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RESEARCH

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Prospective evaluation of the diagnostic efficacy of multiparametric MRI clear cell Likelihood Score in small solid renal masses and its predictive value for tumor grade

Osama M. Soliman[1*], Amani Ezzat Mousa[2], Mona Zaky[2] and Abdalla Abdelhamid[1]

Abstract

Background The detection of small renal masses has significantly increased due to the widespread use of cross-sectional imaging in recent years. Among these masses, clear cell renal cell carcinoma (ccRCC) is the most common subtype and progresses quickly, resulting in the advancement of the disease and the development of metastases. In this prospective study, our goal is to assess the effectiveness of multiparametric MRI clear cell Likelihood Score in small solid renal masses and its utility in predicting tumor grade.

Results In total, 103 patients (mean age 52.5 ± 13.16 years) with small solid renal masses of stage T1a (≤ 4 cm) were identified. Mean tumor size was 3.4 ± 0.6 cm. According to our study results, the clear cell Likelihood Score (ccLS) had sensitivity of 75.6%, specificity of 93.5%, PPV of 88.6%, NPV of 85.3% and accuracy of 86.4% in diagnosing ccRCC using a ccLS threshold of 4 and 5. As regard the assessment of ccLS threshold of 1 or 2 in excluding ccRCC pathological subtype, our study found that out of 29 patients with ccLS 1 or 2, there was only 1 ccRCC case with false result (3% false positive). It was also noted that there is significant relation between Arterial-to-delayed-enhancement-ratio (ADER) value and the grade of the ccRCC. The median interquartile range (IQR) of ADER parameter was statistically significant higher in grade II compared to grade I (Median was 1.6 and 0.9 respectively) and much higher in grade III compared to grades I and II (Median was 2.9) with P value < 0.001.

Conclusion This ccLS showed promising efficacy in prediction and exclusion of ccRCC subtype. Moreover, it aids in predicting the ccRCC grade.

Keywords Multiparametric MRI, Renal cell carcinoma, Clear cell likelihood score (ccLS), Clear cell renal cell carcinoma (ccRCC), Fuhrman grade

Background

The identification of small renal masses (SRMs) measuring less than 4 cm has seen a significant rise in recent decades, primarily due to the extensive utilization of cross-sectional imaging techniques. A considerable proportion of these masses exhibit either minimal growth or no growth at all over time. Both American and European guidelines on managing small renal masses now contemplate active surveillance as a viable option, particularly for patients with existing comorbidities [1].

*Correspondence:
Osama M. Soliman
drosoliman@yahoo.com
[1] Radiology department, Urology and Nephrology Center, Mansoura University, Mansoura, Egypt
[2] Radiology Department, Faculty of Medicine, Mansoura University, Mansoura, Egypt

Clear cell renal cell carcinoma (ccRCC) stands out as the most prevalent subtype among various renal cell carcinoma (RCC) types. It exhibits rapid growth, leading to disease progression and metastasis, particularly in populations under active surveillance [2]. Distinguishing the benign from malignant small renal masses (SRMs) based solely on imaging findings can be a challenging task. For instance, fat-poor angiomyolipoma (fpAML) and oncocytoma are benign tumors that closely resemble renal cell carcinoma (RCC) and are often challenging to differentiate [3].

Renal mass biopsy (RMBs) has been suggested as a standard procedure for distinguishing between benign and malignant small renal masses (SRMs). However, it poses invasiveness as a challenge, making it unfeasible for all patients, and it can yield nondiagnostic results in up to 20% of renal masses [4].

Employing noninvasive imaging for diagnosing solid renal masses serves as an alternative to biopsy, showcasing a certain level of accuracy in diagnosing specific histopathologic subtypes. Multiparametric Magnetic Resonance Imaging (mpMRI) is often used to characterize solid renal tumors. It helps in tumor staging and assist in planning subsequent therapeutic interventions [5].

The clear cell Likelihood Score (ccLS) on MRI was created to assess the likelihood that a mass will be identified as clear cell renal cell carcinoma (ccRCC) upon final pathologic analysis. It is a five-tier Likert scale and is defined as: (ccLS1) Definitely not ccRCC, (ccLS2) Probably not ccRCC, (ccLS3) Equivocal for ccRCC, (ccLS4) Probably ccRCC, and (ccLS5) Definitely ccRCC [6]. Prior studies have indicated the strong diagnostic performance of ccLS with moderate-to-good interreader agreement [1, 7, 8]. Additionally, in many cases, this algorithm can narrow down the imaging differential diagnosis to one to three favored diagnoses, enhancing diagnostic accuracy [9].

Tumor stage and grade serve as the most critical prognostic indicators for 5-year survival rates [10]. The traditional Fuhrman nuclear grade classification system is widely recognized as the most commonly utilized grading system in clear cell renal cell carcinoma (ccRCC) [11].

The majority of the previous studies used a retrospective approach in evaluation the ccLS algorithm, and some of these studies couldn't establish a clear link between ccLS and tumor grading [8, 12, 13].

The goal of our study is to validate the diagnostic performance of ccLS scores in small solid renal masses assigned prospectively in clinical practice and its utility in predicting the tumor grade.

Methods

Patient selection

This prospective study was approved by the institutional research and ethical committee and was approved by the international review board (MS. MS.23.01.2271.RI). Consents were obtained from all patients prior to examination. The study includes 103 patients with small solid renal masses of T1a stage, based on clinical suspicion, ultrasonography or non-contrast computed tomography (CT) studies in the period from April 2023 to January 2024.

Adequate sample size was calculated using Yamane's formula. Inclusion criteria: Patients with solid parenchymal renal masses of stage T1a (size ≤ 4 cm), scheduled for biopsy or surgical resection. Exclusion criteria: Masses excluded by the ccLS algorithm (such as presence of macroscopic fat and masses with less than 25% solid component), infiltrative renal masses and masses more than 4 cm, patients with known histopathological diagnosis by previous biopsy or surgical resection, contraindications for MRI. Studies with low image quality or non-standard scan sequences were excluded.

Data regarding age, gender, clinical presentation of all cases were collected. Assessment of the mpMRI findings was done using ccLS. Patients were monitored and their histopathological results after surgical resection were compared with the initial assigned MRI findings.

Technical information

Regarding MRI examination, all mpMRI exams were performed at a single institution using 3-Tesla MRI machine *(Philips Ingenia 3T, Netherlands)* with abdominal phased array coil, in supine position. The protocol of examination briefly included; coronal and axial non fat-suppressed and fat-suppressed T2- weighted imaging, Dixon based multiphasic contrast enhanced imaging (pre-contrast, corticomedullary, early and late nephrographic, and excretory phases). Diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) (b value = 800). Axial chemical shift (in and opposed phases). The used MRI sequences are illustrated in Table 1.

Interpretation and application of clear cell Likelihood Score

Interpretation: The MRI analysis was conducted by proficient academic radiologist. Each study was transferred and reviewed using a picture archiving and communication system (PACS) called Magic View, GE, WI, USA. As part of the structured clinical report, a clear cell Likelihood Score (ccLS V2.0) was prospectively assigned to each renal tumor. The algorithm flow chart is shown at (Fig. 1) [14].

