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Risk of Nephrogenic Systemic Fibrosis Is Low in Patients With Chronic Liver Disease Exposed to Gadolinium-Based Contrast Agents

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Abstract

Purpose—To determine the risk of nephrogenic systemic fibrosis (NSF) in a cohort of patients with chronic liver disease.

Materials and Methods—This retrospective, Institutional Review Board (IRB)-approved, Health Insurance Portability and Accountability Act (HIPAA)-compliant study was performed at a single tertiary liver center. The study cohort comprised 1167 patients with chronic liver disease followed in a liver clinic and exposed to gadolinium-based contrast agents (GBCAs) between February 2004 and October 2007. A retrospective review of medical records was performed. For each patient, data were collected on demographics, history of GBCA exposure, presence of purported risk factors for NSF, and histopathological evidence of NSF.

Results—Of the 1167 patients with chronic liver disease, 58% ($n = 678$) had cirrhosis. The patients had a total of 2421 separate GBCA exposures. Fifty-five percent ($n = 646$) had a single exposure, 19% ($n = 218$) had two exposures, and 26% ($n = 303$) had three or more exposures. Seventy-two percent ($n = 843$) of patients had renal insufficiency, 25 patients (2.1%) had hepatorenal syndrome, 80 patients (6.8%) were in the perioperative liver transplant period, and 49 patients (4.2%) had one or more additional risk factors for NSF. None of the 1167 patients developed NSF.

Conclusion—Chronic liver disease does not appear to be a significant risk factor for NSF.

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Keywords

nephrogenic systemic fibrosis; chronic liver disease

Nephrogenic Systemic Fibrosis (NSF) is a rare systemic disease primarily reported in patients with severe renal impairment and exposure to gadolinium-based contrast agents (GBCAs). The first cases of NSF were identified in 1997 and published in a case series of 15 hemodialysis patients in 2000 (1). The link of NSF to GBCA exposure was first reported in two case series in 2006 (2,3). Subsequent studies have isolated gadolinium, a highly toxic rare earth metal, in affected soft tissue and bone of NSF patients (4–6). Following the initial reports, a rush of articles ensued documenting the association between GBCA exposure and NSF, with more than 1100 cases reported globally as of 2009 (7).

In June of 2006 the United States Food and Drug Administration (FDA) released a public health advisory cautioning against the use of GBCAs in patients requiring dialysis or having glomerular filtration rates (GFR) <15 mls/min/1.73m² (8). The following year, May 2007, the FDA ordered the addition of a “black box warning” to GBCAs and expanded the prior advisory to include patients with GFR <30 mls/min/1.73m², patients with any degree of renal insufficiency due to hepatorenal syndrome, and patients in the perioperative liver transplantation period (9). Although the expanded black box warning referred specifically to patients with hepatorenal syndrome and those in the perioperative liver transplant period, it raised concern that chronic liver disease in general may confer risk of NSF.

In September 2010 the FDA removed explicit mention of liver disease from the required black box warning. This decision was consistent with the available literature as summarized by a systematic review by Mazhar et al published in December 2009 (10). Nevertheless, some concerns regarding the use of GBCA in patients with chronic liver disease may have persisted. The review by Mazhar et al was compiled exclusively from published case series and reports and it was inherently limited by the paucity of liver-specific data provided in each publication. Furthermore, as the case reports included clinical information only on patients who contracted NSF, data were not available on the entire population of patients with chronic liver disease exposed to GBCA, including those who did not contract NSF, and so the per-patient risk could not be assessed. To better understand the risk of NSF in such patients, studies are needed that include the entire cohort of GBCA-exposed patients with chronic liver disease, not just the subset who developed the disease. The purpose of this retrospective single-center study was to estimate the risk of NSF development after GBCA exposure in patients with chronic liver disease, stratified by severity of renal disease and other purported risk factors (10,12–15).

