BMJ Open

Investigation of renal perfusion and pathological changes in patients with acute kidney disease and tubulointerstitial nephritis using intravoxel incoherent motion and arterial spin labelling MRI: a prospective, observational study protocol

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ABSTRACT

Introduction Acute kidney injury (AKI) is a critical condition with a complex aetiology and different outcomes, where haemodynamic dysfunction, renal hypoperfusion and inflammation serve as key contributors to its development and progression. Early and accurate diagnosis is vital for initiating targeted treatments like fluid resuscitation, vasoactive agents or steroid therapy, which are essential for improving patient outcomes. Intravoxel incoherent motion (IVIM) MRI assesses both capillary perfusion and tissue water diffusion, while arterial spin labelling (ASL) MRI measures renal blood flow without the need for contrast. Research on combined use of IVIM and ASL MRI in patients with AKI is rare. This study aims to investigate the MRI characteristics of IVIM and ASL in patients with tubulointerstitial nephritis (TIN) and to explore their relationship with pathological findings and renal recovery.

Methods and analysis Single-centre, prospective, observational cohort study of 30 patients with biopsy-proven TIN. Participants will undergo renal IVIM and ASL MRI within 7 days post-biopsy. The pathological assessments of active and chronic tubulointerstitial injuries will be semiscored using modified Banff criteria. The estimated glomerular filtration rate (eGFR) during follow-up and prevalence of chronic kidney disease at 3 and 6 months will be reported. An eGFR below 45 mL/min is considered a poor renal outcome.

Ethics and dissemination The study has been reviewed and approved by the Ethics Committee of Peking University First Hospital and written informed consent will be obtained from all participants (2022Y503). The study results will be disseminated through publication in a relevant peer-reviewed journal and presentation at academic meetings to increase awareness and share findings with the scientific community.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Employs intravoxel incoherent motion (IVIM) and arterial spin labelling (ASL) MRI to assess renal capillary perfusion and microstructures in patients with acute kidney injury (AKI), allowing for accurate quantitative analysis.

⇒ Studies combining IVIM and ASL MRI to explore the pathophysiological mechanisms in patients with AKI are scarce.

⇒ Examines IVIM and ASL MRI in patients with tubulointerstitial nephritis, a disease model for AKI, to correlate imaging with pathology, recovery, and enhance AKI diagnostic accuracy and clinical relevance.

⇒ Semiscoring of active and chronic tubulointerstitial injury indices using modified Banff criteria enhances study result standardisation and comparability.

⇒ The study's limited sample size due to biopsy requirements and the cost/availability of imaging techniques may affect broader applicability and clinical utility.

BACKGROUND

Acute kidney injury (AKI) is a clinical syndrome characterised by a rapid and progressive decline in glomerular filtration rate. It is highly prevalent in critically ill patients, with a reported incidence rate of 65% in the literature.1 AKI is closely associated with increased mortality and the risk of dialysis dependence. Kidney perfusion is contingent upon systemic blood pressure and sufficient intravascular blood volume. However, previous studies have indicated that prerenal hypoperfusion can lead to kidney
injury in normotensive patients in the intensive care unit (ICU), potentially due to a redistribution of intrarenal microcirculation and a disrupted cortex-to-medulla ratio. Injured vascular endothelium, resulting from exposure to circulating endotoxins, can decrease the expression of intercellular junctions, leading to plasma protein leakage and reduced intravascular volume. This may account for the occurrence of ischaemia and hypoxia at the onset of AKI, in addition to tubular injury caused by endotoxins and other nephrotoxins. A better understanding of the haemodynamics during AKI is essential for improving kidney outcomes, and interventions such as fluid resuscitation and vasoactive agents may be beneficial. However, critically ill patients often present with multiple complicating factors, complicating differential diagnosis and targeted treatment. For example, drug hypersensitivity-induced tubulointerstitial nephritis (TIN) requires immunosuppressive therapy in addition to fluid supportive therapy, contingent upon timely drug withdrawal.

Currently, AKI is primarily diagnosed and staged according to the Kidney Disease: Improving Global Outcomes guidelines, which rely on changes in serum creatinine and urine volume over time. However, there are limitations to diagnosing AKI using serum creatinine increases, especially in patients with biopsy-proven thrombotic microangiopathy, crescentic glomerulonephritis and acute TIN. The creatinine increase induced by various renal lesions, such as ischaemic tubular necrosis, nephrotoxins or immune-mediated inflammation, can vary significantly. Additionally, making an accurate differential diagnosis is challenging without a baseline serum creatinine level or in patients with pre-existing chronic kidney disease (CKD). While kidney pathology remains the gold standard for diagnosing primary kidney diseases, kidney biopsy is an invasive procedure that is not suitable for ICU patients at high risk of bleeding and cannot be used for dynamic monitoring. Limited kidney sampling can affect the accuracy of diagnosis and may not represent the whole kidney.

