Radiomics features for differentiating clear cell sarcoma of the kidney from Wilms' tumor in children based on contrast-enhanced computed tomography: a case-control study

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February 22, 2024

Abstract

Background: Clear cell sarcoma of the kidney (CCSK) is a rare but the second common renal malignant tumor mimicking Wilms' tumor. Radiomics is helpful for differentiating CCSK from Wilms' tumor preoperatively through analyzing the pixel distribution of lesions on medical images quantitatively. Procedure: In this study, the regions of interest (ROIs) of lesions were delineated on corticomedullary phase (CMP) and nephrographic phase (NP) images to extract radiomics features. Dimensionality reduction and Logistic Regression (LR) algorithm were used to construct the classification models. The area under the receiver operator characteristic curve (AUC), sensitivity and specificity were calculated for evaluation, and Delong test was used to compare the performance of the most meaningful features and LR models. Results: Lower skewness was observed in Wilms' tumor, and higher skewness in CCSK. Skewness transformed by exponential and squareroot filters from NP images achieved moderate to good diagnostic performance for CCSK with AUCs of 0.707 (95%CI: 0.573, 0.840) and 0.705 (95%CI: 0.572, 0.839) in the training set, and 0.818 (95%CI: 0.608, 1.000) and 0.803 (95%CI: 0.585, 1.000) in the validation set, respectively. Delong test showed no significant difference between LR model, exponential-skewness and squareroot-skewness based on NP images in both training and validation sets. Conclusion: Skewness from nephrographic phase at exponential and squareroot filters is helpful to discriminate between CCSK and Wilms' tumor in children, and higher skewness on NP images may be a potential imaging biomarker for diagnosing CCSK from Wilms' tumor.

1 INTRODUCTION

Clear cell sarcoma of the kidney (CCSK) is a rare but the second common renal malignant tumor in childhood between 2 and 4 years of age, accounting for about 2-5% of primary pediatric renal tumors, while Wilms' tumor has a high incidence of approximately 95%.[1,2] Despite of its low incidence, CCSK has an inferior prognosis than Wilms' tumor, although in recent years the treatment outcomes of CCSK have been improved due to the use of more intensive chemotherapy and radiotherapy.[2] CCSK is notorious for its frequent bone metastasis, while the brain has now been replaced to be the most common site of late relapse.[3,4] Therefore, it is necessary to differentiate CCSK from Wilms' tumor for the purpose of improving diagnostic workup, planning treatment regimen and predicting the prognosis.

However, misdiagnosis of CCSK as Wilms' tumor is not uncommon, resulting in mismatched chemotherapy in CCSK.[3] It is difficult to distinguish CCSK from Wilms' tumor in terms of clinical and radiographic features.[5-7] The differential diagnosis of CCSK and Wilms' tumor is generally finally confirmed by histopathological analysis and immunophenotyping; however, this poses challenges to pathologists due to the diverse histology, unavailable immunohistological markers and invalid molecular genetics of CCSK.[4] The accurate diagnosis of CCSK with biopsy is hindered by tumor heterogeneity and sampling error, and the biological characteristics of CCSK cannot be revealed comprehensively and accurately by pathological examination.[4,8]

Hence, the identification and development of new imaging biomarkers and assessing methods is meaningful for differentiating CCSK from Wilms' tumor in pediatric patients.

Radiomics is helpful to diagnosis and differential diagnosis of tumor phenotypes through analyzing the pixel distribution of lesions on medical images quantitatively.[9] In previous literatures, radiomics analysis has been widely used in adult renal tumors.[10,11] There is only one study on assessing the feasibility of texture analysis to differentiate pediatric renal malignancies using gray-scale ultrasonography images.[5]Computed tomography plays a pivotal role in assessing and staging pediatric renal tumors in clinical practice. A recent study showed some qualitative and semi-quantitative imaging features on contrast-enhanced computed tomography can distinguish CCSK from Wilms' tumor.[7] To our best knowledge, the feasibility of using CT-based radiomics for differentiating CCSK from Wilms' tumor has not been addressed.