Materials and Methods

Design

This single-center retrospective, longitudinal, observational cohort study was performed following approval by the Institutional Review Board with waiver of informed consent. Compliance with the Health Insurance Portability and Accountability Act was maintained

throughout the study. The selected study period was between February 2004 and October 2007. This time period was selected for the following reasons: First, prior to 2004, electronic radiology records were not searchable at our institution, a factor that would hamper efforts to collect relevant study data. Second, prior to October 2007 our institution did not restrict the use of GBCAs in patients with risk factors for NSF; these agents were assumed to be safe and routinely were administered during contrast-enhanced magnetic resonance imaging (MRI) examinations regardless of patients' risk factors for NSF. In 2007, our institution implemented a policy to prevent NSF in light of emerging evidence that linked GBCAs exposure to NSF; GBCA use was virtually eliminated in patients with stage 4 or 5 chronic kidney disease (estimated glomerular filtration rate [eGFR] <30 ml/min/1.73 m²) and became less frequent in patients with stage 3 chronic kidney disease ($30 \leq \text{eGFR} < 60$ ml/min/1.73 m²).

Selection of Study Cohort

A list of all patients seen in a hepatology clinic during the study period was generated from the liver center's database. Separately, a list of all patients imaged with GBCAs during the study period was generated from the radiology database. The two lists were cross-referenced to yield a list of hepatology clinic patients imaged with GBCAs between February 2004 and October 2007. Electronic medical records of these patients were retrospectively reviewed, as described further below. Using the data collected by this review, we applied the following eligibility criteria to yield the final study cohort of patients:

Inclusion criteria: electronic medical record documentation of chronic liver disease, defined as cirrhosis from any etiology, chronic hepatitis B and/or C viral infection, alcoholic or nonalcoholic fatty liver disease, veno-occlusive disease, cholestatic liver disease, and autoimmune hepatitis.

Exclusion criteria: the only indication for MRI or for hepatology clinic visit was assessment of focal liver disease—such as hepatocellular adenoma, hepatic hemangioma, focal nodular hyperplasia, or cysts—and the absence of documentation in the electronic medical record of chronic liver disease.

The final study cohort consisted of patients with documented chronic liver disease who had undergone MRI with GBCAs between February 2004 and October 2007.

Data Collection

Electronic medical records from February 2003 to October 2008 for each patient in the study cohort were retrospectively reviewed by three authors (D.S.S., Z.W.F., S.M.M.) under the supervision of the first author (E.S.) and the senior author (C.B.S.). Reviewed medical records included patient clinic notes, consult reports, operative reports, discharge summaries, laboratory data, pathology reports, and imaging reports. The following data were extracted from this review and entered manually into an electronic spreadsheet.

Patient Characteristics—Demographic information (age at time of first GBCA exposure, sex, and ethnicity), etiology of liver disease, presence of cirrhosis, diagnosis of HCC, and history and date(s) of liver transplantation were recorded.

GBCA Exposure—For each GBCA exposure, the GBCA formulation, dose, and date of administration were recorded from the radiology report. If the formulation of GBCA was not documented in the report, it was recorded as “unknown.” If the dose of GBCA was omitted, the standard dose for the particular type of imaging examination at our institution during the study period was used as an estimate. For each patient, the total number of separate GBCA exposures, cumulative volumetric dose of GBCA (in mL), cumulative weight-adjusted gadolinium dose (in mmol/kg of body weight), and time interval between each separate GBCA exposure were determined. To estimate the cumulative weight-adjusted gadolinium dose, the documented weight of each patient most contemporaneous to the first GBCA exposure was used, with a maximum of 1 year between the dates of GBCA exposure and weight measurement. For patients in whom weight was not documented in the electronic medical record within 1 year of the first GBCA exposure, the cumulative weight-adjusted gadolinium dose was not calculated. The type of MRI examination association with each GBCA exposure was recorded.

NSF Risk Factors—To characterize the presence and severity of renal disease at the time of each GBCA exposure, the serum creatinine value most contemporaneous to each GBCA exposure was recorded, as was the time interval between the corresponding blood draw and the GBCA exposure. The eGFR was calculated from each serum creatinine value using the formula based on the Modification of Diet in Renal Disease (MDRD) study (11). If a serum creatinine value was not documented within 1 year of any given GBCA exposure, eGFR was not calculated for that exposure. Additionally, each patient's dialysis requirement at the time of each GBCA exposure was recorded.

