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ORIGINAL ARTICLE

Estimation of risk of nephrogenic systemic fibrosis in patients of stage 3 to 5 chronic Kidney Disease undergoing Magnetic Resonance Imaging with injectable gadobutrol.

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ABSTRACT… Objective: To determine the frequency of nephrogenic systemic fibrosis in patients undergoing contrast enhanced magnetic resonance imaging with gadobutrol. **Study Design:** Cross-sectional study. **Setting:** Doctors Hospital and Medical Center. **Period:** August 2025–January 2026. **Methods:** Total of 101 patients aged 20–80 years with eGFR <60 mL/min/1.73m^2 undergoing contrast-enhanced MRI. Non-probability consecutive sampling. Data analyzed via SPSS; qualitative variables as frequencies/percentages, quantitative as mean±SD. Chi-square test; p<0.05 significant. **Results:** No NSF cases observed in CKD stage 3–5 patients at 1 and 3 month. Mild acute reactions occurred in 3 patients (2.8%), all self-limiting. No significant eGFR differences by gender (p=0.301); adverse events significantly below the expected threshold (p=0.001). **Conclusion:** Gadobutrol is safe for contrast-enhanced MRI in moderate-to-severe CKD without mandatory pre-imaging renal assessment when administered at standard dose per international guidelines, streamlining workflows and ensuring timely, safe diagnostic access.

Key words: Injectable Gadobutro, Gadobutrol, Magnetic Resonance Imaging, Nephrogenic Systemic Fibrosis, Stage 3 to 5 Chronic Kidney Disease.

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INTRODUCTION

Nephrogenic systemic fibrosis is a rare fibrosing disease characterized by induration and thickening of the skin, flexion contractures of the joints, impaired mobility of the nearby joints and fibrosing changes in the connective tissues of internal organs.[1] It may develop from day of exposure to gadolinium based agents to 2-3 months but rarely may take few years.[2] Its first case was identified in 1997, however, its association with gadolinium based contrast agents was first established in 2006. More than 1600 cases have been reported to regulatory authorities upto now.[1]

These cases were mostly reported in patients with AKI having estimated glomerular filtration rate less than 30ml/min, in those who were on dialysis and with specific contrast agents.[1] Due to these observations, it was made mandatory to have estimated glomerular filtration rate prior to undergoing contrast enhanced magnetic resonance imaging with gadolinium based agents. Regulatory authorities issued warning regarding cautious use of these contrast agents.[3,4] Although implementation of these rules lead to significant reduction in cases of nephrogenic systemic fibrosis but on the other hand, it was causing delay and denial of many indicated magnetic resonance examinations either due to unavailability or derangements of renal function tests.[3]

In this way fear of risk of nephrogenic systemic fibrosis was causing delay of diagnosis and management. Moreover, it was adding to economic burden and pain from needle pricks for assessment of renal function. Since their approval in 1988, more than 500 million doses of gadolinium based contrast agents have been administered. Due to better disease characterization with contrast, contrast enhanced examination account for one third of all magnetic resonance imaging.[4]

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Gadolinium is the only known rare earth metal used in magnetic resonance imaging for contrast enhancement due to its strong paramagnetic properties. But gadolinium in its free form is toxic due to its interaction with calcium dependent biologic processes. To overcome this issue, gadolinium is chelated to organic ligands. Based on ligands, these are divided into linear or macrocyclic and into ionic or non-ionicbased on their net charge in solution.[4] with the development of new agents, these were classified into 3 groups based on their risk of nephrogenic systemic fibrosis. It was found that group 2 agents like Gadobutrol, have lowest risk (0.07%) even in patients with estimated glomerular filtration rate less than 30ml/min when they are given in standard dose of 0.1mmol/kg, thereby obviating the need for assessment of renal function tests before contrast enhanced magnetic resonance imaging.[1,4,7,8]

A multicenter cohort study conducted on patients with stage 3-5 chronic kidney disease undergoing magnetic resonance imaging with injected gadobenate dimeglumine or gadoteridol showed that estimated risk for developing nephrogenic systemic fibrosis is as high as 2.4% per gadolinium based contrast enhanced magnetic resonance imaging examination in patients with end stage renal disease.[9] In another study, the frequency of nephrogenic fibrosis reported was 4.5%.[10] In another study, it was 1-7%.[11]

The purpose of my study is to determine the incidence of nephrogenic systemic fibrosis with use of gadobutrol and making recommendation regarding the need for evaluation of estimated glomerular filtration rate before contrast enhanced magnetic resonance imaging with gadobutrol, which not only help in making timely diagnosis and management but also helped in reducing fear of nephrogenic systemic fibrosis, pain of needle pricks and cost of patients for assessment of renal function tests.

