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Title: Update on MRI of cystic renal masses including Bosniak version 2019

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Abstract:

Incidental cystic renal masses are common, usually benign, and almost always indolent. Since 1986, the Bosniak classification has been used to express the risk of malignancy in a cystic

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renal mass detected at imaging. Historically, magnetic resonance imaging (MRI) was not included in that classification. The proposed Bosniak v.2019 update has formally incorporated MRI, included definitions of imaging terms designed to improve inter-observer agreement and specificity for malignancy, and incorporated a variety of masses that were incompletely defined or not included in the original classification. For example, at unenhanced MRI, homogeneous masses markedly hyperintense at T2-weighted imaging (similar to cerebrospinal fluid) and homogeneous masses markedly hyperintense at fat suppressed T1-weighted imaging (approximately ≥2.5 times more intense than adjacent renal parenchyma) are classified as Bosniak II and may be safely ignored, even when they have not been imaged with a complete renal mass MRI protocol. MRI has specific advantages and is recommended to evaluate masses that at CT a) have abundant thick or nodular calcifications; b) are homogeneous, hyperattenuating, ≥3 cm, and non-enhancing; or c) are heterogeneous and non-enhancing. Although MRI is generally excellent for characterizing cystic renal masses, there are unique weaknesses of MRI that bear consideration. These details and others related to MRI of cystic renal masses are described in this review, with an emphasis on Bosniak v.2019. A website (https://bosniak-calculator.herokuapp.com/) and mobile phone apps named 'Bosniak Calculator' have been developed for ease of assignment of Bosniak classes.

Keywords: cystic renal mass; MRI; Bosniak classification; renal cell carcinoma; renal cyst

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Introduction

Incidental cystic renal masses are commonly detected during cross-sectional abdominal imaging examinations, with one or more identified in approximately 50% of patients older than 50 years of age [1]. Although usually benign, a small percentage are malignant. When malignant, most are indolent [2]. The risk of malignancy can be predicted by their appearance on cross-sectional imaging using the Bosniak classification. This classification, originally developed for computed tomography (CT), has been used clinically for over 30 years, but until recently did not formally incorporate magnetic resonance imaging (MRI) criteria [1, 3]. To address this need as well as other shortcomings of the original classification, an update to the Bosniak classification was proposed in 2019 [4]. This update proposal (i.e., Bosniak v.2019) includes formal criteria for MRI, provides definitions of imaging terms designed to improve inter-observer agreement and specificity for malignancy, incorporates masses that are incompletely evaluated but highly likely benign, and addresses cystic masses not included in previous versions of the Bosniak classification. The purpose of this review is to update readers regarding key concepts and changes in Bosniak v.2019 as they pertain to the MRI evaluation of cystic renal masses and to provide insights about the potential implications for patient management.

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Shortcomings of the Original Bosniak Classification with an Emphasis on MRI

Although the Bosniak classification of cystic renal masses is preferred by radiologists and urologists [5], some limitations have been identified [4]. The original classification did not include definitions for terms (e.g., thin vs. thick, smooth vs. irregular), which contributed to high interobserver variability and variable reported malignancy rates within each class. There is a historical high prevalence of benignity among resected Bosniak III masses (historically considered 'surgical lesions'), contributing to the overdiagnosis and overtreatment of cystic renal masses [6-8]. In addition, the original classification was largely applicable only to masses that had been completely characterized by a renal mass protocol CT. Common incompletely characterized masses (e.g. too small to characterize) were not classifiable, and masses identified at other imaging modalities (i.e., ultrasound, MRI) required ad hoc extrapolation.

Formal incorporation of MRI criteria into the Bosniak framework was necessary. Since the original classification was conceived, MRI has become a clinical standard in the evaluation of renal masses [9]. However, studies have shown that application of the original CT-based Bosniak classification at MRI resulted in migration to a higher or lower Bosniak class in approximately 20-30% of cases [10-12]. Migration to a lower class usually was due to non-visibility of calcification at MRI [10], whereas migration to a higher class usually was due to visualizing more or thicker septa, or detecting new areas of enhancement [13, 14]. The lack of definitions in the original Bosniak classification made the determination of number of septa at

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MRI challenging. Internal cyst architecture at T2-weighted imaging (i.e., debris vs. septa) that did not enhance at T1-weighted imaging (i.e., debris) could artificially increase septa number at MRI. It is unclear how these class migrations affected clinical outcomes. Kim et al. described two patients in whom migration from Bosniak II (CT) to Bosniak IV (MRI) in the original classification identified RCC [14]; however, other studies have shown that prevalence of malignancy in MRI-identified Bosniak III masses has been lower (20-30%) than CT-identified Bosniak III masses (50%), increasing the likelihood of overtreatment [10, 12]. Importantly, these class migrations had the potential to change recommendations for management in approximately 7% of patient using the original Bosniak classification [13].

Update in Understanding of Cystic Renal Masses

Cystic renal masses are often overdiagnosed and overtreated [15-17]. Historically, Bosniak I and II masses were ignored; Bosniak IIF masses were followed with serial imaging; Bosniak III masses were considered indeterminate and generally resected; and Bosniak IV masses were considered malignant and required surgical resection. In addition to the low positive predictive value for malignancy of Bosniak IIF and Bosniak III masses, resulting in unneeded follow-up imaging and unnecessary extirpative therapy (respectively); cystic RCC rarely metastasizes or has adverse outcomes [6, 18]. Greater cystic change in clear cell RCC has

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been shown to independently predict improved survival and a lower risk of cancer progression [2, 19].

Histopathological definitions of cystic renal masses have changed since 1986 [20, 21]. For example, multilocular cystic RCC (previously considered malignant) is now classified as a multilocular renal neoplasm of low malignant potential (i.e., not RCC) [20, 21]. The 2016 World Health Organization (WHO) now includes several indolent RCC variants (e.g. tubulocystic RCC, clear cell tubulopapillary RCC) which were undefined in 1986 and often contain cystic change at imaging [21]. Although partial nephrectomy has become more common, radical nephrectomy is still often performed for benign and malignant cystic renal masses. This is problematic because loss of nephrons is associated with renal insufficiency and decreased survival [22]. These data emphasize the need to improve specificity and reduce overtreatment associated with the Bosniak classification.

MRI Technique

General information

Bosniak v.2019 does not include minimum technical requirements for MRI, but the same authors (Society of Abdominal Radiology Disease Focused Panel on Renal Cell Carcinoma) released MRI pulse sequence recommendations for a variety of renal mass scenarios, including

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cystic renal mass characterization [23]. Adequate MRI of cystic renal masses relies upon high-quality pre- and post-contrast (gadolinium-enhanced) MRI [23]. This is because the Bosniak v.2019 class is predominantly based on the presence and morphology of enhancing components [4]. The highest Bosniak v.2019 class which can be assigned at MRI to a non-enhancing mass is IIF, and this is reserved for masses with heterogeneously increased signal intensity at fat-suppressed T1-weighted (T1W) imaging. The highest Bosniak v.2019 class which can be assigned at unenhanced MRI is II [4].

In most clinical practices, multiphasic MRI is performed using fat saturated 3-dimensional (3D) volume-interpolated T1W spoiled gradient recalled echo (GRE) sequences during patient breath-hold [23]. Fat saturation can be achieved with frequency-selective saturation pulses or with fat-water separation Dixon techniques, the latter offering more homogenous attenuation of the fat signal [24]. Through the application of modest parallel imaging (i.e. acceleration factor of 2), breath-held 3D interpolated T1W GRE sequences can be acquired in approximately 16-20 seconds. Breath-holds can be performed during end-expiration or end-inspiration; the latter enables a better capacity for the patient to hold their breath while the former enables better fixation of diaphragm positioning [9]. These considerations are important because if a patient is not able to suspend respiration, the imaging will be degraded by motion artifacts and potentially become non-diagnostic. If a patient can suspend respiration, but cannot do so consistently (i.e. inconsistent diaphragm position), misregistration artifact will

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compromise the quality of subtraction imaging [25]. The use of hyperventilatory preparations prior to suspension of respiration can increase an individual's breath-hold capacity by up to 30% [26].

In general, acquisitions during an effective breath-hold offer the best image quality for evaluation of cystic renal masses. Fortunately, in recent years, hardware and software advances have substantially shortened MRI examination times. Through parallel imaging (using acceleration factors >2, with or without compressed sensing), acquisition times can be shortened dramatically by reducing the number of phase-encoding steps (i.e. under-sampling k-space). This can facilitate shorter breath-holds, improving patient tolerance and minimizing motion artifacts, but carries the penalties of decreased signal-to-noise and parallel imaging artifacts. Signal-to-noise decrements are generally unimportant due to the signal gain from gadolinium-based contrast media.

High-quality free-breathing T1W images are now feasible using motion compensation techniques [27, 28]. Prospective or retrospective motion-compensated imaging techniques have been described and are now commercially available on most clinical scanners, enabling free-breathing 3D T1W GRE. Radial under-sampled K-space acquisitions using golden angle techniques are particularly robust to suppress artifacts caused by respiratory motion [28]. It has been shown that use of free-breathing navigator-triggered 3D T1W GRE enables quality subtraction images that can be analyzed when breath-hold subtraction is degraded by motion

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[29]. If free-breathing motion-compensated techniques are combined with advanced parallel imaging and compressed sensing, completely free-breathing studies including dynamic contrast enhanced (DCE)-MRI is possible [27, 28]. Machine learning techniques are expected to reduce exam times and artifacts even further. Currently, these techniques are often reserved for patients with limited breath-hold capacity.

Enhancement and subtraction imaging

The original Bosniak classification categorized enhancement as absent, "perceived", or "measurable". These designations affected classification. For example, all masses with "measurable" enhancement were considered at minimum Bosniak III. In Bosniak v.2019, a feature within a cystic renal mass is considered enhancing if there is unequivocal visible enhancement (e.g., at subtraction imaging) or unequivocal quantitative enhancement (within a structure large enough to be sampled with region of interest [ROI] analysis). It has been shown that qualitative assessment of high-quality subtraction images is as accurate as quantitative assessment of signal intensity for determination of enhancement [30]. Quantitative enhancement at MRI is defined as an increase in signal intensity ≥15% comparing enhanced and unenhanced imaging: $(SI_{post} - SI_{pre})/SI_{pre} \times 100\%$ [SI_{pre} : unenhanced T1W signal intensity, SI_{post} : enhanced T1W signal intensity; both pre- and post-contrast T1W sequences must use identical pre-scan and acquisition parameters] [4, 31]. A reported sensitivity of 100% and specificity of 98% was achieved with this method when post-contrast images were acquired at least 2

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minutes after intravenous gadolinium-based contrast media administration [31]. However, care should be taken in interpretation due to scanner and pulse sequence differences as well as differences in amount, timing, and non-linear T1 effects of gadolinium.

