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ESTIMATION OF RISK OF NEPHROGENIC SYSTEMIC FIBROSIS IN PATIENTS OF STAGE 3-5 CHRONIC KIDNEY DISEASE UNDERGOING MAGNETIC RESONANCE IMAGING WITH INJECTABLE GADOBUTROL

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ABSTRACT

Background: Nephrogenic systemic fibrosis is a rare but serious fibrosing disorder associated with gadolinium-based contrast agents, particularly in patients with impaired renal function. Newer macrocyclic agents such as gadobutrol have greater chelate stability and are considered to have a very low risk of nephrogenic systemic fibrosis. However, local clinical data in patients with stage 3–5 chronic kidney disease remain limited, making post-contrast safety assessment important for practical radiology decision-making.

Objective: To determine the frequency of nephrogenic systemic fibrosis among patients with stage 3–5 chronic kidney disease undergoing contrast-enhanced magnetic resonance imaging with injectable gadobutrol.

Methods: This prospective descriptive follow-up study was conducted in the Department of Diagnostic Radiology, Doctors Hospital and Medical Center, Lahore, from September 2025 to April 2026, after approval from the College of Physicians and Surgeons Pakistan. A total of 101 patients aged 20–80 years with estimated glomerular filtration rate below 60 mL/min/1.73 m² were enrolled through non-probability consecutive sampling. All patients underwent contrast-enhanced magnetic resonance imaging with intravenous gadobutrol at a standard dose of 0.1 mmol/kg. Immediate adverse reactions were observed for one hour after contrast administration. Clinical follow-up was performed at 1, 3, and 6 months to assess symptoms suggestive of nephrogenic systemic fibrosis. Data were analyzed using SPSS, and a p-value <0.05 was considered statistically significant.

Results: Of 101 patients, 59 were male (58.4%) and 42 were female (41.6%). The mean age was 61.4 ± 10.8 years. Stage 3, stage 4, and stage 5 chronic kidney disease were present in 49 (48.5%), 36 (35.6%), and 16 (15.8%) patients, respectively. Diabetes mellitus was present in 74 patients (73.3%), hypertension in 89 (88.1%), and 15 (14.9%) were on dialysis. Follow-up was completed in 95 patients (94.1%). No patient developed clinical features suggestive of nephrogenic systemic fibrosis. Mild transient adverse reactions occurred in 3 patients (3.0%), while no moderate or severe reaction was recorded.

Conclusion: No case of nephrogenic systemic fibrosis was observed after standard-dose gadobutrol-enhanced magnetic resonance imaging in patients with stage 3–5 chronic kidney disease during the follow-up period. These findings support the low observed clinical risk of gadobutrol in renal impairment, although larger multicenter studies with longer follow-up are needed.

KEYWORDS: Chronic Kidney Disease; Contrast Media; Follow-Up Studies; Gadolinium; Magnetic Resonance Imaging; Nephrogenic Fibrosing Dermopathy; Prospective Studies.

INTRODUCTION

Nephrogenic systemic fibrosis (NSF) is an uncommon but potentially disabling fibrosing disorder that primarily affects the skin and subcutaneous tissues, although involvement of joints and internal organs may also occur. Clinically, it is characterized by skin induration, thickening, patterned plaques, joint contractures, reduced mobility, and progressive fibrosis of connective tissues. The condition has particular relevance in radiology because its occurrence has been linked to exposure to gadolinium-based contrast agents in patients with impaired renal function (1). NSF may appear within days to months after gadolinium exposure, most commonly within the first 2–3 months, although delayed presentations have also been reported (2).

The first recognized case of NSF was identified in 1997, while its association with gadolinium-based contrast agents was established later, in 2006. Since then, more than 1600 cases have been reported to regulatory authorities worldwide (1). Most cases were observed in patients with acute kidney injury, end-stage renal disease, dialysis dependence, or an estimated glomerular filtration rate below 30 mL/min/1.73 m², particularly after exposure to certain high-risk gadolinium agents (1). These observations led to stricter safety protocols, including routine assessment of renal function before contrast-enhanced magnetic resonance imaging (MRI) and caution in the use of gadolinium-based contrast agents among patients with renal impairment (3,4).

Although these precautions contributed to a marked reduction in NSF cases, they also created practical challenges in clinical imaging. Requirement of pre-imaging renal function assessment may delay urgently needed MRI examinations, increase patient anxiety, add financial burden, and expose patients to repeated needle pricks for laboratory testing. In many clinical settings, such delays may affect timely diagnosis and management, especially in patients who require contrast-enhanced MRI for neurological, musculoskeletal, abdominal, vascular, or oncological indications (3). Therefore, the balance between patient safety and timely diagnostic imaging remains an important issue in radiology practice.