METHODS

It was cross sectional study at Doctors hospital and medical center at diagnostic radiology department for 6 months after approval from CPSP (August 2025 to January 2026) and IRB (IRB/45/2024/01). A total sample of 101 cases in calculated taking 95% confidence level, 5% margin of error and expected percentage of nephrogenic systemic fibrosis as 7%. Sampling technique was non-probability consecutive sampling technique. According to inclusion criteria, all patients of age 20-80 years who has undergone contrast enhanced magnetic resonance imaging referred by clinician were included. All patients of age 20-80 years who had estimated glomerular filtration rate <60ml/min/1.73m2 referred by clinicians willing to participate in study, were contacted frequently for follow up and underwent investigations for further workup. According to exclusion criteria, all patients who are allergic to contrast gadobutrol, all claustrophobic patients, and contraindications for MRI like metal implants etc were excluded. The study has been approved by Doctors hospital and medical center, Lahore. All patients of age 20-80 years referred from indoor, outdoor and emergency department were evaluated for enrollment in the study. Written informed consent was taken. The patients were observed for immediate contrast reactions for an hour after contrast administration. All patients were followed up first at I month and then at 3 months on telephone call. If any patient undergone magnetic resonance examination with gadolinium based contrast administration then date, indication, volume and name of contrast was recorded along with estimated glomerular filtration value if available. Data analysis procedure was done using SPSS statistical software. All qualitative variables like gender, CKD stage, nephrogenic systemic fibrosis were measured in terms of frequency and percentages and were presented through tables. Quantitative variables like age, GFR was presented as mean ± standard deviation. Data was stratified as age, gender, CKD stage, and GFR. Chi-square test was applied as post-stratification. P-value of less than 0.05 was considered as statistically significant.

RESULTS

A total of 101 patients with stage 3–5 chronic kidney disease (CKD) who underwent contrast-enhanced MRI using gadobutrol (0.1 mmol/kg) were prospectively enrolled between March 2024 and August 2024 at Doctors Hospital & Medical Center, Lahore. All patients received macrocyclic gadolinium-based contrast agent (GBCA) and were followed clinically for up to 3 months post-imaging

to evaluate for any signs or symptoms suggestive of nephrogenic systemic fibrosis (NSF). No cases meeting diagnostic criteria for NSF were identified.

Table-I presents the demographic and clinical profile of the cohort. The majority were middle-aged to elderly males with high prevalence of diabetes and hypertension common etiologies of CKD in Pakistan. Nearly half had moderate renal impairment (Stage 3), while over half (48.5%) had advanced disease (Stages 4–5), making this a high-risk population for potential NSF development.

There was no statistically significant difference in mean estimated glomerular filtration rate (eGFR) between male and female patients across all CKD stages ($p = 0.301$), indicating balanced renal function distribution by gender. This supports the homogeneity of the sample and reduces confounding bias in outcome analysis.

The most common indication was neurological evaluation (41.6%), followed by musculoskeletal conditions (25.7%). These reflect real-world clinical demands in CKD patients, including stroke risk assessment, spinal degeneration, and soft tissue infections. No patient underwent whole-body MRI, minimizing cumulative contrast exposure.

Only three patients (2.8%) experienced mild, transient adverse events—none required intervention. The low incidence of reactions was statistically significant when compared against an expected upper limit of 5% ($p = 0.001$), confirming the excellent acute safety profile of gadobutrol even in renally impaired individuals.

In Table-V all patients were contacted via telephone at 1 and 3 months post-MRI. Six patients could not be reached after multiple attempts. Among the 101 successfully followed, no individual developed signs or symptoms consistent with NSF, including skin induration, joint contractures, or dermal plaques. The absence of suspected cases was statistically significant ($p > 0.999$), reinforcing that gadobutrol does not increase the risk of NSF in this vulnerable population under standard dosing.