Subtraction images are derived by mathematically removing signal intensity of an unenhanced T1W acquisition from the signal intensity of a contrast-enhanced T1W acquisition. Accurate subtraction imaging depends on both the unenhanced and enhanced datasets having identical acquisition parameters and pre-scan settings. If there is perfect spatial registration between the unenhanced and enhanced data, any signal unequivocally visible at subtraction imaging should represent enhancement (i.e., any brighter signal intensity than non-enhancing reference tissue, such as bile within the gallbladder or enteric content within bowel) [30]. Subtraction images are critical for the evaluation of renal masses that are hyperintense on unenhanced T1W imaging. Without subtraction data, it is difficult to discriminate enhancement from background T1W hyperintensity [9]. Adequate spatial registration is improved by use of end-expiration breath-holds and shorter acquisition (i.e., breath-hold) times. Despite efforts, misregistration artifacts are common and must be differentiated from enhancement. Misregistration usually manifests as edge or ringing artifacts at the interface of structures.

If misregistration occurs, manual subtraction may be an option (i.e., the user [rather than the scanner] selects a common spatial reference point on the two image sets). In those cases where this is not possible due to substantial misregistration, the radiologist must perform

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a “mental subtraction” to rule out or confirm enhancement. Non-vascularized hemorrhagic or proteinaceous material shortens T1 and can resemble enhancing tissue on contrast-enhanced T1W imaging. Therefore, any apparent enhancement on subtraction imaging should be confirmed on the non-subtracted acquisitions by identifying: 1) an area that is hypointense to the material that is hyperintense on unenhanced T1W imaging but becomes isointense or hyperintense to it on contrast-enhanced T1W imaging; or 2) an area that is isointense to the material that is hyperintense on unenhanced T1W imaging but becomes hyperintense to it on contrast-enhanced T1W imaging (Figure 1).

T2W and diffusion-weighted imaging

T2W imaging is commonly performed using a version of spin echo-train imaging, including single-shot half-Fourier turbo or fast spin echo techniques, with or without respiratory-triggering [9]. Multi-shot T2W acquisitions theoretically offer superior soft-tissue contrast due to a shorter echo train length compared to single-shot acquisitions. However, longer acquisition times necessitate interleaved acquisition of data, leading to motion-related ghosting artifacts even during adequate breath-hold (i.e., fluid motion within the cyst). Conversely, single-shot sequences allow for sequential acquisition of images, with each image acquisition taking about 1 second, facilitating robust imaging without motion artifacts. With single shot T2W imaging, blurring can result from the extended echo train and prolonged

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effective echo time (TE) in moieties with relatively shorter T2 (e.g. nodules, septa, debris) [9]. However, the long T2 relaxation time of 'simple fluid' within cystic renal masses offers an excellent contrast mechanism between septa or nodules and fluid, resulting in sharp delineation of internal architecture within a cystic mass. This excellent contrast resolution, when combined with the superior sensitivity of MRI for gadolinium vs. CT for iodine, likely improves the diagnostic accuracy of MRI vs. CT for small cystic masses.

Flow artifacts may occur in cystic masses with large fluid components at T2W imaging and should be distinguished from heterogeneity (by noting their absence on orthogonal planes) or solid tissue (by reviewing enhanced images). Balanced steady-state free precession (bSSFP) sequences are an alternative to T2W imaging. They provide greater signal-to-noise and spatial resolution and are insensitive to motion and flow artifacts [32], but they cause banding artifacts, and their signal intensity reflects a ratio of T2 to T1 (i.e., they are not purely T2W) [32].

Diffusion-weighted imaging (DWI) has been explored in cystic renal masses [33, 34], but it is not required for nor incorporated into the Bosniak v.2019 classification. Its utility in characterizing cystic renal masses is low. A comprehensive explanation of DWI as it applies to oncologic imaging is beyond the scope of this manuscript but is available elsewhere [33, 35-37]. When used, moderate or high b-value imaging (e.g. ≥ 600 mm/sec^2) is needed to suppress unwanted signal from urine and simple fluid. It usually is performed with single-shot echo

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planar imaging (EPI) techniques that are sensitive to susceptibility artifacts. Therefore, if DWI is performed after contrast media administration, it must occur before the pyelographic phase to avoid artifacts [38].

MRI Elements in Bosniak v.2019

Bosniak v.2019 formally incorporated MRI (Table 1) and defined a cystic renal mass as having less than approximately 25% enhancing tissue [4]. The Bosniak classification cannot be applied to patients with a congenital kidney cancer syndrome, and should only be used after infectious, inflammatory and vascular etiologies have been excluded. If a mass has features of more than one Bosniak class, the highest Bosniak class should be assigned. Below is a summary of Bosniak v.2019 with an emphasis on MRI. A key principle of Bosniak v.2019 is that features (e.g., septa, nodules) must enhance for a mass to be upgraded to Bosniak IIF, III, or IV. Therefore, apparent septa at T2W imaging that do not enhance cannot be used to upgrade a mass beyond Bosniak II. Full details of Bosniak v.2019 are available at [4].

Bosniak I

Bosniak I masses are benign simple cysts with a thin (≤2 mm thickness) wall, no septa, and no calcification. They are composed of 'simple' fluid (homogeneous signal intensity similar

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to cerebrospinal fluid [CSF] at T2W imaging). The wall may or may not enhance (Figure 2). Cysts that are incompletely characterized (e.g., unenhanced MRI) cannot be placed in this class.

Bosniak II

Bosniak II masses are highly likely benign and do not warrant additional management. Bosniak v.2019 expanded this class to include some masses that are incompletely characterized (e.g., at unenhanced MRI). This should decrease the number of unneeded confirmatory tests [39]. All Bosniak II masses are well-defined with thin (≤2 mm) smooth walls, and all incompletely characterized Bosniak II masses must be homogeneous. The following types of Bosniak II masses exist in Bosniak v.2019:

- Thin (≤2 mm) few (1-3) enhancing septa, any non-enhancing septa, may have calcification (Figure 3)
- Unenhanced MRI: Markedly hyperintense at T2W imaging (similar to CSF)
- Unenhanced MRI: Markedly hyperintense at fat-saturated T1W imaging (approximately ≥2.5 more intense than renal parenchyma) (Figure 4) [40-42]

Bosniak IIF

Bosniak IIF masses are likely benign and almost always indolent. They are generally followed by imaging (6 months, 12 months, annually for 5 years) in patients without significant comorbidities due to a <10% risk of cystic RCC [6]. Upgrade in morphology over time is a strong

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(80-90%) predictor of malignancy [43, 44]. The following types of Bosniak IIF masses exist in Bosniak v.2019:

- Smooth minimally thickened (3 mm) enhancing wall (Figure 5)
- Smooth minimal thickening (3 mm) of one or more enhancing septa (Figure 6)
- Many (≥4) smooth thin (≤2 mm) enhancing septa (Figure 7)
- Unenhanced MRI: Heterogeneously hyperintense at fat-suppressed T1W imaging (Figure 8)

The rationale for the latter type is papillary RCC may have this presentation [45-47].

Bosniak III

Bosniak III masses are approximately 50% likely to be malignant [6]. Historically, Bosniak III masses have been treated surgically, but there is an expanding role for active surveillance, especially in older patients and patients with comorbidities [48, 49]. The following types of Bosniak III masses exist in Bosniak v.2019:

- Thick (≥4 mm) enhancing walls or septa
- Irregular (≤3 mm obtusely margined convex protrusion[s]) enhancing walls or septa (Figure 9)

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A protrusion is a focal thickening or outgrowth from the wall or septa. Protrusions are measured perpendicular to the wall or septum of origin. If a protrusion is seen on both sides of a wall or septum, then the cumulative perpendicular distance is used. In both cases, the thickness of the underlying wall or septum is excluded. In Bosniak v.2019, enhancement must be present for a cystic mass to be classified as Bosniak III or Bosniak IV. However, unlike in the original classification, enhancement does not necessitate a specific class in Bosniak v.2019 (i.e., the thin wall of a Bosniak I simple cyst may enhance in Bosniak v.2019).

Bosniak IV

Bosniak IV masses are approximately 90% likely to be malignant [6]. Most Bosniak IV masses are resected in patients without significant comorbidities. The following defines a Bosniak IV mass in Bosniak v.2019:

- Enhancing nodule(s) (≥4 mm obtuse- or any size acute-margin convex protrusion[s]) (Figure 10)

A website (https://bosniak-calculator.herokuapp.com/) and mobile phone apps for both android and iOS named 'Bosniak Calculator' have been developed for ease of assignment of appropriate Bosniak classes and imaging recommendations.

Advantages of MRI for Evaluating Cystic Renal Masses

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There are several advantages of MRI over CT for the characterization of cystic renal masses, and MRI is specifically recommended by Bosniak v.2019 in certain clinical scenarios. Those include:

- Thick or nodular calcification at CT (Figure 11)
- Hyperattenuating, homogeneous, nonenhancing, and >3 cm at CT
- Heterogeneous and nonenhancing at CT (Figure 12)

The primary rationale in the above scenarios relates to the insensitivity of MRI to calcification, and the greater sensitivity of MRI to gadolinium than CT to iodine.

Insensitivity to calcification

MRI is less sensitive than CT to calcification. This is an advantage because the presence of calcification, or the change in the amount or configuration of calcification, are not useful independent predictors of malignancy in cystic renal masses [50]. In the original Bosniak classification, thick or nodular calcification was a feature of Bosniak IIF, and all other types of calcification were a feature of Bosniak II. In Bosniak v.2019, calcification of any type is a feature of Bosniak II. However, thick or nodular calcification at CT may obscure enhancing features that could affect the Bosniak class. Therefore, Bosniak v.2019 recommends that when thick or nodular calcification is identified at CT, MRI should be considered to determine the final Bosniak class (Figure 11).

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Increased sensitivity to enhancement

MRI is more sensitive to gadolinium than CT is to iodine [51-53]. This is an advantage because clinically important masses that do not enhance at CT may enhance at MRI. Failure to accurately diagnose enhancement can result in misclassifying a solid mass or a hemorrhagic Bosniak IV mass as a Bosniak II mass. For example, papillary RCC can exhibit equivocal (10-20 HU) or absent (<10HU) enhancement at CT, but definitive enhancement at MRI [51]. In addition, subtraction imaging at MRI helps identify small enhancing nodules in an otherwise non-enhancing hyperattenuating or heterogeneous cystic renal mass, which may be challenging to identify by attenuation measurements at CT. Therefore, Bosniak v.2019 recommends that MRI be used to characterize the following types of masses at CT:

- Hyperattenuating, homogeneous, nonenhancing, and >3 cm
- Heterogeneous and nonenhancing (Figure 12)

No pseudoenhancement

CT is affected by pseudoenhancement and MRI is not. This is an advantage for MRI because pseudoenhancement can result in misdiagnosis of a benign cyst as a solid mass. Pseudoenhancement is an artifactual increase in attenuation at CT due to inadequate algorithmic correction for beam-hardening artifact [54]. It is common in small (<1.5 cm) endophytic cysts near avidly enhancing parenchyma [54]. Pseudoenhancement cannot be

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differentiated from enhancement at CT, but it can be suspected in small endophytic lesions. Dual energy CT can mitigate or eliminate pseudoenhancement, but dual energy CT is not widely used and has its own technical limitations [55]. MRI can be used to confirm or exclude pseudoenhancement when it is suspected at CT (Figure 13). Pre-emptive use of MRI instead of CT for the evaluation of small masses can eliminate this serial imaging strategy and reduce cost.