For each GBCA exposure, data were also collected for the presence of the following purported risk factors for NSF (10,12–15): presence of hepatorenal syndrome at the time of exposure (based on CPT code and verified by electronic record review), exposure in the peri-operative liver transplantation period (defined for this study as 6 months before to 6 months after transplantation, as this is a time period in which patients may be severely ill and at high risk for hepatic and extrahepatic complications of liver disease), exposure within 6 weeks of the diagnosis of a thrombotic event, and exposure within 6 weeks of the diagnosis of other inflammatory event(s). A thrombotic event was defined as any major venous or arterial thrombosis resulting in hospitalization or occurring in a hospitalized patient and included deep vein thrombosis, portal vein thrombosis, and mesenteric artery thrombosis. An inflammatory event was defined as a major inflammatory condition—such as pancreatitis, cholangitis, osteomyelitis, meningitis, pneumonia, and pyelonephritis—resulting in hospitalization or occurring in a hospitalized patient and meeting criteria for systemic inflammatory response syndrome (SIRS) or sepsis.

Outcome

To identify patients who developed NSF, all dermatopathology reports from February 2003 through June 2013 in cohort patients were reviewed. Additionally, manual review of clinic notes, consult reports, operative reports, and discharge summaries from February 2003 to October 2008 for mention of NSF or nephrogenic fibrosing dermopathy was performed. The electronic medical record through June 2013 was also queried to generate for each patient in

the cohort the date of the last clinic note or hospitalization and whether the patient was, as of June 2013, deceased or lost to follow-up. A record was considered sufficient for follow-up if it occurred more than 60 days after exposure to GBCA, in order to allow symptoms to manifest (12). Lastly, the hospital electronic medical record was queried with ICD-9 codes from February 2003 to June 2013, to generate all cases of NSF seen at our institution. This list was cross-referenced against patients in our cohort.

Data Analysis

Data were summarized descriptively on a per-exposure basis or a per-patient basis, as appropriate. Some of the data were stratified by eGFR value or dialysis requirement at the time of GBCA exposure. We used eGFR thresholds (<90 , <60 , <30 , <15 ml/min/1.73m²) commonly used in staging of chronic kidney disease (16) as well as an eGFR threshold (<40 ml/min/1.73³) for which the ACR Committee on Drugs and Contrast Media recommends caution in the use of GBCAs (17). Finally, we identified all patients who met the FDA's 2007 expanded "black box warning" specific to liver disease (i.e., any degree of renal insufficiency due to hepatorenal syndrome or in the perioperative liver transplantation period) that were not already considered at risk by virtue of having eGFR <30 mls/min/1.73m². The upper bound risk estimates for developing NSF after exposure to gadolinium in subgroups of patients stratified by renal function and purported risk factors for NSF were calculated using the 95% Agresti-Coull binomial confidence intervals (18).

Results

Patient Characteristics

From February 2004 to October 2007, 1167 patients with chronic liver disease underwent 2421 GBCA-enhanced MRI examinations (2334 [96.4%] abdomen, 3 [0.1%] pelvis, 75 [3.1%] brain or spine, 7 [0.3%] musculoskeletal, 2 [0.1%] thoracic). Patient characteristics are summarized in Tables 1 (demographics) and 2 (liver disease data). Mean age at first GBCA exposure was 53.5 years (range 12–87 years) and 57.8% of the population was male. The three most common etiologies of liver disease were hepatitis C virus infection, alcoholic liver disease, and hepatitis B virus infection. In all, 239 patients (20.5%) had liver disease due to more than one cause. Over half the patients had cirrhosis, and 143 (12.3%) underwent liver transplantation.

Documented GBCA Exposures

Data on GBCA exposures are summarized in Table 3. The majority of patients (646/1167, 55.4%) had a single documented GBCA exposure, 218 patients (18.7%) had two exposures, and 303 patients (26%) had three or more exposures to GBCA (maximum, 10 exposures) during the study period. Nineteen patients (1.6%) had two exposures on the same calendar day or within 2 consecutive calendar days, and one patient had three exposures within 3 consecutive calendar days. Of the 521 patients (44.6%) with multiple GBCA exposures, the mean time interval between exposures was 194.7 days (range, 0–1087 days). Across all patients, the average single dose of GBCA volumetrically was 19.8 mL. The average cumulative dose of GBCA volumetrically was 39.0 mL per patient (range, 10–200 mL). In the 1014 subjects in whom weight was recorded within 1 year of the first GBCA exposure,

