Heliyon 10 (2024) e33702

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Integrating MR radiomics and dynamic hematological factors predicts pathological response to neoadjuvant chemoradiotherapy in esophageal cancer

Yunsong Liu [a], Zeliang Ma [a], Yongxing Bao [a], Xin Wang [a], Yu Men [b], Xujie Sun [c], Feng Ye [d], Kuo Men [a], Jianjun Qin [e], Nan Bi [a], Liyan Xue [c], Zhouguang Hui [b,*]

[a] *Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*
[b] *Department of VIP Medical Services, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*
[c] *Department of Pathology, National Cancer Center/ National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*
[d] *Department of Diagnostic Radiology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*
[e] *Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

ARTICLE INFO

Keywords:
Esophageal neoplasms
Magnetic resonance
Hematologic tests
Treatment outcome
Neoadjuvant chemoradiotherapy

ABSTRACT

Purpose: We aimed to integrate MR radiomics and dynamic hematological factors to build a model to predict pathological complete response (pCR) to neoadjuvant chemoradiotherapy (NCRT) in esophageal squamous cell carcinoma (ESCC).

Methods: Patients with ESCC receiving NCRT and esophagectomy between September 2014 and September 2022 were retrospectively included. All patients underwent pre-treatment T2-weighted imaging as well as pre-treatment and post-treatment blood tests. Patients were randomly divided to training set and testing set at a ratio of 7:3. Machine learning models were constructed based on MR radiomics and hematological factors to predict pCR, respectively. A nomogram model was developed to integrate MR radiomics and hematological factors. Model performances were evaluated by areas under curves (AUCs), sensitivity, specificity, positive predictive value and negative.

Results: A total of 82 patients were included, of whom 39 (47.6 %) achieved pCR. The hematological model built with four hematological factors had an AUC of 0.628 (95%CI 0.391–0.852) in the testing set. Two out of 1106 extracted features were selected to build the radiomics model with an AUC of 0.821 (95%CI 0.641–0.981). The nomogram model integrating hematological

Abbreviations: ESCC, Esophageal squamous cell carcinoma; NCRT, Neoadjuvant chemoradiotherapy; pCR, Pathological complete response; AUC, Area under the curve; T2WI, T2-weighted imaging; ROI, Region of interest; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index; PNI, prognostic nutritional index; RF-RFE, Random Forest-Recursive Feature Elimination; ROC, Receiver operating characteristics; PPV, Positive predictive value; NPV, Negative predictive value; DCA, Decision curve analysis.

* Corresponding author. Department of VIP Medical Services, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. Panjiayuan Nanli #17, Chaoyang District, Beijing, 100021, China.

E-mail address: drhuizg@163.com (Z. Hui).

https://doi.org/10.1016/j.heliyon.2024.e33702
Received 31 January 2024; Received in revised form 8 June 2024; Accepted 25 June 2024
Available online 26 June 2024

factors and MR radiomics had best predictive performance, with an AUC of 0.904 (95%CI 0.770–1.000) in the testing set.
Conclusion: An integrated model using dynamic hematological factors and MR radiomics is constructed to accurately predicted pCR to NCRT in ESCC, which may be potentially useful to assist individualized preservation treatment of the esophagus.

1. Introduction

For esophageal squamous cell carcinoma (ESCC), neoadjuvant chemoradiotherapy (NCRT) followed by surgery has become a standard of care, with improved survival and surgical outcomes compared to surgery alone [1,2]. Randomized controlled trials showed the pathological complete response (pCR) rate of more than 40 % for ESCC after neoadjuvant chemoradiotherapy [1,2]. For those patients, active surveillance instead of instant esophagectomy can be a proper option to preserve organ function with the guarantee of salvage surgery, which has similar survival compared to trimodality treatment [3]. Besides, pCR has been proved to be a most valuable prognostic factor with significant correlation with survival outcomes [4,5]. Therefore, early prediction of pCR is of great importance to guide individualized treatment.

Although previous efforts using clinical factors and medical images has been made to predict pCR of ESCC receiving NCRT, none of those methods can be applied to clinical practice due to unsatisfactory accuracy [6]. For instance, CT scans have demonstrated a sensitivity of only 33%–55 % and a specificity of 50%–70 % for detecting pCR, according to a systematic review [7]. Similarly, a meta-analysis of 44 studies indicated that endoscopy with biopsy had a specificity of just 33 %, while quantitative PET-CT analysis yielded pooled sensitivity and specificity of around 70 % [6]. In contrast, radiomics, which involves the quantitative extraction of features from medical images to produce high-dimensional, analyzable data, has shown significant promise in developing personalized treatment plans and understanding disease mechanisms [8]. In predicting pCR after NCRT for esophageal cancer, radiomics based on CT and PET/CT improved predictive performance with areas under the curves (AUCs) reaching approximately 0.8(9). However, those studies used traditional imaging modalities like CT and PET-CT, which have low soft-tissue resolution, reducing the amount of detailed tumor information available. Besides, the accuracy of these methods has not been satisfactory enough to meet clinical demands.

Emerging evidence has shown the high value of MR in predicting neoadjuvant treatment response. It is broadly studied in breast and rectal cancer that radiomics using MR can predict pCR after NCRT accurately, with satisfactory reproductivity [9–12]. Preliminary research focusing on esophageal cancer suggested that MRI sequences, such as T2-weighted imaging (T2WI) and diffusion-weighted imaging (DWI), might be valuable tools for predicting pCR, with AUCs between 0.7 and 0.9 [13, 14]. However, those studies relying solely on imaging may overlook important information about the overall body status and response. While existing imaging studies have provided valuable insights, they haven't fully explored the integration of other biomarkers.

Dynamic hematological factors derived from multi-timepoint blood tests indicate inflammation and nutritional status and have been associated with treatment responses and prognoses in various cancer types, including ESCC [15–17]. However, although these studies have established correlations, the precise predictive value of these hematological factors in cancer outcomes remains to be conclusively determined.

Few studies have explored the potential of MR radiomics in predicting the response to neoadjuvant treatment in ESCC [18]. Furthermore, the potential additive value of hematological factors alongside radiomics remains an area ripe for investigation. Our study aimed to bridge this gap by combining MR radiomics and dynamic hematological factors to develop and validate a model to precisely predict pCR to NCRT in ESCC, potentially offering a more comprehensive and accurate tool for treatment planning and prognosis assessment in this patient population.