Lack of ionizing radiation

MRI has no ionizing radiation. This can be an advantage during initial multiphasic characterization of a renal mass as well as during surveillance. Bosniak IIF masses are routinely imaged multiple times over a 5-year period (F: "follow-up"). Bosinak III masses, and Bosniak IV masses with small nodules, especially in patients with competing risks, are increasingly being considered for surveillance as well. The benefits of eliminating ionizing radiation are greatest in younger patients and in patients without substantial co-morbidities.

Disadvantages of MRI for Evaluating Cystic Renal Masses

MRI has some disadvantages relative to CT for the characterization of cystic renal masses.

More motion artifacts

MRI is more sensitive than CT to motion because the images take longer to acquire. This is a limitation because degraded images can impair diagnosis. Motion artifacts at MRI can result

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from gross patient movement or biological functions (e.g., respiratory motion, pulsation artifact, peristalsis). It manifests as blurring, obscuration, and overlapping or indistinct margins. Across sequences (e.g., unenhanced and enhanced images), motion can result in misregistration that causes edge or ringing artifacts at subtraction imaging. Misregistration may simulate enhancement and exaggerate the thickness of a wall or septa, causing erroneous Bosniak class assignment (usually higher than it should be). There are a variety of methods to reduce motion artifacts (Figure 14) [56].

Lower spatial resolution

MRI has a lower spatial resolution than CT. This is a limitation because lower spatial resolution can limit assessment of small structures. Accurate Bosniak v.2019 class assignment relies on determining the number and thickness (mm) of small features (septa, convex protrusions). The lower spatial resolution of MRI may cause partial volume effects that impair characterization and measurements. The in-plane resolution for most MRI sequences is different than the slice thickness (anisotropic voxels) even when 3D acquisitions with interpolation strategies are used. Small features may be overlooked if they are perpendicular to the scan plane. To avoid this, multiplanar acquisitions in at least two planes is recommended, especially for T2W imaging and enhanced T1W sequences. 3D acquisitions with isotropic voxels and near-millimeter resolutions are feasible, but 3D sequences suffer from propagation of

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artifacts across the entire image volume and—for fast spin echo imaging—image blur due to an extended echo train.

Potential limitations of gadolinium-based contrast media

MRI generally uses gadolinium-based contrast media (GBCM) and CT uses iodinated contrast media. Use of GBCM is a potential limitation in certain clinical scenarios. Although iodinated contrast media are more likely to cause hypersensitivity reactions and reaction-related death, GBCM may be contraindicated in patients who previously had a severe reaction to GBCM [57]. Nephrogenic systemic fibrosis (NSF) used to be a major consideration for GBCM, but the risk of NSF from group II GBCM has been found to be extremely low (0 of 4,931 administrations, 0% [upper bound 95% CI: 0.07%]) [27, 58, 59]. Gadolinium retention is a potential concern, especially in young patients and in patients receiving repeated administrations of GBCM (e.g., follow-up of Bosniak IIF), but the clinical significance remains unclear [39, 60]. In general, group II GBCM are well tolerated and have an excellent safety profile.

More technically demanding – variable image quality

MRI protocols are more technically demanding than CT protocols. Lack of standardization is a potential limitation because it results in a wider range of image quality compared to CT. Bosniak v.2019 does not include minimum technical requirements for MRI, but

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the same authors (Society of Abdominal Radiology Disease Focused Panel on Renal Cell Carcinoma) released MRI pulse sequence recommendations for a variety of renal mass scenarios, including renal mass characterization [23]. Heterogeneity in magnet strength, choice of pulse sequences, and individual scan parameters (e.g. field of view, slice thickness, matrix size etc.) may impact resolution (spatial and contrast) and diagnostic accuracy. In many institutions, 1.5T scanners are used interchangeably with 3T scanners for kidney mass imaging. However, Rosenkrantz *et al.* found that readers using the original Bosniak Classification tended to upgrade cystic mass complexity at 3T vs. 1.5T [61]. This tendency was associated with changes in patient management, especially when a Bosniak IIF mass was upgraded to a Bosniak III mass (Figure 15) [61]. Interchangeable use of 1.5T and 3T also can result in problems during active surveillance. For example, changing to a higher field strength can increase the apparent complexity of internal features and promote overtreatment.

Update in Management of Cystic Renal Masses

It is now recognized that cystic RCC is indolent with a very low likelihood of local recurrence or metastatic disease [6]. Although resection remains the standard for Bosniak IV masses in patients without significant comorbidities, the management of Bosniak III masses and even some Bosniak IV masses with small nodules is shifting toward active surveillance [17, 62].

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There is growing evidence that active surveillance of cystic renal masses is safe [17, 62]. Shaish et al showed that approximately half of Bosniak III and IV masses (using the original classification) were downgraded to a lower Bosniak class during follow-up [49]. Active surveillance is favored in older patients with limited life expectancy and surgical co-morbidities. This approach requires well-informed patients capable of understanding the risks and benefits of avoiding treatment. The ideal follow-up scheme and ideal imaging-based triggers for intervention remain uncertain [63]. In high-risk surgical candidates for whom active surveillance is not being contemplated, thermal ablation is a safe alternative [64, 65]. Biopsy is generally avoided because it is low yield [66].

Conclusion

Bosniak v.2019 formally incorporates MRI into the risk-stratification of cystic renal masses. MRI offers specific advantages (e.g., insensitivity to calcification, sensitivity for enhancement) and can be used alone or as an adjunct to CT. The goals of the updated classification are to improve inter-rater agreement, improve specificity for malignancy, and to enable a greater proportion of benign masses to enter lower-risk classes. These goals are important because cystic RCC is indolent and overtreated. Active surveillance is emerging as a

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promising management strategy for many Bosniak III masses and some Bosniak IV masses.

Further refinement of the Bosniak classification is anticipated as new data emerge.

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Table 1: Summary of the Bosniak version 2019 classification of cystic renal masses as it pertains to MRI.

Adapted from [4]. Italicized elements indicate changes from the original Bosniak classification.

Class	MRI: Proposed Bosniak Classification v.2019[1]
I	Well-defined, *thin* (*≤2 mm*) smooth wall; homogeneous simple fluid *(signal intensity similar to cerebrospinal fluid)*; no septa or calcifications; *the wall may enhance*
II	*Three* types, *all well-defined with thin (≤2 mm) smooth walls*: 1. Cystic masses with thin (*≤2 mm*) few (*1-3*) *enhancing* septa; *any nonenhancing septa*; may have *calcification of any type*[2] *2. Unenhanced MRI: Homogeneous masses markedly hyperintense on T2W imaging (similar to cerebrospinal fluid)* *3. Unenhanced MRI: Homogeneous masses markedly hyperintense on T1W imaging (approximately 2.5-times normal parenchyma signal intensity)*
IIF	Two types: 1. Cystic masses with a smooth minimally thickened (*3 mm*) enhancing wall, or smooth minimal thickening (*3 mm*) of one or more enhancing septa, or *many (≥4*) smooth thin *enhancing* septa 2. *Cystic masses that are heterogeneously hyperintense at unenhanced fat saturated T1W imaging*
III	One or more enhancing thick (*≥4 mm width*) or enhancing irregular (*≤3 mm obtusely margined convex protrusion(s)*) walls or septa
IV	One or more *enhancing nodule(s) (≥4 mm convex protrusion with obtuse margins, or a convex protrusion of any size that has acute margins)*

1 – The Bosniak classification is intended for cystic renal masses in patients without a congenital kidney cancer syndrome after exclusion of necrotic solid masses and infectious, inflammatory, and vascular etiologies. If a cystic mass has features described in more than one Bosniak class, the highest Bosniak class is assigned. In rare cases, a mass may have an unusual combination of features (undefined, not fitting a specific Bosniak class) that may warrant inclusion into Bosniak IIF. Other than for the diagnosis of Bosniak I simple cysts, the role of ultrasound with or without contrast material in assigning a Bosniak class is uncertain.
2 – Renal masses that at CT have abundant thick or nodular calcifications; are hyperattenuating, homogeneous, nonenhancing, and larger than 3 cm; or are heterogeneous might best be visualized at MRI prior to the assignment of a Bosniak class to determine if there are occult enhancing elements that might affect classification.

Figure legends

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Figure 1: Examples of cystic renal masses in 2 different patients to demonstrate the concept of “mental subtraction”.

74-year-old man with papillary RCC. (a) Coronal T2W image shows >50% exophytic cystic renal mass with a heterogeneous hypointense component along the medial wall (arrow). (b) Coronal fat saturated (FS) T1W image shows the mass is heterogeneously hyperintense, with a hypointense component along the medial wall (arrow). (c) Coronal FS T1W nephrographic phase image shows the signal intensity of the two components has become closer following contrast material administration, indicating enhancement demonstrated by “mental subtraction”. (d) Coronal FS T1W nephrographic phase subtraction image confirms enhancing nodules (arrows; i.e,, Bosniak IV).

63-year-old woman with papillary RCC. (e) Coronal T2W image shows >50% exophytic hypointense renal mass with an apparent nodule along the medial aspect (arrow). (f) Coronal fat saturated (FS) T1W image shows the mass is heterogeneously hyperintense, with isointensity of the apparent nodule to the remainder of the mass (arrow). (g) Coronal FS T1W nephrographic phase image shows relative increase in signal intensity of the apparent nodule compared to the remainder of the mass, confirming an enhancing nodule by “mental subtraction” (i.e., Bosniak IV). (h) Coronal FS T1W nephrographic phase subtraction image is degraded by motion artifact and uninterpretable (arrow).

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Figure 2: Examples of Bosniak v2019 class I cyst at MRI in two patients.

43-year-old man with an incidental cyst identified on MRI. (a) Axial T2-weighted (T2W) image shows a cyst (arrow) with simple fluid intensity (defined as homogeneous signal intensity similar to that of cerebrospinal fluid) without septa or nodule. (b) Axial fat-suppressed (FS) T1-weighted (T1W) nephrographic phase (NP) image shows a smooth thin (≤2 mm) wall (arrow).

65-year-old woman with an incidental cyst identified on MRI. (c) Axial T2W image shows a cyst with simple fluid intensity (arrow). (d) Axial FS T1W NP image shows smooth thin (≤2 mm) enhancing wall (arrow).

Wall enhancement is permissible in Bosniak v.2019 class I cysts when smooth and thin (≤2 mm).

Figure 3: 54-year-old man with Bosniak v.2019 class II cyst at MRI. (a) Axial T2W image shows a ≥50% exophytic left renal cystic mass with numerous apparent septa (arrows). (b) Axial fat-saturated T1W nephrographic phase image shows no internal enhancement. The cystic mass is well-defined with a smooth thin (≤2mm) wall (arrow). Bosniak II cystic masses can have any number of non-enhancing septa. Only enhancing septa can be used to upgrade a mass to Bosniak IIF-IV.

