. Kang SH, Kim DY, Jeon SM, et al. Clinical characteristics and prognosis of hepatocellular carcinoma with different sets of serum AFP and PIVKA-II levels. Eur J Gastroen Hepat 2012;24:849-856.
48. Chang SK, Hlaing WW, Yu RQ, Lee TW, Ganpathi IS, Madhavan KK. Value of alpha-foetoprotein for screening of recurrence in hepatocellular carcinoma post resection. Singap Med J 2012;53:32-35.
49. Wang D, Bai N, Hu X, et al. Preoperative inflammatory markers of NLR and PLR as indicators of poor prognosis in resectable HCC. PeerJ 2019;7:e7132.
50. Li Z, Zhao X, Jiang P, et al. HBV is a risk factor for poor patient prognosis after curative resection of hepatocellular carcinoma: A retrospective case-control study. Medicine 2016;95:e4224.
51. Gao F, Li X, Geng M, et al. Pretreatment neutrophil-lymphocyte ratio: an independent predictor of survival in patients with hepatocellular carcinoma. Medicine 2015;94:e639.
52. Meng Y, Zhang Y, Dong D, et al. Novel radiomic signature as a prognostic biomarker for locally advanced rectal cancer. Journal of magnetic resonance imaging : JMRI. 2018.
53. Li W, Zhang L, Tian C, et al. Prognostic value of computed tomography radiomics features in patients with gastric cancer following curative resection. Eur Radiol 2018.
54. Kitao A, Matsui O, Yoneda N, et al. Hypervascular hepatocellular carcinoma: correlation between biologic features and signal intensity on gadoxetic acid-enhanced MR images. Radiology 2012;265:780-789.