Table 1 Sample protocol for Renal MRI

Sequence Name	Section thickness	Matrix (pixels)	TR (ms)	TE (ms)	NSA	Acquisition time	Notes
Coronal T2W single shot fast SE	6	320 × 320	1000	100	1	90 (multiple breath holds)	Whole-abdomen coverage
Axial 3D Dixon T1W spoiled GRE	3	260 × 320	6.68	2.39, 4.77	1	14 (single breath hold)	Acquire in-phase and opposed phase images, reconstruct fat-only and water-only images
Axial T2W singleshot fast SE	4	320 × 320	1000	100	1	120 (multiple breath holds)	Whole-abdomen coverage
Axial T2W fast SE	6	260 × 320	3000	93	1	40 (multiple breath holds)	Cover kidneys only; not part of DFP recommendations, optional sequence
Axial T2W fat-suppressed fast SE	6	260 × 320	3000	93	1	60 (multiple breath holds)	Cover kidneys only; not part of DFP recommendations, optional Sequence
Axial single-shot DWI	6	256 × 268	9500	56	2, 4, 10	180 (free breathing)	Obtain *b* values of 50, 400, and 800 s/mm2; reconstruct ADC map
Axial 3D precontrast T1W spoiled GRE	3	260 × 320	5.09	2.33	1	12 (single breath hold)	–
Coronal 3D precontrast T1W spoiled GRE	3	260 × 320	5.09	2.33	1	12 (single breath hold)	–
Axial 3D T1W CMP spoiled GRE	3	260 × 320	5.09	2.33	1	12 (single breath hold)	30-s delay or late arterial phase by bolus tracking or test bolus methods; generate subtraction images from precontrast acquisition
Axial 3D T1W venous phase spoiled GRE	3	260 × 320	5.09	2.33	1	12 (single breath hold)	70-s delay; generate subtraction images from precontrast acquisition
Axial 3D T1W nephrographic phase spoiled GRE	3	260 × 320	5.09	2.33	1	12 (single breath hold)	150-s delay; generate subtraction images from precontrast acquisition
Coronal 3D T1W delayed phase spoiled GRE	3	320 × 320	4.67	2.39	1	14 s (single breath hold)	210-s delay; generate subtraction images from precontrast acquisition
Axial 3D T1W delayed phase spoiled GRE	3	320 × 320	4.67	2.39	1	14 s (single breath hold)	300-s delay; generate subtraction from precontrast acquisition

To assign a ccLS, specific steps must be followed, which are divided into three categories:

a. *Eligibility criteria*; (excluding lesions with macroscopic fat and lesions with less than 25% enhancing solid components).
b. *Major criteria*; which are necessary in evaluation of each renal mass.

    1. *T2-weighted Signal Intensity*: assessing the signal intensity of the solid component of the mass [that will be the most enhancing component at dynamic contrast enhancement (DCE)] comparing to renal cortex.
    2. *Corticomedullary phase enhancement*: The evaluation of degree of solid lesion enhancement is assessed at the corticomedullary phase (CMP). The degree of enhancement can be visually assessed by comparing it to the normal renal cortex or quantitatively if visually the degree of enhancement is uncertain by using the following formula. $\frac{Tumor\ (CMP-Pre)/Pre}{Cortex\ (CMP-Pre)/Pre}$. [Values > 75% = intensely enhancing, values 40–75% = moderately enhancing and values < 40% = mildly enhancing [14].
    3. *Microscopic Fat*: Can be qualitatively evaluated by observing a significant signal intensity drop on opposed-phase sequences compared to in-phase sequences of chemical shift images (CSI). However, in uncertain cases, quantitative assessment may be employed using the following formula. $\left(SI_{in\ phase} - SI_{opposed\ phase}\right) > (Std\ dev_{in\ phase} + Std\ dev_{opposed\ phase})$ [14].

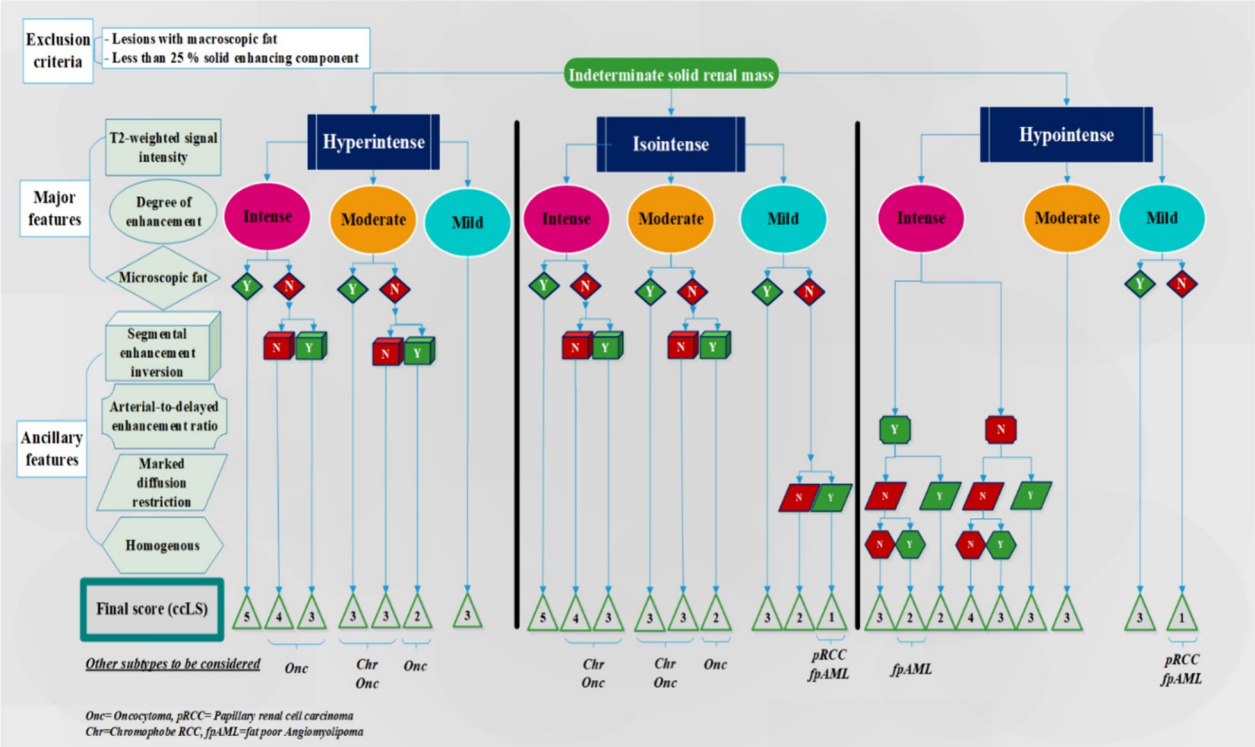

Fig. 1 This simplified flowchart illustrates the ccLS algorithm including the latest updates and modifications of ccLS V2.0. Renal masses that meet the eligibility criteria are evaluated in a stepwise manner through the major and the ancillary parameters according to their specific pathway to determine their ccLS; which ranges from 1 (very unlikely to be ccRCC) to 5 (very likely to be ccRCC). Alternative diagnoses based on imaging features are listed below the ccLS scores [Y = yes and N = No] [14]

c. *Ancillary features*; which are used in specific scenarios.