Gadolinium is used in MRI because of its strong paramagnetic properties, which improve lesion detection and tissue characterization. However, free gadolinium is toxic; therefore, it is bound to organic chelating ligands before clinical use. These agents are broadly classified according to their chemical structure as linear or macrocyclic, and according to their charge as ionic or non-ionic. The stability of the gadolinium chelate is clinically important because less stable agents are more likely to release free gadolinium, particularly in patients with delayed renal clearance (4). With improved understanding of NSF risk, gadolinium-based contrast agents have been categorized into different risk groups. Group II agents, including gadobutrol, are considered to have very low NSF risk because of their higher kinetic and thermodynamic stability, especially when used at the standard dose of 0.1 mmol/kg (5-8).

Previous literature has shown that the estimated risk of NSF varies according to the type of contrast agent, renal function status, dose, and repeated exposure. A multicenter cohort study involving patients with stage 3–5 chronic kidney disease who underwent MRI with injected gadobenate dimeglumine or gadoteridol reported a low but measurable estimated risk of NSF in patients with advanced renal disease (9). Other studies have reported variable frequencies of NSF, ranging from 1% to 7%, particularly in populations exposed to older or less stable gadolinium-based agents (10,11). However, data regarding the clinical safety of gadobutrol in patients with stage 3–5 chronic kidney disease remain limited in local clinical practice, where radiology departments often face the dual pressure of ensuring contrast safety while avoiding unnecessary diagnostic delays.

The central research question of the present prospective descriptive follow-up study was whether patients with stage 3–5 chronic kidney disease who undergo contrast-enhanced MRI with standard-dose injectable gadobutrol develop clinical features of nephrogenic systemic fibrosis during follow-up. Addressing this question is important because reliable local evidence may help guide safer and more practical MRI contrast protocols for patients with renal impairment. Therefore, the objective of this study was to determine the frequency of nephrogenic systemic fibrosis among patients with stage 3–5 chronic kidney disease undergoing contrast-enhanced magnetic resonance imaging with injectable gadobutrol.

METHODOLOGY

This was a prospective descriptive follow-up study conducted in the Department of Diagnostic Radiology, Doctors Hospital and Medical Center, Lahore, after approval from the College of Physicians and Surgeons Pakistan, Research Evaluation Unit, under approval reference number CPSP/REU/RAD-2022-088-3940. The study was carried out over a period of eight months, from September 2025 to April 2026. Written informed consent was obtained from all participants before enrollment, and confidentiality of patient information was maintained throughout the study.

A total of 101 patients were included through non-probability consecutive sampling. Patients aged 20–80 years with stage 3–5 chronic kidney disease who were referred from indoor, outdoor, or emergency departments for contrast-enhanced magnetic resonance imaging were evaluated for eligibility. The sample size of 101 was calculated using an expected NSF frequency of 7%, 95% confidence level, and 5% margin of error. Chronic kidney disease was staged according to estimated glomerular filtration rate, with stage 3 defined as eGFR 30–59 mL/min/1.73 m², stage 4 as eGFR 15–29 mL/min/1.73 m², and stage 5 as eGFR <15 mL/min/1.73 m². The eGFR value was obtained from the hospital laboratory record and was calculated using the CKD-EPI equation. Patients were included if they were willing to participate, available for follow-up, and had an eGFR <60 mL/min/1.73 m². Patients with a known allergy to gadobutrol, claustrophobia, metallic implants or other contraindications to MRI, previous fibrotic skin disease suspicious for NSF, or a history of moderate to severe reaction to gadolinium-based contrast media were excluded.

All eligible patients underwent contrast-enhanced MRI using injectable gadobutrol at a standard dose of 0.1 mmol/kg, administered intravenously. The name/brand of the gadobutrol preparation, dose, volume, indication for MRI, anatomical region examined, and baseline renal function were recorded on a structured data collection proforma. Patients were observed for one hour after contrast administration to identify any immediate adverse reaction such as nausea, metallic taste, warmth at the injection site, bronchospasm, hypotension, or anaphylaxis. Dialysis status was

also documented. Patients who were already on maintenance dialysis continued their routine dialysis schedule after MRI, and no additional dialysis session was mandated solely because of gadobutrol administration unless advised by the treating nephrologist.