2. Method

2.1. Patients

Clinical and image records of ESCC patients between September 2014 and September 2022 were reviewed. In patients received MR scanning, most only had sequences of plain T1WI and T2WI. However, given the enhanced sensitivity of T2WI in detecting and characterizing tumor tissues, it was selected as the primary imaging modality for our analysis. Patients were enrolled based on the following inclusion criteria [1]: histological confirmation of esophageal or gastro-esophageal junction squamous cell carcinoma [2]; underwent neoadjuvant chemoradiation followed by esophagectomy [3]; had pretreatment T2WI, and [4] were aged between 18 and 80. This study was approved by the institutional review boards and the patient informed consent was waived for the retrospective design.

Patients were randomly divided into the training and testing set at a ratio of 7:3.

2.2. Treatment and Histopathological response evaluation

Platinum plus paclitaxel based or 5-fluorouracil based regimen were adopted. Radiotherapy was administered using intensity-modulated radiation therapy or volumetric modulated arc therapy technique, with prescribed dose of 2Gy per fraction (PTV) by 20∼25 fractions or 2.14Gy (PGTV)/1.8Gy (PTV) per fraction by 20∼23 fractions.

Patients received curative esophagectomy within 16 weeks after the completion of NCRT. Each patient's surgical specimens were assessed by at least two pathologists specialized in esophageal cancer and pCR was defined as ypT0N0.

2.3. Measures of hematological factors

The blood samples of patients were collected at two time points: within 1 month prior to NCRT and within 1 week prior to surgery after NCRT. The following items were recorded: white blood cell count, neutrophil count, lymphocyte count, monocyte count, platelet count, and albumin. The definitions for the ratios and indices were calculated as follows: neutrophil to lymphocyte ratio (NLR) = neutrophil counts/lymphocyte counts; monocyte to lymphocyte ratio (MLR) = monocyte counts/lymphocyte counts; platelet to lymphocyte ratio (PLR) = platelet counts/lymphocyte counts; systemic immune-inflammation index (SII) = platelet counts × neutrophil counts/lymphocyte counts; prognostic nutritional index (PNI) = albumin level + 5 × total lymphocyte counts. The values of pre-NCRT, post-NCRT and delta-NCRT (values of post-NCRT minus pre-NCRT) of albumin, NLR, MLR, PLR, SII, and PNI were used as hematological factors for further analysis. These factors resulted in a total of 18 variables (eTable 1).

MR image acquisition and Regions of interest (ROIs)

MR scanning was performed within two weeks prior to the initiation of treatment. T2WI were scanned on either two MR scanners: GE Discovery MR750w (3.0 T, TR/TE: 11250/88 ms, echo train length: 32, flip angel: 90°/142°) and GE Discovery MR750 (3.0 T, TR/TE: 18000/99 ms, echo train length: 32, flip angel: 90°). The primary tumor was delineated on axial T2WI by two experienced radiologists (L.Y. and H. Z.) to generate 3D-ROIs on ITK-SNAP. Ten randomly selected patients in the training set were independently segmented by another experienced radiologist (Z. M.) to calculate inter-class coefficients (ICC).

Table 1
Patients' characteristics.

Characteristics	Training set		P-value	Testing set		P-value
	pCR (N = 27)	Non-pCR (N = 30)		pCR (N = 12)	Non-pCR (N = 13)	
Age, years (median, IQR)	64 (55, 66)	59 (55, 65)	0.128	63 (59, 70)	62 (59, 69)	0.841
Sex			0.167			>0.999
Female	7 (25.9)	3 (10.0)		3 (25.0)	3 (23.1)	
Male	20(74.1)	27 (90.0)		9 (75.0)	10 (76.9)	
ECOG PS			>0.999			0.238
1	16 (59.3)	18 (60.0)		5 (41.7)	9 (69.2)	
0	11 (40.7)	12 (40.0)		7 (53.8)	4 (30.8)	
Location			0.793			0.861
Upper thoracic	4 (14.8)	2 (6.7)		2 (16.7)	1 (7.7)	
Middle thoracic	10 (37.0)	11 (36.7)		4 (33.3)	4 (30.8)	
Lower thoracic	12 (44.4)	16 (53.3)		6 (50.0)	8 (61.5)	
GEJ	1 (3.7)	1 (3.3)		0 (0.0)	0 (0.0)	
Length, cm (median, IQR)	5.0 (4.0, 6.0)	5.5 (4.0, 7.0)	0.438	6.0 (4.0, 6.0)	5.0 (4.5, 6.0)	0.836
cT			0.761			0.140
1	0 (0.0)	1 (2.3)		0 (0.0)	1 (7.7)	
2	2 (7.4)	2 (6.7)		0 (0.0)	0 (0.0)	
3	16 (59.3)	21 (70.0)		6 (50.0)	10 (76.9)	
4	9 (33.3)	7 (23.3)		6 (50.0)	2 (15.4)	
cN			0.975			0.809
0	3 (11.1)	4 (13.3)		1 (8.3)	1 (7.7)	
1	7 (25.9)	9 (30.0)		4 (33.3)	2 (15.4)	
2	14 (51.9)	15 (50.0)		5 (41.7)	8 (61.5)	
3	3 (11.1)	2 (6.7)		2 (16.7)	2 (15.4)	
cM			0.599			>0.999
0	25 (92.6)	29 (96.7)		11 (91.7)	11 (84.6)	
1	2 (7.4)	1 (3.3)		1 (8.3)	2 (15.4)	
Chemotherapy regimen			>0.999			>0.999
Platinum and paclitaxel based	22 (81.5)	24 (80.0)		8 (66.7)	8 (61.5)	
5-fluorouracil based	5 (18.5)	6 (20.0)		4 (33.3)	5 (38.5)	
Radiotherapy technique			>0.999			>0.999
IMRT	4 (14.8)	5 (16.7)		2 (16.7)	2 (15.4)	
VMAT	23 (85.2)	25 (83.3)		10 (83.3)	11 (84.6)	
Radiation dose, Gy (median, IQR)	41.4 (37.8, 41.4)	41.4 (37.4, 41.4)	0.430	41.4 (37.8, 41.4)	41.4 (37.8, 46.9)	0.836
Application of SIB radiation	18 (66.7)	25 (83.3)	0.218	10 (83.3)	10 (76.9)	>0.999
Interval between NCRT and surgery, days (median, IQR)	55 (49, 83)	58 (47, 81)	0.797	56 (48, 78)	58 (47, 78)	0.758

Data are the number of patients and those in parentheses are percentages unless otherwise indicated. pCR, pathological complete response; IQR, interquartile range; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GEJ, gastroesophageal junction; cT, clinical T stage; cN, clinical N stage; cM, clinical M stage; IMRT, Intensity-Modulated Radiation Therapy; VMAT, Volumetric Modulated Arc Therapy; SIB, simultaneously integrated boost; NCRT, neoadjuvant chemoradiotherapy.