Therefore, we aimed to identify and assess the potential valuable quantitative radiomics features for differentiating CCSK from Wilms' tumor in pediatric patients based on contrast-enhanced computed tomography.

2 METHODS

2.1 Patients

The Ethics Committee of Children's Hospital Affiliated with Chongqing Medical University approved this retrospective study and waived the need for informed patient consent. 29 patients with CCSK diagnosed from January 2013 through February 2021 were enrolled. Considering the imbalance ratio between CCSK and Wilms' tumor, 66 patients with Wilms' tumor diagnosed consecutively were selected as control group, and then 51 patients were finally enrolled according to the including and excluding criterions. Workflow of patient enrollment for this retrospective case-control study was demonstrated in**Supplementary Fig. 1** . The patients' cohort (n=80) was randomly separated into the training set (n=63) and validation set (n=17) at the ratio of 8:2, and the random seeds is 138.

2.2 CT Technique

The pediatric patients in this study were examined in a quiet state, and for those who could not cooperate with the CT examinations, oral administration of 10% chloral hydrate (0.5 mL/kg) or intramuscular injection of phenobarbital sodium (5 mg/kg) was used. GE Lightspeed VCT 64 or Philips Brilliance ICT 256 was used to obtain the CT images. The scanning parameters were: tube voltage, 90-120 kV; tube current, automatic; slice thickness, 5.0 mm; slice interval, 5.0 mm; pitch, 0.984:1. The patients were injected with 2 mL/kg of nonionic contrast material (Omnipaque or Visipaque, GE Healthcare) at a rate of 2 mL/s via the peripheral vein of the forearm by a power injector. Corticomedullary phase (CMP) and nephrographic phase (NP) of post-contrast scanning were performed at 15-30s and 50-60s after contrast material injection, respectively.

2.3 Image Preprocessing and Regions of Interest (ROIs) Segmentation

CT images were acquired according to standardized scanning protocols. Preprocessing of the images before ROIs segmentation was performed by a radiologist, and the mean standard deviation of the images was normalized. Lesions of all slices were delineated on the CT images manually by a radiologist who was blinded to the clinical information of the patients, then all contours were reviewed by the other senior radiologist. If the discrepancy was [?]5%, the senior radiologist decided on the tumor borders. Examples of ROIs of CCSK and Wilms' tumor were shown in **Supplementary Fig. 2** .

2.4 Extraction and Selection of Quantitative Features

After image preprocessing, a number of 1409 quantitative imaging features were extracted from CT images based on CMP or NP using the Pyradiomics v.2.1.2 package, and so a total of 2818 features from CMP+NP were obtained. These features can be grouped into three groups. Group 1 (first order statistics) quantitatively delineates the distribution of voxel intensities within the CT image through commonly used and basic metrics. Group 2 (shape- and size-based features) reflects the shape and size of the region. Calculated from grey level run-length and grey level co-occurrence texture matrices, textural features that can quantify region heterogeneity differences were classified into group 3 (texture features).

As described above, a large number of image features may be computed. However, all these extracted features may not be useful for a particular task. Therefore, dimensionality reduction and selection of task-specific features for best performance are necessary steps. To reduce the redundant features, the feature selection methods included the variance threshold (variance threshold = 0.8), SelectKBest and the least absolute shrinkage and selection operator (LASSO) were used for this purpose. For the variance threshold method, the threshold is 0.8, so that the eigenvalues of the variance smaller than 0.8 were removed. The SelectKBest method, which belongs to a single variable feature selection method, uses p value to analysis the relationship between the features and the classification results, so all the features with $p < 0.05$ will be used. For LASSO model, L1 regularizer was used as the cost function, and the error value of cross validation is 5, and the maximum number of iterations is 1000.

2.5 Classification Models Setup

Based on the final selected features, there are several supervised learning classifiers available for classification analysis, which creates models that attempt to separate or predict the data with respect to an outcome or phenotype. In this study, the classification models based on CMP, NP and CMP+NP were constructed with Logistic Regression (LR) algorithm in testing set, and then the effectiveness of the models was confirmed in validation set.