All patients were followed clinically at 1 month, 3 months, and 6 months after MRI through telephone follow-up. The follow-up focused on symptoms suggestive of nephrogenic systemic fibrosis, including skin thickening, induration, patterned plaques, puckering, joint stiffness, contractures, reduced mobility, or new fibrotic skin changes. Initial follow-up assessment was performed by the radiology team using the structured proforma. Any patient reporting suspicious symptoms was to be recalled for clinical examination and referred to a dermatologist for detailed assessment, clinical scoring, photographic documentation of skin lesions where applicable, and decision regarding deep skin biopsy. The diagnosis of nephrogenic systemic fibrosis was based on the Yale NSF Registry clinical and histopathological criteria, including major and minor clinical features and histological findings where biopsy was clinically indicated (6). Nephrology consultation was considered where renal status, dialysis timing, or progression of kidney disease required clarification.

Data were entered and analyzed using SPSS statistical software. Qualitative variables, including gender, CKD stage, comorbidities, dialysis status, MRI indication, adverse reactions, follow-up status, and development of nephrogenic systemic fibrosis, were summarized as frequencies and percentages. Quantitative variables, including age and eGFR, were reported as mean ± standard deviation. Data were stratified by age, gender, CKD stage, and eGFR category. The chi-square test or Fisher's exact test was used for categorical variables where appropriate, while independent-samples t-test was used to compare mean eGFR between male and female patients. Patients who could not be contacted after repeated follow-up attempts were considered lost to follow-up; they were included in baseline descriptive analysis but were not counted as NSF-free in complete follow-up outcome analysis. A p-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 101 patients with stage 3–5 chronic kidney disease underwent contrast-enhanced magnetic resonance imaging using intravenous gadobutrol at a standard dose of 0.1 mmol/kg. The patients were prospectively enrolled from Doctors Hospital and Medical Center, Lahore, and were followed clinically for up to 6 months after imaging for symptoms suggestive of nephrogenic systemic fibrosis.

The study population included 59 males and 42 females, representing 58.4% and 41.6% of the cohort, respectively. The mean age of the patients was 61.4 ± 10.8 years. Among the included patients, 12 were aged 20–40 years (11.9%), 45 were aged 41–60 years (44.6%), and 44 were older than 60 years (43.6%). Based on renal function, 49 patients had stage 3 chronic kidney disease with eGFR 30–59 mL/min/1.73 m² (48.5%), 36 had stage 4 chronic kidney disease with eGFR 15–29 mL/min/1.73 m² (35.6%), and 16 had stage 5 chronic kidney disease with eGFR <15 mL/min/1.73 m² (15.8%). Diabetes mellitus was present in 74 patients (73.3%), hypertension in 89 patients (88.1%), and 15 patients (14.9%) were on dialysis.

The mean eGFR across the cohort was recorded as 38.2 ± 12.6 mL/min/1.73 m². The mean eGFR among male patients was 39.1 ± 12.4 mL/min/1.73 m², while the mean eGFR among female patients was 36.8 ± 13.0 mL/min/1.73 m². No statistically significant difference in mean eGFR was observed between male and female patients ($p = 0.301$). Across chronic kidney disease stages, the mean eGFR was 47.3 ± 7.1 mL/min/1.73 m² in stage 3, 23.6 ± 4.8 mL/min/1.73 m² in stage 4, and 11.2 ± 2.7 mL/min/1.73 m² in stage 5. Gender-based comparison within each stage did not show statistically significant differences, with p-values of 0.382, 0.291, and 0.417 for stages 3, 4, and 5, respectively.

The most frequent indication for contrast-enhanced MRI was neurological evaluation involving the brain or spine, which was recorded in 42 patients (41.6%). Musculoskeletal indications were present in 26 patients (25.7%), abdominal pathology in 19 patients (18.8%), breast imaging in 8 patients (7.9%), and vascular magnetic resonance angiography in 6 patients (5.9%). Regarding anatomical regions examined, brain MRI was performed in 34 patients (33.7%), spine MRI in 22 patients (21.8%), joints or limbs MRI in 26 patients (25.7%), and abdomen or pelvis MRI in 19 patients (18.8%). No patient underwent whole-body MRI.