2.4. Radiomics analysis

All images were resampled to isotropic voxel-dimensions of 1 × 1 × 1 mm with normalization of density distribution using Z-scores method. Feature extraction was performed by PyRadiomics package on Python 3.9. Radiomics features were extracted from each region of interest (ROI), including shape features (e.g., volume, surface area), first-order features (e.g., mean intensity, standard deviation), Neighborhood Gray Tone Difference Matrix features, Gray Level Co-occurrence Matrix features, Gray Level Run Length Matrix features, Gray Level Size Zone Matrix features, Gray Level Dependence Matrix features, wavelet features, and Laplacian of Gaussian features (eTable 2). Feature selection was performed independently in the training set. First, features with low reproductivity (i.e., ICC<0.75) were removed. The remaining features were then subjected to a selection process using Random Forest-Recursive Feature Elimination (RF-RFE). This method involves recursively removing the least important features based on their importance scores until the optimal subset of features is obtained. The selection aimed to retain the top two most predictive features, as determined by their ability to distinguish between classes, following the dimensionality guidelines stipulated in the ARISE guideline [19] to prevent overfitting given the instances of each class in the training set. A radiomics model using random forest was trained based on the final two features, with 5-fold cross-validation in the training set to tune the hyperparameters using the Grid-search method.

2.4.1. Integrated model construction

Clinical and hematological factors were filter using Mann-Whittney *U* test with a threshold of $P < 0.1$ to construct a hematological model. The probability of pCR predicted by the radiomics model was calculated as RFprob. We combined the filtered hematological factors with RFprob to develop an integrated nomogram model by multivariable logistic regression. The workflow of study process is depicted in Fig. 1.

2.5. Statistical analysis

Statistical analysis was conducted using Python 3.9 and R 4.1.2 software. To compare differences between two groups, Fisher exact test was used for categorical variables and the Mann-Whitney *U* test for continuous variables. Receiver operating characteristics (ROC) curve and AUC were utilized to assess model performance. The optimal cut-offs were determined based on the top-left method, which allowed for the calculation of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Calibration curves were used to assess the calibration performance and decision curve analysis (DCA) was used to quantify the clinical benefits. To generate the 95 % confidence interval (95 % CI), 1000 bootstrap samples were utilized. Logistic regression analysis was applied to calculate the odds of achieving pCR. A two-tailed $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

Eighty-two patients were enrolled, including 57 in the training group and 25 in the testing group, respectively. Baseline characteristics were summarized in Table 1 and eTable 3. Among all included patients, 16 (19.5 %) were female and 66 (80.5 %) were male, with median age of 62 (interquartile range 56–67). Sixty-two(75.6 %) patients received platinum-based chemotherapy and 63 (76.8 %) patients received simultaneously integrated boost radiotherapy. pCR rates were 47.4 % (27/57) and 48.0 % (12/25) in the training and testing sets, respectively. None of the clinical factors were significantly different between pCR and non-pCR groups in both training and testing sets.

3.2. Predictive performance of hematological model

Based on the Mann-Whitney *U* test ($P < 0.1$), the hematological model was constructed with post-NCRT NLR (NLRpost), post-treatment minus pre-treatment value of MLR (deltaMLR), post-treatment minus pre-treatment value of PLR (deltaPLR) and post-treatment minus pre-treatment value of SII (deltaSII). In the training set, the model showed an AUC of 0.990 (95 % CI

Table 2
Predictive performance of different models.

	AUC	Accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Hematological model						
Training set	0.990 (0.970–1.000)	94.7 (91.2–100)	96.3 (88.9–100)	93.3 (86.7–100)	92.9 (87.1–100)	96.6 (90.0–100)
Testing set	0.628 (0.391–0.853)	64.0 (52.0–84.0)	66.7 (41.7–100)	61.5 (38.5–100)	61.5 (50.0–100)	66.7 (53.9–100)
Radiomics model						
Training set	0.984 (0.953–1.000)	92.9 (89.5–100)	96.2 (85.2–100)	90.0 (86.7–100)	89.7 (86.7–100)	96.4 (88.2–100)
Testing set	0.821 (0.641–0.981)	82.2(72.0–96.0)	91.7 (83.3–100)	76.9 (46.2–92.3)	78.6 (63.2–92.3)	84.0 (76.9–100)
Nomogram						
Training set	0.991 (0.973–1.000)	96.5 (93.0–100)	96.3 (88.9–100)	96.7 (86.7–100)	96.3 (87.1–100)	96.7 (90.9–100)
Testing set	0.904 (0.770–1.000)	84.0 (76.0–96.1)	83.3 (74.8–100)	84.6 (61.5–100)	83.3 (70.6–100)	84.6 (75.0–100)

Data in brackets are 95 % CIs. AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value.

