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Diagnostic value of texture analysis of apparent diffusion coefficient maps for differentiating fat-poor angiomyolipoma from non-clear-cell renal cell carcinoma

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ABSTRACT

Purpose: To investigate the feasibility of texture analysis of apparent diffusion coefficient (ADC) maps for differentiating fat-poor angiomyolipomas (fpAMLs) from non-clear-cell renal cell carcinomas (non-ccRCCs).

Methods: In this bi-institutional study, we included two consecutive cohorts from different institutions with pathologically confirmed solid renal masses: 67 patients (fpAML = 46; non-ccRCC = 21) for model development and 39 (fpAML = 24; non-ccRCC = 15) for validation. Patients underwent preoperative magnetic resonance imaging (MRI), including diffusion-weighted imaging. We extracted 45 texture features using a software with volumes of interest on ADC maps. Receiver operating characteristic curve analysis was performed to compare the diagnostic performance between the random forest (RF) model (derived from extracted texture features) and conventional subjective evaluation using computed tomography and MRI by radiologists.

Results: RF analysis revealed that grey-level zone length matrix long-zone high grey-level emphasis was the dominant texture feature for diagnosing fpAML. The area under the curve (AUC) of the RF model to distinguish fpAMLs from non-ccRCCs was not significantly different between the validation and development cohorts ($p = .19$). In the validation cohort, the AUC of the RF model was similar to that of board-certified radiologists ($p = .46$) and significantly higher than that of radiology residents ($p = .03$).

Conclusions: Texture analysis of ADC maps demonstrated similar diagnostic performance to that of board-certified radiologists for discriminating between fpAMLs and non-ccRCCs. Diagnostic performances in the development and validation cohorts were comparable despite using data from different imaging device manufacturers and institutions.

Abbreviations: ADC, Apparent diffusion coefficient; AUC, Area under the curve; CI, Confidence interval; CT, Computed tomography; DWI, Diffusion-weighted imaging; fpAML, Fat-poor angiomyolipoma; GLCM, Grey-level co-occurrence matrix; GLZLM, Grey-level zone length matrix; HGRE, High grey-level run emphasis; MRI, Magnetic resonance imaging; NGLDM, Neighbourhood grey-level different matrix; RCC, Renal cell carcinoma; RF, Random forest; ROC, Receiver operating characteristic; ROI, Region of interest.

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1. Introduction

Approximately 20% of solid small renal masses measuring less than 4 cm are benign, and differentiating them from malignancy is an important issue [1]. A particular challenge in this setting is the preoperative imaging diagnosis of fat-poor (fp) angiomyolipoma (AML), defined as AML with no visible fat on imaging because of limited fat content in the tumour, which accounts for 5% of AMLs [1–3]. A recent meta-analysis of 23 studies by Wilson et al. revealed that preoperative magnetic resonance imaging (MRI) showed promising accuracy for discriminating between fpAMLs and clear-cell renal cell carcinomas (ccRCCs) (area under the receiver operating characteristic curve [AUC], 0.96) [4]. Their results indicated the potential to replace biopsy in such situations. Nevertheless, as Silverman et al. reported, differentiation between fpAMLs and non-ccRCCs is often not possible based on conventional computed tomography (CT) and MRI [5]. In such cases, a percutaneous biopsy may be useful for diagnosis [6]. If the results of preoperative imaging and percutaneous biopsy are not definitive, surgery is warranted [7].

Diffusion-weighted imaging (DWI) differs from conventional MRI in that it measures water mobility within tissues to generate contrast [8]. Because the apparent diffusion coefficient (ADC) value calculated from DWI is a quantitative scale of water-molecule diffusion in tissues that are affected by the cellularity of a tumour, the ADC value may be reflective of tumour histological subtypes and grades [8,9]. Nevertheless, the role of DWI with ADC mapping in discriminating between fpAML and renal cell carcinoma (RCC) is still unclear.

Recently, research has been conducted on the use of texture analysis techniques, which extract quantitative pixel- or voxel-based tumour features from image data, for the differential diagnosis of renal masses. Texture analysis allows objective evaluation of imaging features that are more detailed and comprehensive than the traditional subjective evaluation of images. The utility of CT texture analysis in the differential diagnosis of RCC subtypes has been reported [10–13]. The application of this new technique to the evaluation of the DWI signal, which provides functional imaging information, is expected to be useful in the differential diagnosis of renal tumour subtypes.

The purpose of this study was to develop and validate a diagnostic model to discriminate between fpAML and non-ccRCC on the basis of texture features of ADC maps.