1. *Segmental Enhancement Inversion (SEI)* A phenomenon observed in parts of a mass, where there is a differential enhancement pattern. Initially hyperenhancing components transition to become hypoenhancing, while initially hypoenhancing components shift to become hyperenhancing.
2. *Arterial-to-Delayed Enhancement Ratio* The positive value of parameter (ADER) describes a small renal mass (SRM) that shows intense enhancement during the corticomedullary phase (CMP) imaging, followed by comparatively reduced enhancement during the delayed phase. Quantitatively, a threshold ratio of 1.5 or higher is utilized in the subsequent calculation to signify a positive outcome. $ADER = \frac{CMP-Pre}{Delayed-Pre}$ [14].
3. *Diffusion-weighted Imaging* by assessing the diffusion restriction pattern as regard the enhancing solid component of the mass.
4. *Homogeneity and Heterogeneity* The homogeneity of a small renal mass (SRM) is utilized as a tie-breaker in cases of lesions with low T2 weighted signal intensity (T2WSI) and intense enhancement.

Pathological diagnosis

All diagnosed lesions underwent surgical resection either partial or radical nephrectomy, and histopathological evaluation was done according to the World Health Organization classification of renal neoplasms [11].

Statistics

IBM SPSS Statistics for Windows, Version 25.0, was used for the statistical analysis (IBM Corp, 2017). Categorical data are presented as number and percentage of total. While normally distributed continuous data are expressed as mean and standard deviation. Non-normally distributed data are presented as median (Interquartile Range). Significance of the obtained results is considered at P value ≤ 0.05. A receiver operator characteristic (ROC) curve was constructed to detect ccLS score diagnostic performance for predicting clear cell carcinoma or malignancy presence. To compare non-normally distributed data between the 3 groups, Kruskal–Wallis test was

employed, while Mann–Whitney test was used to compare between each two groups.

Results

In this prospective study, there were 163 patients with a total of 163 solid renal masses. 56 renal masses were excluded from the study due to lack of pathological results (managed by active surveillance). 4 other cases were excluded due to degraded imaging quality and unavailability of specific sequences. 103 solid renal masses were included in the final analysis (Fig. 2). In this study, the age of patients ranges from 18 to 83 years, with a mean age of 52.5 (standard deviation (SD) ± 13.16). The most prevalent age group was between 48- and 58-years accounting for (30.09%) of the participants. Among the patients, there were 69 males (67% of total cases) and 34 females.

The mean size of the studied renal masses was 3.4 cm (SD ± 0.6 cm). Most of them were isointense at T2WIs (54.4%). About half of the masses showed intense enhancement (48.5%). Only one third of the cases showed intralesional microscopic fat. The distribution of cases among the different ccLS scores were; ccLS1 = 17.5%, ccLS2 = 10.7%, ccLS3 = 37.9%, ccLS4 = 12.6%, ccLS5 = 21.4%), ccLS3 was the predominant score group (Table 2).

Of the total masses, 82 out of 103 cases (79.6%) were histopathologically confirmed as malignant, with 41 out of those 82 (50%) diagnosed as ccRCC. In contrast, benign lesions accounted for 21 out of 103 (20%) of total masses, distributed as follows: 17 cases of oncocytoma, 2 cases of fpAML, 1 case of papillary adenoma, and 1 case of metanephric adenoma (Table 3).

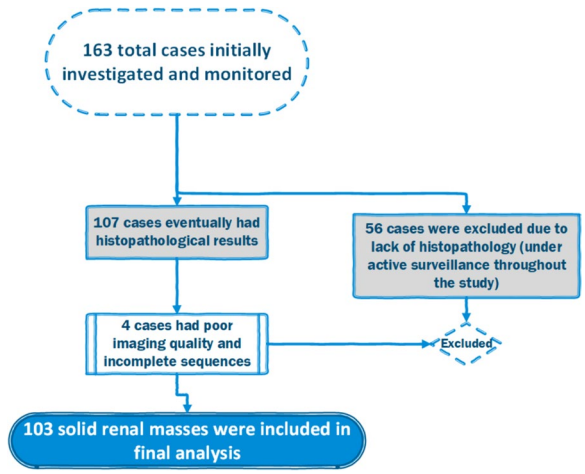

Fig. 2 The flow chart of participants in the study

Table 2 MRI criteria of renal masses

Variable	N (%) N = 103
Signal intensity on T2W images	
Hypointense	28 (27.2%)
Isointense	56 (54.4%)
Hyperintense	19 (18.4%)
Degree of enhancement at CMP	
Mild enhancing	33 (32%)
Moderate enhancing	20 (19.4%)
Intense enhancing	50 (48.5%)
Microscopic fat at CSI	
Drop of signal	30 (29.1%)
No drop of signal	73 (70.8%)
Final ccLS	
ccLS 1	18 (17.5%)
ccLS 2	11 (10.7%)
ccLS 3	39 (37.9%)
ccLS 4	13 (12.6%)
ccLS 5	22 (21.4%)

Most of the lesions had a pathology of clear cell carcinoma (39.8%), with papillary cell carcinoma (22.3%) and oncocytoma (16.5%) following behind. The majority of the cases with ccLS 4 and 5 shows pathological results of clear cell carcinoma. Specifically, 92.3% of ccLS 4 cases and 86.4% of ccLS 5 cases were of the clear cell carcinoma subtype (Table 3 and Fig. 3).

The ROC curve results of ccLS in prediction of clear cell carcinoma and any type of renal malignancy. (AUC 0.89 and 0.58 respectively) (Table 4 and Fig. 4).

Among the conducted cases, 31 out of 41 cases with clear cell carcinoma pathological diagnosis, had ccLS score 4 and 5. In contrast, 58 out of 62 cases with pathological diagnosis other than clear cell carcinoma, had ccLS 1,2 and 3 (Table 5). The false positive rate for SRM graded as ccLS 4–5 is 12.9%. Among these false positives, there were 4 cases: 2 were fpAML, 1 was oncocytoma (yielded ccLS4), and 1 was renal cell carcinoma Xp11.2 translocation (Table 3) (Figs. 5, 6).

According to this study, the ccLS demonstrates a sensitivity of 75.6%, specificity of 93.5%, positive predictive value (PPV) of 88.6%, negative predictive value (NPV) of 85.3%, and an accuracy of 86.4% when using a ccLS score of 4–5 to diagnose clear renal cell carcinoma (Table 6).

It was revealed that out of 29 cases with ccLS 1 and ccLS 2, there was only 1 case diagnosed as ccRCC (false omission rate 3%) (Table 7). It was also noted that the papillary renal cell carcinoma (pRCC) histological subtype was predominant at the ccLS1 and 2 groups accounting for 17/29 (58.6%) (Fig. 7).