Functional MRI techniques have garnered substantial research evidence, demonstrating their enhanced diagnostic capabilities for kidney diseases. The apparent diffusion coefficient value, derived from diffuse-weighted imaging (DWI), reflects the pathophysiological features of tissue structures. Intravoxel incoherent motion (IVIM) MRI, a novel DWI-based sequence, shows promise in being more sensitive and accurate for evaluating renal microstructures and function. IVIM applies a biexponential model to analyse magnetic resonance signal intensity decay and yields information on both capillary perfusion and water molecular diffusion within tissues. It measures parameters including true diffusion coefficient (D), pseudo-diffusion coefficient (D*), and pseudo-diffusion component fraction (f). However, evidence is still lacking from studies using IVIM MRI for the diagnosis and prognostic prediction of AKI. Arterial spin labelling (ASL) MRI is a non-invasive technique for quantifying blood perfusion. Unlike conventional contrast-enhanced MRI that depends on exogenous contrast agents, ASL uses endogenous arterial blood as a tracer, making it suitable for detecting changes in renal blood flow and providing quantitative measurements. This technique is particularly beneficial when contrast agents are contraindicated or when repeated imaging sessions are necessary.

TIN, a frequent cause of AKI, is marked by autoimmune-mediated inflammation. Pathological findings typically include inflammatory cell infiltration, interstitial oedema, tubulitis and tubular epithelial cell degeneration, with the glomeruli remaining largely unaffected. In addition to TIN-related inflammation, locally activated renin–angiotensin–aldosterone systems and imbalances in prostaglandin and nitric oxide production contribute to altered intrarenal microcirculation, exacerbating the decline in glomerular filtration rate. TIN serves as an ideal disease model for studying the pathogenesis of AKI. This study aims to use IVIM and ASL MRI, in combination with clinicopathological parameters, to examine renal perfusion and pathological changes in patients with acute kidney disease and TIN. The study will also explore the potential of this diagnostic approach in evaluating kidney outcomes.

METHODS AND ANALYSIS
Study design and timeline
This study is a prospective observational cohort study designed to examine the MRI features of IVIM and ASL in patients with acute kidney disease caused by TIN. The study aims to explore the clinical relevance of these MRI findings in relation to pathology and renal outcomes. Recruitment will include patients who have undergone kidney biopsies from November 2022 to May 2024. Participants will undergo IVIM and ASL MRI within 7 days after kidney biopsy. Routine laboratory examinations will be conducted to obtain sequential data, including serum creatinine levels on admission, at the time of peak creatinine, and at 1, 3 and 6 months post-peak, along with urinalysis and systemic inflammation markers. Figure 1 depicts the timeline of data collection.

Study population
Inclusion criteria:
► Patients with acute kidney disease who have biopsy-proven active TIN.
► Informed consent is obtained.
Exclusion criteria:
► Age <18 years or pregnant women.
► Patients with a transplanted kidney.
► Patients clinically diagnosed with CKD or those with pathologically confirmed chronic TIN.
► Patients with concurrent glomerular or vascular diseases which obviously contribute to severity of kidney injury, such as diabetic nephropathy, IgA nephropathy, lupus nephritis, etc.
► Patients with comorbid diseases, including:
  - Cystic kidney disease.

TIN, tubulointerstitial nephritis
IVIM, Intravoxel incoherent motion
MRI, magnetic resonance imaging
SCr, serum creatinine
eGFR, estimated glomerular filtration rate

- Renal malignancies.
- Renal artery stenosis.
- Systemic inflammatory diseases, for example, vasculitis, pyelonephritis and IgG4-related disease.
  ► Patients who are critically ill and cannot cooperate to undergo the MRI.
  ► Patients with obesity or other reasons at high risk of poor quality of imaging.
  ► Contraindications for MRI examination, such as claustrophobia, metallic implants, etc.
  ► Life expectancy less than 6 months.