the average single weight-adjusted dose of gadolinium was 0.12 mmol/kg (range 0.05–0.27 mmol/kg) and the average cumulative weight-adjusted gadolinium dose was 0.26 mmol/kg (range 0.05–2.1 mmol/kg) (Table 6). Of 2421 exposures, the GBCA formulation was documented in 1761 (72.7%). Of the 1761 documented formulations, gadobenate dimeglumine was used in 1145 (65.0%) and gadoversetamide in 607 (34.5%). Of the exposures to gadobenate dimeglumine, 33 occurred at eGFR <30 ml/min/1.73m² and 7 occurred at eGFR <15 ml/min/1.73m², none at doses greater than 0.2 mmol/kg. Of the exposures to gadoversetamide, 18 occurred at eGFR <30 ml/min/1.73m² (14 of these at doses greater than 0.1 mmol/kg), and seven occurred at eGFR <15 ml/min/1.73m² (6 of these at doses greater than 0.1 mmol/kg). In all, 675 (57.8%) patients were exposed only to gadobenate dimeglumine, 301 (25.8%) only to gadoversetamide, 5 (0.4%) only to gadopentetate dimeglumine, and 186 (15.9%) to more than one agent. No patient had a documented exposure to gadodiamide or gadoteridol, as these agents were not on the institutional formulary during the study period.

Risk Factor Analysis

In all, 324 (27.8%) patients had eGFR $\geq$ 90 ml/min/1.73m² at the time of all GBCA exposures; in these patients, the median time interval from serum collection (for eGFR measurement) to exposure was 18 days (range, 0–974 days) and total number of separate exposures was 2,421. A total of 843 patients (72.2%) had eGFR <90 ml/min/1.73m² at the time of one or more GBCA exposures; in these patients, the median time interval from serum collection to exposure was 2 days (range, 0–442 days). Figure 1 plots for these 843 patients the number of GBCA exposures in which eGFR <90 ml/min/1.73m² or in which the patient was on dialysis, stratified by the severity of renal disease. Renal disease severity was defined by eGFR threshold values (<90, <60, <40, <30, <15 ml/min/1.73m²) or hemodialysis requirement (16). For data organized on a per-patient, rather than per-exposure, basis, in order to conservatively approximate the patient's renal function for those with more than one GBCA exposure, the highest eGFR value was used to determine the eGFR stratum. For example, a patient with three GBCA exposures with corresponding eGFRs of 12, 18, and 28 would be plotted as having three exposures at an eGFR threshold of <30 ml/min/1.73m². Similarly, only patients on dialysis at the time of every GBCA exposure would be plotted as being on dialysis. Thus, Fig. 1 underreports the severity of renal disease in patients with GBCA exposures at different eGFR thresholds.

Table 4 summarizes the severity of renal disease on a per-exposure basis. There were a total of 1129 (46.6%) exposures in the setting of eGFR <90 ml/min/1.73m², including 95 (3.9%) in the setting of severe renal failure (eGFR <15 ml/min/1.73m² or dialysis requirement).

As summarized in Fig. 2, 100 patients (8.6%) had an eGFR <90 ml/min/1.73m² as well as at least one additional purported risk factor (perioperative liver transplant period, hepatorenal syndrome, inflammatory event, and thrombotic event) at the time of GBCA exposure, and 12 patients (1%) had severe renal failure (eGFR <15 ml/min/1.73m² or dialysis requirement) as well as an additional purported risk factor. Additional details on these additional risk factors are provided in Table 5.

Sixty-seven patients (5.7%) met FDA's expanded "black box warning" specific to liver patients (any degree of renal insufficiency due to hepatorenal syndrome or in the perioperative liver transplantation period) that were not already considered at risk by virtue of having $\text{GFR} < 30 \text{ mls/min/1.73m}^2$. Of these, 24 patients (2.1%) had hepatorenal syndrome with $30 \text{ eGFR} < 90 \text{ mls/min/1.73m}^2$ and 49 patients (4.2%) were in the perioperative liver transplantation period (median time interval between transplantation and exposure, -53 days; range, -165 to 159 days) with $30 \text{ eGFR} < 90 \text{ mls/min/1.73m}^2$. Six patients (0.5%) both had hepatorenal syndrome and were in the perioperative liver transplantation period with $30 \text{ eGFR} < 90 \text{ mls/min/1.73m}^2$.