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Figure 4: 47-year-old man with Bosniak v.2019 class II hemorrhagic or proteinaceous cyst at MRI. (a) Coronal unenhanced CT image shows an endophytic mass in right kidney (arrow) with indeterminate attenuation (35 HU). Further evaluation was done with MRI. (b) Coronal T2W image shows the mass is iso- to hypointense (arrow) relative to the renal parenchyma and does not have simple fluid signal. (c) Coronal fat saturated (FS) unenhanced T1W image shows homogeneous hyperintensity (≥2.5x renal parenchyma) (arrow). (c) Coronal FS T1W nephrographic phase subtraction image shows no enhancement (arrow). (e) Ultrasound shows anechoic cyst (arrow) with increased posterior through transmission. Homogeneous masses markedly hyperintense at unenhanced FS T1W imaging (approximately ≥2.5x normal parenchymal signal intensity) are Bosniak II.

Figure 5: 44-year-old woman with Bosniak v.2019 class IIF mass at MRI. (a) Axial contrast-enhanced CT (CECT) image shows a <50% exophytic right renal mass with a minimally thickened (3 mm) wall (arrow). It is unclear whether the internal contents excluding the wall are enhancing. (b) Axial fat saturated (FS) T2W image shows the cystic mass with internal simple fluid signal with a smooth minimally thickened (3 mm) wall (arrow). (c) Axial FS T1W nephrographic phase image shows a smooth minimally thickened (3 mm) enhancing wall (arrow) and no septa or nodule. Smooth minimal thickening (3 mm) of a wall or septa without irregularity or nodule is consistent with Bosniak IIF. The mass remained stable for 2 years without morphologic change. Annual follow-up for 3 more years is planned.

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Figure 6: 66-year-old man with Bosniak v.2019 class IIF mass at MRI. (a) Coronal T2W image shows a <50% exophytic cystic right renal mass with many (≥4) thin (≤2 mm) and minimally thickened (3 mm, arrow) septa. (b) Axial fat saturated T1W nephrographic phase image shows many (≥4) enhancing septa, one of which is minimally thickened (3 mm, arrow). Many (≥4) enhancing septa and smooth minimal thickening (3 mm) of the wall or septa, are each features of a Bosniak IIF mass. The mass remained stable for 7 years without morphologic change.

Figure 7: 54-year-old man with Bosniak v.2019 class IIF mass at MRI. (a) Axial fat saturated T2W image shows a ≥50% exophytic cystic right renal mass with many (≥4) apparent septa (arrow). (b) Axial fat saturated T1W nephrographic phase image confirms many (≥4) thin (≤2 mm) smooth enhancing septa (big arrow) and a minimally thickened (3 mm) posteromedial wall (small arrow). Smooth minimal thickening (3 mm) of the wall or septa, and many (≥4) enhancing septa, are each features of a Bosniak IIF mass. The mass remained stable for 5 years without morphologic change.

Figure 8: 72-year-old man with papillary renal cell carcinoma (RCC) type 1, diagnosed at partial nephrectomy, presenting as a Bosniak v.2019 class IIF mass. (a) Coronal fat saturated unenhanced T1W image shows a ≥50% exophytic heterogeneously hyperintense cystic mass arising from the medial interpolar region of the right kidney (arrow). (b) Coronal T2W image shows heterogeneously hypointense signal (arrow). (c) Coronal fat saturated T1W

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nephrographic phase subtraction image shows no definitive enhancement (arrow). Heterogeneous hyperintensity at fat saturated unenhanced T1W imaging is a feature of a Bosniak IIF mass, regardless of enhancement. Papillary renal cell carcinoma (as in this case) may present this way.

Figure 9: 58-year-old woman with papillary RCC type 1, diagnosed at partial nephrectomy, presenting as a Bosniak v.2019 class III mass. (a) Axial contrast-enhanced CT shows a ≥50% exophytic heterogeneous left renal mass (arrow). (b) Axial fat saturated T1W nephrographic phase subtraction image shows an enhancing thick (≥4 mm) irregular (≤3mm obtusely marginated convex protrusions) medial wall (arrow). Enhancing thickened wall or septa, and enhancing irregular thickening of the wall or septa, are each features of a Bosniak III mass.

Figure 10: Examples of Bosniak v.2019 class IV masses in two patients, illustrating nodules with obtuse (a and b) and acute (c and d) margins.

45-year-old woman with clear cell RCC diagnosed at partial nephrectomy. (a) Axial T2W image shows a <50% exophytic cystic left renal mass with many (≥4) septa and a 6 mm septal nodule (≥4 mm and obtuse margins) (arrow). (b) Axial fat saturated T1W nephrographic phase image confirms the nodule enhances (arrow).

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74-year-old man with clear cell RCC diagnosed at partial nephrectomy. (c) Axial T2W image shows a <50% exophytic cystic left renal mass with a 5 mm mural nodule (convex protrusion of any size with acute margins to the wall or septa) (arrow). (d) Axial fat saturated T1W nephrographic phase image confirms the nodule enhances (arrow).

Enhancing nodules are features of a Bosniak IV cystic masses, and may have obtuse margins (≥4 mm) or acute margins (any size) with the wall or septa.

Figure 11: Examples of cystic renal masses with abundant calcification at CT in 2 different patients.

54-year-old man with incidental left renal mass. (a) Axial unenhanced CT shows a <50% exophytic left renal mass with abundant calcification (arrow). (b) Contrast-enhanced CT cannot confirm or exclude the presence of enhancing elements due to obscuration by calcification (arrow). (c) Axial fat saturated T1W nephrographic phase subtraction image shows an enhancing irregular (≤3mm obtusely marginated convex protrusions) wall (arrow). An enhancing irregular wall is a feature of a Bosniak III mass. The patient was placed on active surveillance.

66-year-old man with incidental left renal mass. (d) Axial unenhanced CT shows a ≥50% exophytic left renal mass with abundant calcification (arrow). (e) Contrast-enhanced CT cannot

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confirm or exclude the presence of enhancing elements due to obscuration by calcification (arrow). (f) Axial fat saturated T1W nephrographic phase subtraction image shows a thin (≤2mm) smooth wall and few (1-3) smooth thin (≤2mm) enhancing septa (arrow). Few thin septa is a feature of a benign Bosniak II mass.

Masses with abundant calcification at CT generally require renal mass protocol MRI prior to Bosniak v.2019 class assignment to ensure enhancing elements are not obscured by calcification.

Figure 12: 63-year-old woman with papillary RCC type 1, diagnosed at partial nephrectomy, presenting as a heterogeneous non-enhancing mass at CT. (a) Coronal unenhanced CT shows a <50% exophytic heterogenous left upper pole renal mass with attenuation 51 HU (arrow). Three homogeneous simple-cyst-appearing masses with attenuations -9 to 20HU are also present (arrowheads). (b) Coronal contrast-enhanced nephrographic phase CT shows no measurable enhancement in the heterogeneous mass (arrow; 59HU; difference from unenhanced CT is 8HU). The 3 simple cysts do not enhance (arrowheads; Bosniak I). (c) Coronal fat saturated unenhanced T1W image shows the heterogeneous mass is heterogeneously hyperintense. (d) Coronal fat saturated T1W nephrographic phase subtraction image shows an enhancing 12 mm nodule (acute margins, enhancing, any size) along the medial aspect of the wall (arrow). Enhancing nodule is a feature of a Bosniak IV mass.

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MRI is indicated prior to Bosniak v.2019 class assignment for heterogeneous non-enhancing renal masses at CT. Papillary renal cell carcinoma (as in this case) may present this way.

Figure 13: 23-year-old woman with incidental cystic left renal mass. (a) Coronal unenhanced CT shows an endophytic renal mass with attenuation 11HU (arrow). (b) Coronal contrast-enhanced nephrographic phase image shows the mass is 32HU (arrow; increase of 21HU, consistent with enhancement). However, given the size of the mass and its endophytic location, pseudoenhancement was favored and MRI was performed. (c) Coronal T2W image shows well-defined cystic mass with simple fluid signal (arrow). (d) Coronal fat saturated T1W nephrographic phase subtraction image shows a simple Bosniak I cyst with a smooth thin (≤2mm) wall and no other features (arrow).

Figure 14: 45-year-old man with papillary RCC, type 1 diagnosed at partial nephrectomy, presenting as a hypoenhancing mass at MRI confounded by misregistration artifact. (a) Axial fat saturated T1W nephrographic phase subtraction image acquired using breath-hold technique shows a <50% exophytic mass in the anterior interpolar region of the right kidney (arrow). Solid enhancement (≥25% enhancing volume) was suspected but confounded by misregistration artifact from respiratory motion. (b) Axial fat saturated T1W nephrographic phase subtraction image acquired using free-breathing navigator-triggered technique shows unequivocal solid

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enhancement consistent with a solid mass (arrow). Compare the hypoenhancing solid mass (arrow) with the nonenhancing Bosniak I simple cyst (arrowhead).

Figure 15: 47-year-old man with an incidental left renal mass. (a) Axial T2W image performed on a 1.5T scanner shows an endophytic cystic renal mass with many (≥4) septa (arrow). (b) Axial fat saturated T1W nephrographic phase image performed on 1.5T scanner confirms many (≥4) thin (≤2 mm) smooth enhancing septa (arrow). Many thin enhancing septa are a feature of a Bosniak IIF mass. MRI was performed at 3T for an unrelated indication 3 months later. Increased resolution at 3T is also obvious by the better delineation of individual nerve roots in the spinal canal compared to 1.5T (c) Axial T2W image performed on a 3T scanner shows many (≥4) septa, some of which are irregular (arrow; ≤3mm obtusely marginated convex protrusions). (d) Axial fat saturated T1W nephrographic phase image performed on a 3T scanner shows enhancement of the irregular septa (arrow). Therefore, the mass was reclassified as Bosniak III and placed on active surveillance.