2. Materials and methods

The study protocol was approved by the medical ethics committee of our institution (study ID: 20200003). The requirement for written informed consent was waived owing to the retrospective nature of the study. Patient/tumour characteristics including clinical presentations and pathological findings were obtained from the medical records.

2.1. Patients

Consecutive patients with a solid renal tumour that was histologically diagnosed as non-ccRCC (papillary and chromophobe RCC) or AML in either institution A or B and who had undergone preoperative MRI (including DWI) were eligible for inclusion. Of these, patients with (1) prominent artefacts on MRI, (2) renal tumours of less than 65 voxels (since the software requires a VOI of at least 65 voxels for accurate calculation of texture features), and (3) the presence of visible macro fat on thin-section unenhanced CT were excluded. Exploratory texture feature analysis and prediction model development were performed using patient data from institution A (development cohort), and the validation analysis was performed using patient data from institution B (validation cohort).

2.2. MRI protocol

In institution A, an Intera Achieva 1.5-T MRI system (Philips, Best, the Netherlands) was used to perform DWI. The maximum gradient strength was 33 mT/m, and the slew rate was 160 T/m/s. DWI data were obtained in the axial plane using a spin echo-based single-shot echo-planar imaging sequence with the following parameters: repetition time 4500–5000 ms; echo time 82 ms; b-value = 0 and 1000 s/mm². In institution B, a Signa HDx 1.5-T MRI system (GE Healthcare, Waukesha, WI, USA) was used to perform DWI. The maximal gradient strength was 33 mT/m, and the slew rate was 120 T/m/s. DWI data were obtained in the axial plane using a spin echo-based single-shot echo-planar imaging sequence with the following parameters: repetition time 4500–5000 ms; echo time 60 ms; b-value = 0 and 1000 s/mm². Other MR parameters for both institutions A and B are shown in Table S1.

2.3. Texture analysis using ADC maps

To extract the texture features of the renal tumours on ADC maps, the Local Image Feature Extraction (LIFEx) software (version 4.00; Inserm, Orsay, France; <https://www.lifexsoft.org>) was used. ADC maps were generated from DWI with a b-value of 0 and 1000 s/mm² (for both cohorts). VOIs were drawn around each renal tumour on the axial ADC maps. For patients with multiple renal tumours, only the largest tumour was included for the analysis. Two board-certified radiologists with 17 and 31 years of experience in urogenital and body radiology (H. A. and S. O. in consensus) who were blinded to the clinical information and histological diagnosis of the tumour manually drew the tumour VOIs to include the whole tumour volume on multiple slices. From each VOI, 45 quantitative texture features were extracted, including 10 first-order and 35 higher-order statistics. First-order features included general statistical indices (mean and standard deviation of grey levels) and histogram features (skewness, kurtosis, excess kurtosis, entropy_log10, entropy_log2, and energy). Higher-order features, which reveal spatial relationships between voxels, included the grey-level co-occurrence matrix (GLCM), neighbourhood grey-level different matrix (NGLDM), grey-level run length matrix, and grey-level zone length matrix (GLZLM). The details of each texture feature are available in the appendix of the LIFEx software [14]. The settings used for feature extraction were as follows: (a) spatial resampling using 2.0 × 2.0 × 2.0 mm for spacing, (b) intensity discretisation using 64 as the number of grey levels, and (c) intensity rescaling using the 64 grey levels between the absolute minimum and maximum values in the VOI. An outline of imaging analysis and model development is shown in Fig. 1.

2.4. Subjective evaluation using CT and MRI by radiologists

Two board-certified radiologists with 7 and 34 years of experience in urogenital and body radiology (Y. A. and M. J. in consensus) and two radiology residents both with 2 years of experience in urogenital and body radiology (K. M. and Y. I. in consensus) determined the probability of fpAML on a 5-point scale (1 indicates fpAML to be less likely, 5 indicates fpAML to be highly likely) based on the presence or absence of the following imaging findings, which suggested fpAML high attenuation on unenhanced CT: a lower signal intensity in the renal cortex than in renal masses on T2WI, the absence of a pseudocapsule on T2WI, and less enhancement than the renal cortex in the corticomedullary phase of dynamic contrast-enhanced CT [15].