Table 3 Distribution of pathological results in relation to Clear cell Likelihood Score

Pathology	Total N = 103	Clear cell Likelihood Score				
		ccLS 1 N = 18	ccLS 2 N = 11	ccLS 3 N = 39	ccLS 4 N = 13	ccLS 5 N = 22
	N (%)					
Malignant lesions (N = 82)						
Clear cell carcinoma	41 (39.8%)	–	1 (9.1%)	9 (23.1%)	12 (92.3%)	19 (86.4%)
Chromophobe cell carcinoma	11 (10.7%)	1 (5.6%)	–	10 (25.6%)	–	–
Papillary cell carcinoma	23 (22.3%)	14 (77.8%)	3 (27.3%)	6 (15.4%)	–	–
RCC unclassified	2 (1.9%)	1 (5.6%)	–	1 (2.6%)	–	–
Mixed Tubular & spindle cell carcinoma	3 (2.9%)	1 (5.6%)	–	2 (5.1%)	–	–
RCC Xp11.2 translocation	1 (0.97%)	–	–	–	–	1 (4.5%)
Small cell neuroendocrinal carcinoma	1 (0.97%)	–	1 (9.1%)	–	–	–
Benign lesions (N = 21)						
Oncocytoma	17 (16.5%)	–	6 (54.5%)	10 (25.6%)	1 (7.7%)	–
Metanephric Adenoma	1 (0.97%)	–	–	1 (2.6%)	–	–
Papillary Adenoma	1 (0.97%)	1 (5.6%)	–	–	–	–
Fat Poor Angiomyolipoma	2 (1.9%)	–	–	–	–	2 (9.1%)

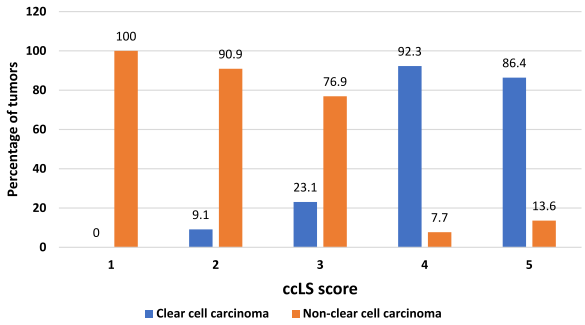

Fig. 3 Distribution of pathology according to ccLS score

Table 4 ROC curve analysis of ccLS score determining clear cell carcinoma or any type of renal malignancy

	AUC
ccLS score diagnosing clear cell carcinoma	0.89
ccLS score detecting any type of renal malignancy	0.58

Interestingly, this study discovered a clear link between the ccLS and the tumor grading of cases with ccRCC. Among the different parameters of the ccLS, the median (IQR) of arterial-to-delayed enhancement ratio (ADER) is remarkably statistically significant higher in grade II compared to grade I (Median was 1.6 and 0.9 respectively). Furthermore, it is much higher in grade III compared to grades I and II. (Median was 2.9) where P value < 0.001 (Table 8) (Fig. 8).

Discussion

The potential of magnetic resonance imaging (MRI) in histologic subtyping of renal cell carcinoma (RCC) has been established, along with its value in distinguishing between benign and malignant renal masses [6]. Despite renal mass biopsy being an alternative diagnostic method, it remains invasive and not suitable for all patients, and it yields nondiagnostic results in up to 20% of cases [4].

The clear cell Likelihood Score (ccLS) is regarded as a non-invasive, MRI-based tool used to predict the likelihood of a mass being identified as clear cell renal cell carcinoma (ccRCC) upon final pathological analysis. Previous studies have shown its good diagnostic performance and moderate-to-good interreader agreement [1, 7, 8].

The prospective design of this study offers an advantage over previous retrospective studies. This is due to the potential for selection bias and variations in techniques and study protocols that can influence the outcomes. Study protocols often change over time, impacting studies performed on cases examined over years. For instance, variations in contrast agent timing methods and differences in b-values for diffusion-weighted imaging (DWI). Such limitations inherent in retrospective designs can ultimately result in less accurate results [15].

We aimed in this study to evaluate the effectiveness of the clear cell Likelihood Score (ccLS) as a non-invasive diagnostic imaging tool for determining the likelihood of clear cell subtype renal cell carcinoma and predicting tumor grade. By applying the ccLS algorithm in our

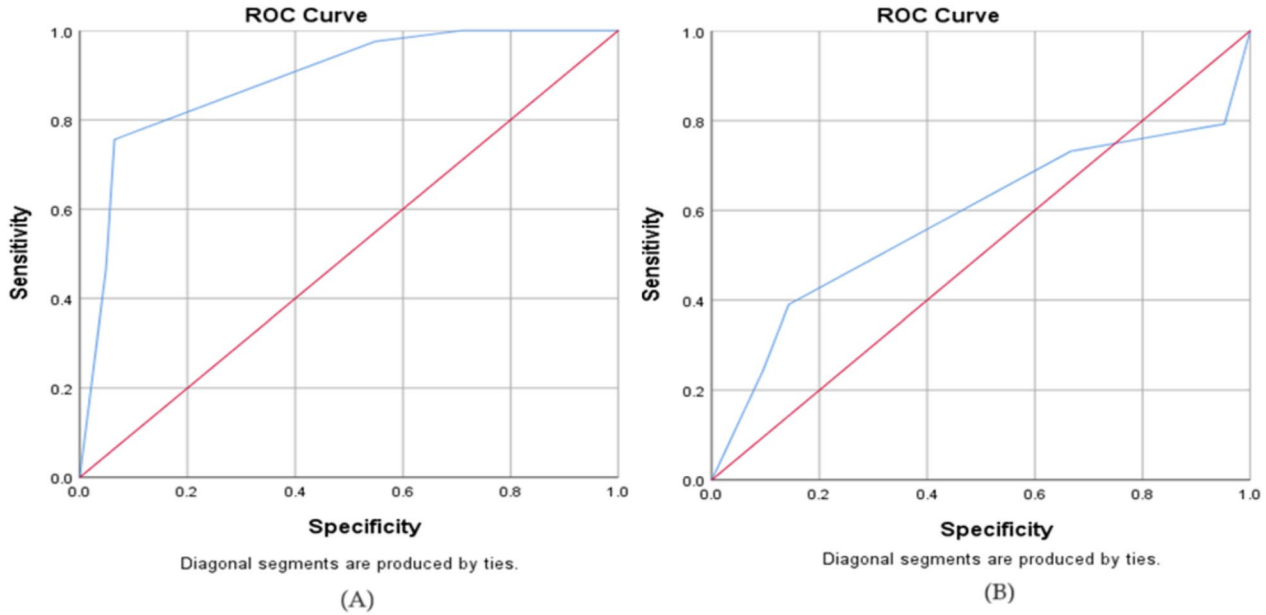

Fig. 4 **A** ROC curve for of ccLS score determining clear cell carcinoma, **B** ROC curve for of ccLS score determining any type of renal malignancy

Table 5 Relation between ccLS score of 4–5 and diagnosed clear cell renal masses

ccLS score	Final diagnosis		Total
	Clear cell	Non clear cell	
ccLS score 4–5	31	4	35
ccLS score 1–3	10	58	68

daily clinical practice, we were able to assess both its utility and its limitations.