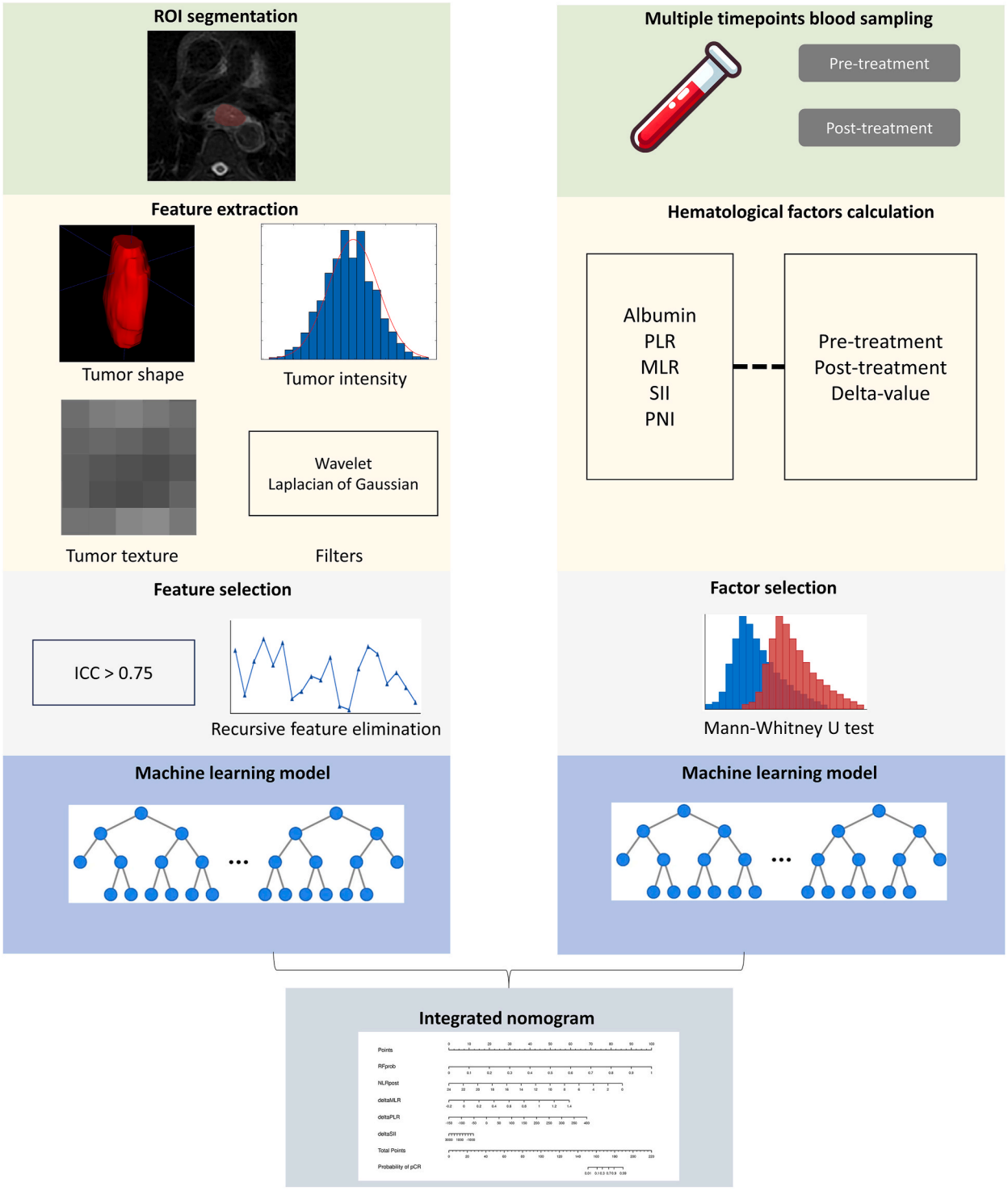

Fig. 1. Workflow of the study. ROI, regions of interest; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index; PNI, prognostic nutritional index; ICC, inter-class coefficients.

0.970–1.000), with a sensitivity of 96.3 % (95 % CI 88.9–100 %) and specificity of 93.3 % (95 % CI 86.7–100 %). In the testing set, the model showed an AUC of 0.628 (95%CI 0.391–0.853), with sensitivity of 66.7 % (95%CI 41.7–100 %) and specificity of 61.5 % (95%CI 38.5–100 %) (Fig. 2, Table 2).

3.3. Predictive performance of radiomics model

Totally 1106 features were extracted for each patient, of which 928 exhibited satisfactory reproductivity according to ICC. Based on the rank of features' predictive value by RF-RFE, top two features were retained for model construction using random forest (eTable 4). The radimics model achieved AUCs of 0.984 (95%CI 0.953–1.000) in the training set and 0.821 (95%CI 0.641–0.981) in the testing set (Fig. 3, Table 2). In the testing set, the sensitivity, specificity, PPV and NPV were 91.7 % (95%CI 83.3–100 %), 76.9 % (95%CI 46.2–92.3 %), 78.6 % (95%CI 63.2–92.3 %) and 84.0 % (95%CI 76.9–100 %). The predicted probabilities of pCR in both the training and testing sets were recorded as RFprob.

3.4. Predictive performance of nomogram

The nomogram integrating five variables, including RFprob, NLRpost, deltaMLR, deltaPLR, and deltaSII, was constructed (Fig. 4), achieving an AUC of 0.991 (95 % CI 0.973–1.000) in the training set and 0.904 (95 % CI 0.770–1.000) in the testing set (Fig. 5, Table 2). The confusion matrix demonstrated accurate predictions in both the training and testing sets, correctly identifying 55 out of 57 patients in the training set and 21 out of 25 patients in the testing set (eFig. 1). In the training set, the sensitivity, specificity, PPV and NPV were 96.3 % (95%CI 88.9–100 %), 96.7 % (95%CI 86.7–100 %), 96.3 % (95%CI 87.1–100 %) and 96.7 % (95%CI 90.9–100 %). In the testing set, the sensitivity, specificity, PPV and NPV were 83.3 % (95%CI 74.8–100 %), 84.6 % (95%CI 61.5–100 %), 83.3 % (95% CI 70.6–100 %) and 84.6 % (75.0–100 %). The nomogram was significantly associated with the odds of achieving pCR (OR 39.73, 95 % CI 3.90–513.00, P = 0.005) (eTable 5). Favorable correspondence was show between true probability and predicted probability in calibration curves (eFig. 2) and clinical benefit was demonstrated through DCA curves (eFig. 3).

4. Discussion

The present study validates that an integrated nomogram built on MR radiomics and dynamic hematological factors can precisely predict pCR after NCRT in patients with ESCC accurately. To the best of our knowledge, this is the first study combining MR radiomics and hematological factors to predict neoadjuvant therapy response of esophageal cancer.

Our study selected two radiomics features from 1106 extracted MR radiomics features to build a radiomics model. In consistence with previous studies, our radiomics model achieved an AUC of 0.821 in the testing set. By combining four valuable hematological factors, the integrated nomogram showed favorable AUC of 0.904 in the testing set, which surpassed those reported in previous studies on the same topic [20] and can be potentially helpful to apply to clinical practice.