Figures

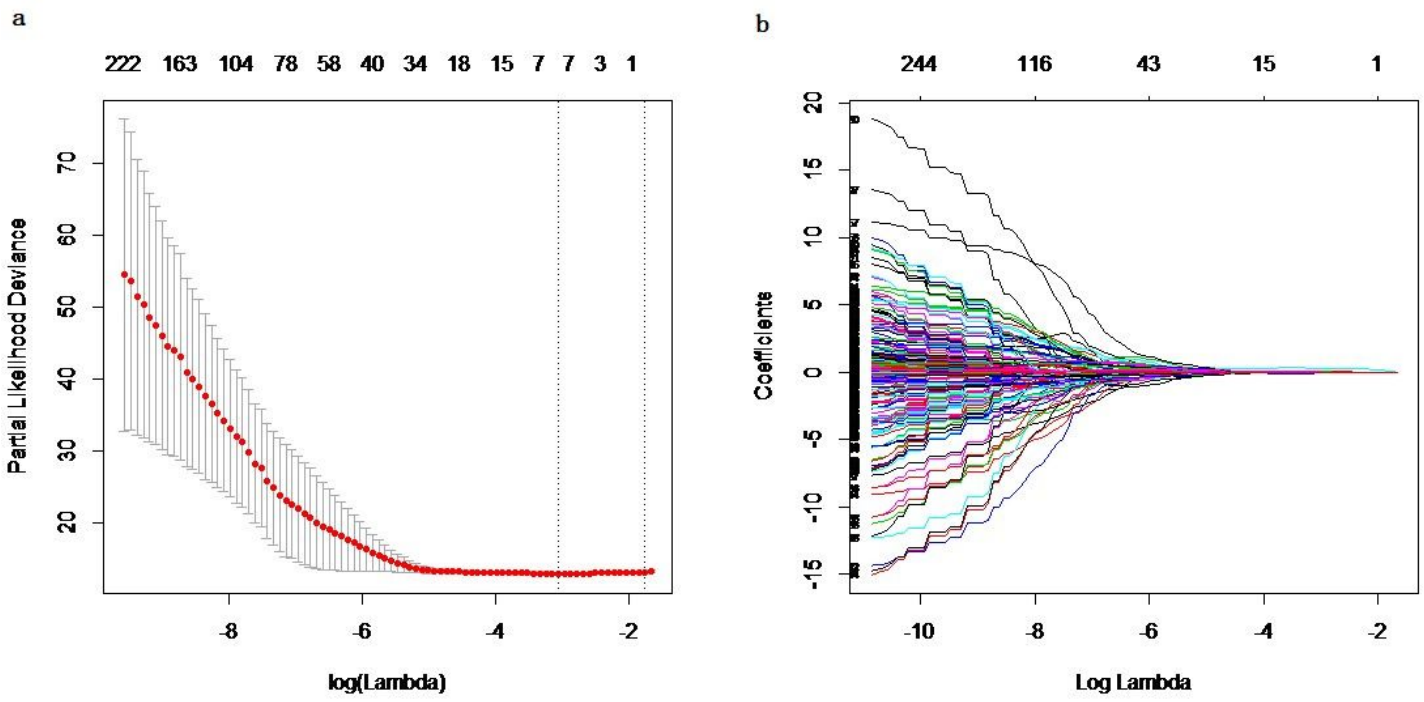

Figure 1

Radiomics feature selection using the LASSO Cox regression model. a Tuning parameter (λ) was selected in the LASSO model via 10-fold cross-validation based on minimum criteria. b The coefficients of the 269 radiomics features were examined and 7 features with nonzero coefficients were selected to build the radiomics signature.

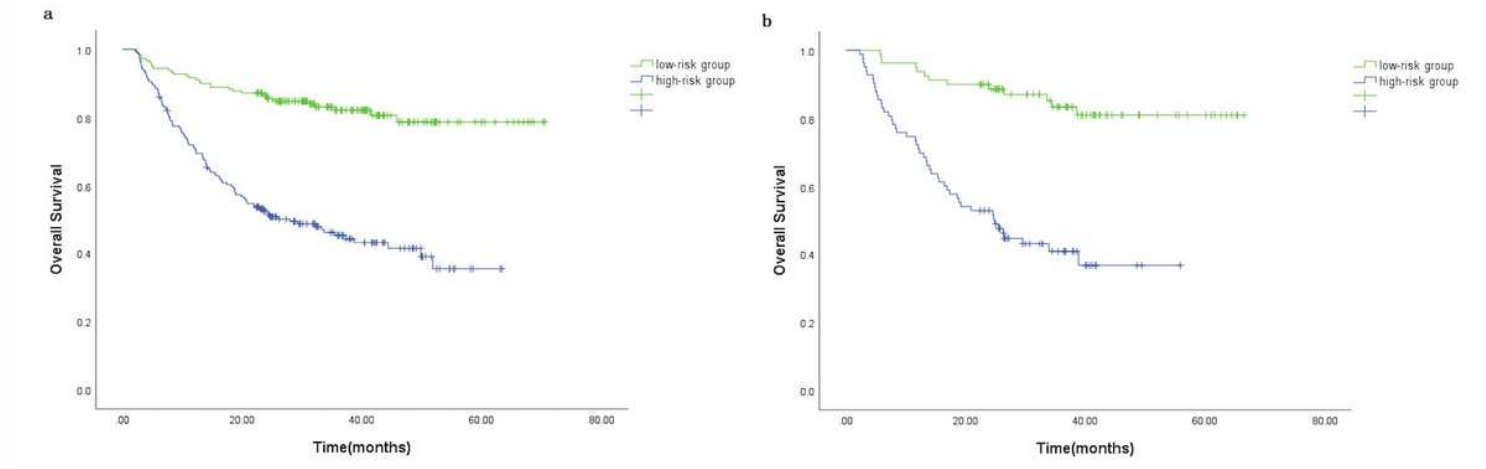

Figure 2

Kaplan-Meier survival analysis for the patients in the high- and low-risk groups in the training cohorts (a) and validation cohort (b).