2.5. Development and validation of a diagnostic model using texture and statistical analyses

Random forest (RF) analysis was performed to develop a diagnostic model to differentiate fpAMLs from non-ccRCCs; 500 models were evaluated by varying the extracted parameters from texture analysis and selecting the best-performing model as the final model. The feature

Fig. 1. Schematic presentation of the study workflow. Abbreviations: non-ccRCC, non-clear-cell renal cell carcinoma; fpAML, fat-poor angiomyolipoma; ROI, region of interest.

importance of each texture feature was calculated as the percentage increase in the misclassification rate, and the texture features that did not contribute to improving the diagnostic performance or that highly correlated with other features were removed from model building, as reported previously [14,16]. Unsupervised hierarchical cluster analysis was used to identify tumour clusters among the extracted texture features in the validation cohort. Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic performance of each texture feature and developed RF model in differentiating fpAMLs from non-ccRCCs in both the development and validation cohorts. The optimal cut-off points for maximum accuracy were determined using the Youden index. The areas under the curves (AUCs) of both cohorts and subjective radiologists' assessment were compared using the two-variable chi-square test. The sensitivity and specificity values of subjective radiologists' assessment for an fpAML diagnosis were calculated using a cut-off score of 3. All p -values were two-sided, and p -values < 0.05 were considered significant. RF analysis was performed using XLSTAT software (version 2018.7; Addinsoft, New York, NY, USA; <https://www.xlstat.com>). ROC curve analysis was performed using SPSS®, version 20 (IBM Corp., Armonk, NY, USA) and the R-package pROC, v1.15.3 (R Foundation for Statistical Computing, Vienna, Austria). Other statistical analyses were performed using SAS software (version 9.0; SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient and tumour characteristics

Of the 78 potentially eligible patients (non-ccRCC, $n = 51$; fpAML, $n = 27$) in institution A and 47 (non-ccRCC, $n = 28$; fpAML, $n = 19$) in institution B, 67 cases (non-ccRCC, $n = 46$; fpAML, $n = 21$) in institution A and 39 (non-ccRCC, $n = 24$; fpAML, $n = 15$) in institution B were finally included in this study (Fig. 2). Among the five patients with multiple renal tumours ($n = 3$ in Cohort A, and $n = 2$ in Cohort B), only the largest tumour was included in the analysis. Table 1 shows the patient and tumour characteristics of the development cohort ($n = 67$) and validation cohort ($n = 39$) available for analysis of the texture features. Age ($p = .002$ and 0.005), proportion of males ($p < .001$), and median tumour size among patients with non-ccRCC ($p = .002$ and 0.046) were significantly higher than those among patients with fpAML in both cohorts (Table 1).

3.2. Exploratory texture feature analysis of the development cohort

Among the 45 imaging features calculated using texture analysis in the development cohort, the dominant 20 features were used to create the RF model (Table 2). Of these, the following three features were significantly higher in fpAML than in non-ccRCC: GLZLM_LZHGE (distribution of long homogeneous zones with high grey levels) ($p = .001$), GLZLM_SZLGE (distribution of short homogeneous zones with low grey levels) ($p = .009$), and HISTO_kurtosis (shape of the grey-level

Fig. 2. Flowchart of patient selection and exclusion. Abbreviations: non-ccRCC, non-clear-cell renal cell carcinoma; fpAML, fat-poor angiomyolipoma.

Table 1

Patient and tumour characteristics.

Institution A (development cohort)			
Parameter	Fat-poor AML (n = 21)	Non-clear-cell RCC (n = 46)	P-value
Median age, years (range)	46 (32–79)	62.5 (30–88)	0.002*
Sex, female/male	17 (81.0%)/4 (19.0%)	9 (19.6%)/37 (80.4%)	<0.001*
Median tumour size (mm, range)	25 (15–43)	35 (19–102)	0.002*
Clinical T stage	20 (95.2%)/1 (4.8%)/	30 (65.2%)/7	0.14
1a/1b/2a/2b/3a	0 (0.0%)/0 (0.0%)/0 (0.0%)	(15.2%)/4 (8.7%)/1 (2.2%)/4 (8.7%)	
Fuhrman grade		1 (2.2%)/23 (50.0%)/17 (37.0%)/5 (10.9%)	
1/2/3/4			
Institution B (validation cohort)			
Parameter	Fat-poor AML (n = 15)	Non-clear-cell RCC (n = 24)	P-value
Median age, years (range)	48 (27–79)	66.5 (38–78)	0.005*
Sex, female/male	10 (66.7%)/5 (33.3%)	4 (16.7%)/20 (83.3%)	0.002*
Median tumour size (mm, range)	23 (15–39)	31 (15–101)	0.046*
Clinical T stage	15 (100.0%)/0 (0.0%)/	16 (66.7%)/3	0.26
1a/1b/2a/2b/3a	0 (0.0%)/0 (0.0%)/0 (0.0%)	(12.5%)/2 (8.3%)/1 (4.2%)/2 (8.3%)	
Fuhrman grade		2 (8.3%)/13 (54.2%)/8 (33.3%)/1 (4.2%)	
1/2/3/4			

Abbreviations: AML, angiomyolipoma; RCC, renal cell carcinoma.