The ccLS was implemented in a prospective manner in this study, where patients were followed up after initial diagnosis using primary modalities [such as ultrasound or Computed Tomography (CT)]. Subsequently, MRI imaging was conducted using specific protocol, and the ccLS was applied to each patient, resulting in a final ccLS result.

Following the initial patient selection, their management was categorized into two groups: those under active surveillance (excluded from the study) and those undergoing surgical intervention with histopathological examination. The approved histopathological results were then correlated with the previously assigned ccLS results.

Furthermore, this study established correlation between the algorithm parameters and the grade of clear cell renal cell tumors. This correlation will aid in predicting the grade and aggressiveness of the tumor, thereby facilitating quicker clinical management when necessary to reduce the risk of invasion or metastasis in high-grade cases.

Regarding the demographic findings of our study, a significant proportion of patients with renal masses were males, accounting for 67% of the total cases. This indicates a male-to-female distribution ratio of approximately 2:1. The mean age of the patients included in the study was 52.5 years with a standard deviation of 13.16 years. These findings align with those reported in previous studies [7, 9].

Small solid renal masses of stage T1a (i.e. ≤ 4 cm) were the target group of this study, with mean size (3.4 ± 0.6 cm). The mean mass size is close to prior studies [8, 9].

Our study clearly demonstrates the predominance of the clear cell carcinoma (ccRCC) subtype in final pathological diagnoses, accounting for (39.8%) of cases, followed by the papillary cell carcinoma subtype (pRCC) at (22.3%). This pattern aligns with the prevalent intensely enhancing patterns observed among the studied cases. These results and the pathological distribution mirror findings from previous studies [12, 16].

In terms of the highest two ccLS categories (ccLS 4 and 5), our study revealed that 92.3% (12/13) of cases with ccLS 4 were diagnosed with clear cell carcinoma subtype (ccRCC), while 86.4% (19/22) of cases with ccLS 5 were also identified as clear cell carcinoma subtype (ccRCC). These findings closely resemble the results reported in a previous study [15].

When using a ccLS 4 and 5 to diagnose clear cell renal cell carcinoma (ccRCC), our study found a sensitivity

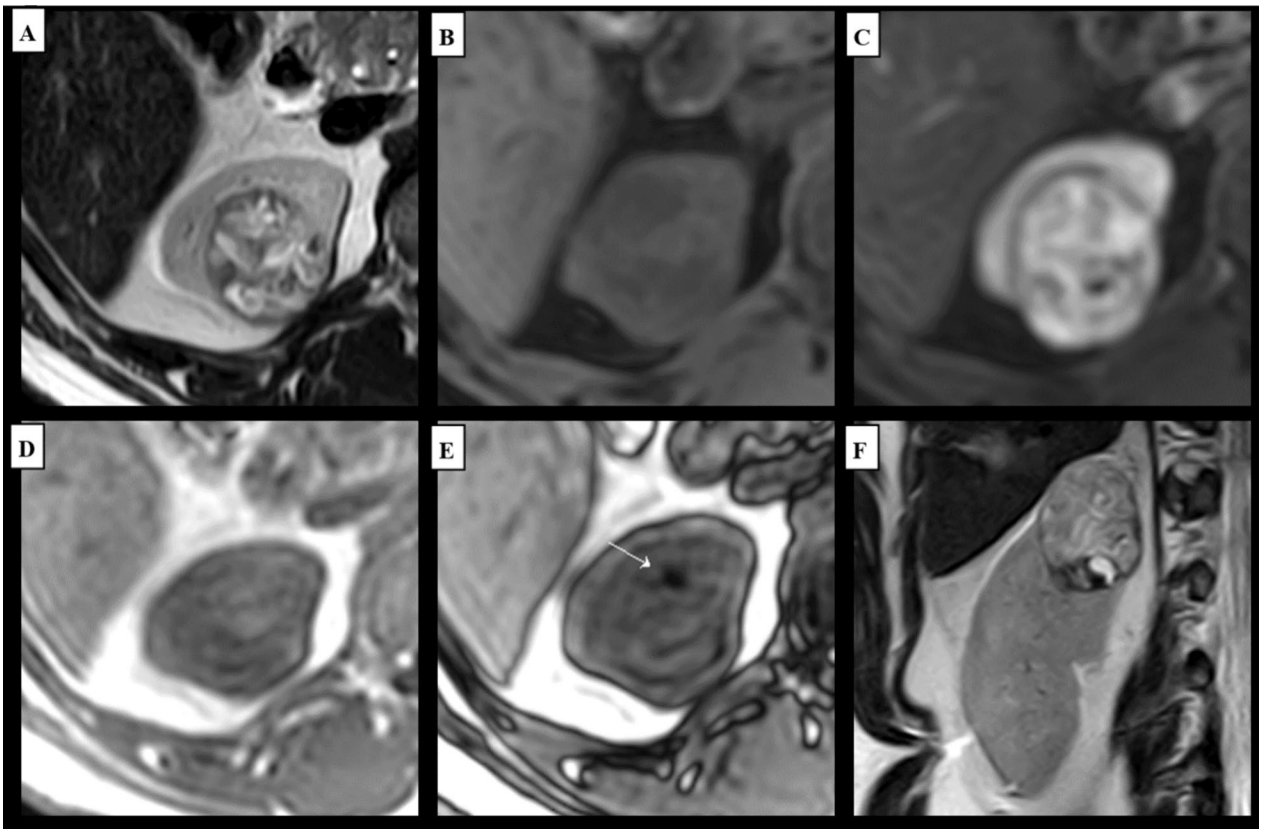

Fig. 5 A 47-years-old male patient, with incidental discovered right renal upper polar mass on non-contrast CT, measuring 3.8 cm. **A** Axial T2-WI, showing predominantly isointense lesion comparing to renal cortex. **B**, **C** Axial pre-contrast and corticomedullary phases of DCE MRI image respectively, showing intense enhancement of the mass (the solid component of the mass enhances ≥ the renal cortex). **D**, **E** Chemical shift images, showing areas of signal drop at opposed phase (Arrowed) represents intracellular fat. **F** Coronal T2-WI, showing the location and relations of the lesion. Application of ccLS algorithm revealed a final score of ccLS 5. Histopathological result clear renal cell carcinoma (Grade III)

of 75.6%, specificity of 93.5%, positive predictive value (PPV) of 88.6%, negative predictive value (NPV) of 85.3%, and an overall accuracy of 86.4%. Interestingly, Johnson et al. also reported similar findings in their research, with a sensitivity of 79%, specificity of 86%, PPV of 84%, NPV of 85%, and accuracy of 84% [8]. Schieda's study, which was done retrospectively on a larger sample volume, reported slightly superior specificity and PPV values with sensitivity, specificity, PPV, and NPV for the diagnosis of ccRCC when ccLS was 4 or 5 as 75%, 78%, 76%, and 77%, respectively [15].

