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ADVANCED IMAGING BIOMARKERS: THE ROLE OF APPARENT DIFFUSION COEFFICIENT FOR EVALUATING ACUTE RENAL INJURY

Radio-Diagnosis

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ABSTRACT

Background: To evaluate the role of magnetic resonance imaging (MRI) in acute renal injury and correlate MRI findings with the degree of renal function derangement. **Methods:** The study included patients admitted with acute renal injury from August 2022 to October 2023 at a tertiary care center. Serum creatinine levels were obtained on the day of the MRI examination. MRI was conducted using a 1.5 T system (Symphony, Siemens Medical Solutions) with a phased array body coil. The protocol included axial T1WI, T2WI, T2 HASTE coronal images, and diffusion-weighted imaging (DWI) with 'b' values of 100, 500, and 750 along with ADC maps. **Results:** The study included 39 patients diagnosed with ARI, with mean age 49.3 years ± 16.09, with 25 (64%) males and 14 (36%) females. The mean ADC value for the renal cortex was $1.91 \pm 0.30 \times 10^{-3}$ mm²/s, while for the renal medulla, it was $1.82 \pm 0.25 \times 10^{-3}$ mm²/s. The medullary ADC values showed a significant inverse correlation with serum creatinine ($r = -0.67$, $p < 0.001$). The correlation between cortical ADC and serum creatinine was also inverse ($r = -0.61$, $p < 0.001$). **Conclusion:** MRI, particularly DWI, provides valuable information on renal function. ADC values correlated significantly with serum creatinine, suggesting its utility as a non-invasive indicator of renal dysfunction.

KEYWORDS

Acute renal injury, apparent diffusion coefficient, MRI, AKI, DWI, diffusion weighted images

INTRODUCTION

Acute renal injury (ARI), also known as acute kidney injury (AKI), represents a rapid decline in kidney function, characterized by an abrupt increase in serum creatinine levels, reduction in urine output, or both.[1] ARI is a prevalent condition in clinical settings, particularly in hospitalized patients, and is associated with significant morbidity and mortality.[2] The underlying causes of ARI are multifactorial, encompassing pre-renal factors such as hypovolemia and hypotension, intrinsic renal factors including acute tubular necrosis and glomerulonephritis, and post-renal factors like urinary obstruction.[2] Early and accurate diagnosis is critical for managing ARI effectively and mitigating potential long-term renal damage.[1,2]

Traditionally, the evaluation of renal function in ARI has relied heavily on biochemical markers, particularly serum creatinine and blood urea nitrogen (BUN).[3,4] While these markers are widely used, they have notable limitations. Serum creatinine, for instance, is influenced by factors such as muscle mass, age, and sex, and may not accurately reflect real-time changes in kidney function.[1-4] Furthermore, creatinine levels often do not rise until significant kidney damage has occurred, delaying the diagnosis of ARI.[3,4] Consequently, there is a pressing need for more sensitive and specific diagnostic tools that can detect ARI at an earlier stage and provide more detailed information about renal pathology.

Magnetic Resonance Imaging (MRI) has emerged as a valuable imaging modality in the evaluation of renal diseases due to its high spatial resolution and ability to provide both anatomical and functional information.[5] MRI is particularly advantageous because it does not involve ionizing radiation, making it suitable for repeated use, which is often necessary in the management of chronic and acute kidney conditions.[6] Among the various MRI techniques, Diffusion-Weighted Imaging (DWI) has garnered considerable attention for its potential in assessing renal pathology.[5-7]

DWI is an MRI technique that measures the random Brownian motion of water molecules within tissues.[5-7] This motion can be influenced by tissue cellularity, the integrity of cell membranes, and the presence of interstitial and intracellular edema, all of which are pertinent in the context of renal injury.[5-7] By applying DWI, it is possible to generate Apparent Diffusion Coefficient (ADC) maps, which provide quantitative measurements of water diffusion in tissues.[6,7] ADC values are inversely correlated with tissue cellularity and directly correlated with the amount of extracellular space, thus offering insights into tissue structure and pathology.[5-7]