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May 11, 2020

Satheesh Krishna
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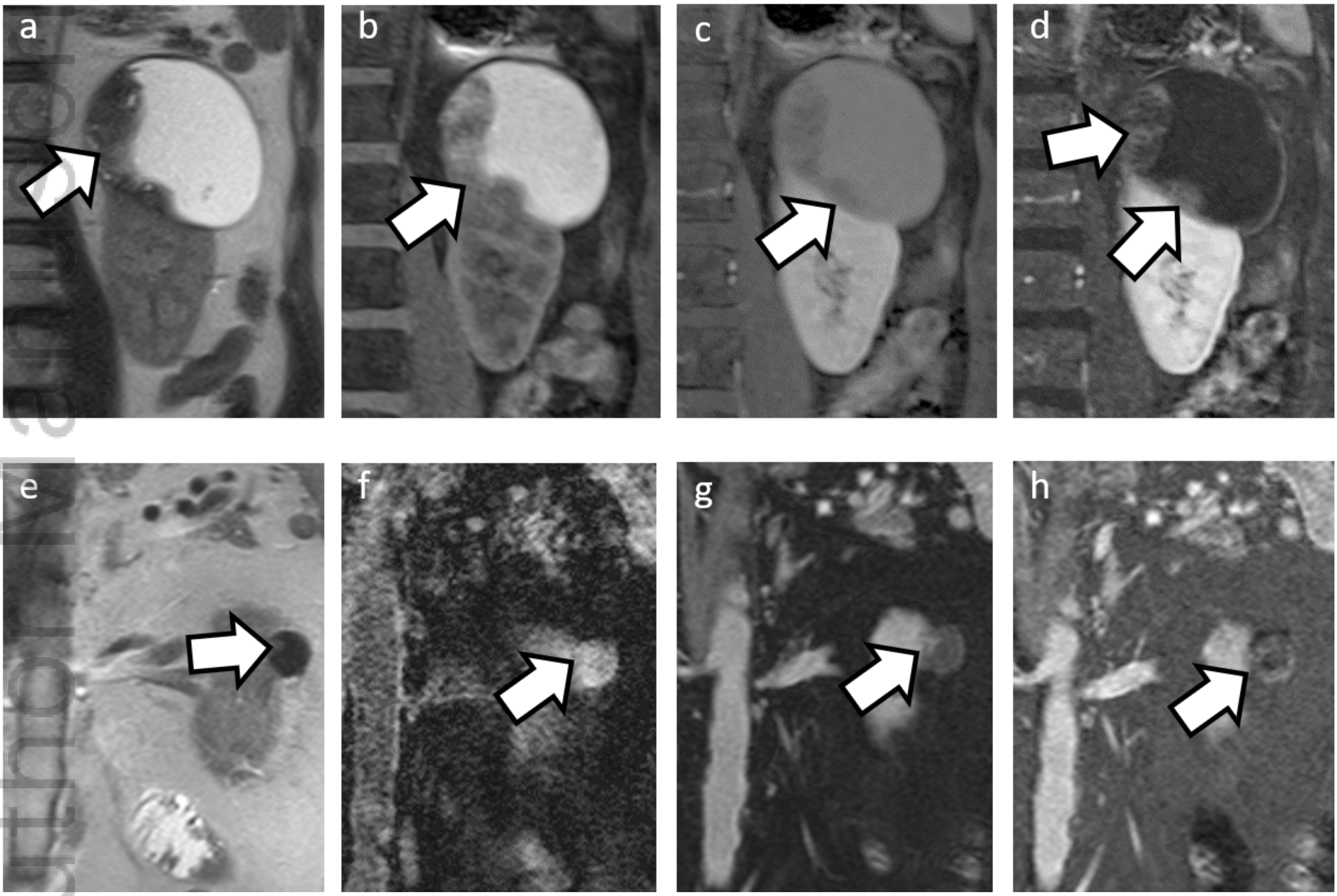

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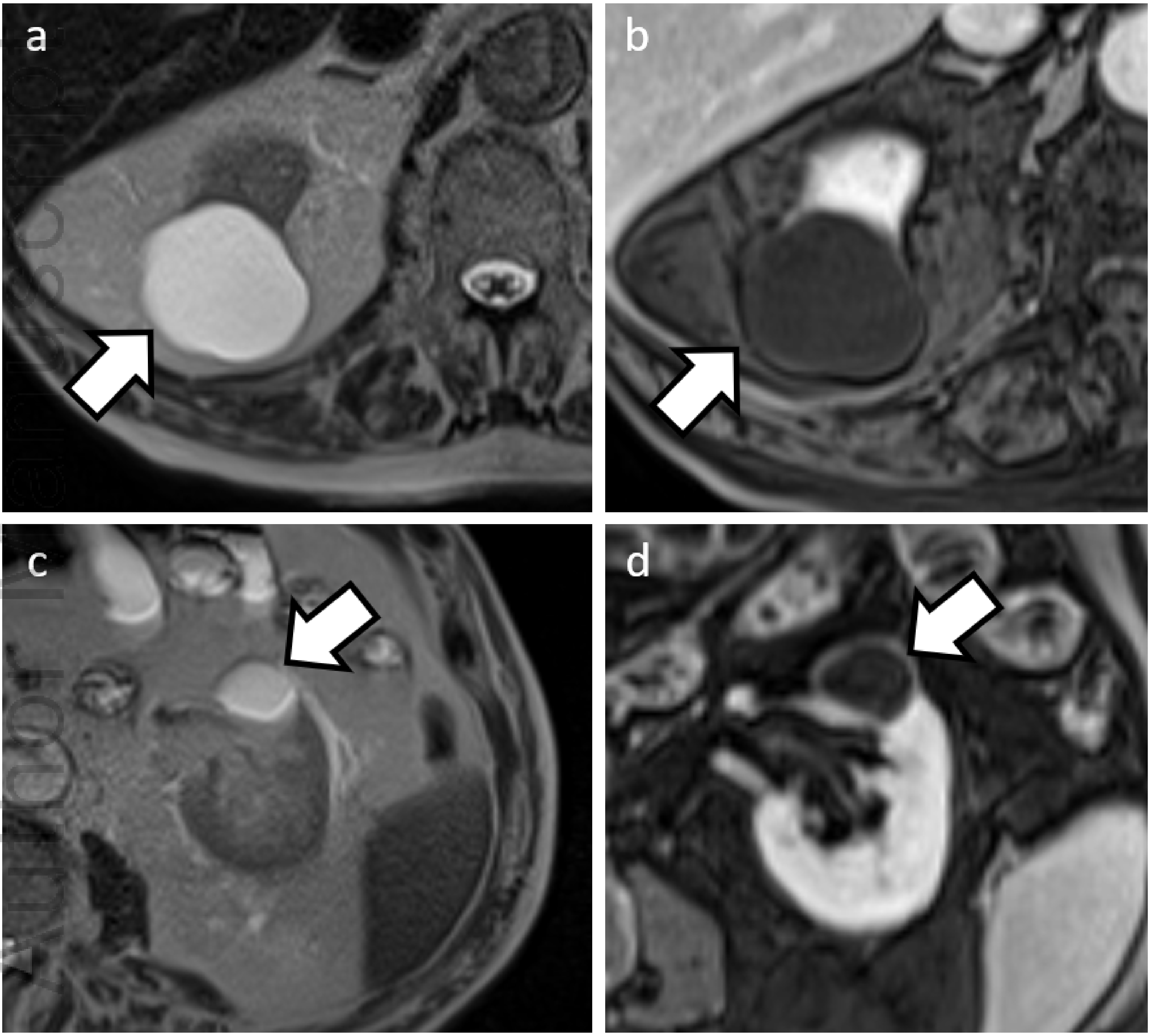

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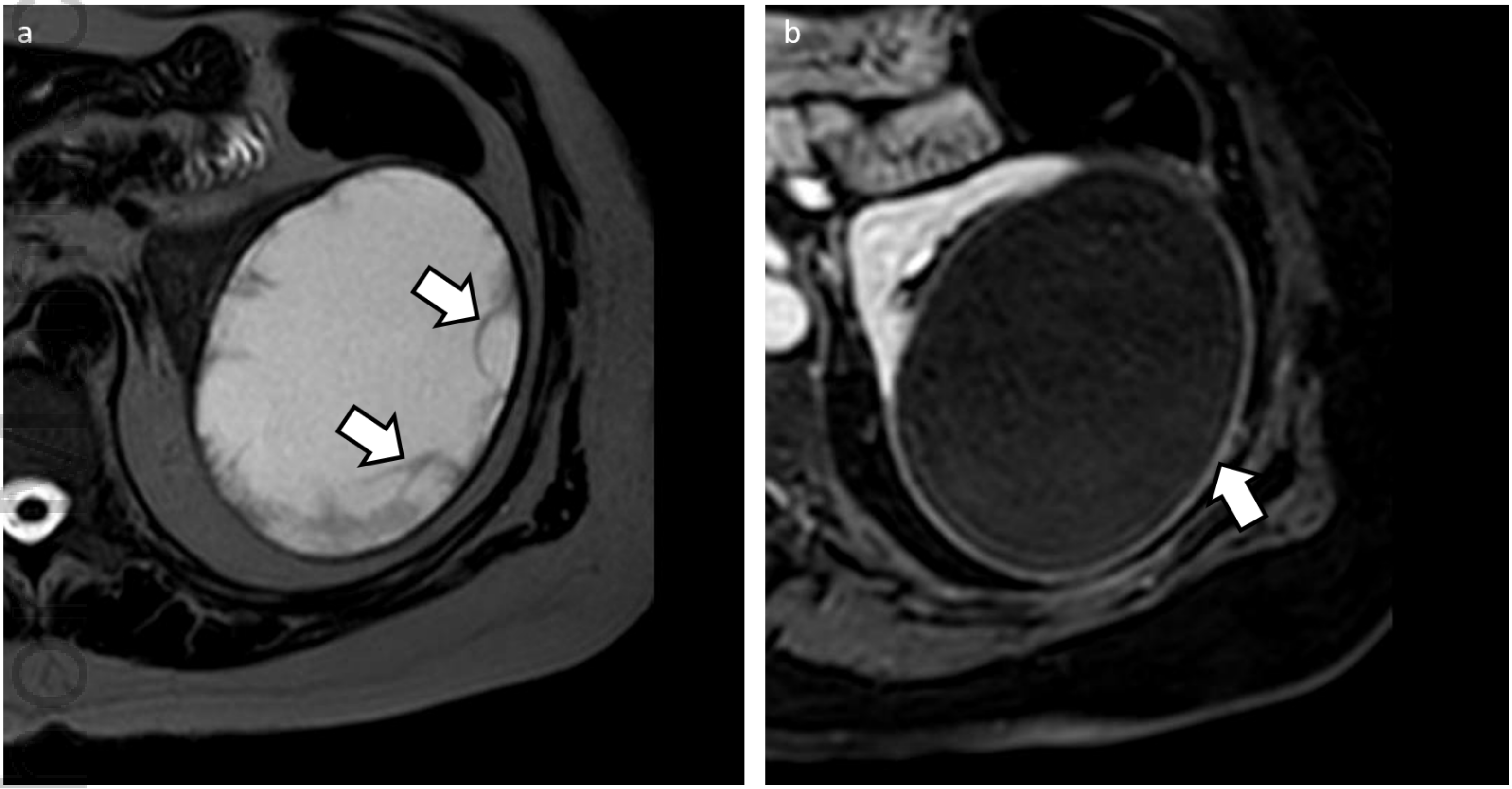

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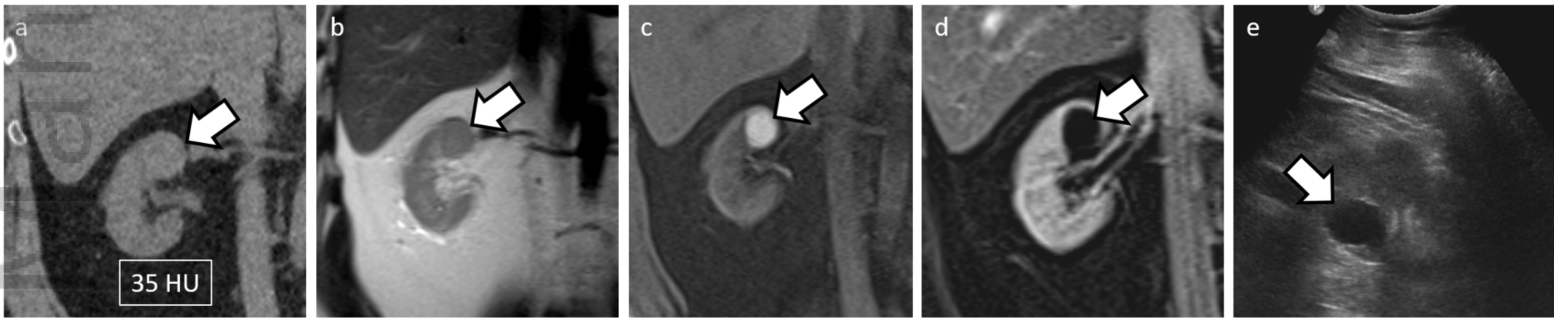