Duration of Follow-up

In all, 955 patients (81.8%) had follow-up clinic visits or hospitalizations (mean 1505 days; range 61 to 3400 days); 64 patients (5.5%) were dead.

Outcome

Forty-eight patients (4.1%) in the study cohort had dermal biopsies between 2003 and 2013 for evaluation of skin conditions after GBCA exposure. The dermatopathology reports described a fibrotic process in 11 patients, none consistent with NSF, and nonfibrotic processes in the rest. ICD-9 code search through June 2013 revealed four patients with the diagnosis of NSF seen at our institution, none of whom were in our cohort. Additionally, there was no documented diagnosis of NSF or suggestion that a diagnosis of NSF was made or was pending at an outside institution in the reviewed clinic notes, consult reports, operative reports, or discharge summaries. As there were no documented cases of NSF in our cohort, the observed risk of NSF after GBCA exposure in our cohort of patients was 0%.

Based on this observed frequency, the upper 95% confidence estimate for the risk of developing NSF in patients with chronic liver disease exposed on one or more occasions to GBCA—using the formulations and at the doses described above—is 0.4% overall ($n = 1167$), 0.55% in those ($n = 843$) with $\text{eGFR} < 90 \text{ mls/min/1.73m}^2$, 1.5% in those ($n = 306$) with $\text{eGFR} < 60 \text{ mls/min/1.73m}^2$, 2.8% in those ($n = 162$) with $\text{eGFR} < 40 \text{ mls/min/1.73m}^2$, 5.5% in those ($n = 80$) with $\text{eGFR} < 30 \text{ mls/min/1.73m}^2$, 6.4% in those ($n = 44$) with $\text{eGFR} < 15 \text{ mls/min/1.73m}^2$, and 6.5% in those ($n = 67$) who meet the FDA's expanded black box warning and have $30 \text{ eGFR} < 90 \text{ mls/min/1.73m}^2$. The upper 95% confidence estimates for developing NSF after exposure to GBCAs in subgroups of patients with additional purported risk factors for NSF are summarized in Table 6.

Discussion

This retrospective study evaluated the risk of NSF in 1167 patients with chronic liver disease exposed to 2421 doses of GBCA. None of the patients in the study cohort were diagnosed with NSF. These results suggest that chronic liver disease is not a strong independent risk factor for NSF development, in contrast to early reports on NSF that suggested a link between liver disease and NSF development (14,19) and the 2007 FDA warning, which implied that liver disease may be contributory (9). Our results are consistent with more recent literature (20–22) and the latest edition of the ACR Manual on Contrast Media (17),

neither of which support the notion that patients with chronic liver disease are at risk of NSF in the absence of severe renal failure. The study also justifies the FDA's decision in September 2010 to remove explicit mention of liver disease in the black box warning instituted in May 2007.

The patients in our study cohort had a broad spectrum of liver disease severity, liver disease etiology, associated comorbidities, and purported risk factors. The cohort's distribution of liver disease etiologies are representative of the distribution of liver disease etiologies in the West in general (23,24), although the proportion of patients with nonalcoholic liver disease in our cohort was smaller than might be expected. Severity of liver disease in the study cohort was substantial. More than 50% of patients had a diagnosis of cirrhosis, and many underwent liver transplantation. The patients also had a substantial burden of renal disease and 67 (5.7%) met FDA's May 2007 extended black box warning pertaining to liver patients. The study cohort also had other purported risk factors for NSF development including exposure to higher-than-approved doses of GBCA, multiple exposures to GBCA, and exposures in association with inpatient status, major inflammatory events, and thrombotic events (12,14,15).