This study showed that 32/35 (91.4%) of the renal masses with ccLS 4 or 5 had a malignant histopathological diagnosis. This result is comparable to that of previous study which reported a ratio of 84% malignant masses among cases with ccLS 4 or 5 [15].

Among the ccLS 1 and 2 groups, malignant lesions accounted for 44% of the cases. A majority of these lesions were confirmed to be papillary renal cell carcinoma (pRCC), comprising 63% of the malignant pathologies, which was expected since pRCC was a top differential subtype during the application of the algorithm. However, these findings impacted the sensitivity of ccLS 4 and 5 groups in detecting all malignant lesions. Notably, a prior study reported a similar proportion of pRCC among the ccLS 1 and 2 groups (67%) [15].

Among the ccLS 3 (equivocal) group, malignant lesions accounted for 28/39 cases (71%). The majority of these lesions were pathologically diagnosed as chromophobe renal cell carcinoma (chrRCC) (25%), followed closely by clear cell renal cell carcinoma (ccRCC) (23%). In contrast, the benign lesions in this group numbered 11/39 cases (29%), with oncocytoma representing the majority at 10 out of 11 cases (91%). These findings align closely with a prior multicentric study that reported 33% of the ccLS 3 group being diagnosed as ccRCC [15].

A previous study conducted by Johnson et al. found that using a ccLS 1 or 2 to rule out a diagnosis of ccRCC resulted in no lesions being identified as ccRCC among the ccLS 1 and 2 groups (0% false positive) [8]. These results align closely with our study, with a subtle

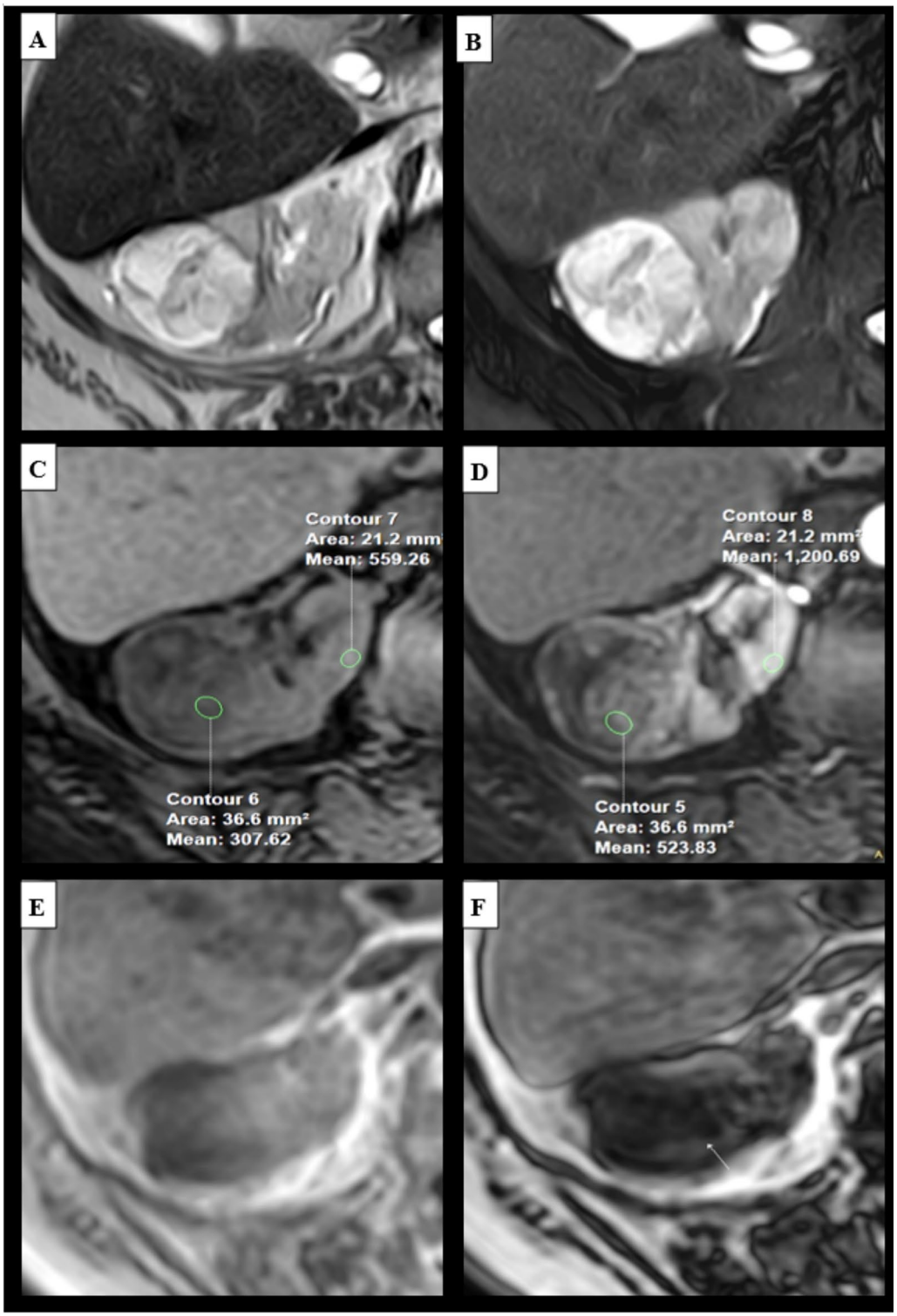

Fig. 6 A 73-years-old male patient, presented with incidentally discovered right renal mass, measuring 3.3 cm. **A** Axial T2-WI, showing hyperintense lesion. **B** Axial fat saturated T2-WI, the mass showing no signal drop excluding presence macroscopic fat. **C**, **D** Axial pre-contrast and corticomedullary phases respectively, showing moderate (63%) enhancement of the mass. **E**, **F** Chemical shift images, showing areas of intracellular fat. Application of ccLS algorithm revealed a final score of ccLS 3. Histopathological result was oncocytoma

Table 6 ccLS score 4–5 performance in diagnosing clear cell carcinoma

Diagnostic performance	ccLS score 4–5 detecting clear cell-carcinoma (%)
Sensitivity	75.6
Specificity	93.5
PPV	88.6
NPV	85.3
Accuracy	86.4

Table 7 Relation between ccLS score of 1–2 and pathologically diagnosed non-clear cell renal malignant lesions

ccLS score	Final diagnosis		Total
	Non clear cell N = 62	Clear cell N = 41	
ccLS score 1–2	28	1	29
ccLS score 3–5	34	40	74

difference. In our study, we found that 1 out of 29 masses with ccLS 1 or 2 was confirmed to have ccRCC diagnosis after pathological examination (3% false positive rate). This discrepancy can be attributed to the atypical radiological presentation of this solitary mass, characterized by low T2-weighted signal intensity and the absence of intralesional microscopic fat.