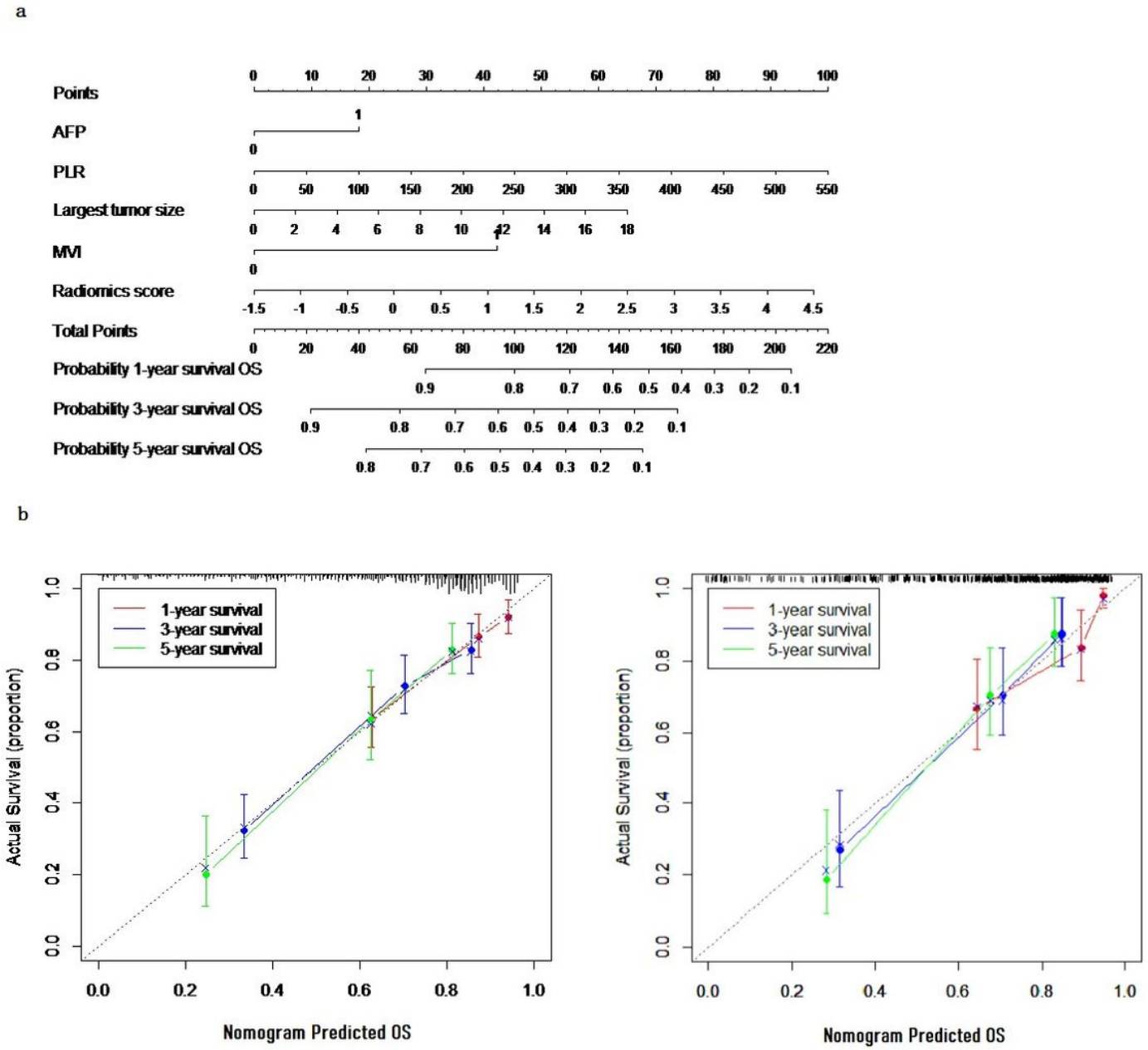

Figure 3

The radiomics nomogram for the prediction of survival status(a). The calibration curves of the radiomics nomogram in the training cohorts (b) and validation cohort (c).