Although our study is underpowered to draw definitive conclusions, the results are consistent with two recently published case series of liver transplant recipients exposed to GBCA in the peritransplant period ($n = 327$ and $n = 656$), none of whom developed NSF (20,25). Similarly, a systematic review of 335 cases of NSF reported in the medical literature found that, with a single exception, all patients with liver disease who developed NSF did so in the setting of severe renal insufficiency at baseline prior to GBCA exposure (10,12). This single known case of NSF in a patient with liver disease without known underlying severe renal insufficiency prior to first exposure to GBCA was highly atypical. This was a liver transplant recipient with severe postoperative complications of hepatic artery thrombosis, graft failure, bile leak, peritonitis, and internal hemorrhage. While the patient did not have known renal failure prior to first GBCA exposure, the patient developed acute kidney injury attributed to hepatorenal syndrome, with progressive decline of eGFR from 69.6 to 34.6 mL/min/1.73 m² over a 10-week period during which the patient received four double-dose (cumulative dose, 0.76 mmol/kg) injections of gadodiamide. Given the presence of multiple other risk factors for NSF development (acute kidney injury, high individual and cumulative doses of GBCA, thrombosis, and inflammatory state), it is unclear that underlying liver disease or perioperative transplantation period per se were contributory (12,14,15).

In addition to evidence that chronic liver disease does not play a significant role, there is compelling evidence that if the eGFR ≥ 30 mL/min/1.73m², the risk of NSF is extremely low, regardless of liver disease status. In an effort to quantify risk factors for NSF, Prince et al (15) reviewed 290 cases of NSF from the available literature and found only three cases with eGFR >30 mL/min/1.73m². In these three cases, the patients had acute kidney injury, a condition in which eGFR values derived from serum creatinine underestimate the true degree of renal impairment (15). Similarly, the Adverse Event Reporting System (AERS) notes only four cases of biopsy-proven NSF with eGFR ≥ 30 mL/min/1.73m² in the United States (7). These findings suggest that severe renal failure is virtually a sine qua non for development of NSF. The ACR Manual on Contrast Media recommends caution in patients

with an eGFR between 30 and 40 mL/min/1.73 m² out of concern for potential fluctuation in renal function from serum collection to exposure (17). It is known that eGFR tends to underestimate the true degree of renal dysfunction in patients with chronic liver disease (26,27), suggesting that caution may be necessary in gauging NSF risk based on eGFR values in such patients. While such caution may seem reasonable, neither our study nor the literature provides empirical evidence that eGFR values are unreliable for gauging NSF risk in this context; future research in this area is needed. An unresolved question that our study does not address is the maximum time interval between serum collection and exposure that may be considered adequate for gauging the degree of impairment at the time of exposure.

In our cohort of liver patients, a strict interpretation of the FDA's May 2007 black box warning would have precluded the use of GBCAs in 67 patients (5.7%). Extrapolated to a national or global scale, strict interpretation of this warning may unnecessarily deny many patients from undergoing GBCA-enhanced MRI based on an unsubstantiated risk. Denying the use of GBCA-enhanced MRI in such patients is problematic because alternative imaging modalities such as unenhanced MRI have limited efficacy for tumor diagnosis and staging, while contrast-enhanced computed tomography (CT) has well-documented risks including radiation exposure and nephrotoxic effects of iodinated contrast agents. Instead, our study suggests that patients with chronic liver disease are not at elevated risk for developing NSF after GBCA exposure and the presence of chronic liver disease should not deter radiologists from performing GBCA-enhanced MRI examinations in such patients. However, patients with chronic liver disease frequently have concomitant renal disease and caution should be exercised in patients with renal comorbidity.

In evaluating potential factors in disease pathogenesis, biological plausibility is a relevant consideration, not just epidemiological associations. When gadolinium, a highly toxic rare earth metal (6,28), is bound to one of the proprietary chelating agents, it is considered virtually inert on the time scale during which it may be found in the circulation of patients with normal kidney function (29,30). In severe renal insufficiency, however, the half-life of GBCAs, which are primarily renally excreted, may increase from hours to days (31,32). While the mechanism is yet to be fully clarified, it is thought that the extended exposure provides time for the process of transmetallation, in which gadolinium ions are released from their chelates in exchange for endogenous ions (29,33,35). The subsequent deposition of free gadolinium in tissue triggers a fibrotic response through activation of circulating fibroblasts (35,36). Many of the endogenous ions that promote transmetallation, including calcium, phosphates, hydrogen, zinc, and copper are elevated in patients with severe renal failure (37,38). Therefore, renal disease plausibly contributes to the pathogenesis of NSF by promoting greater systemic exposure to GBCAs and altering the biochemical environment in a manner that promotes deposition of free gadolinium in tissue.