The application of DWI and ADC mapping in renal imaging provides a unique opportunity to non-invasively evaluate changes in kidney tissue associated with ARI. Several studies have suggested that DWI can detect early renal changes before they are evident on conventional imaging or through serum biomarkers.[5-7] For instance, lower ADC values have been associated with acute tubular necrosis and other forms of acute kidney damage, reflecting restricted water diffusion due to cellular swelling and interstitial edema.[5-7]

This study aims to explore the utility of DWI and ADC values obtained through MRI in evaluating patients with acute renal injury. The primary objective is to determine the correlation between these imaging parameters and traditional biochemical markers, such as serum creatinine. By establishing this correlation, we hope to validate DWI as a reliable and sensitive tool for the early detection and assessment of ARI. Moreover, this research seeks to enhance the understanding of the pathophysiological changes occurring in the kidneys during ARI, which could lead to improved diagnostic and therapeutic strategies.

METHODS

This study was designed as a prospective observational study conducted at a tertiary care hospital, from August 2022 to October 2023. The study was conducted in accordance with the tenets of declaration of Helsinki. The study protocol was approved by the institutional review board (reg. no.: IEC/02/2022/03), and written informed consent was obtained from all participants. All patient data were anonymized to ensure confidentiality. Patients had the right to withdraw from the study at any time without any impact on their medical care.

The study included patients who were diagnosed with acute renal injury based on the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, which define ARI as an increase in serum creatinine by ≥0.3 mg/dL within 48 hours, an increase in serum creatinine to ≥1.5 times baseline within the prior 7 days, or urine volume <0.5 mL/kg/h for 6 hours.[8]

Inclusion Criteria:
1. Adults aged 18 years and older.
2. Patients meeting KDIGO criteria for ARI.
3. Patients willing and able to provide informed consent.

Exclusion Criteria:
1. Patients with chronic kidney disease (CKD) stages 4-5.
2. Patients with contraindications to MRI, such as implanted metallic devices or severe claustrophobia.
3. Pregnant or breastfeeding women.
4. Patients with a history of renal transplantation.

Age and sex-matched healthy volunteers were also included as controls.

Imaging Protocol

All MRI scans were performed using a 1.5 Tesla MRI scanner. The imaging protocol included conventional sequences such as T1-weighted and T2-weighted images, as well as diffusion-weighted imaging (DWI). The DWI was acquired using a single-shot echo-planar imaging sequence with b-values of 0, 500, and 800 s/mm².

Imaging Parameters:
- **Repetition time (TR):** 3500 ms
- **Echo time (TE):** 85 ms
- **Slice thickness:** 5 mm
- **Matrix size:** 128 x 128
- **Field of view (FOV):** 380 mm

Image Analysis

The Apparent Diffusion Coefficient (ADC) maps were generated from the DWI images using the MRI scanner's software. ADC values were calculated by fitting the data to a mono-exponential decay model using the following equation:

ADC = [AntiLog10 (S1/S2)] /(b2-b1)

Where S0 is the signal intensity without the diffusion weighting, S is the signal with the gradient (b= 750 sec/ sq mm), S1 is the signal with the gradient b1 and S2 with that of b2, ADC is the Apparent diffusion-coefficient. The resultant values were expressed in Mean ± SD.

Regions of interest (ROIs) were manually drawn on the renal cortex and medulla on ADC maps by two experienced radiologists who were blinded to the patients' clinical information. The mean ADC values for each ROI were recorded.

Biochemical Analysis

BUN levels were measured at baseline and at 48 hours post-MRI. Urine output was monitored for 24 hours before and after the MRI to assess kidney function. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[9]

Statistical Analysis

The primary outcome was the correlation between ADC values and serum creatinine levels. Secondary outcomes included the correlation of ADC values with BUN, eGFR, and urine output. Statistical analyses were performed using SPSS software (version 23.0). The Pearson correlation coefficient was used to assess the strength and direction of the linear relationships between ADC values and biochemical markers. Correlation coefficients were interpreted as follows- 0.00-0.19: Very weak; 0.20-0.39: Weak; 0.40-0.59: Moderate; 0.60-0.79: Strong; 0.80-1.00: Very strong. Student's t-test was used to compare variables between cases and healthy controls. Multiple linear regression analysis was conducted to adjust for potential confounding variables such as age, sex, and baseline kidney function. The level of statistical significance was set at $p < 0.05$.