Sample size calculation
Our renal pathology centre annually diagnoses around 50 new TIN cases, but nearly half may have concurrent glomerulonephritis, a condition that could lead to AKI and thus exclude them from this study. Aiming for an observational preliminary study, we plan to recruit 100 patients. Enrolment began in November 2022 and will continue until we have enrolled a minimum of 30 eligible participants.

Data collection and outcomes
Baseline data collection
Clinical information
The study will collect data including demographic information such as age, sex and body mass index, as well as medical histories, causes of TIN and comorbidities. Laboratory assessments will encompass haemoglobin, serum creatinine (on admission and at peak), urea, electrolytes, albumin levels, and urinalysis parameters like urinary sediment, glucose, albumin-to-creatinine ratio, N-acetyl-β-D-glucosaminidase and α1-microglobulin. Systemic inflammation markers, such as C reactive protein and erythrocyte sedimentation, will be documented.

MRI protocol and image analysis
For the control group, healthy individuals will be selected at a 10:1 ratio. All the participants are required to fast for at least 6 hours before MRI examinations and will be scanned using a 3.0 T MRI scanner (Ingenia, Philips Healthcare, Best, The Netherlands) with a 32-channel body array coil. Conventional MRI sequences, including T2-weighted imaging breath-hold examinations will be performed. IVIM images will be acquired in the coronal plane with 10 b values (0, 25, 50, 80, 100, 150, 300, 500, 800 and 1000 s/mm²) using respiratory-triggered single-shot echo-planar imaging sequence with the following parameters: slice thickness, 8 mm; number of slices, 20; repetition time: depending on respiratory frequency/echo time, shortest ms; matrix size, 128×126; field of view (FOV), 380×380 mm². The pulsed continuous arterial spin labelling technique, two-dimensional fast field echo echo-planar imaging sequence and background suppression, will be used for renal ASL MRI. The labelling plane will be located 10 cm above the FOV centre, oriented axially and perpendicular to the aorta to label blood in the abdominal aorta. Before

Figure 1 Timeline of data collection. ASL, arterial spin labelling; eGFR, estimated glomerular filtration rate; IVIM, intravoxel incoherent motion; SCr, serum creatinine; TIN, tubulointerstitial nephritis.
image acquisition, labelling will be applied for 2000 ms followed by a 2000 ms post-labelling delay. Multiple coronal slices covering both kidneys will be acquired with the following imaging parameters: slice thickness, 8 mm; number of slices, 7; repetition time/echo time, 5000 ms/shortest ms; matrix size, 200×199; FOV, 380×380 mm².

IVIM and ASL images post-processing will be performed using in-house-developed software in MatLab (R2015b, MathWorks, Natick, Massachusetts, USA). Three IVIM parameters, D, D* and f, will be calculated using a biexponential model according to the equation: $S_b/S_0=(1-f)\times\exp(-b\times D)+f\times\exp(-b\times(D+D*))$, where $S_b$ represents the signal intensity at a given b value and $S_0$ represents the signal intensity for b=0 mm²/s. All the IVIM and ASL images will be analysed and regions of interest (ROIs) will be drawn by one radiologist and confirmed by another radiologist with 12 years of experience in interpreting renal MRIs. Both radiologists will be blinded to the clinical and renal pathological information of the participants. ROIs will be drawn free-hand on the b=0 images, carefully avoiding the collecting system. The T2-weighted images, IVIM and renal blood flow (RBF) maps will be combined to differentiate the cortex and medulla. Three ROIs, approximately 20 mm² in each area, will be carefully placed in the medulla of the upper, middle and lower poles of bilateral kidneys separately. An ROI of 60–120 mm² will cover the cortex. These ROIs will then be copied to the D, D*, f and RBF maps at the same level, and the mean D, D*, f and RBF values for the cortex and medulla will be calculated from the average of these separate ROI values.

Kidney pathology
The biopsied kidney samples will undergo a comprehensive analysis using standard direct immunofluorescence, light microscopy and electron microscopy techniques. The specimens will be stained with H&E, periodic acid–Schiff, Masson trichrome and Jones methenamine silver to enable visual observation of the tissues under light microscopy. Two experienced pathologists will independently make the diagnosis and grade tubulointerstitial injuries based on the Peking University First Hospital working criteria, which have been modified according to Banff criteria (online supplemental table 1). Both active and chronic injuries will be scored separately. Acute pathological injuries will be identified by the presence of degeneration or necrosis of tubular epithelial cells, oedema or infiltration of inflammatory cells in the interstitium. Chronic pathological scores will be determined based on the severity of tubular epithelial cell atrophy and the extent of interstitial fibrosis.