A plausible explanation for involvement of liver disease in the pathogenesis of NSF is less clear. Unlike the kidneys, the liver does not play a primary role in the clearance of most GBCAs and liver dysfunction is not associated with elevated levels of endogenous ions (10). Although renal dysfunction is common in patients with endstage liver disease, the literature suggests that such patients are at risk for NSF only to the extent that they are physiologically predisposed to renal insufficiency or acute kidney injury. The hepatobiliary GBCA agents,

gadobenate dimeglumine and gadoxetate disodium, are cleared by the liver in addition to the kidneys; however, even severe liver dysfunction will not plausibly elevate the risk associated with these dual-elimination agents beyond that associated with extracellular agents with single-elimination pathways.

Our study was limited by its retrospective design, which did not permit the collection of data prospectively in a standardized fashion. Moreover, patients underwent dermal biopsies only at the discretion of the treating physician for clinical indications, not routinely, and therefore the true prevalence of NSF in this cohort may be underestimated, especially for subclinical cases of NSF or cases associated with mild symptoms. Conceivably, some patients may have been diagnosed with NSF at other institutions, which also would contribute to risk underestimation. However, ours is the largest liver center in our geographic region, and most patients with chronic liver disease in the region receive their clinical follow-up at our institution. Moreover, our hepatologists communicate closely with community hepatologists, so it is likely that any diagnosis of NSF made at other centers in the region would have been brought to light. It also is conceivable that some patients may have developed NSF but been lost to follow-up without a documented diagnosis of the disease. This situation is unlikely, however, as liver center patients are followed closely by their hepatologists and are seen in clinic every 3–6 months; in our cohort, over 80% of patients had documented follow-up. Other limitations in our study may have contributed to underestimation of GBCA exposure. For example, although they receive their hepatology clinic follow-up at our institution, some of our liver center patients are required by third-party contractual agreements to undergo imaging, including GBCA-enhanced MRI, at other centers; for this study, we were not able to review GBCA examinations performed at other centers. Similarly, we focused only on patients followed in hepatology clinics at our institution. Many patients exposed to GBCA may have undiagnosed chronic liver disease or may not be followed at a hepatology clinic for a variety of reasons. Hence, our study likely underestimated the true number of GBCA-exposed patients with chronic liver disease and possibly the average and cumulative GBCA exposure in the enrolled patients. Another limitation is our institution's historical practice of using almost exclusively gadobenate dimeglumine or gadoversetamide for GBCA-enhanced MRI during the study period; thus, our results may not be generalizable to other GBCA formulations. Moreover, while higher-than-approved doses of GBCAs were used during the study period, our study was not designed to evaluate the safety of such doses and our results should not be interpreted as an endorsement for high-dose use of GBCAs.

In conclusion, our study is consistent with the growing body of knowledge suggesting that liver disease is not a major risk factor in development of NSF and that the “black box warning” issued in 2007 may have been overly cautious.

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Figure 1.

GBCA exposures in patients with eGFR <90 ml/min/1.73m² or dialysis requirement. Bar graph plots the number of GBCA exposures on a per-patient basis, stratified by eGFR threshold (<90, <60, <40, <30, or <15 ml/min/1.73 m²) or dialysis requirement. As explained in the text, for patients with more than one exposure the highest eGFR was used to define their eGFR stratum. eGFR = estimated glomerular filtration rate (in mL/min/1.73 m²).

Figure 2.

GBCA exposures in patients with additional purported risk factors. Bar graph plots the number of GBCA exposures for each type of additional purported risk factor, stratified by eGFR thresholds (60 < eGFR < 90, 40 ≤ eGFR < 60, 30 ≤ eGFR < 40, 15 ≤ eGFR < 30 mL/min/1.73 m²) or dialysis requirement. eGFR = estimated glomerular filtration rate (in mL/min/1.73 m²). Peritransplant period = perioperative liver transplant period.