RESULTS

A total of 39 patients diagnosed with ARI were included in this study. The mean age of the participants was 49.3 years ± 16.09, with 25 (64%) males and 14 (36%) females. The baseline characteristics, including serum creatinine levels, BUN, and eGFR, are summarized in Table 1.

Figure 1 (a), (b) and (c) show a case of emphysematous pyelonephritis. True restriction of diffusion is noted on DWI and ADC map. Gas is seen within the renal parenchyma and collecting system; while figure 1 (d), (e) and (f) show a case of post partum ARF. True restriction of diffusion is noted on DWI and ADC map. No abnormality is seen on T2WI.

The mean ADC value for the renal cortex was $1.91 \pm 0.30 \times 10^{-3}$ mm²/s, while for the renal medulla, it was $1.82 \pm 0.25 \times 10^{-3}$ mm²/s.

Table 2 summarizes the correlation coefficients between ADC values and renal function markers. A strong inverse correlation was observed between cortical ADC values and serum creatinine levels ($r = -0.61$, $p < 0.001$) [Table 3] [Graph 1(a)]. Similarly, medullary ADC values showed a significant inverse correlation with serum creatinine ($r = -0.67$, $p < 0.001$) [Table 3] [Graph 1(b)].

Subgroup analysis was performed to evaluate the correlation between ADC values and renal function markers across different age groups and sexes. In patients under 50 years old (n=22), the correlation between cortical ADC and serum creatinine was slightly stronger ($r = -0.70$, $p < 0.001$) compared to those aged 50 and above ($r = -0.64$, $p < 0.001$).

When stratified by sex, the correlation coefficients for males and females were similar, with cortical ADC vs. serum creatinine showing $r = -0.66$ ($p < 0.001$) in males and $r = -0.68$ ($p < 0.001$) in females. This indicates that the inverse relationship between ADC values and serum creatinine is consistent across different demographic groups. The patient with pyelonephritis had the most substantial differences between the kidneys for both the cortex and the medulla and for all calculated ADC values which ranged from 30 to 40 percent. For the patients with ureteral obstructions, no substantial differences were found in the ADC when compared with the contralateral kidney. The patient with renal cell carcinoma in the right kidney showed a substantial difference for ADC when compared with the contralateral kidney for both the cortex and the medulla and for all calculated ADC values which ranged from 29.8 to 30.9 percent. Kidneys in which renal failure was diagnosed (n =20), there was a significant inverse correlation between ADC values of renal parenchyma and S Cr levels (Pearson's correlation coefficient. Cortex- $R = -0.518$; $P = 0.001$, Medulla- $R = -0.518$; $P = 0.001$). When dividing the group of patients with renal failure into two groups according to serum creatinine level (an arbitrary threshold of 2.5 mg/dL was used), the group of patients with a creatinine level lower than this threshold (n =11) had ADC values lower than those in the group of patients with a creatinine level higher than the threshold (n =9).

Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of ADC values. The area under the ROC curve (AUC) for cortical ADC was 0.92 (95% CI: 0.85-0.97), indicating high diagnostic accuracy [Table 4]. The optimal cutoff value for cortical ADC to diagnose ARI was 1.45×10^{-3} mm²/s, with a sensitivity of 85% and a specificity of 90% [Table 4].

DISCUSSION

This study aimed to evaluate the correlation between Apparent Diffusion Coefficient (ADC) values obtained from Diffusion-Weighted Imaging (DWI) and serum creatinine levels in patients with acute renal injury (ARI). We found a significant inverse correlation between ADC values and serum creatinine, suggesting that lower ADC values are associated with higher serum creatinine levels. This finding supports the hypothesis that DWI and ADC values can serve as non-invasive biomarkers for assessing renal function in ARI.

The significant inverse correlation between ADC values and serum creatinine levels ($r = -0.67$, $p < 0.001$) is observed in our study.

The findings are supported by prior studies, which demonstrated a similar inverse relationship between ADC values and serum creatinine in patients with chronic kidney disease (CKD).[10-20] This consistency across different renal conditions suggests that ADC values might universally reflect changes in renal pathology. Lower ADC values indicate restricted diffusion, which may reflect tissue edema, inflammation, or cell death in the renal parenchyma, all of which are characteristic of ARI.[21] Serum creatinine, a well-established marker of kidney function, rises as renal impairment progresses.[22] Therefore, the significant inverse relationship between ADC and serum creatinine

reinforces the potential of ADC as a surrogate marker for renal function.