As regard the evaluation of ccLS 1 or 2 in diagnosing all non-clear cell renal cell carcinoma (ccRCC) histopathological subtypes, this study showed a sensitivity of 45.2%, specificity of 97.6%, positive predictive value (PPV) of 96.6%, negative predictive value (NPV) of 54.1%, and an overall accuracy of 66.02% in. These results show difference in some aspects comparing to the results of Johnson et al. [8], which reported a sensitivity of 68%, specificity and PPV of 100%, NPV of 80%, and accuracy of 86%. The NPV differs from another study conducted by Schieda et al. (88%) [15]. This moderate NPV (54.1%) of ccLS 1 and 2 to diagnose non-clear cell carcinomas was observed in the context of a higher prevalence of the

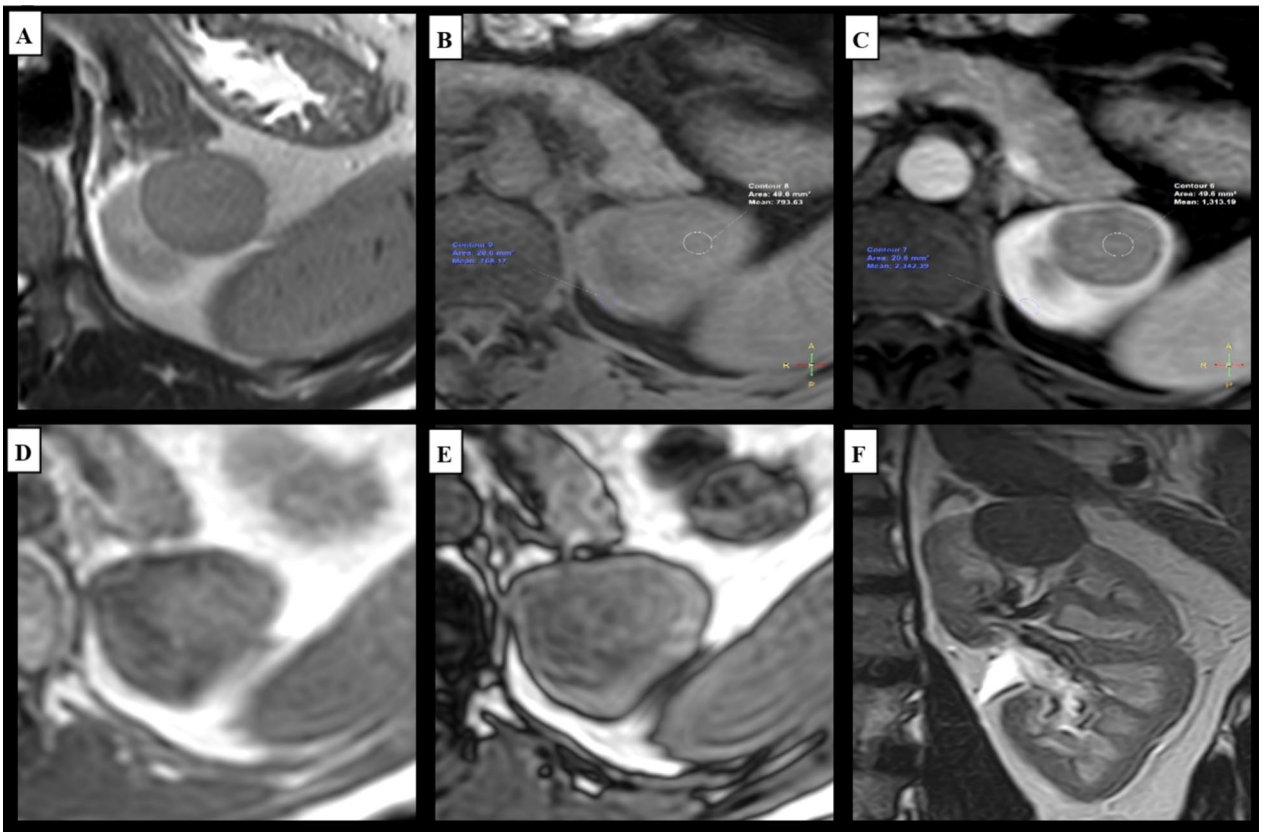

Fig. 7 A 57-years-old male patient, presented with lower urinary tract symptoms, during routine pelviabdominal ultrasound, an incidental left renal mass, measuring 3.3 cm was noted at the lateral aspect of the upper zone. **A** Axial T2-WI, showing predominantly hypointense lesion comparing to renal cortex. **B**, **C** Axial pre-contrast and corticomedullary phases of DCE MRI image respectively, showing mild enhancement of the mass (quantitative assessment of the degree of enhancement using the corresponding formula revealed 31.8% enhancement ratio). **D**, **E** Chemical shift images, showing no drop of signals at opposed phase. **F** Coronal T2-WI, showing the location and relations of the lesion. Application of ccLS algorithm revealed a final score of ccLS 1. Histopathological result papillary renal cell carcinoma

Table 8 Relation between ADER and grade of clear cell carcinoma patients (N = 40)

Parameters	Grade I N = 17 Median (IQR)	Grade II N = 16	Grade III N = 8	P value
Pre-contrast intensity value	146 (131–189)	154 (127–179)	225.5 (132.7–243.5)	0.2
Arterial phase intensity value	342 (263–484)	464 (354–500.3)	640 (436.5–918.3)*	0.01
Delayed phase intensity value	358 (269.5–454)	361 (271–439.5)	341.5 (250.3–377.5)	0.6
(Arterial – Pre) intensity value	141 (117.5–278.5)	315.5 (204.3–355)*	405 (313.3–626.3)*	**0.004**
(Delayed – Pre) intensity value	211 (152.5–298.5)	201.5 (135–264.3)	99 (74–178.3)*#	0.03
ADER	0.9 (0.6–1.3)	1.6 (1.1–2.1)*	2.9 (1.9–9.5)*#	**< 0.001**