Table 1**Study Cohort Characteristics**

Characteristic	Number of patients (%)
Gender	
Male	675 (57.8)
Female	492 (42.2)
Age	
Mean	53.5 years
Range	12–87 years
Ethnicity	
Caucasian	549 (47.0)
Hispanic/Latino	311 (26.6)
Asian/Pacific Islander	117 (10.0)
African American	65 (5.6)
American Indian/Eskimo	12 (1.0)
Other/Not Mentioned	113 (9.7)

Table 2
Liver Disease Profile in Study Cohort ($n = 1167$ patients)

	Number of patients (%)
Etiology	
HCV	599 (51.3)
HBV	146 (12.5)
Alcoholic liver disease	237 (20.3)
Non-alcoholic fatty liver disease	76 (6.5)
Primary sclerosing cholangitis	11 (0.9)
Auto-immune hepatitis	28 (2.4)
Primary biliary cirrhosis	17 (1.5)
Cryptogenic	39 (3.3)
Other	295 (25.3)
Patients with >1 etiology	
2 etiologies	239 (20.5)
3 etiologies	18 (1.5)
4 etiologies	2 (0.2)
Cirrhosis	678 (58.1)
Hepatocellular carcinoma	202 (17.3)
Hepatorenal syndrome	77 (6.6)
Liver transplantation	143 (12.3)

HCV = hepatitis C virus, HBV = hepatitis B virus.

Table 3
GBCA Exposure Summary in Study Cohort

Exposures per patient	
1	646 (55.4%)
2	218 (18.7%)
>3	303 (26%)
Doses per Patient (mL)	
Average Volumetric Single Dose	19.8 ml
Average Cumulative Volumetric Dose	39.0 ml
Average Weight-Adjusted Single Dose ^a	0.12 mmol/kg
Average Weight-Adjusted	0.26 mmol/kg
Cumulative Volumetric Dose ^a	
Days Between GBCA Exposure (days)	
Mean	195
Median	161
Range	0–1087
GBCA Formulation (number of doses) ^b	
gadobenate dimeglumine	1145 (65%)
gadoversetamide	607 (34.5%)
gadopentetate dimeglumine	8 (0.5%)
gadodiamide	0
gadoteridol	0
Not Recorded	661 (27.3%)

^aIn the $n = 1013$ patients (86.8%) in whom weight was documented within 1 year of the first GBCA exposure.

^bGBCA formulation percentages are out of the 1761 exposures in which GBCA formulation was documented.

Table 4
Severity of Renal Disease per GBCA Exposure

Severity of renal disease	Number of exposures
60 eGFR < 90	586 (24.1%)
40 eGFR < 60	363 (15%)
30 eGFR < 40	56 (2.3%)
15 eGFR < 30	62 (2.6%)
eGFR < 15	27 (1.1%)
Hemodialysis	35 (1.4%)
Total	1129 (46.6%)

Table 5
Characteristics of Additional Purported Risk Factors

Purported risk factor	Comments
Perioperative transplant period	Median time interval between transplantation and exposure: 80.5 days prior to exposure; range, 165 days prior to 159 days after
Hepatorenal syndrome	Median time interval from first documented diagnosis of hepatorenal syndrome to exposure, 4 days prior; range, 371 days prior to 38 days after
Inflammatory event	Sepsis in 9 patients, pneumonia in 8, spontaneous bacterial peritonitis in 5, cholangitis in 5 and other in 18; median time interval between diagnosis of event and exposure, 6.9 days; range, 1 to 26 days
Thrombotic event	Deep venous thrombosis in 3 patients, portal vein thrombosis in 1, superior mesenteric artery thrombosis in 1, hepatic artery thrombosis in 1; median time interval between diagnosis of event and exposure, 26 days; range, 0 to 40 days

Table 6
Upper Bound Risk Estimates for Purported Risk Factors for NSF

Risk factor at time of exposure	N	Agresti-Coull 95% CI UB^a(%)
Total	1167	0.4
Hepatorenal syndrome	25	15.8
Peri-operative period	80	5.5
Thrombotic event	6	44.3
Inflammatory event	45	9.4
eGFR<90 or on dialysis	843	0.55
eGFR<60 or on dialysis	306	1.5
eGFR<40 or on dialysis	162	2.8
eGFR<30 or on dialysis	80	5.5
eGFR<15 or on dialysis	68	6.4

No patient in study cohort developed NSF. Hence, upper bound 95% confidence limits were calculated based on the observed frequency of 0%. These were calculated on a per-patient rather than per-exposure basis.

^aCI UB = confidence interval upper bound.