These findings align with those of other studies that have demonstrated similar relationships between DWI parameters and renal function markers.[10-20]

The use of DWI and ADC values in the clinical setting offers several advantages. First, MRI is a non-invasive imaging modality that does not involve ionizing radiation, making it safer for repeated assessments compared to CT scans.[21] Second, DWI can be performed without the need for contrast agents, which is particularly beneficial for patients with renal impairment who are at risk of contrast-induced nephropathy[21]. Third, ADC values can provide quantitative data that may detect subtle changes in renal function earlier than traditional markers like serum creatinine.[21]

The ability to detect early renal impairment is crucial for timely intervention. Traditional biomarkers such as serum creatinine often lag behind actual renal injury, as their levels only rise after significant nephron loss.[22] ADC values, however, may reflect early microstructural changes, allowing for prompt diagnosis and management of ARI.[21]

The pathophysiological mechanisms underlying the observed correlation may include alterations in renal microstructure due to edema, ischemia, and inflammation.[21] These changes can restrict water diffusion, leading to lower ADC values.[21] In ARI, renal tubules and interstitial spaces often become edematous, which increases the extracellular water content but restricts the movement of water molecules, thus lowering the ADC. [22] This study's findings are consistent with this mechanistic explanation and highlight the sensitivity of ADC to such microstructural changes.[22]

Renal ischemia, a common cause of ARI, leads to cellular swelling and interstitial edema, which are detectable through decreased ADC values.[21,22] Similarly, inflammatory processes can disrupt normal tissue architecture, further limiting water diffusivity.[21] These microstructural changes precede clinical symptoms and elevated serum biomarkers, emphasizing the diagnostic value of DWI.

Several limitations should be noted. The study's single-center design and relatively small sample size may limit the generalizability of the findings. Additionally, manual delineation of regions of interest (ROIs) can introduce inter-observer variability. Future research should consider larger, multi-center studies to validate these findings. Automated or semi-automated methods for ROI selection could also be employed to reduce variability. Longitudinal studies are needed to assess the utility of ADC in monitoring disease progression and response to therapy.

Another limitation is the potential influence of various confounding factors such as age, sex, and baseline kidney function, although we adjusted for these in our analysis. Further research should explore the impact of these variables in greater detail. For instance, age-related changes in renal microstructure might affect ADC values, necessitating age-specific reference ranges.

Moreover, the study did not account for other potential confounders such as hydration status, which can influence both serum creatinine and ADC values. Hydration can affect renal blood flow and, consequently, the diffusivity of water within the renal parenchyma. Future studies should control for hydration levels to isolate the effect of renal pathology on ADC values.

The use of advanced MRI techniques such as DWI presents certain technical challenges. Variations in imaging parameters, magnetic field strength, and scanner types can affect ADC measurements. Standardizing these parameters is crucial for the reproducibility and comparability of results across different institutions.

Advancements in MRI technology, such as the development of higher field strength magnets (e.g., 3 Tesla) and improved diffusion sequences, could enhance the sensitivity and specificity of DWI. Furthermore, the integration of machine learning algorithms for automated image analysis could reduce observer bias and improve the accuracy of ADC measurements.

The findings of this study have broader implications for the field of nephrology and medical imaging. The non-invasive nature of DWI could facilitate large-scale screening programs for early detection of renal impairment, particularly in high-risk populations such as those with diabetes or hypertension. Additionally, DWI could be used to monitor renal function in patients undergoing nephrotoxic treatments, such as chemotherapy, providing a means to prevent irreversible kidney damage.

In the context of personalized medicine, ADC values could be integrated into clinical decision-making algorithms to tailor treatments based on individual renal function. For instance, dose adjustments for nephrotoxic drugs could be guided by ADC measurements, optimizing therapeutic efficacy while minimizing renal toxicity.

Furthermore, the application of DWI extends beyond ARI to other renal pathologies such as chronic kidney disease, renal fibrosis, and transplant nephropathy. By providing a window into renal microstructure, DWI can offer insights into the pathogenesis and progression of these conditions, potentially leading to novel therapeutic targets.