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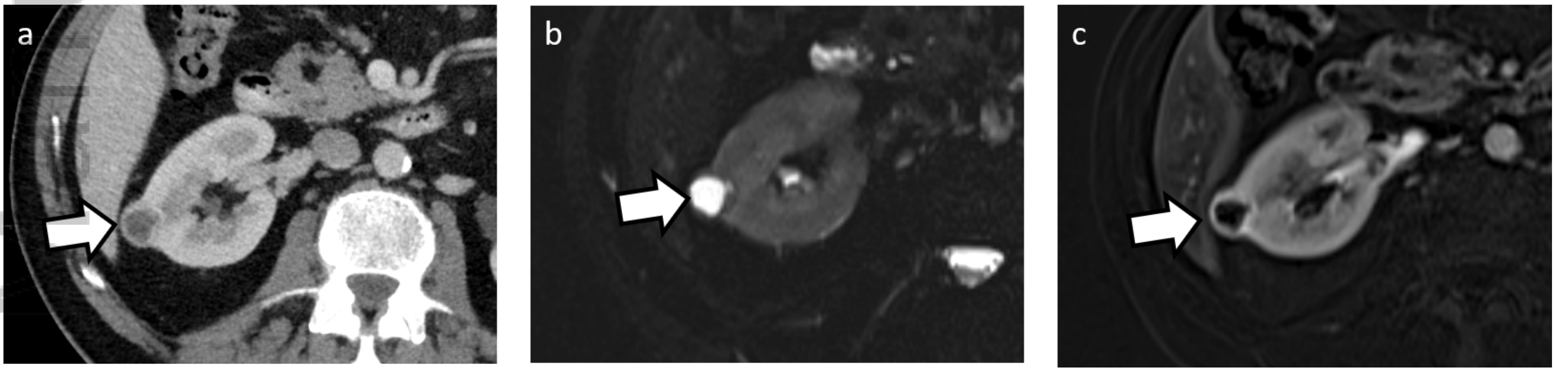

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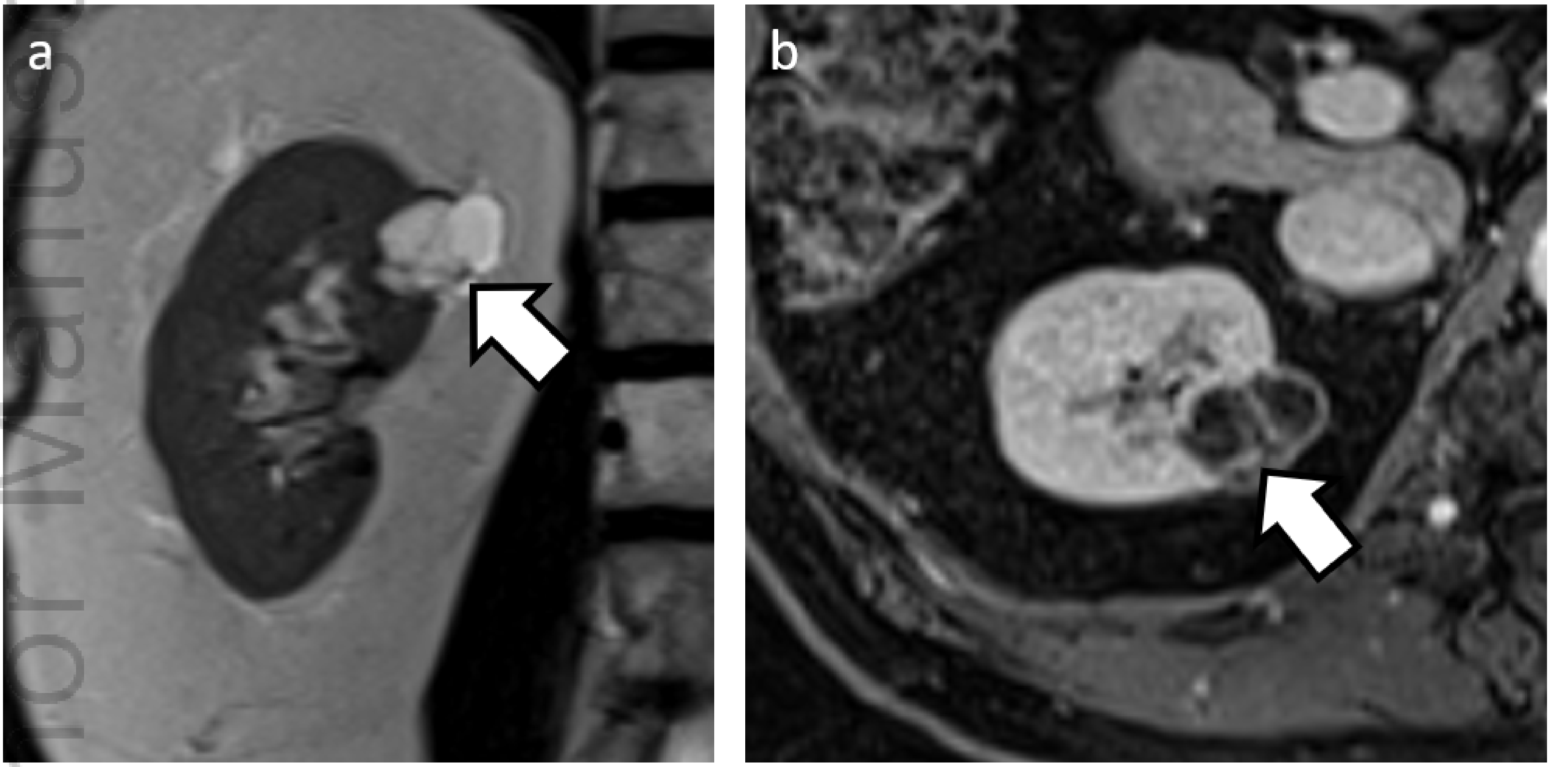

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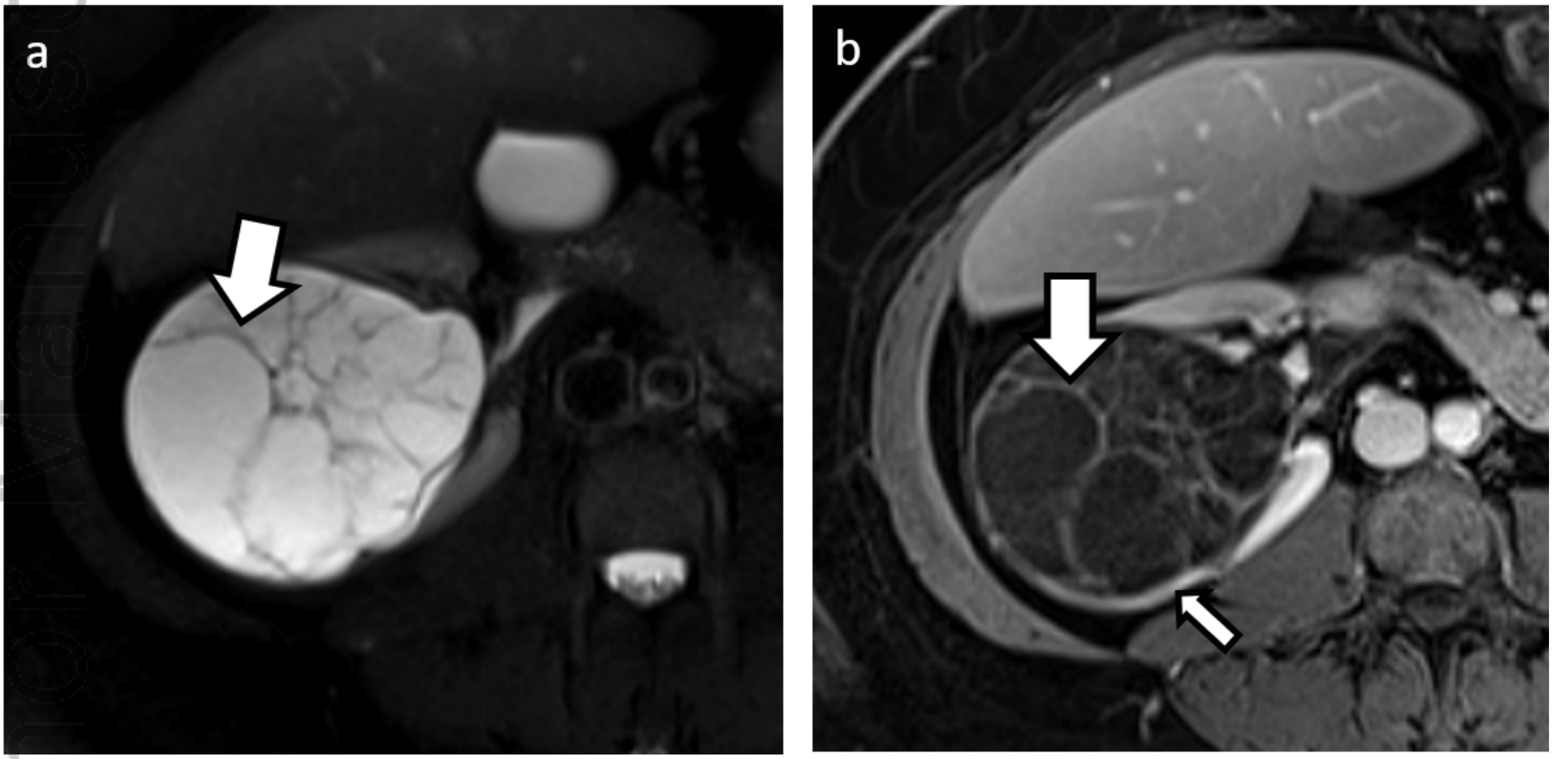