Explorations on traditional qualitative or quantitative methods using CT or PET/CT to predict pCR after neoadjuvant chemo-radiotherapy in ESCC have showed low accuracy, with sensitivity and specificity less than 70 % in most studies [6]. Gene expression analysis distinguished several predictive genetic markers but accuracy was not reported or satisfactory in most studies, with the lack of validation [21–25]. The recent development of radiomics shed light on the promising role of this new approach in treatment response prediction. Hu et al. [26] combined intratumoral and peritumoral radiomics features from CT images to build a support vector machine model, with AUC reaching 0.852 in the testing set in predicting pCR. Another study integrated pretreatment CT and PET images of 68

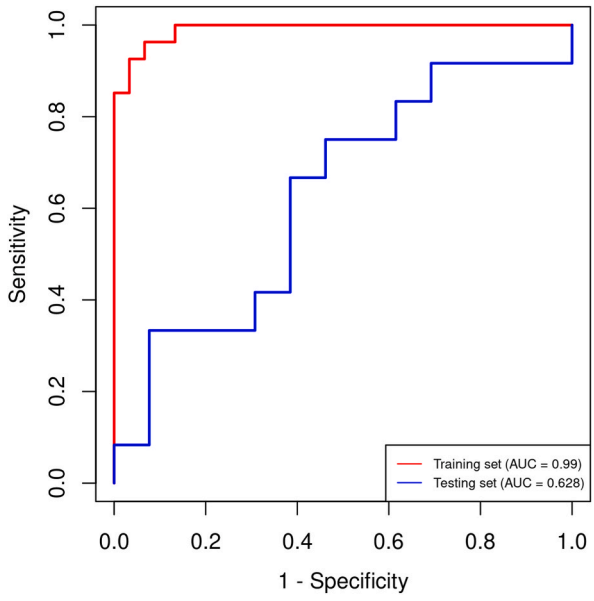

Fig. 2. Receiver operating characteristic curve analysis of the hematological model. AUC, area under the curve.

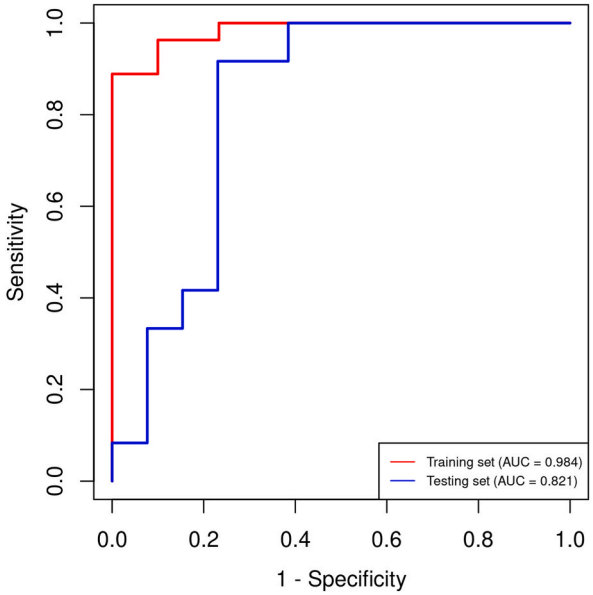

Fig. 3. Receiver operating characteristic curve analysis of the radiomics model. AUC, area under the curve.

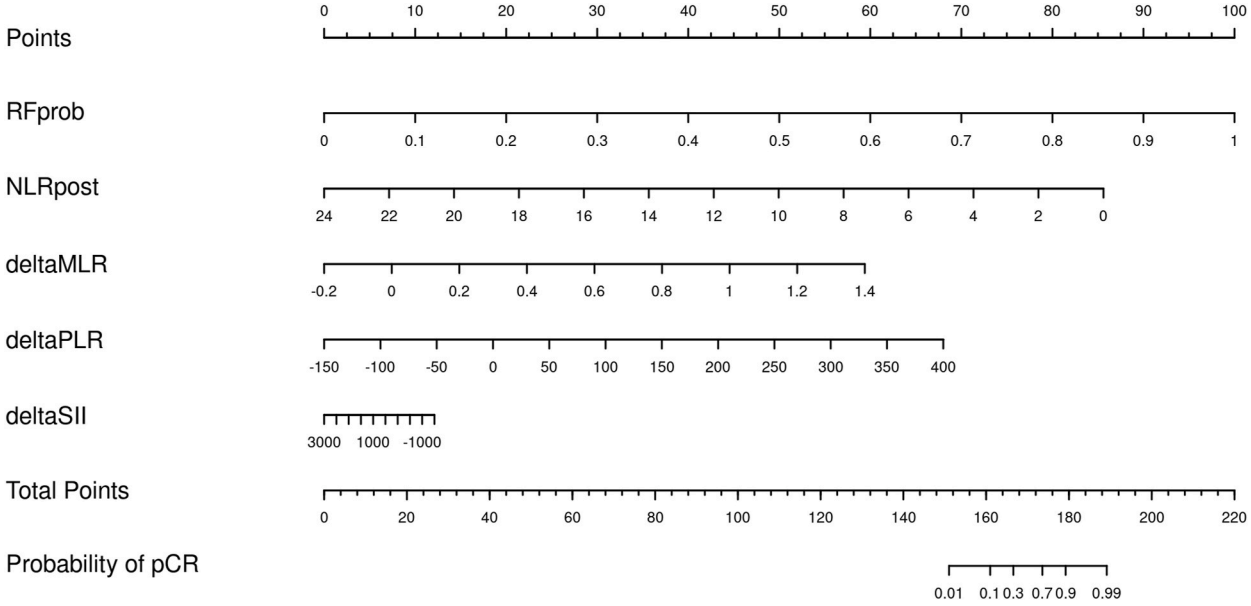

Fig. 4. Nomogram integrating MR radiomics and hematological factors. The nomogram combines the radiomics model and four hematological factors. Each predictor is assigned a score on the points scale, and the total score corresponds to the probability of achieving pCR, as indicated on the bottom scale. RFprob, probability of pCR predicted by the radiomics model; NLRpost, post-treatment neutrophil to lymphocyte ratio; deltaMLR, post-treatment minus pre-treatment value of monocyte to lymphocyte ratio; deltaPLR, post-treatment minus pre-treatment value of platelet to lymphocyte ratio; deltaSII, post-treatment minus pre-treatment value of systematic immune-inflammation index; pCR, pathological complete response.

patients to build a radiomics model with an AUC of 0.87 in internal cross-validation [27]. Wang et al. [28] used contrast-enhanced CT images of 112 ESCC patients to develop a radiomics model that achieved an AUC of 0.817 in the testing set. These studies relied solely on traditional medical imaging, and enhancing accuracy has proven to be challenging. In contrast, our model demonstrates superior performance by leveraging comprehensive information from both novel MR imaging and dynamic hematological factors.