2.6 Statistical Analysis

Python software (PyRadiomics, v2.1.2) and IBM SPSS Statistics software (version 23.0, IBM Corp.) were used for statistical analysis. A value of $p<0.05$ was meant statistically significant. To assess the performance of the radiomics features and LR models, the receiver operating characteristic (ROC) curve was used both in training and validation set, and the area under the receiver operator characteristic curve (AUC), sensitivity and specificity were calculated in the two sets respectively. Delong test was used to compare the diagnostic performance of LR model, exponential-skewness and squareroot-skewness based on NP images in both training and validation sets. The Mann–Whitney U-test was used to determine how the most statistically significant features distributed in training and validation sets.

3 RESULTS

3.1 Features Extraction and Selection

Based on single-phase and two-phase CT images, 1409 features were extracted from CMP and NP respectively, and 2818 features from CMP+NP. Firstly, a number of 347, 349 and 699 features were screened from CMP, NP and CMP+NP using variance threshold method, respectively. Then with the SelectKBest method, we selected 28, 20 and 30 features from CMP, NP and CMP+NP, respectively. Finally, 6, 5 and 6 optimal features were identified with LASSO algorithm from CMP, NP and CMP+NP, respectively (**Fig. 1**).

3.2 Comparison of Radiomics Features Between CCSK and Wilms' tumor

Based on the final features from CMP, NP and CMP+NP, ROC curves of each feature were demonstrated in **Fig. 2** , and the values of AUC, sensitivity and specificity were listed in **Table 1** . The results showed first-order features from NP images have a better diagnostic performance than those from CMP images. Generally, a value of AUC between 0.8 and 0.9 indicates good diagnostic efficacy, and between 0.7 and 0.8 moderate diagnostic efficacy. Skewness from NP images filtered by exponential and squareroot filters were the most meaningful features to differentiate CCSK from Wilms' tumor.

3.3 Classification Performance of the LR models

ROC curves of LR models based on CMP, NP and CMP+NP were shown in**Fig. 3** and the corresponding results were illustrated in**Table 2** for training set and validation set. When training with LR classifier, the AUCs of the CMP, NP and CMP+NP models were 0.676 (95%CI:0.546, 0.789), 0.780 (95%CI:0.658, 0.875), and 0.779 (95%CI:0.657, 0.874) in the training set, respectively, which were confirmed in the validation set by AUCs of 0.788 (95%CI:0.526, 0.944), 0.803 (95%CI:0.543, 0.952), and 0.803 (95%CI:0.543, 0.952), respectively. Because NP-based skewness filtered by exponential and squareroot filters showed meaningful in

differentiating CCSK from Wilms' tumor, the performance of these features and LR model based on NP was compared by Delong test, and the results showed there was no significant difference among them (p>0.05). The Mann–Whitney U-test showed the distribution of skewness differs between CCSK and Wilms' tumor. Lower skewness was observed in Wilms' tumor, and higher skewness in CCSK.

4 DISCUSSION

CCSK, with unclear histological and immunohistological features, is an unusual pediatric renal malignancy secondary to Wilms' tumor.[4] The main clinical manifestations of CCSK include abdominal mass, abdominal pain, hematuria and other atypical symptoms similar to Wilms' tumor, and the lack of specificity of these symptoms can result in misdiagnosis of CCSK as Wilms' tumor preoperatively.[3] Thus, the accurate preoperative differentiation between CCSK and Wilms' tumor is helpful for clinical decision making in children. Kang et al found perinephric vessel engorgement and higher tumor enhancement on CT images are useful in differentiating CCSK from Wilms' tumor.[7] However, these qualitative and semi-quantitative features cannot reflect intra-tumoral heterogeneity comprehensively. Recently, radiomics provides a promising method to evaluate tumor phenotypes quantitatively.[12,13] In this study, we used CT-based radiomics analysis to differentiate CCSK from Wilms' tumor for the first time. Some differences were confirmed in radiomics features between CCSK and Wilms' tumor.