*P < .05, significant.

Table 2

Feature importance from random forest model for differentiating fat-poor AML from non-clear-cell RCC.

Selected feature	Feature importance
GLZLM_LZHGE	11.54
GLZLM_SZLGE	9.85
HISTO_Kurtosis	9.58
NGLDM_Coarseness	6.36
GLCM_Entropy_log10	5.90
HISTO_Skewness	5.13
GLCM_Homogeneity	4.55
HISTO_Energy	4.29
GLRLM_LRHGE	3.44
GLCM_Entropy_log2	2.78
HISTO_Entropy_log10	1.93
GLZLM_ZLNU	1.74
GLRLM_SRLGE	1.72
CONVENTIONAL_max	1.68
GLZLM_SZHGE	1.62
GLCM_Dissimilarity	1.60
GLRLM_LGRE	1.56
CONVENTIONAL_Q1	1.43
CONVENTIONAL_Q3	1.41
GLRLM_HGRE	1.33

Abbreviations: AML, angiomyolipoma; RCC, renal cell carcinoma; GLZLM, grey-level zone length matrix; LZHGE, long-zone high grey-level emphasis; SZLGE, short-zone low grey-level emphasis; NGLDM, neighbourhood grey-level different matrix; GLCM, grey-level co-occurrence matrix; GLRLM, grey-level run length matrix; LRHGE, long-run high grey-level emphasis; ZLNU, zone length non-uniformity; SRLGE, short-run low grey-level emphasis; SZHGE, short-zone high grey-level emphasis; LGRE, low grey-level run emphasis; HGRE, high grey-level run emphasis.

distribution [peaked or flat] relative to a normal distribution) ($p = .013$). NGLDM_Coarseness (level of spatial rate of change in intensity) ($p < .001$) and GLCM_Entropy_log10 (randomness of the distribution) ($p =$

.004) were significantly lower in fpAML than in non-ccRCC (Fig. 3). There was no difference in the remaining 15 imaging features between fpAML and non-ccRCC.

3.3. Diagnostic performance of the RF model and ADC values in the development cohort

The feature importance of mean ADC was -0.74 , and it contributed little to the differentiation between fpAML and non-ccRCC. In the development cohort, the AUC to distinguish fpAML from non-ccRCC in the RF model was 0.83 (sensitivity 85.7%, specificity 71.7%), which was significantly higher than the 0.61 of the model with ADC values alone ($p < .001$, sensitivity 81.0%, specificity 50.0%).

3.4. Validation of the developed model

Unsupervised hierarchical cluster analysis (an algorithm that groups similar objects into groups called clusters) of texture features included in the RF model of the validation cohort helped identify clusters (similar groups) characteristic of fpAML (Fig. 4).

The AUCs of the developed model and radiologists' subjective reading in the validation cohort are shown in Fig. 5. The AUC of the RF model to distinguish fpAML from non-ccRCC was 0.82 (sensitivity 86.7%, specificity 69.2%), which was similar to that of the board-certified radiologists' subjective readings (AUC = 0.86, $p = .46$, sensitivity 80.0%, specificity 79.2%) and significantly higher than that of the radiology residents' subjective readings (AUC = 0.69, $p = .03$, sensitivity 66.6%, specificity 62.5%) and the ADC-alone model (AUC = 0.52, $p < .001$, sensitivity 86.7%, specificity 33.3%). The AUC of the RF model was not significantly different between the development and validation cohorts (0.83 vs. 0.82, $p = .19$).

4. Discussion

This is the first study to investigate the feasibility of ADC map-based texture features for differentiating fpAML from non-ccRCC. The developed diagnostic model demonstrated a diagnostic performance comparable to that of board-certified radiologists and was validated in both intracross and independent external cohorts. The DWI signal, which provides functional tissue information, has potential as a biomarker for tumour characteristics [8,9]. According to a meta-analysis reported by Wilson et al., the sensitivity, specificity, and AUC values of DWI for differentiating fpAML from ccRCC were 0.89, 0.87, 0.94, respectively [4]. In this study, a diagnostic model derived from texture ADC map features improved the diagnostic performance of conventional ADC analysis. The diagnostic model using ADC-based texture features can be considered useful as an objective evaluation tool to maximise the diagnostic potential of DWI for differentiating fpAML from non-ccRCC.