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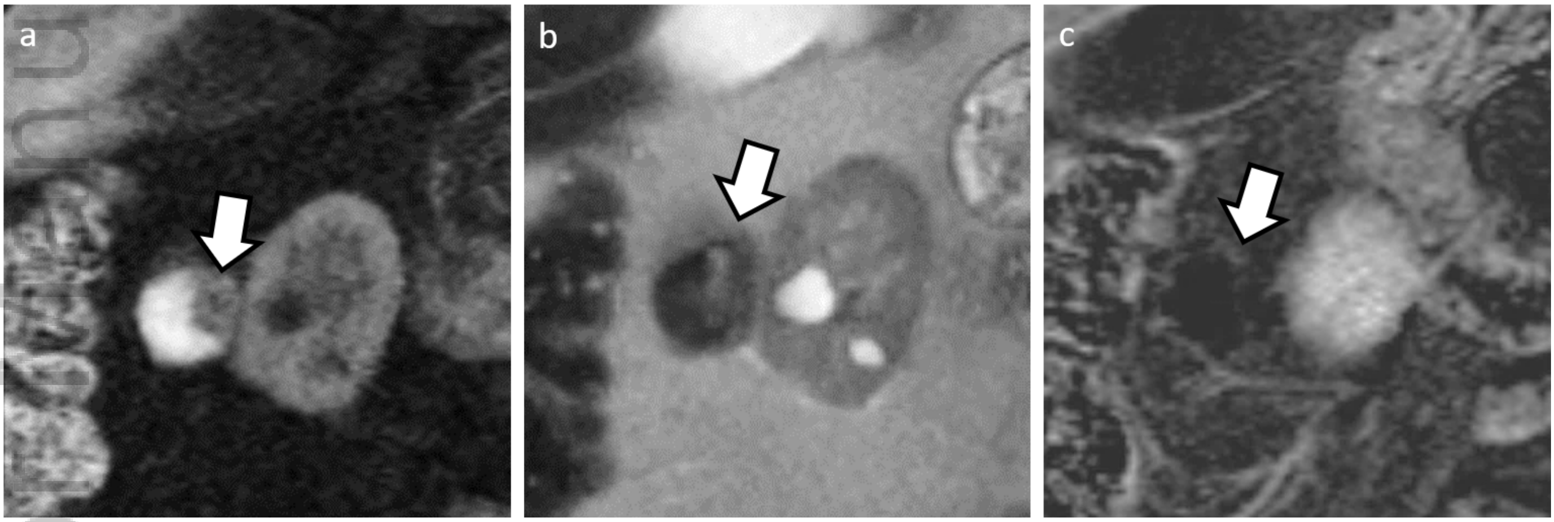

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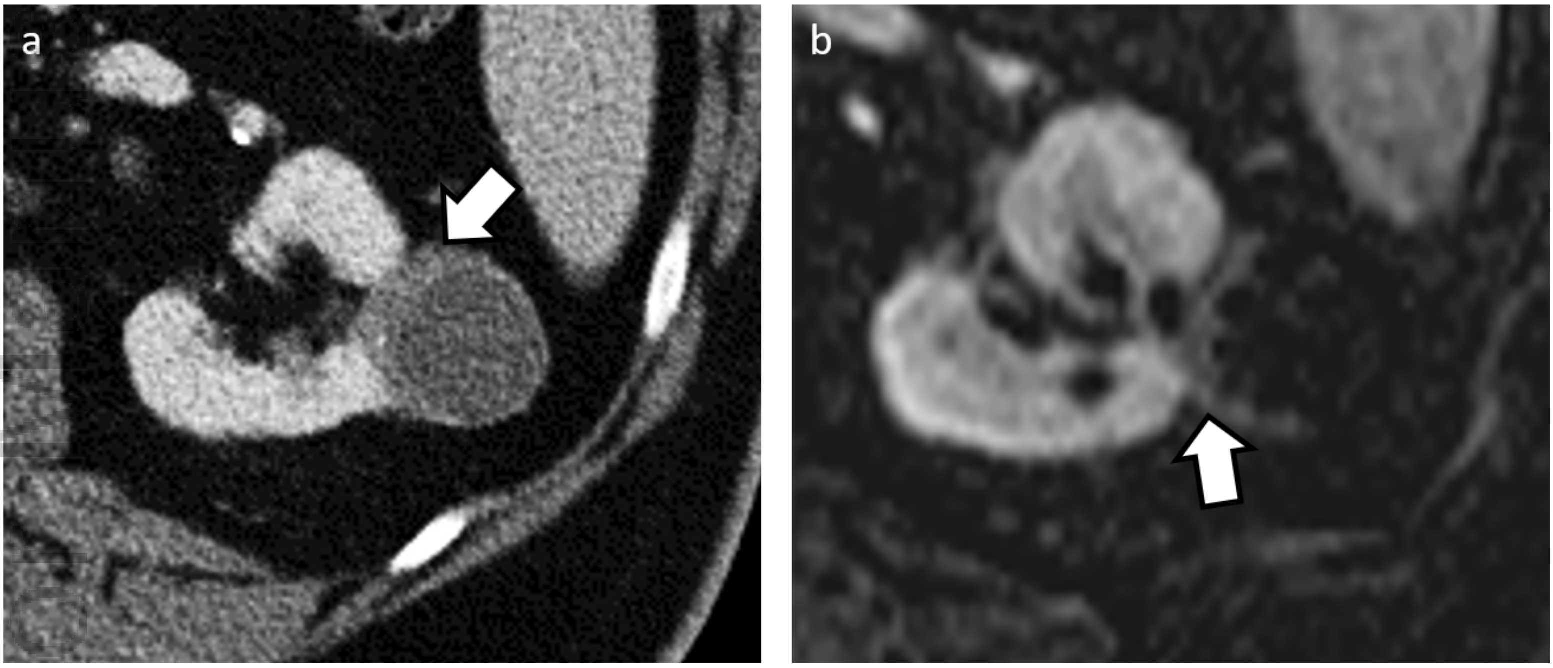

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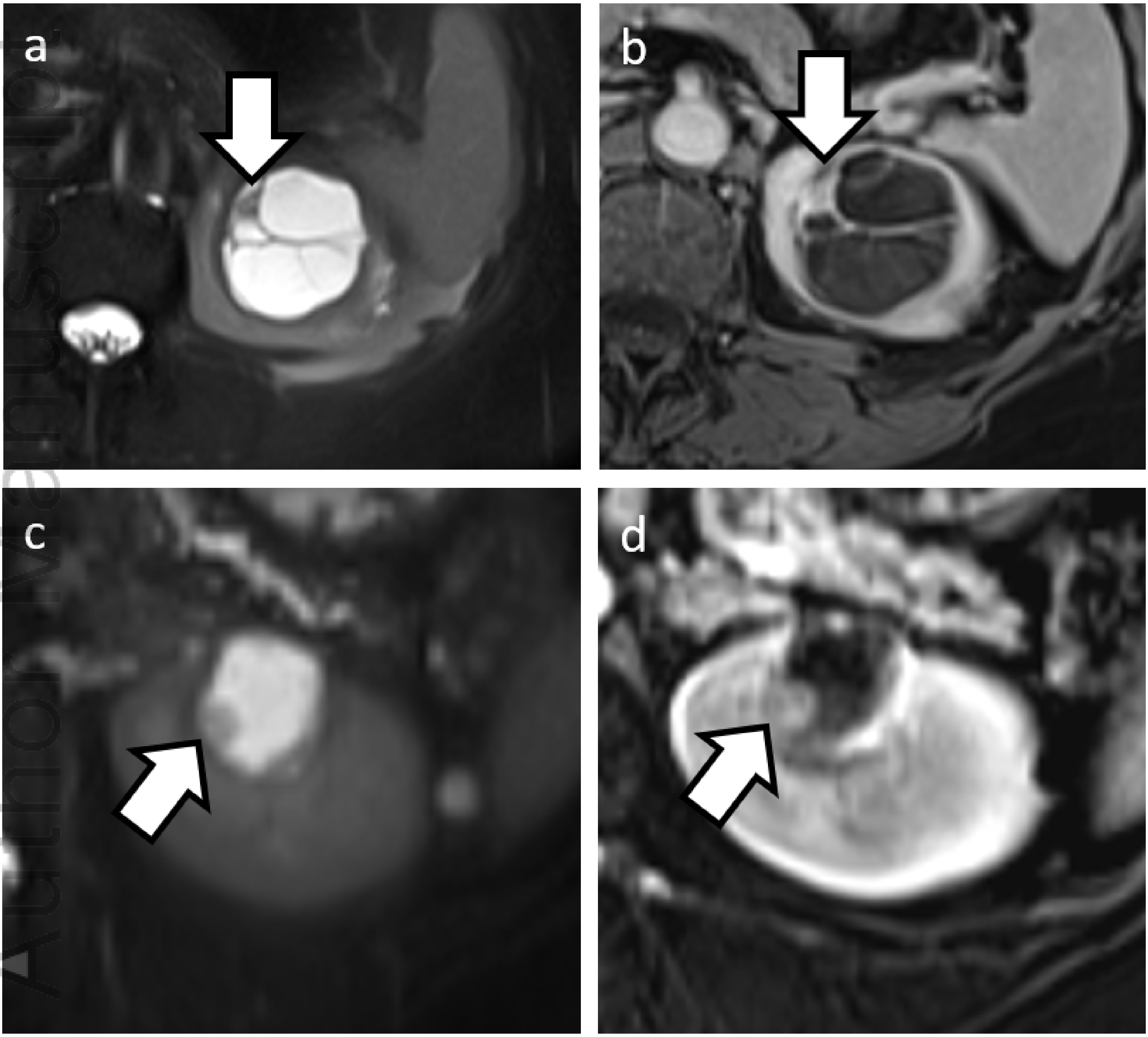

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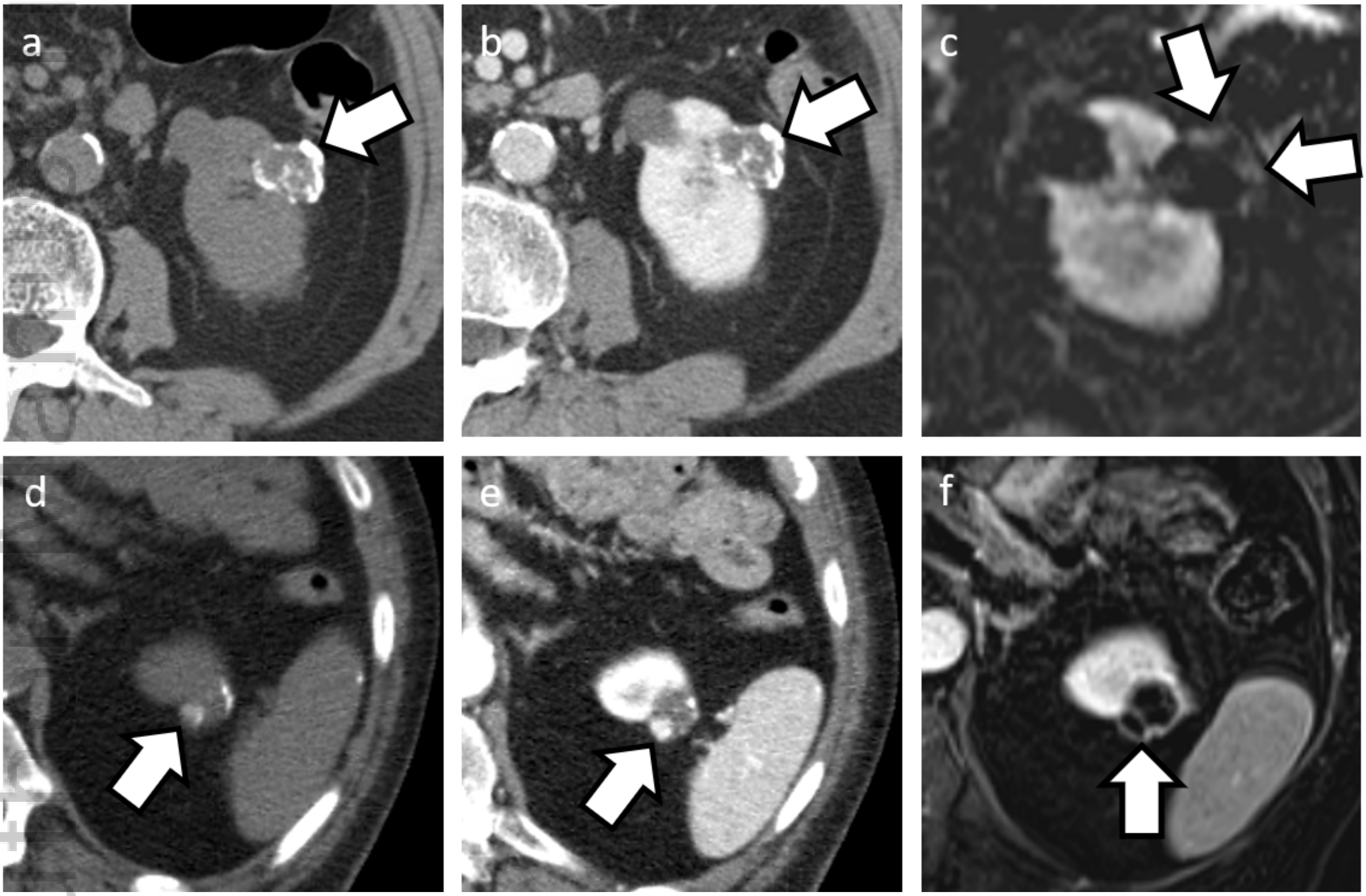