MR has become increasingly applied for patients with esophageal cancer due to its high soft tissue resolution and abundant types of sequences with various information. T2WI is the most common sequence in clinical practice. Although not widely explored, a few studies have shown its remarkable predictive value of treatment response. Hou et al. [29] constructed a radiomics model using T2WI,

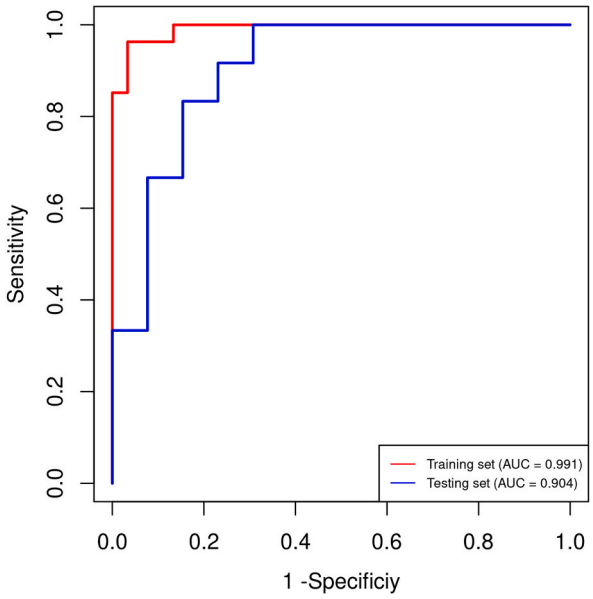

Fig. 5. Receiver operating characteristic curve analysis of the nomogram. AUC, area under the curve.

which accurately predicted treatment response to definitive chemoradiotherapy assessed by RECIST. Lu et al. [30] utilized T2-TSE-BLADE images to construct radiomics model to predict pathological response of neoadjuvant chemotherapy in ESCC with the highest AUC of 0.831 using post-treatment images. Our study demonstrated that pre-treatment T2WI with radiomics can be a useful biomarker to predict pathological response of neoadjuvant chemoradiotherapy, which is the standard care in locally advanced ESCC and more widely adopted in clinical practice. Specifically, the radiomics model utilized Small Area Emphasis features, which quantify the distribution of small-sized homogeneous zones and reflect intratumor heterogeneity. These features, extracted from CT images, have been shown to be effective in predicting prognosis and response to chemoradiotherapy in lung cancer and gastric cancer [31–33]. In our study, these features were identified as the most predictive through the use of RF-RFE and were effectively utilized using reliable machine learning methods. Given the high soft-tissue resolution of MR images, our model is likely to capture specific patterns of intratumor heterogeneity, which can be instrumental in predicting the response to chemoradiation in ESCC.

Correlations between hematological factors and prognosis of esophageal cancer has been reported in many studies [34]. Lawati et al. [35] found that pre-treatment and post-treatment NLR was associated with OS and DFS in patients with esophageal cancer, most of whom received neoadjuvant chemotherapy. MLR, PLR and SII were also found related to pathological response and survival outcomes of esophageal cancer [17,36,37]. However, performances of predicting pathological response to NCRT using hematological factors in independent testing set were not investigated, with only few studies reported AUC of 0.6–0.7 in in the entire patient cohort [16,38]. The hematological model in our study had an AUC of 0.628 when predicting pCR, which also indicated limited clinical applicability. Zhang et al. [39] demonstrated the added value of hematological factors that combining NLR, MLR, Albumin with CT-based radiomics showed superior performance (AUC = 0.857) compared to radiomics alone (AUC = 0.718–0.786). However, their study did not utilize dynamic hematological factors, and the field of CT radiomics itself is not new, having been extensively explored previously [20]. In our study, dynamic hematological factors were valuable when adding to MR radiomics model, which improved AUC from 0.821 to 0.904 in the testing set. This enhancement is likely attributed to the various values that hematological factors reflect systematic inflammation and host adaptive immune status [40,41], while MR reveals features of the primary tumor.

This study has several limitations. Firstly, as an exploratory single-center study with a relatively limited sample size, the generalizability of the findings is not well guaranteed and requires further validation. Secondly, the results may be influenced by potential confounding factors such as variations in patient characteristics or treatment protocols. The possibility of false positives/negatives and measurement variability of imaging and hematological biomarkers can also affect the reliability. A multi-center prospective study will be conducted in the future to further validate the model. Thirdly, contrast-enhanced MR sequences and DWI were not applied in this study. These techniques are not standard protocols in the clinical management of ESCC, and have significant time and financial implications, so they were not utilized in the majority of patients in our study. Prospective study with predefined MR sequences will integrate multiple sequences to further improve the predictive performance. Fourthly, manual delineation was adopted in this study, which was time-consuming and outmoded. Automatic contouring system will be investigated in the future. Fifthly, the radiomics approach has its own limitations of dependence on image quality and variability in feature extraction methods, which could affect model's performance and generalization. Lastly, the underlying biological mechanisms of the model's predictions are not fully understood. To address this, we plan to integrate gene expression data in future studies to better interpret these mechanisms.

5. Conclusions

In conclusion, an integrated model combining hematological factors with MR radiomics was developed to accurately predict pCR to NCRT in ESCC, potentially useful in guiding individualized esophageal preservation treatments. However, further validation in larger datasets is essential.

Ethics statement

The research is approved by the Institutional Review Boards of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (ethics approval number 23/163–3905). Written informed consent was waived.

Funding

This work was supported by National Key R&D Program of China (2022YFC2705000,2022YFC2705001); Beijing Hope Run Special Fund of Cancer Foundation of China (LC2022R03).

Data availability statement

Data associated with this study are not deposited into a publicly available repository for the authors do not have permission to share data due to relevant laws and hospital policies. All data and materials are only available through reasonable request to the corresponding author.

CRediT authorship contribution statement

Yunsong Liu: Writing – original draft, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Zeliang Ma:** Writing – original draft, Methodology. **Yongxing Bao:** Validation, Formal analysis. **Xin Wang:** Resources, Methodology. **Yu Men:** Writing – review & editing, Data curation. **Xujie Sun:** Resources. **Feng Ye:** Resources, Investigation. **Kuo Men:** Software, Methodology. **Jianjun Qin:** Writing – review & editing, Resources, Investigation. **Nan Bi:** Supervision, Investigation. **Liyan Xue:** Writing – review & editing, Supervision. **Zhouguang Hui:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33702.