Immediate post-contrast monitoring showed that 98 patients (97.0%) had no acute adverse reaction after gadobutrol administration. Mild transient adverse reactions were recorded in 3 patients (3.0%), including metallic taste in 1 patient (1.0%), nausea in 1 patient (1.0%), and warmth at the injection site in 1 patient (1.0%). No moderate or severe adverse reaction was observed. No patient developed anaphylaxis, bronchospasm, hypotension, or required medical intervention after contrast administration.

Follow-up was completed in 95 patients (94.1%), while 6 patients (5.9%) could not be reached after repeated contact attempts and were considered lost to follow-up. Among the patients who completed follow-up at 1, 3, and 6 months, no patient reported symptoms suggestive of nephrogenic systemic fibrosis. No skin induration, rash, thickening, patterned plaques, joint contractures, or mobility restriction consistent with NSF was documented. No patient required dermatology referral for suspected NSF, and no biopsy was recommended because no participant fulfilled clinical criteria for nephrogenic systemic fibrosis. The observed NSF frequency among patients who completed follow-up was 0/95 (0%). When compared with the expected NSF frequency of 7% used for sample size estimation, the absence of

observed NSF cases was statistically significant on exact binomial testing (p = 0.001). The upper 95% confidence limit for the zero-event NSF rate was approximately 3.2% using the rule-of-three approach.

Table 1: Demographic and baseline characteristics of the study population

Variable	Category	Frequency (n)	Percentage (%)
Gender	Male	59	58.4
	Female	42	41.6
Age group	20–40 years	12	11.9
	41–60 years	45	44.6
	>60 years	44	43.6
Mean age	—	61.4 ± 10.8 years	—
CKD stage	Stage 3, eGFR 30–59 mL/min/1.73 m²	49	48.5
	Stage 4, eGFR 15–29 mL/min/1.73 m²	36	35.6
	Stage 5, eGFR <15 mL/min/1.73 m²	16	15.8
Comorbidities	Diabetes mellitus	74	73.3
	Hypertension	89	88.1
	On dialysis	15	14.9

Table 2: Distribution of eGFR across CKD stages and comparison by gender

CKD stage	n (%)	Mean eGFR (mL/min/1.73 m²) ± SD	Male mean ± SD	Female mean ± SD	p-value
Stage 3	49 (48.5%)	47.3 ± 7.1	47.8 ± 6.9	46.6 ± 7.4	0.382
Stage 4	36 (35.6%)	23.6 ± 4.8	24.1 ± 5.0	22.9 ± 4.5	0.291
Stage 5	16 (15.8%)	11.2 ± 2.7	11.5 ± 2.9	10.6 ± 2.3	0.417
Total cohort	101 (100%)	38.2 ± 12.6	39.1 ± 12.4	36.8 ± 13.0	0.301

Table 3: Indications and anatomical regions for contrast-enhanced MRI

Parameter	Subcategory	Frequency (n)	Percentage (%)
Primary indication	Neurological, brain/spine	42	41.6
	Musculoskeletal	26	25.7
	Abdominal pathology	19	18.8
	Breast imaging	8	7.9
	Vascular/MRA	6	5.9
Anatomical region imaged	Brain	34	33.7
	Spine	22	21.8
	Joints/limbs	26	25.7
	Abdomen/pelvis	19	18.8
	Multiple regions/whole-body MRI	0	0.0