Treatment and kidney outcomes
The information on fluid resuscitation, administration of steroids and renal replacement therapy will be recorded. Patients will be regularly followed up after hospital discharge. During follow-up, estimated glomerular filtration rates (eGFRs) are calculated by the Chronic Kidney Disease-Epidemiology Collaboration Group equation based on sequential measurement of serum creatinine at 1, 3 and 6 months post-peak to track the changes over time.12 The CKD staging will be determined according to the Kidney Disease Outcomes Quality Initiative guideline.13 The prevalence of CKD at the 3 and 6 months will be reported. Patients having an eGFR less than 45 mL/min/1.73 m² are confirmed having poor outcome.

Data analysis plan
Measurement data that are normally distributed will be described using mean and SD. Data that are not normally distributed will be described using the median. Categorical variables will be analysed using χ² tests. Paired t-tests or one-way analysis of variance will be used to compare patients with TIN and healthy controls, and serum creatinine levels on admission and during follow-up. The test used will depend on the normality of the data. Logistic regression will be performed to identify factors that influence kidney outcomes. Receiver operating characteristic curves will be generated using MedCalc to determine thresholds for influential factors. A multifactor diagnostic and outcomes prediction model will be built based on the identified factors and thresholds. SPSS (version 25.0) and MedCalc software will be used to perform the statistical analyses.

Safety monitoring
The IVIM and ASL MRI are non-enhanced techniques of MRI. No additional risk and adverse reaction have been reported. For safety of participants, adverse events will be promptly reported to the principal investigator of this study and handled within 24 hours. Patients will receive timely medical care if necessary.

Patient and public involvement
Patients and the public will not be involved in the design of the study.

Study status
The study has been initiated in November 2022. Study participants have undergone the ongoing follow-up since February 2023. The project is anticipated to close in May 2024.

Ethics and dissemination
The study protocol has been approved by the Ethics Committee of Peking University First Hospital. A paper reporting the main results of the study will then be submitted for publication in a relevant peer-reviewed journal, presented to academic meetings and not directly distributed to study participants.

DISCUSSION
AKI is a critical condition with complex pathogenesis and variable outcomes, where haemodynamic dysfunction and renal hypoperfusion are key contributors to its development and progression. In addition, common causes
include nephrotoxins and immune-mediated inflammation, leading to tubular necrosis/injury and active interstitial nephritis. Early and accurate diagnosis is vital for initiating targeted treatments like fluid resuscitation or steroid therapy, which are essential for improving patient outcomes.14,19 Although kidney biopsy is the gold standard for diagnosing kidney diseases, its invasive nature and limitations in assessing intrarenal perfusion make it less ideal for early disease evaluation.

Functional MRI techniques, including IVIM and ASL, offer non-invasive quantitative assessments of renal blood flow, glomerular filtration rate, and microvascular permeability in the cortex and medulla.14–19 These methods provide additional physiological insights crucial for early detection of kidney abnormalities, lesion characterisation and treatment response evaluation, enhancing the diagnosis and management of kidney diseases.20–22 In this study, we will apply IVIM and ASL MRI to examine renal capillary perfusion and microstructures in patients with TIN, a disease model for AKI. This approach aims to correlate imaging findings with pathological changes and recovery, thereby improving the accuracy and clinical applicability of AKI diagnosis. By using semisemicing of active and chronic TIN indices based on modified Banff criteria, we further enhance the standardisation and comparability of our study results, contributing to a more comprehensive understanding of AKI. However, the sample size of our study is constrained by the need for biopsies, which may reduce the statistical power of the findings. Nonetheless, the valuable parameters obtained from this preliminary research hold promise for informing future, well-designed prospective studies in patients with AKI.

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Contributors TS, RW and JG conceived and planned the study protocol. JL wrote the draft. RW and TS revised the draft. All authors approved the final manuscript.

Funding This study was supported by the National High Level Hospital Clinical Research Funding (Interdepartmental Clinical Research Project of Peking University First Hospital; grant number: 2022CR09), CAMS Innovation Fund for Medical Sciences (grant number: 2019-IZM-5-046) and National Natural Science Foundation of China (grant number: 82202092).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES
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Acute tubulointerstitial score = Acute tubular injury + Acute interstitial injury
Chronic tubulointerstitial score = Chronic tubular injury + Chronic interstitial injury

[a]: detachment of brush border, flat change of cell, vacuolar degeneration, granular degeneration, bare basement membrane