References

[1] H. Yang, H. Liu, Y. Chen, C. Zhu, W. Fang, Z. Yu, et al., Neoadjuvant chemoradiotherapy followed by surgery versus surgery alone for locally advanced squamous cell carcinoma of the esophagus (NEOCRTEC5010): a phase III multicenter, randomized, open-label clinical trial, J. Clin. Oncol. 36 (27) (2018) 2796–2803.
[2] P. van Hagen, M.C. Hulshof, J.J. van Lanschot, E.W. Steyerberg, M.I. van Berge Henegouwen, B.P. Wijnhoven, et al., Preoperative chemoradiotherapy for esophageal or junctional cancer, N. Engl. J. Med. 366 (22) (2012) 2074–2084.
[3] B.J. van der Wilk, B.M. Eyck, W.L. Hofstetter, J.A. Ajani, G. Piessen, C. Castoro, et al., Chemoradiotherapy followed by active surveillance versus standard esophagectomy for esophageal cancer: a systematic review and individual patient data meta-analysis, Ann. Surg. 275 (3) (2022) 467–476.
[4] J.I. Geh, A.M. Crellin, R. Glynne-Jones, Preoperative (neoadjuvant) chemoradiotherapy in oesophageal cancer, Br. J. Surg. 88 (3) (2001) 338–356.
[5] T. Taketa, K. Sudo, A.M. Correa, R. Wadhwa, H. Shiozaki, E. Elimova, et al., Post-chemoradiation surgical pathology stage can customize the surveillance strategy in patients with esophageal adenocarcinoma, J. Natl. Compr. Cancer Netw. 12 (8) (2014) 1139–1144.
[6] B.M. Eyck, B.D. Onstenk, B.J. Noordman, D. Nieboer, M.C.W. Spaander, R. Valkema, et al., Accuracy of detecting residual disease after neoadjuvant chemoradiotherapy for esophageal cancer: a systematic review and meta-analysis, Ann. Surg. 271 (2) (2020) 245–256.
[7] M. Westerterp, H.L. van Westreenen, J.B. Reitsma, O.S. Hoekstra, J. Stoker, P. Fockens, et al., Esophageal cancer: CT, endoscopic US, and FDG PET for assessment of response to neoadjuvant therapy–systematic review, Radiology 236 (3) (2005) 841–851.
[8] M.E. Mayerhoefer, A. Materka, G. Langs, I. Häggström, P. Szczypiński, P. Gibbs, et al., Introduction to radiomics, J. Nucl. Med. 61 (4) (2020) 488–495.
[9] L. Feng, Z. Liu, C. Li, Z. Li, X. Lou, L. Shao, et al., Development and validation of a radiopathomics model to predict pathological complete response to neoadjuvant chemoradiotherapy in locally advanced rectal cancer: a multicentre observational study, The Lancet Digital Health 4 (1) (2022) e8–e17.
[10] A.G.V. Bitencourt, P. Gibbs, C. Rossi Saccarelli, I. Daimiel, R. Lo Gullo, M.J. Fox, et al., MRI-based machine learning radiomics can predict HER2 expression level and pathologic response after neoadjuvant therapy in HER2 overexpressing breast cancer, EBioMedicine 61 (2020) 103042.
[11] L. Boldrini, J. Lenkowicz, L.C. Orlandini, G. Yin, D. Cusumano, G. Chiloiro, et al., Applicability of a pathological complete response magnetic resonance-based radiomics model for locally advanced rectal cancer in intercontinental cohort, Radiat. Oncol. 17 (1) (2022) 78.
[12] N.M. Braman, M. Etesami, P. Prasanna, C. Dubchuk, H. Gilmore, P. Tiwari, et al., Intratumoral and peritumoral radiomics for the pretreatment prediction of pathological complete response to neoadjuvant chemotherapy based on breast DCE-MRI, Breast Cancer Res. 19 (1) (2017) 57.