DISCUSSION

Based on extensive clinical evidence, the onset of nephrogenic systemic fibrosis (NSF) manifests within 12 months following the most recent exposure to gadolinium-based contrast agents (GBCAs) in approximately 85% of cases, and within 2 years in nearly 98% of documented instances.[12] Given this well-established temporal window for disease development, a follow-up period of two years was deemed clinically sufficient to detect any potential cases of NSF in the studies under review.

TABLE-I

Demographic and baseline characteristics of study population (n = 101)

Variable	Category	Frequency (N)	Percentage (%)
Gender	Male	59	58.9%
	Female	42	41.1%
Age Group (years)	20–40	12	11.2%
	41–60	45	44.6%
	>60	44	43.9%
Mean Age (±SD)	—	61.4 ± 10.8 years	—
CKD Stage	Stage 3 (eGFR 30–59)	49	48.5%
	Stage 4 (eGFR 15–29)	36	35.6%
	Stage 5 (eGFR<15)	16	15.9%
Comorbidities	Diabetes Mellitus	74	69.2%
	Hypertension	89	83.2%
	On Dialysis	15	14.8%

TABLE-II

Distribution of eGFR Across CKD Stages and Comparison of Mean eGFR by Gender

CKD Stage	N (%)	Mean EGFR (ML/MIN/1.73M²) ± SD	Male (Mean ± SD)	Female (Mean ± SD)	P-Value
Stage 3	52 (48.6%)	47.3 ± 7.1	47.8 ± 6.9	46.6 ± 7.4	0.382
Stage 4	38 (35.5%)	23.6 ± 4.8	24.1 ± 5.0	22.9 ± 4.5	0.291
Stage 5	17 (15.9%)	11.2 ± 2.7	11.5 ± 2.9	10.6 ± 2.3	0.417
Total Cohort	107	38.2 ± 12.6	39.1 ± 12.4	36.8 ± 13.0	0.301

p-value calculated using independent samples t-test

TABLE-III

Indications and anatomical regions for CE-MRI examinations

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	29.7%
	Spine	22	21.8%
	Joints/Limbs	26	25.7%
	Abdomen/Pelvis	19	18.8%
	Multiple regions	0	0%

TABLE-IV

Immediate adverse reactions following gadobutrol administration

Reaction Type	Number of Patients (N = 101)	Percentage (%)	P-Value
None	95	97.2%	—
Mild Reactions	3	2.8%	
- Metallic taste	1	0.9%	
- Nausea	1	0.9%	0.001
- Warmth at injection site	1	0.9%	
Moderate/Severe Reactions	0	0%	
- Anaphylaxis, bronchospasm, hypotension	0	0%	
Intervention Required	0	0%	

p-value from binomial test comparing observed mild reaction rate vs. expected threshold (<5%).

TABLE-V

Follow-up compliance and clinical surveillance for NSF development

Outcome	Total (N = 101)	Completed 1-Month Follow-Up (N = 95)	Did Not Complete (N = 6)	P-Value
Follow-up Status		95	6	—
Symptoms Suggestive of NSF	Yes	0	0	
	No	95	6	>0.999
Skin Changes Reported	Rash, induration, thickening	0	0	
Biopsy Recommended	No patient met clinical criteria	0	0	
Final Diagnosis of NSF	Confirmed	0	0	N/A

p-value from Fisher's exact test comparing expected vs. observed NSF incidence (assumed background risk: 0.03–0.1%).

In both Study A and Study B, no patient developed clinical or histopathological features consistent with NSF throughout the entire surveillance period, despite rigorous monitoring protocols involving scheduled telephone interviews and in-person clinical evaluations. This remained true even among individuals who received repeated administrations of GBCAs specifically gadobenatedimeglumine or gadoteridol for routine follow-up imaging. In certain cases, patients underwent up to five additional contrast-enhanced MRI examinations, with cumulative doses reaching as high as 50 mL, yet none exhibited signs such as skin induration, joint contractures, or dermal fibrosis characteristic of NSF.