Table 4: Immediate adverse reactions following gadobutrol administration

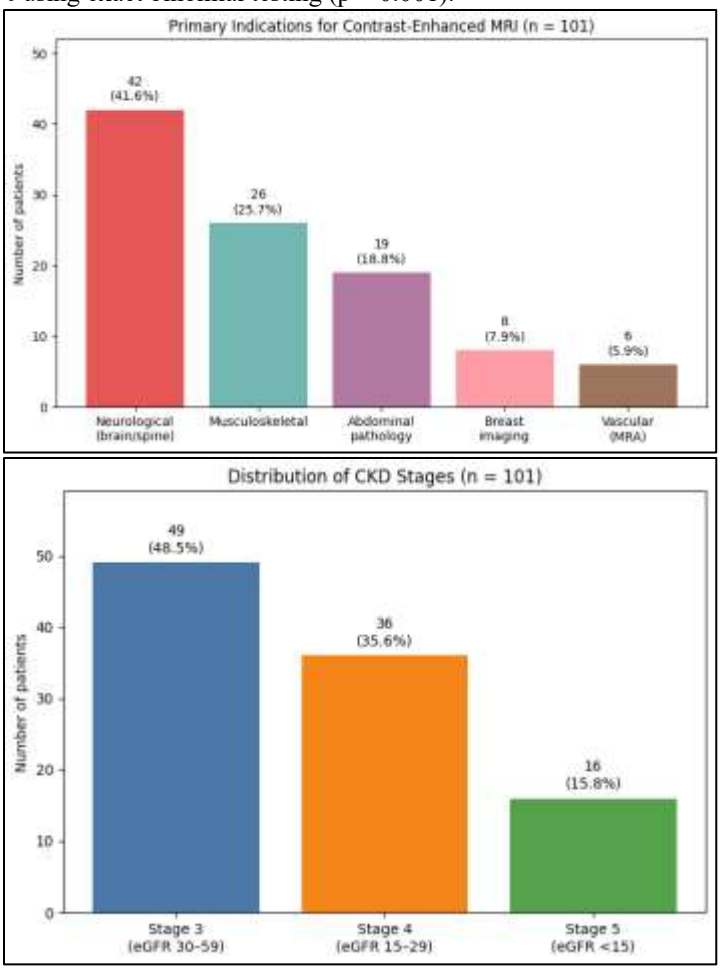
Reaction type	Number of patients	Percentage (%)
No immediate adverse reaction	98	97.0
Any mild transient reaction	3	3.0
Metallic taste	1	1.0
Nausea	1	1.0
Warmth at injection site	1	1.0
Moderate/severe reaction	0	0.0
Anaphylaxis, bronchospasm, or hypotension	0	0.0
Intervention required	0	0.0

Table 5: Follow-up compliance and clinical surveillance for NSF

Outcome	Category	Completed follow-up (n = 95)	Lost to follow-up (n = 6)
Follow-up status	—	95	6
Symptoms suggestive of NSF	Yes	0	Not assessed
	No	95	Not assessed

Skin changes reported	Rash, induration, thickening, plaques, or contractures	0	Not assessed
Dermatology referral/biopsy	Required	0	Not assessed
Final diagnosis of NSF	Confirmed	0	Not assessed

The absence of NSF among patients who completed follow-up was statistically significant when compared with the expected frequency of 7% using exact binomial testing ($p = 0.001$).



DISCUSSION

The present prospective descriptive follow-up study found no clinically suspected or confirmed case of nephrogenic systemic fibrosis among patients with stage 3–5 chronic kidney disease who underwent contrast-enhanced magnetic resonance imaging with standard-dose intravenous gadobutrol. This finding is clinically relevant because the study population included patients with moderate to severe renal impairment, including individuals with stage 4 and stage 5 chronic kidney disease, who are traditionally considered more vulnerable to complications related to gadolinium-based contrast agents. During follow-up at 1, 3, and 6 months, no patient developed skin induration, patterned plaques, joint contractures, restricted mobility, or other clinical features suggestive of NSF. These findings support the observed short-term safety of gadobutrol in this high-risk renal population when used at the recommended diagnostic dose.

The absence of NSF in this cohort is consistent with previous evidence showing that the risk of NSF has markedly declined with the use of more stable gadolinium-based contrast agents and stricter contrast safety protocols. Earlier reports linked most NSF cases to patients with severe renal dysfunction, dialysis dependence, acute kidney injury, or repeated exposure to less stable linear gadolinium agents (12). In contrast, more recent studies involving group II and macrocyclic agents have shown an extremely low risk of NSF, even among patients with advanced chronic kidney disease (3,4). A systematic review and meta-analysis also reported that the pooled risk of NSF after exposure to group II gadolinium-based contrast agents in patients with stage 4 or 5 chronic kidney disease was very low, supporting the safety profile of these agents when used appropriately (13). The findings of the present study therefore align with the growing body of evidence that gadobutrol and other high-stability agents are associated with a negligible observed risk of NSF in routine clinical practice.

The biological explanation for the low NSF risk with gadobutrol is related to its macrocyclic structure and high chelate stability. Gadolinium in its free ionic form is potentially toxic; therefore, it is administered in a chelated form to reduce

dissociation and tissue deposition. Less stable linear agents are more likely to release free gadolinium, particularly when renal clearance is delayed, which may increase the potential for tissue retention and fibrotic responses (14). In patients with markedly reduced estimated glomerular filtration rate, prolonged circulation of gadolinium-based contrast agents may theoretically increase the opportunity for transmetallation, gadolinium release, deposition in tissues, macrophage activation, and recruitment of circulating fibrocytes, all of which have been proposed as mechanisms in the pathogenesis of NSF (9,15). Gadobutrol, being a macrocyclic agent, has greater kinetic and thermodynamic stability, which likely reduces gadolinium dissociation and may explain its very low clinical association with NSF, even in patients with renal impairment (2,16).