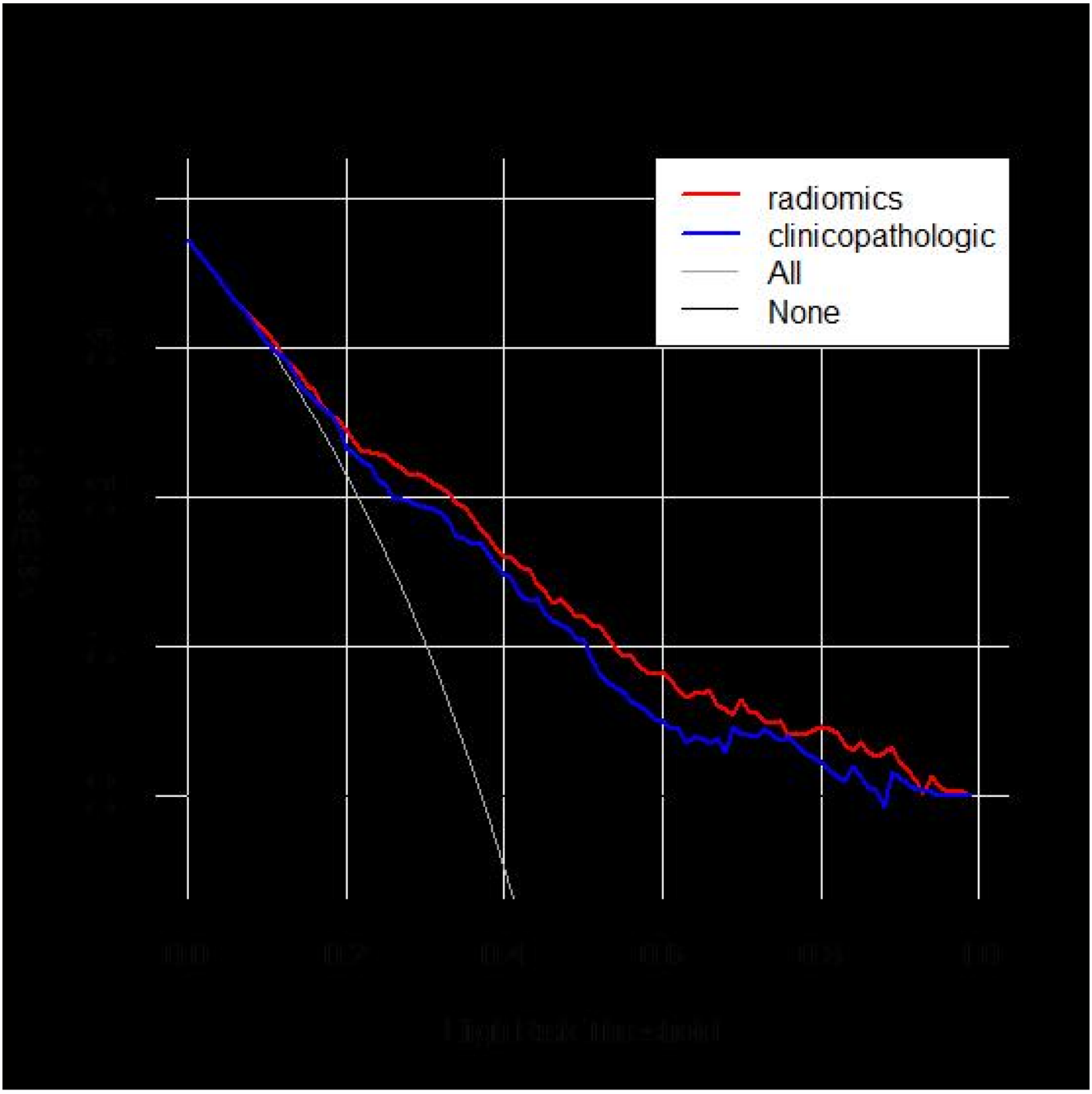

Figure 4

Decision curve analysis for the radiomics and clinicopathologic nomogram in the entire cohort(n=544). The y-axis represents the net benefit, and the x-axis represents the threshold probability. The black line represents the assumption that no patients had long-term overall survival (OS). The grey line represents the assumption that all patients had long-term OS. The decision curves indicated that radiomics nomogram (red line) showed better clinical utility than clinicopathologic nomogram (blue line).

Supplementary Files

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- table.pdf