According to our results, among the final optimal features screened through the variance threshold, SelectKBest and LASSO methods, all of them were first-order features depicting the distribution of voxel intensities, of which skewness from NP images achieved moderate to good diagnostic performance for CCSK. A skewness is about the asymmetry of the distribution of voxel intensities,[14] indicating that there are differences in the asymmetry of the voxel intensity histogram between CCSK and Wilms' tumor. Additionally, the performance of skewness transformed by exponential and squareroot filters is obviously superior to that of original skewness, suggesting advanced features filtered by filters could reveal more invisible meaningful information about tumoral heterogeneity.[15] In previous literatures, first-order histogram characteristics of renal tumors differed in various pathological types.[10,16,17] Deng et al investigated the role of CT texture analysis in differentiating major renal cell carcinoma subtypes, and the first-order entropy was found to be the most meaningful biomarker in differentiating clear cell from papillary renal neoplasms.[17] Likewise, skewness and kurtosis were demonstrated to be helpful for differentiating clear cell renal carcinoma from oncocytoma.[16] However, in other studies on texture analysis of non-renal tumors, second-order features, such as gray level size zone matrix or gray level difference matrix, seem to play a more important role in characterizing heterogeneity of non-renal tumors.[18-20]

When training with LR model, all the selected features from each phase were used to construct classification model for diagnosing CCSK. The results showed LR models combining all chosen features perform better than the majority of single feature. Because it is hard to delineate the boundary of tumor lesion from kidney on non-contrast-enhanced CT images, we only chose CMP and NP images to perform radiomics analysis. Compared to CMP images, NP images provided more useful data to the CCSK-associated radiomics characteristics. When combining CMP and NP images, an interesting finding was that all the optimal features are extracted from the NP images. Meanwhile, the performance of the composite model was similar to that of NP model, suggesting two-phase CT images have no additional value in differentiating between CCSK and Wilms' tumor. Meng et al demonstrated NP features are the most sensitive features for characterizing sarcomatoid from clear cell renal carcinoma, the reason for which may be that sarcomatoid differentiation causes changes in intra-tumoral enhancement patterns.[11] Boo et al found there are some unique vascular patterns in CCSK, in which regularly-spaced fibrovascular septa separates the nests of tumor cells, and this may cause late enhancement in CCSK compared with Wilms' tumor.[21]

Despite LR model based on NP images had moderate to good performance in diagnosing CCSK, the results of Delong test showed no significant difference between LR model, exponential-skewness and squareroot-skewness based on NP in training and validation set, which further confirms the important role of skewness in differentiating CCSK from Wilms' tumor. The distribution of exponential-skewness and squareroot-skewness in CCSK was different from Wilms' tumor. And higher skewness was statistically associated with CCSK, and

lower skewness with Wilms' tumor. Although NP-based skewness performed moderate to good in our study, this feature may be a supplementary biomarker contributing to the differential diagnosis between CCSK and Wilms' tumor. However, the exact utility of skewness in the CCSK and Wilms' tumor differentiation still needs further investigation.

Admittedly, there were some limitations in the present study. First, due to the rarity of CCSK, as a tertiary referral children's medical center, only 29 pediatric patients with CCSK were enrolled in this study. Second, considering the predominant prevalence of Wilms' tumor, 51 patients with Wilms' tumor were selected consecutively as control group, which may cause selection bias to our results. Third, the slice thickness of CT images in our study was 5 mm in order to include more patients as possible, and thin slice thickness may help to reflect more meaningful radiomics features between CCSK and Wilms' tumor. Finally, the CT scans performed in our study were obtained on two different scanners. Although preprocessing of the images was performed, the radiomics features derived from different scanners may have some influence on the diagnostic performance for CCSK.

In conclusion, radiomics is a promising method to differentiate CCSK from Wilms' tumor in children. Skewness from NP images at exponential and squareroot filters was able to discriminate between CCSK and Wilms' tumor, obtaining moderate to good diagnostic performance for CCSK. And higher skewness on NP images may be a potential biomarker for diagnosing CCSK from Wilms' tumor.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ACKNOWLEDGMENT

None.