The findings also carry practical implications for radiology services. Contrast-enhanced MRI is often essential for accurate diagnosis, disease characterization, treatment planning, and follow-up in neurological, musculoskeletal, abdominal, vascular, and oncological conditions. Excessive fear of NSF may delay clinically indicated MRI examinations, particularly when renal function testing is unavailable or delayed. The present study adds local clinical experience showing that standard-dose gadobutrol was not associated with observed NSF during the follow-up period in patients with stage 3–5 chronic kidney disease. However, these findings should be applied with clinical judgment. The results support careful use of gadobutrol in renal impairment rather than unrestricted use of all gadolinium-based contrast agents. Patient selection, use of the lowest diagnostic dose, avoidance of unnecessary repeated contrast exposure, documentation of renal status, and adherence to institutional and international safety guidance remain important.

The study had several strengths. It was conducted prospectively, included a clearly defined renal-impaired population, used a standard gadobutrol dose of 0.1 mmol/kg, and followed patients after contrast exposure for symptoms suggestive of NSF. The inclusion of patients with stage 4 and stage 5 chronic kidney disease increased the clinical relevance of the findings because this group carries the greatest theoretical concern for NSF. The use of structured follow-up and predefined clinical criteria for suspected NSF also strengthened outcome assessment. In addition, documentation of immediate adverse events allowed the study to report both acute contrast tolerance and delayed clinical surveillance for NSF.

Despite these strengths, the findings should be interpreted with caution. The study was conducted at a single center and had a relatively small sample size for detecting a very rare outcome such as NSF. The absence of observed NSF cases did not completely exclude a very low residual risk. Follow-up was performed partly by telephone, which may have missed subtle skin findings that could have been detected on direct physical examination. Dermatological examination and biopsy were not performed in all participants because no patient developed symptoms suspicious for NSF; however, this approach may limit detection of mild or atypical cases. The follow-up period of 6 months was clinically useful, but some NSF cases in the literature have been reported later, making longer surveillance preferable for stronger risk estimation (17,18). The study also did not include a comparator group exposed to other gadolinium-based contrast agents, so direct comparison between gadobutrol and other agents could not be performed.

Another important consideration is that the study assessed clinically evident NSF rather than gadolinium retention or subclinical tissue deposition. Current evidence suggests that absence of NSF does not necessarily mean absence of gadolinium retention, and the clinical significance of gadolinium deposition remains an area of ongoing investigation (19,20). Therefore, the present findings should be understood as evidence of no observed clinical NSF during follow-up, not as proof that gadobutrol carries absolutely no biological effect or no residual risk in all patients with renal impairment (21,23).

Future research should include larger multicenter cohorts with longer follow-up, preferably extending to at least 12 months or more, to improve detection of delayed NSF manifestations. Studies comparing gadobutrol with other group II macrocyclic agents in patients with stage 4 and stage 5 chronic kidney disease would also be valuable. Further research may also assess the role of dialysis timing, repeated gadolinium exposure, cumulative dose, and standardized dermatological assessment in high-risk patients. Such studies would help refine contrast safety protocols and support evidence-based decisions regarding renal function screening and gadolinium use in patients with chronic kidney disease.

Overall, the present study showed no observed case of nephrogenic systemic fibrosis after standard-dose gadobutrol-enhanced MRI in patients with stage 3–5 chronic kidney disease during the follow-up period. These findings were consistent with published evidence supporting the low NSF risk of macrocyclic and group II gadolinium-based contrast agents. However, because NSF is rare and the study sample was limited, the results should be interpreted as supportive but not definitive evidence of safety. Careful patient selection, standard-dose administration, and continued post-contrast clinical vigilance remain appropriate when gadobutrol is used in patients with impaired renal function.

CONCLUSION

In this prospective descriptive follow-up study, no case of nephrogenic systemic fibrosis was observed among patients with stage 3–5 chronic kidney disease who underwent contrast-enhanced MRI with standard-dose gadobutrol. The findings support the low observed clinical risk of gadobutrol in patients with renal impairment when used appropriately and with standard safety precautions. However, because the study was conducted at a single center and

included a limited sample, broader recommendations regarding omission of renal function assessment should be made cautiously. Larger multicenter studies with longer follow-up are needed to further strengthen the evidence and guide practical contrast-use protocols in high-risk kidney disease patients.

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