CONCLUSION

This study demonstrates that ADC values obtained from DWI are significantly correlated with serum creatinine levels and other markers of renal function in patients with acute renal injury. These findings suggest that DWI and ADC values can serve as non-invasive biomarkers for assessing renal function, offering potential clinical utility in the early detection and monitoring of ARI. Future studies with larger, more diverse populations and advanced imaging techniques are warranted to further validate and refine the use of DWI in renal imaging.

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Table 1: Demographic Characteristics Of Participants

S.No.	Characteristics	Mean ± SD	Range
1	**Age (Years)**	49.3 ± 16.09	20-81
2	**Serum Creatinine (mg/dL)**	3.22 ± 2.02	1.30-10.20
3	**ADC-Avg Cortex** (10^{-3} mm²/s)	1.91 ± 0.30	1.26-2.45
4	**ADC-Avg Medulla** (10^{-3} mm²/s)	1.82 ± 0.25	1.12-2.27

Abbreviations- ADC: Apparent diffusion coefficient; Avg- Average; SD: Standard deviation; GFR: Glomerular filtration rate

Table 2: Correlation Coefficients Between ADC Values and Renal Function Markers

S.No.	Parameter	Correlation Coefficient (r)	p-value
1	**Cortical ADC vs. Creatinine**	-0.6068	0.0002*
2	**Medullary ADC vs. Creatinine**	-0.6743	0.0000*

*Statistically significant; Abbreviations- ADC: Apparent diffusion coefficient

Table 3: ADC Values in ARI Patients and their correlation with serum creatinine levels

S.No.	Parameters	Correlation Coefficient (r)	p-value
1	**Cortical ADC vs. Creatinine**	-0.518	0.001*
2	**Medullary ADC vs. Creatinine**	-0.518	0.001*

*Statistically significant; Abbreviations-ADC: Apparent diffusion coefficient; ARI: Acute renal injury

Table 4: ROC Curve Analysis for ADC Values in Diagnosing ARI

S.No.	Parameter	AUC	95% CI	Optimal Cutoff ($\times 10^{-3}$ mm²/s)	Sensitivity (%)	Specificity (%)
1	**Cortical ADC**	0.92	0.85 - 0.97	1.45	85	90
2	**Medullary ADC**	0.89	0.82 - 0.95	1.35	80	88

Abbreviations- ADC: Apparent diffusion coefficient; ARI: Acute renal injury; CI: Confidence interval

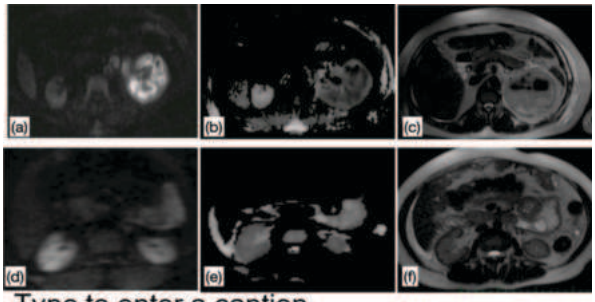

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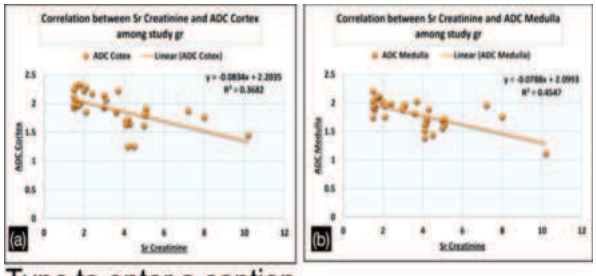
Figure 1: (a), (b), (c): A case of emphysematous pyelonephritis. True restriction of diffusion is noted on DWI and ADC map. Gas is seen within the renal parenchyma and collecting system; (d), (e), (f): A case of post partum ARF. True restriction of diffusion is noted on DWI and ADC map. No abnormality is seen on T2WI; abbreviations- DWI: Diffusion weighted images; ADC: Apparent diffusion coefficient; ARF: acute renal failure



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Graph 1: (a) Correlation between serum creatinine and apparent diffusion coefficient cortex among study group; (b) Correlation between serum creatinine and apparent diffusion coefficient medulla among study group

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