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TABLE 1 The index of AUC, sensitivity and specificity of each selected feature in training and validation set.

	Feature	**Training Set** AUC (95%CI)	**Training Set** p value	**Training Set** Sensitivity	**Training Set** Specificity	**Va** AU
CMP	wavelet-HHL_Energy	0.628 (0.475, 0.781)	0.092	26.1%	100.0%	0.5
	wavelet-HHL_Total Energy	0.628 (0.475, 0.781)	0.092	26.1%	100.0%	0.5
	wavelet-LLL_90Percentile	0.676 (0.537, 0.815)	0.021	78.3%	62.5%	0.4
	wavelet-LLL_Range	0.646 (0.502, 0.789)	0.056	65.2%	65.0%	0.5
	gradient_Energy	0.605 (0.452, 0.758)	0.166	60.9%	65.0%	0.6
	gradient_Total Energy	0.605 (0.452, 0.758)	0.166	60.9%	65.0%	0.6
NP	exponential_Skewness	0.707 (0.573, 0.840)	0.007	78.3%	65.0%	0.8
	squareroot_Skewness	0.705 (0.572, 0.839)	0.007	82.6%	55.0%	0.8
	wavelet-HHL_Energy	0.577 (0.418, 0.736)	0.311	30.4%	97.5%	0.6
	wavelet-HHL_Total Energy	0.577 (0.418, 0.736)	0.311	30.4%	97.5%	0.6
	gradient_Energy	0.605 (0.452, 0.759)	0.166	30.4%	100.0%	0.7
CMP+NP	NP_exponential_Skewness	0.707 (0.573, 0.840)	0.007	78.3%	65.0%	0.8
	NP_squareroot_Skewness	0.705 (0.572, 0.839)	0.007	82.6%	55.0%	0.8
	NP_wavelet-HHL_Energy	0.577 (0.418, 0.736)	0.311	30.4%	97.5%	0.6
	NP_wavelet-HHL_Total Energy	0.577 (0.418, 0.736)	0.311	30.4%	97.5%	0.6
	NP_gradient_Energy	0.605 (0.452, 0.759)	0.166	30.4%	100.0%	0.7
	NP_gradient_Total Energy	0.605 (0.452, 0.759)	0.166	30.4%	100.0%	0.7

TABLE 2 The index of AUC, sensitivity and specificity of LR models based on CMP, NP and CMP+NP in training set and validation set.

LR Model	**AUC (95% CI) Training set**	**AUC (95% CI) Validation set**	**Sensitivity Training set**	**Sensitivity Validation set**	**Specificity Training set**	**Specifi Valida set**

CMP	0.676 (0.546, 0.789)	0.788 (0.526, 0.944)	34.8%	100.0%	95.0%	63.3%
NP	0.780 (0.658, 0.875)	0.803 (0.543, 0.952)	52.2%	83.3%	90.0%	90.9%
CMP+NP	0.779 (0.657, 0.874)	0.803 (0.543, 0.952)	52.2%	83.3%	90.0%	90.9%

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FIGURE 1 LASSO algorithm on feature selection. Fig. 1A, 1C and 1E show Lasso path of CMP, NP and CMP+NP, respectively; Fig. 1B, 1D and 1F demonstrate coefficients in Lasso model of CMP, NP and CMP+NP, respectively. Using Lasso model, 6, 5 and 6 optimal features, corresponding to the optimal alpha value of CMP, NP and CMP+NP respectively, were identified.

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FIGURE 2 ROC curves of each feature from CMP, NP and CMP+NP in training and validation set. Fig. 2A and 2B represent ROC curves from CMP in training and validation set, respectively. Fig. 2C and 2D represent ROC curves from NP in training and validation set, respectively. Fig. 2E and 2F represent ROC curves from CMP+NP in training and validation set, respectively.

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FIGURE 3 ROC curves of LR models based on CMP, NP and CMP+NP in training set (Fig. 3A) and validation set (Fig. 3B).