[13] S.E. Heethuis, L. Goense, P.S.N. van Rossum, A.S. Borggreve, S. Mook, F.E.M. Voncken, et al., DW-MRI and DCE-MRI are of complementary value in predicting pathologic response to neoadjuvant chemoradiotherapy for esophageal cancer, Acta Oncol 57 (9) (2018) 1201–1208.
[14] Q.W. Li, B. Qiu, B. Wang, D.L. Wang, S.H. Yin, H. Yang, et al., Prediction of pathologic responders to neoadjuvant chemoradiotherapy by diffusion-weighted magnetic resonance imaging in locally advanced esophageal squamous cell carcinoma: a prospective study, Dis. Esophagus 31 (2) (2018).
[15] C. Li, J.W. Lin, H.L. Yeh, C.Y. Chuang, C.C. Chen, Good prediction of treatment responses to neoadjuvant chemoradiotherapy for esophageal cancer based on preoperative inflammatory status and tumor glucose metabolism, Sci. Rep. 11 (1) (2021) 11626.
[16] A. Powell, C. Chin, A.H. Coxon, A. Chalishazar, A. Christian, S.A. Roberts, et al., Neutrophil to lymphocyte ratio as a predictor of response to neoadjuvant chemotherapy and survival in oesophageal adenocarcinoma, BJS Open 4 (3) (2020) 416–423.
[17] Y. Wu, J. Chen, L. Zhao, Q. Li, J. Zhu, H. Yang, et al., Prediction of pathologic response to neoadjuvant chemoradiotherapy in patients with esophageal squamous cell carcinoma incorporating hematological biomarkers, Cancer Res Treat 53 (1) (2021) 172–183.
[18] Z. Shi, Z. Zhang, Z. Liu, L. Zhao, Z. Ye, A. Dekker, et al., Methodological quality of machine learning-based quantitative imaging analysis studies in esophageal cancer: a systematic review of clinical outcome prediction after concurrent chemoradiotherapy, Eur. J. Nucl. Med. Mol. Imag. 49 (8) (2022) 2462–2481.
[19] B. Kocak, L.L. Chepelev, L.C. Chu, R. Cuocolo, B.S. Kelly, P. Seebock, et al., Assessment of RadiomIcS rEsearch (ARISE): a brief guide for authors, reviewers, and readers from the Scientific Editorial Board of European Radiology, Eur. Radiol. 33 (11) (2023) 7556–7560.
[20] Y.S. Kao, Y. Hsu, A meta-analysis for using radiomics to predict complete pathological response in esophageal cancer patients receiving neoadjuvant chemoradiation, *In Vivo* 35 (3) (2021) 1857–1863.
[21] M. Fassan, F. Cavallin, V. Guzzardo, A. Kotsafti, M. Scarpa, M. Cagol, et al., PD-L1 expression, CD8+ and CD4+ lymphocyte rate are predictive of pathological complete response after neoadjuvant chemoradiotherapy for squamous cell cancer of the thoracic esophagus, Cancer Med. 8 (13) (2019) 6036–6048.
[22] M. Gusella, E. Pezzolo, Y. Modena, C. Barile, D. Menon, G. Crepaldi, et al., Predictive genetic markers in neoadjuvant chemoradiotherapy for locally advanced esophageal cancer: a long way to go. Review of the literature, Pharmacogenomics J. 18 (1) (2018) 14–22.
[23] P.C. Chen, Y.C. Chen, L.C. Lai, M.H. Tsai, S.K. Chen, P.W. Yang, et al., Use of germline polymorphisms in predicting concurrent chemoradiotherapy response in esophageal cancer, Int. J. Radiat. Oncol. Biol. Phys. 82 (5) (2012) 1996–2003.
[24] F.M. Hsu, J.C. Cheng, Y.L. Chang, J.M. Lee, A.C. Koong, E.Y. Chuang, Circulating mRNA profiling in esophageal squamous cell carcinoma identifies FAM84B as A biomarker in predicting pathological response to neoadjuvant chemoradiation, Sci. Rep. 5 (2015) 10291.
[25] K. Chiam, G.C. Mayne, D.I. Watson, R.J. Woodman, T.F. Bright, M.Z. Michael, et al., Identification of microRNA biomarkers of response to neoadjuvant chemoradiotherapy in esophageal adenocarcinoma using next generation sequencing, Ann. Surg Oncol. 25 (9) (2018) 2731–2738.
[26] Y. Hu, C. Xie, H. Yang, J.W.K. Ho, J. Wen, L. Han, et al., Assessment of intratumoral and peritumoral computed tomography radiomics for predicting pathological complete response to neoadjuvant chemoradiation in patients with esophageal squamous cell carcinoma, JAMA Netw. Open 3 (9) (2020) e2015927.
[27] A. Rishi, G.G. Zhang, Z. Yuan, A.J. Sim, E.Y. Song, E.G. Moros, et al., Pretreatment CT and (18) F-FDG PET-based radiomic model predicting pathological complete response and loco-regional control following neoadjuvant chemoradiation in oesophageal cancer, J Med Imaging Radiat Oncol 65 (1) (2021) 102–111.
[28] J. Wang, X. Zhu, J. Zeng, C. Liu, W. Shen, X. Sun, et al., Using clinical and radiomic feature–based machine learning models to predict pathological complete response in patients with esophageal squamous cell carcinoma receiving neoadjuvant chemoradiation, Eur. Radiol. 33 (12) (2023) 8554–8563.
[29] Z. Hou, S. Li, W. Ren, J. Liu, J. Yan, S. Wan, Radiomic analysis in T2W and SPAIR T2W MRI: predict treatment response to chemoradiotherapy in esophageal squamous cell carcinoma, J. Thorac. Dis. 10 (4) (2018) 2256–2267.
[30] S. Lu, C. Wang, Y. Liu, F. Chu, Z. Jia, H. Zhang, et al., The MRI radiomics signature can predict the pathologic response to neoadjuvant chemotherapy in locally advanced esophageal squamous cell carcinoma, Eur. Radiol. 34 (1) (2024) 485–494.
[31] J. Shin, J.S. Lim, Y.M. Huh, J.H. Kim, W.J. Hyung, J.J. Chung, et al., A radiomics-based model for predicting prognosis of locally advanced gastric cancer in the preoperative setting, Sci. Rep. 11 (1) (2021) 1879.
[32] H. Zhang, Y. Deng, M.A. Xiaojie, Q. Zou, H. Liu, N. Tang, et al., Construction of a radiomics-based model for predicting the efficacy of radiotherapy and chemotherapy for non-small cell lung cancer, Heliyon 10 (1) (2024) e23923.
[33] T. Wang, J. Deng, Y. She, L. Zhang, B. Wang, Y. Ren, et al., Radiomics signature predicts the recurrence-free survival in stage I non-small cell lung cancer, Ann. Thorac. Surg. 109 (6) (2020) 1741–1749.
[34] H. Yodying, A. Matsuda, M. Miyashita, S. Matsumoto, N. Sakurazawa, M. Yamada, et al., Prognostic significance of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in oncologic outcomes of esophageal cancer: a systematic review and meta-analysis, Ann. Surg Oncol. 23 (2) (2016) 646–654.
[35] Y. Al Lawati, J. Cools-Lartigue, J.L. Ramirez-GarciaLuna, J.C. Molina-Franjola, D. Pham, E. Skothos, et al., Dynamic alteration of neutrophil-to-lymphocyte ratio over treatment trajectory is associated with survival in esophageal adenocarcinoma, Ann. Surg Oncol. 27 (11) (2020) 4413–4419.
[36] X. Zhang, A. Gari, M. Li, J. Chen, C. Qu, L. Zhang, et al., Combining serum inflammation indexes at baseline and post treatment could predict pathological efficacy to antiPD1 combined with neoadjuvant chemotherapy in esophageal squamous cell carcinoma, J. Transl. Med. 20 (1) (2022) 61.
[37] G. Cai, J. Yu, X. Meng, Predicting prognosis and adverse events by hematologic markers in patients with locally advanced esophageal squamous cell carcinoma treated with neoadjuvant chemoradiotherapy, Cancer Manag. Res. 12 (2020) 8497–8507.
[38] K. Zhao, C. Wang, F. Shi, M. Li, J. Yu, Lymphocyte-monocyte ratio as a predictive marker for pathological complete response to neoadjuvant therapy in esophageal squamous cell carcinoma, Transl. Cancer Res. 9 (6) (2020) 3842–3853.
[39] M. Zhang, Y. Lu, H. Sun, C. Hou, Z. Zhou, X. Liu, et al., CT-based deep learning radiomics and hematological biomarkers in the assessment of pathological complete response to neoadjuvant chemoradiotherapy in patients with esophageal squamous cell carcinoma: a two-center study, Transl Oncol 39 (2024) 101804.
[40] S.I. Grivennikov, F.R. Greten, M. Karin, Immunity, inflammation, and cancer, Cell 140 (6) (2010) 883–899.
[41] C.I. Diakos, K.A. Charles, D.C. McMillan, S.J. Clarke, Cancer-related inflammation and treatment effectiveness, Lancet Oncol. 15 (11) (2014) e493–e503.