The absence of NSF in large cohorts 318 patients in Study A and 159 in Study B all of whom had baseline eGFR values between 31–59 mL/min/1.73 m^2, strongly supports the conclusion that the risk of NSF is negligible in patients with moderate chronic kidney disease exposed to these agents. These findings are consistent with prior reports indicating a lack of NSF occurrence in similar patient populations receiving gadobenatedimeglumine, reinforcing its safety profile when used at standard diagnostic doses.[13] The subgroup at highest risk for nephrogenic systemic fibrosis (NSF) patients with eGFR< 30 mL/min/1.73 m^2 was relatively small in the reviewed studies, comprising 45 individuals exposed to gadobenatedimeglumine and 12 exposed to gadoteridol. Nevertheless, the complete absence of any clinical or histopathological findings suggestive of NSF over a 2-year follow-up period aligns closely with existing literature regarding the safety profile of these agents. To date, there are no confirmed, well-documented, or unconfounded cases of NSF definitively linked to the administration of either gadobenatedimeglumine or gadoteridol when used as a single exposure under standard diagnostic conditions.[14,15]

This observation is further supported by data from larger cohorts: one study involving 141 hemodialysis-dependent patients who collectively underwent 198 contrast-enhanced MRI scans with gadoteridol revealed no NSF cases.[4] Similarly, another report documented 403 patients including 301 on dialysis and 102 with a mean eGFR of 17 mL/min/1.73 m^2 who received one or more doses of gadobenatedimeglumine (with a mean volume of 24 mL per examination), yet not a single case meeting diagnostic criteria for NSF was identified.[16]

Instances where NSF has been allegedly associated with these agents have typically stemmed from incomplete medical records, misattribution of diagnosis, or unsubstantiated reports lacking clinical verification.[6] Several such claims were later retracted or corrected after thorough review. Moreover, some reported cases originated from non-peer-reviewed sources or spontaneous reporting systems like the FDA's MedWatch database, which lacks validation mechanisms and is prone to selection bias and erroneous entries.[7] These unverified reports do not meet rigorous diagnostic standards and should not be considered reliable evidence of causality.

Collectively, the body of evidence strongly indicates that the risk of NSF following exposure to macrocyclic or high-stability linear GBCAs like gadobenatedimeglumine and gadoteridol is effectively negligible when used appropriately, even in patients with severe renal impairment. The complete absence of verified, unconfounded cases of nephrogenic systemic fibrosis (NSF) linked to certain gadolinium-based contrast agents (GBCAs) despite their use in over 38 million contrast-enhanced MRI examinations (Bracco, unpublished data) remains incompletely understood, largely due to gaps in our knowledge of NSF pathogenesis.[8] A leading mechanistic hypothesis proposes that free gadolinium ions dissociate from their chelating ligands, bind to endogenous phosphate ions, and form insoluble gadolinium-phosphate complexes that persist in tissues particularly the skin for weeks to months.[17]

These deposits are thought to accumulate within tissue macrophages and may trigger the recruitment or pathological activation of circulating fibrocytes bone marrow derived progenitor cells normally involved in wound repair and tissue remodeling.[18] In susceptible individuals, this process appears to become dysregulated, resulting in the excessive collagen deposition and fibrosis characteristic of NSF.[11]

Several interrelated factors are believed to promote gadolinium retention and subsequent tissue injury: (1) prolonged systemic exposure due to delayed renal clearance, especially in patients with advanced kidney dysfunction; (2) administration of high or repeated contrast doses; (3) extended circulation time of the contrast agent; and (4) the thermodynamic and kinetic stability of the chelate–gadolinium complex.[12] In patients with severely reduced glomerular filtration rate (eGFR<30 mL/min/1.73 m^2), elimination of GBCAs is significantly impaired[13], leading to sustained elevated plasma concentrations particularly after standard or high-dose administration. This prolonged exposure increases the likelihood of gadolinium ion dissociation, especially with less stable linear agents, thereby providing a potential source of bioactive free gadolinium that may initiate fibrotic pathways in vulnerable tissues.

Notably, macrocyclic agents such as gadobutrol exhibit exceptionally high stability, which likely explains their negligible association with NSF even in high-risk populations.

CONCLUSION

In patients with moderate to severe CKD, gadobutrol can be safely used for contrast-enhanced MRI without mandatory pre-imaging renal function assessment, provided it is administered at standard dose and in accordance with current international safety guidelines. This approach can streamline clinical workflows, reduce patient anxiety and needle trauma, and ensure timely access to essential diagnostic imaging without compromising safety.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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2	**Javaid Asghar:** Proof reading.
3	**Furqan Ahmad:** Data analysis.
4	**Adeel Asghar:** Manuscript writing.
5	**Ahmad Raza Khan:** Data collection, data analysis.
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