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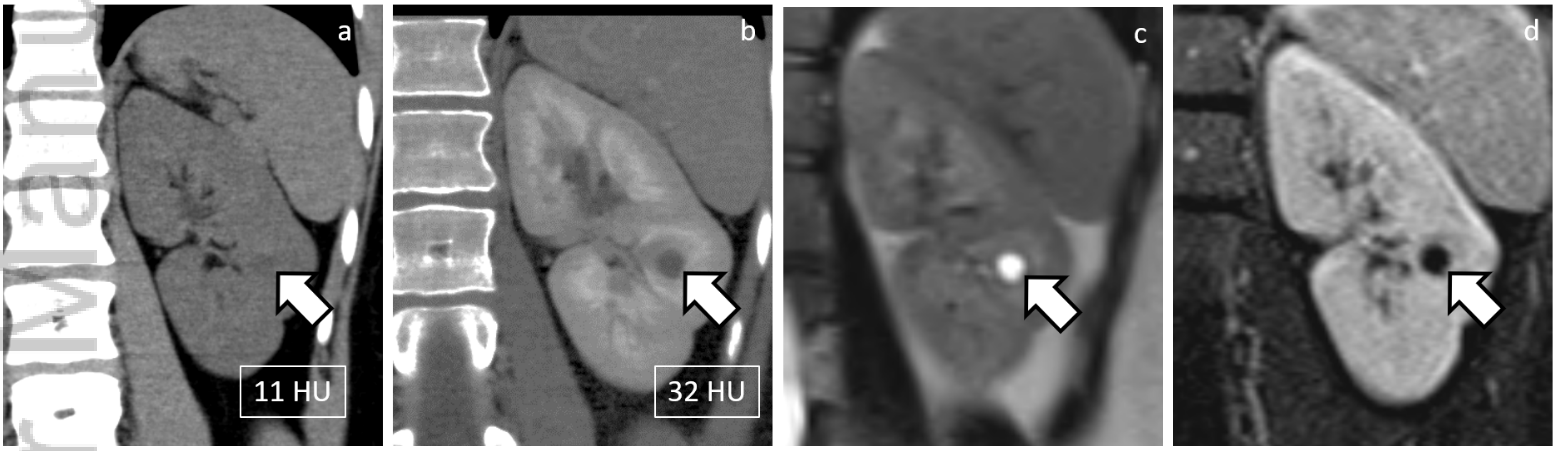

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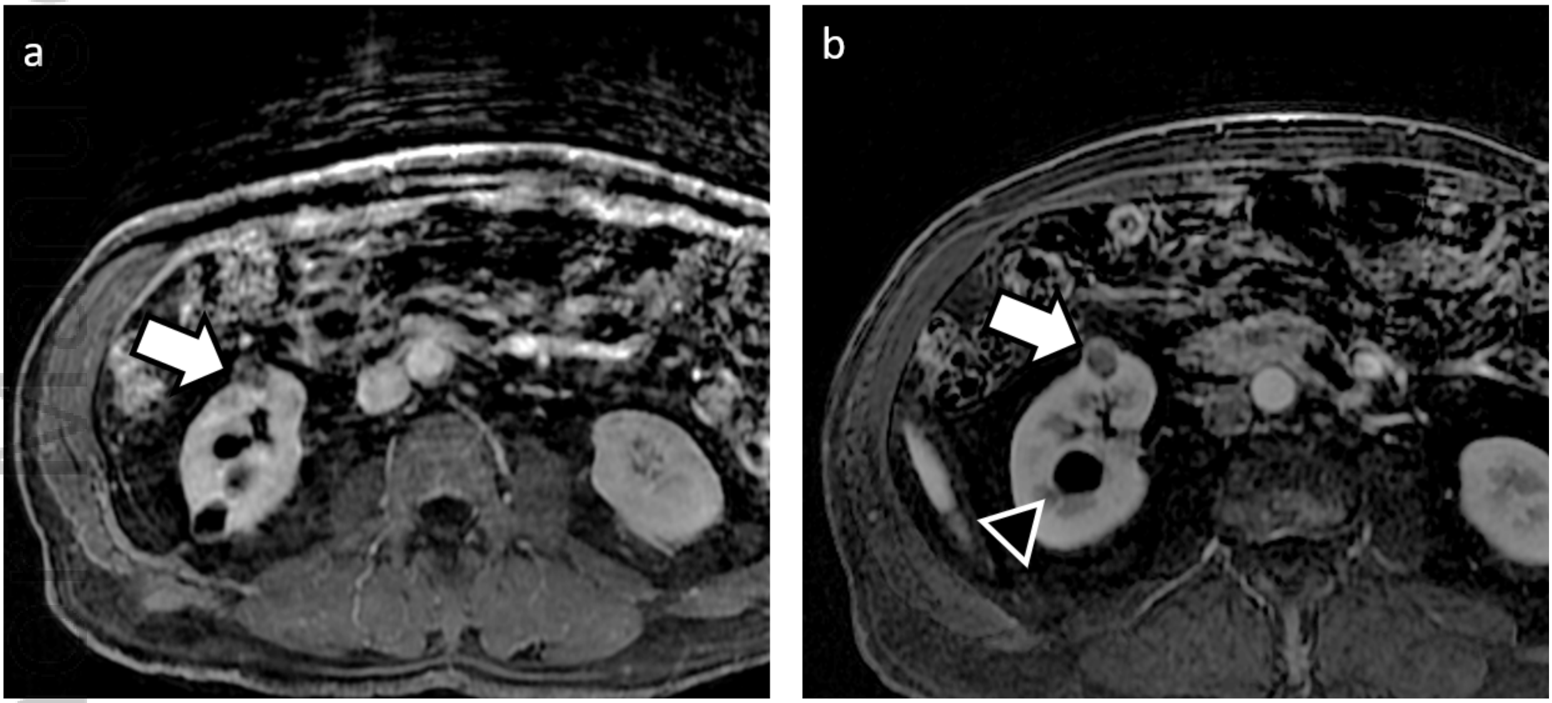

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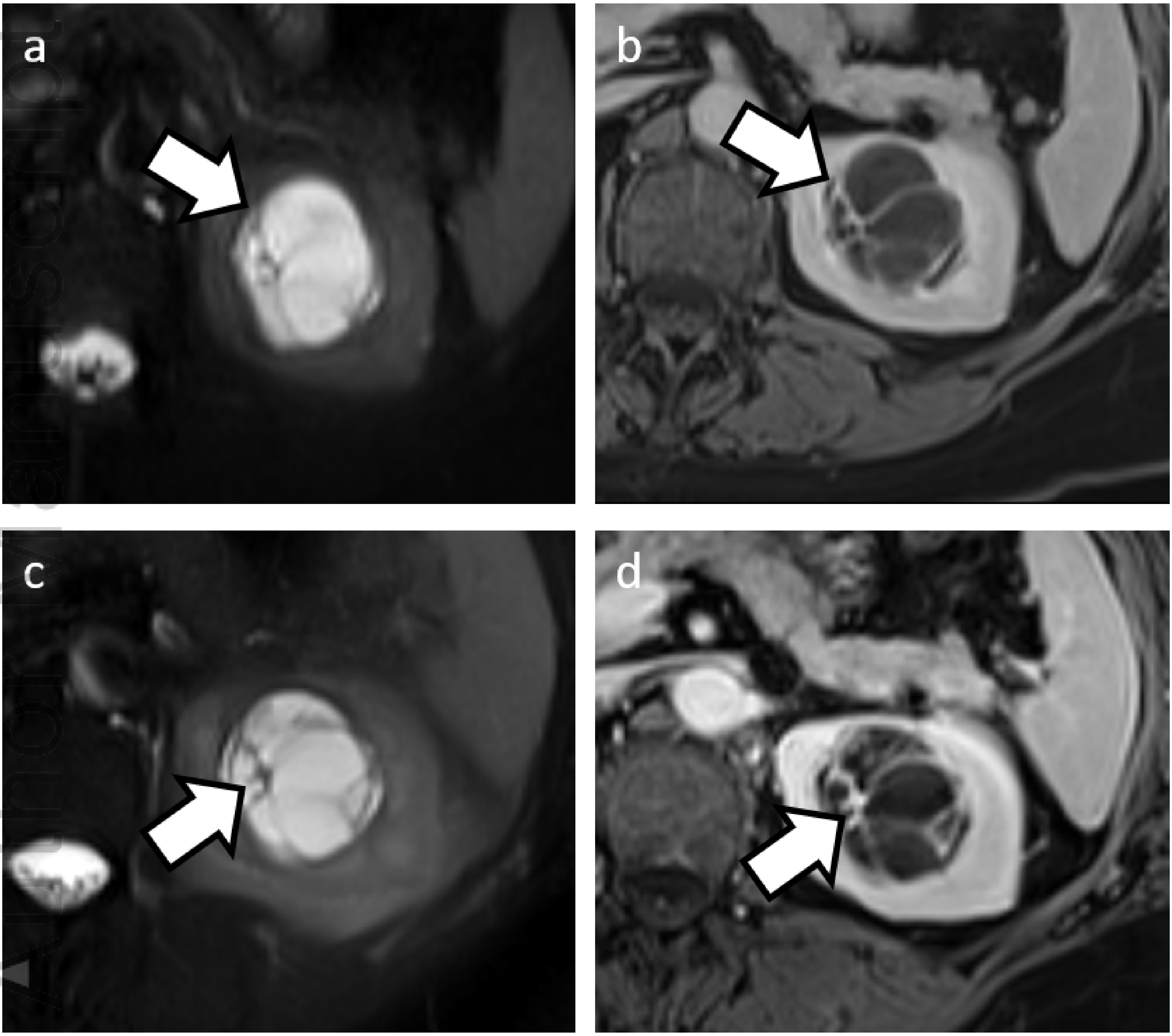

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