Bold values are the statistically significant values

*Means significant difference compared to grade I

Means significant difference compared to grade II

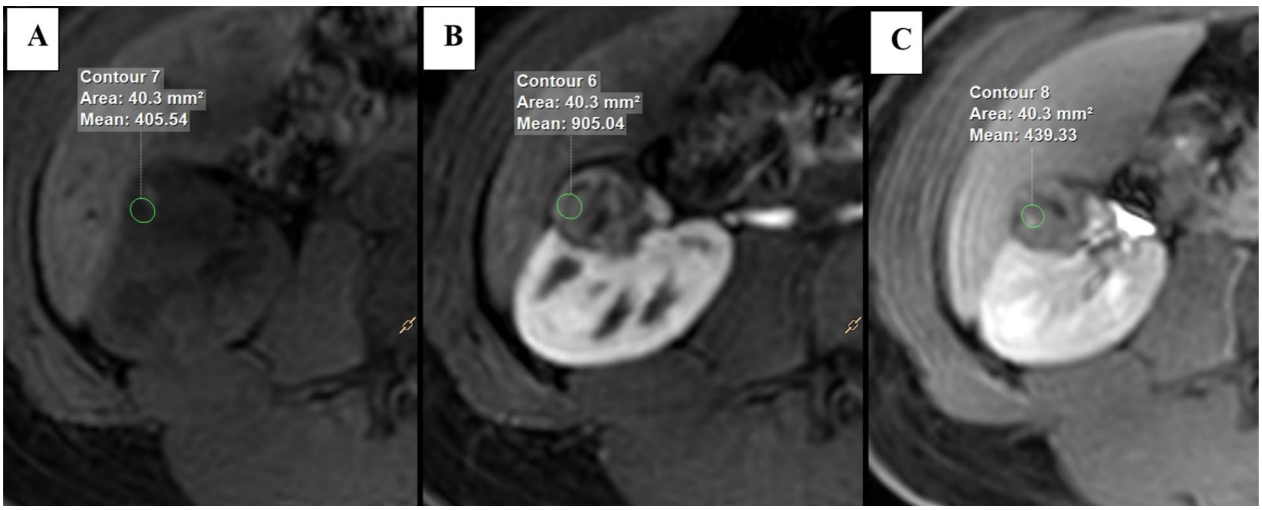

Fig. 8 A 24-years-old male patient with small solid right renal midzonal mass, **A–C** Axial pre-contrast and corticomedullary and delayed phases respectively, showing degree of enhancement at the different phases. histopathological examination revealed clear renal cell carcinoma (Grade III). Calculation of the ADER resulted in high value (= 15). (Positive correlation)

ccLS 3 group among the studied samples, accounting for 39 out of 103 cases (37%), of which 10 cases (25%) were ultimately diagnosed as oncocytoma in the final pathological diagnoses. This prevalence of ccLS 3 cases with a non-clear cell diagnosis significantly impacted the NPV of ccLS 1 and 2.

The percentages of clear cell renal cell carcinoma (ccRCC) according to the clear cell Likelihood Score (ccLS) were 0%, 9%, 23%, 92%, and 86% for ccLS of 1–5, respectively, in our study. Comparing these results with those of previous study which reported percentages of 6%, 38%, 32%, 72%, and 81% for ccLS of 1–5, respectively, we note a similarity in the trends [15]. However, there is a slight difference in our study with a lower percentage in the ccLS 2 group and a higher percentage in the ccLS 4 group. This difference is most likely due to the higher proportion of atypical cases of ccRCC in our study that lack intralesional microscopic fat. According to the fact that absence of intralesional fat downgrades the ccLS5 to ccLS4 according to the ccLS algorithm.

Additionally, we found a relation between the ccRCC pathological grade and ADER value, which is an ancillary parameter in the ccLS algorithm [14]. This parameter have been found to have role in predicting the ccRCC pathological (Fuhrman) grade among masses with high ccLS (4 and 5). Comparing to renal mass biopsy which plays a crucial role in diagnosing indeterminate masses, yet it is associated with a reported complications and a nondiagnostic rate of up to 14% and shows poor performance in determining tumor grade [17].

The available previous studies couldn't establish a correlation between Fuhrman's grade of ccRCC and ccLS

algorithm as Johnson et al. and Steinberg et al. as well as Pedrosa and Cadeddu et al. [8, 12, 13]. In this study we found that there is positive correlation between ADER values and the grade of the ccRCC. The Fuhrman grade consists of 4 pathological grades of ccRCC (I, II, III and IV). The tumor grade categorizing pattern of previous study conducted by Johnson et al., was adopted in our study for standardization of the results, assigning grades I-II as low grade and III-IV as high-grade tumors [8].

By calculation of the ADER parameter (quantitatively) for the masses with final pathological diagnosis of ccRCC, notably, the results showed that the median interquartile range (IQR) of ADER parameter was statistically significant higher in grade II compared to grade I (Median was 1.6 and 0.9 respectively) and much higher in grade III compared to grades I and II. (Median was 2.9) where P value < 0.001. This positive correlation can aid in predicting the behavior of the lesion according to its expected tumor grade.

Although the known traditional MRI features of the ccRCC can give close predictive results about the nature of renal masses, we think that the most beneficial point from the ccLS is to reduce overall benign nephrectomy rate by using a other management strategies (i.e. management with active surveillance) by avoiding initial surgeries in patients with a ccLS of 2 or less and considering biopsy in SRMs with a ccLS of 3, these strategies can be supported by the high privilege of pRCC among the ccLS 1 and 2 groups and the high privilege of oncocytomas among ccLS 3 group, specially that these two subtypes are known to have very low incidence of metastasis (< 1%) while undergoing active surveillance [2]. So that, providing the clinicians the enough radiological support using the ccLS during making the decision of each small solid renal mass they encounter will help the widespread use of the algorithm at the clinical field.

The relation between the ADER and ccRCC tumor grade can be helpful to increase the benefits from the application of ccLS on renal masses as it will not be limited to predict the probability of being ccRCC, but also will help in predicting the grade of the tumor, so that will give initial impression for the further steps of management.

Limitation of this study

The pathological diagnosis of the studied cases who underwent active surveillance couldn't be identified so that they were excluded from our sample and their long term behavior couldn't be assessed due to limited study time, these masses need to be followed up for few years so we recommend further studies to investigate masses with low ccLS and monitor their behavior for longer periods as a part of assessing the low ccLS groups masses in scenarios other than surgical intervention of RMBs.

The two studied histopathologically proven fpAML yielded a high ccLS score, we still think that the ccLS needs more investigations to find a parameter that has the ability to distinguish the both entities by conducting larger sample size of fpAML cases. Although the prospective design of our study has advantage to avoid research bias but on the other hand it resulted in a limited sample size, comparing to the prior retrospective studies.

Conclusions

Through a prospective assessment of the ccLS algorithm, this research demonstrated its strong effectiveness in both predicting and excluding the pathological nature of ccRCC. Furthermore, the ccLS proves advantageous in anticipating the tumor grade (Fuhrman grade) as well.

Abbreviations

ADC	Apparent diffusion coefficient
ADER	Arterial to delayed enhancement ratio
ccLS	Clear cell Likelihood Score
ccRCC	Clear cell renal cell carcinoma
chrRCC	Chromophobe renal cell carcinoma
CMP	Corticomedullary phase
CSI	Chemical shift images
CT	Computed Tomography
DWI	Diffusion weighted imaging
DCE	Dynamic contrast enhancement
fpAML	Fat-poor angiomyolipoma
mpMRI	Multiparametric Magnetic Resonance Imaging
PACS	Picture Archiving and Communication System
pRCC	Papillary renal cell carcinoma
RMBs	Renal mass biopsy
ROC	Receiver operator characteristic
SD	Standard deviation
SEI	Segmental enhancement inversion
SRMs	Small renal masses
T2WSI	T2-weighted Signal Intensity

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Author contributions

OMS contributed to the data collection. OMS and AA performed data analysis and writing. AA, MZ and AEM performed supervision. They all approved the final version of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the Faculty of Medicine at Mansoura University in Egypt on 01/03/2023; reference number of approval: MS.23.01.2271.

Consent for publication
All patients included in this research gave written informed consent to publish the data contained within this study.

Competing interests
The authors declare that they have no competing interests.

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