Although the usefulness of the ADC value as an imaging biomarker has been reported in various malignancies, ADC values are affected by several image-dependent factors, including differences in gradient, coil, pulse-sequence system, and acquisition parameters [17]. The usefulness of skewness and kurtosis, which are less affected by these settings in ADC-related factors, obtained using histogram analysis is being investigated [18]. In this study, the diagnostic model using ADC map-based texture features showed high diagnostic performance comparable to intracross validation, unlike the mean ADC value alone, despite the differences between the two patient cohorts and MRI machines. Therefore, texture analysis may have the potential to solve these disadvantages.

According to the feature importance from the RF analysis, a high GLZLM_LZHGE value, which indicates high signal homogeneity, is the dominant feature for the diagnosis of fpAMLs. From a histopathological perspective, fpAML may be hypercellular with smooth muscle components. In contrast, papillary RCC arises from distal convoluted tubules and may have accompanying intratumoral haemorrhage or necrosis. In

Fig. 3. Boxplot of the significant exploratory texture feature of the development cohort. Abbreviations: fpAML, fat-poor angiomyolipoma; GLZLM, grey-level zone length matrix; LZHG, long-zone low grey-level emphasis; SZLGE, short-zone low grey-level emphasis; NGLDM, neighbourhood grey-level different matrix; GLCM, grey-level co-occurrence matrix.

Fig. 4. Results of the unsupervised hierarchical cluster analysis in the validation cohort. Nine of fifteen (60.0%) fpAML cases are included in Cluster II. Abbreviations: non-ccRCC, non-clear-cell renal cell carcinoma; fpAML, fat-poor angiomyolipoma.

Fig. 5. Receiver operating characteristic curves of the developed model and radiologists' subjective readings in the validation cohort. Abbreviations: RF, random forest; CI, confidence interval.

addition, chromophobe RCC arises from intercalated cells of collecting ducts, and coagulative necrosis may occur [7,19,20]. These histopathological characteristics of non-ccRCCs might have increased their heterogeneity when compared with that of fpAMs. A comprehensive (differential) diagnosis of renal tumours includes clear-cell RCC and oncocytoma as benign tumours and anaplastic and papillary RCC as non-ccRCC entities. Further investigations are warranted to confirm the correlation between texture features and these subtypes.

Our study has some limitations. First, the VOIs were set by two readers in consensus. Reader variability should be assessed in a detailed

study to evaluate interobserver agreement with regard to VOI placement. Second, there is a risk of overfitting in this study (45 variables were used in 67 cases). Third, additional texture features extracted from other major multiparametric MR sequences (T2WI or T1WI) to the model might improve the diagnostic performance, although the reproducibility of VOI placement might decrease during the multiparametric evaluation. Fourth, this study was conducted to create a differential diagnosis model using the textural features of ADC maps, while clinical parameters were not included. However, in both cohorts included in this analysis, there were significant differences in age, sex, and tumour size between non-ccRCC and fpAML. Future studies with larger sample sizes should assess if the diagnostic model can be further improved by incorporating these clinical parameters. Finally, this retrospective study included a relatively small sample size. Further larger validation studies are needed to confirm the results of this study.

5. Conclusions

Texture analysis of ADC maps demonstrated diagnostic performance similar to that of board-certified radiologists and better diagnostic performance than that of radiology residents for differentiating fpAMs from non-ccRCCs. The RF model provided comparable diagnostic performances in both intracross and external validation cohorts despite the use of data from different imaging device manufacturers and different institutions.

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CRedit authorship contribution statement

Yuki Arita: Investigation, Writing – original draft. **Soichiro Yoshida:** Writing – review & editing, Visualization. **Thomas C. Kwee:** Writing – review & editing, Visualization. **Hirohisa Akita:** Data curation. **Shigeo Okuda:** Resources, Data curation. **Yuki Iwata:** Data curation. **Kiyoko Mukai:** Data curation. **Shunya Matsumoto:** Data curation, Visualization. **Ryo Ueda:** Resources, Data curation. **Ryota Ishii:** Resources, Data curation. **Ryuichi Mizuno:** Data curation. **Yasuhisa Fujii:** Supervision, Project administration. **Mototsugu Oya:** Supervision, Project administration. **Masahiro Jinzaki:** Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejrad.2021.109895>.

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