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# Intravenous iodinated contrast is not associated with acute kidney injury in adult patients with nephrotic syndrome

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# Intravenous iodinated contrast is not associated with acute kidney injury in adult patients with nephrotic syndrome

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**ABSTRACT** A critical appraisal and clinical application of Tao SM, Kong X, Schoepf UJ, et al. Acute kidney injury in patients with nephrotic syndrome undergoing contrast-enhanced CT for suspected venous thromboembolism: a propensity score-matched retrospective cohort study. *European Radiology*. 2018;28(4):1585-1593. doi: [10.1007/s00330-017-5109-0](https://doi.org/10.1007/s00330-017-5109-0).

**Keywords:** *intravenous contrast, contrast-enhanced CT, nephropathy, acute kidney injury, nephrotic syndrome*

## Clinical Context

Lisa Moore (pseudonym), a previously healthy 56-year-old female, was admitted to our hospital for generalized edema and fatigue. Initial workup showed proteinuria of 8.7 g/day, hypoalbuminemia, and an estimated glomerular filtration (eGFR) rate of 92 mL/min. While awaiting a renal biopsy, she was started on furosemide and a low salt diet. Two days after admission she complained of shortness of breath and chest pain. Her physical exam was negative for deep venous thrombosis (DVT); however, given her elevated Wells score and nephrotic state, our team suspected a pulmonary embolism (PE) and informed her that a contrast-enhanced CT scan was needed for evaluation. Mrs. Moore's husband, who happened to be a nurse, shared his concerns about the effect the contrast might have on her already compromised kidneys. If she were admitted to the hospital due to kidney dysfunction, wouldn't contrast cause further damage? What would that risk be? Was it safe to proceed? After discussion with her husband and our team, the patient ultimately agreed to the procedure. She was subsequently diagnosed with a PE and treated with anticoagulation. Her renal biopsy showed minimal change disease, and she was given a long tapering course of prednisone and discharged home. Nevertheless, the concerns brought up by Mrs. Moore and her husband deserve to be addressed.

## Clinical Question

Does intravenous contrast administration during CT evaluation of PE put an adult patient with nephrotic syndrome at risk for acute kidney injury (AKI)?

## Research Article

Tao SM, Kong X, Schoepf UJ, et al. Acute kidney injury in patients with nephrotic syndrome undergoing contrast-enhanced CT for suspected venous thromboembolism: a propensity score-matched retrospective cohort study. *European Radiology*. 2018;28(4):1585-1593. doi: [10.1007/s00330-017-5109-0](https://doi.org/10.1007/s00330-017-5109-0)

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## Related Literature

Initially, both “nephrotic syndrome” and “acute kidney injury” were reviewed on UpToDate. PubMed was the primary search engine used to find relevant articles, and search terms were limited to the last 10 years since older studies frequently cite the use of contrast media not routinely used in current clinical practice.<sup>2</sup> The following keywords were initially used in the search: “contrast,” “acute kidney injury,” and “nephrotic syndrome.” When used together, 6 articles were identified. Five of these articles were not relevant to the clinical question. Adding various combinations of “nephropathy” and “proteinuria” did not result in more relevant results. The search terms were broadened, with “contrast” and “acute kidney injury” returning 2077 results, many of which focused on the complications of intra-arterial contrast administration. Subsequently, “contrast” was refined to “intravenous contrast” and resulted in 70 papers. Thirty-two of these articles were excluded due to the population studied and/or irrelevance. The remaining 38 articles were reviewed, and only one relevant paper studying adult patients with nephrotic syndrome was identified.<sup>1</sup> However, two other articles found certainly warrant discussion.

A 2014 study by McDonald, et al. examined a large cohort of patients retrospectively, with half receiving contrast-enhanced CT scans and half receiving non-contrast scans.<sup>3</sup> A propensity score analysis was performed to match patients. The investigators found that the incidence of AKI was not significantly different between the contrast and non-contrast groups. Although this study had a large sample size and control group, it was not stratified to determine if the results were valid in patients with nephrotic syndrome. Furthermore, patients in the high-risk subgroup were given iso-osmolar instead of low osmolar contrast, potentially confounding results. Nevertheless, this study made a strong case that intravenous contrast may not be associated with AKI, as historically taught.

A 2018 meta-analysis by Aycock et al. also found no difference in the rates of AKI between patients receiving contrast-enhanced versus non-contrast scans.<sup>4</sup> All of the studies included in the analysis were observational and most were retrospective, which can inherently be seen as a limitation due to selection bias and lack of randomization. Many of the studies included in this meta-analysis were not matched between contrast and non-contrast groups, limiting the validity of combining the data from individual studies. Additionally, the association between intravenous contrast and AKI specifically in patients with nephrotic syndrome could not be determined from the dataset.

No randomized controlled trials were identified in the literature search. Ultimately, a 2018 article by Tao et al. was selected for critical appraisal because of its specificity. While the two articles mentioned previously had larger sample sizes, this was the only study specific to adult patients with nephrotic syndrome. Additionally, patients in the contrast and non-contrast groups were matched to reduce selection bias, and all patients received the same type of contrast in this study.

## Critical Appraisal

This study was a single-center, retrospective investigation.<sup>1</sup> Because of its retrospective and observational nature, it is classified as a Level 3 study according to the Oxford Centre for Evidence-Based Medicine.<sup>5</sup>

Patients met inclusion criteria if they a) had undergone contrast-enhanced or non-contrast-enhanced CT, b) currently had nephrotic syndrome, and c) had serum creatinine data available to assess for AKI. Exclusion criteria included renal replacement therapy and additional contrast exposure within a 14-day period. Our patient did not meet either exclusion criteria. Seven hundred and one patients (mean age of 39) received contrast-enhanced CT with low-osmolar media, and 1053 patients (mean age of 42) received non-contrast-enhanced CT. The mean age of patients in this study was significantly less than that of our patient, although approximately 25% of the patients studied were 55 and older. To minimize indication bias, a propensity score analysis was performed to match clinical variables between the two groups. The incidence of AKI between contrast and non-contrast groups was compared using the Fisher exact test and Odds ratio. AKI was defined as an increase of 0.5 mg/dL (standard AKI criteria<sup>1</sup>) or 0.3 mg/dL (Acute Kidney Injury Network [AKIN] criteria<sup>6</sup>) over baseline 24-72h after the CT scan.

Using standard criteria, the incidence of AKI was 2.7% in the contrast group and 4.1% in the non-contrast group, with an Odds ratio of 0.65 and a 95% confidence interval of 0.38-1.10 (p=0.15). After propensity matching of 3 clinical variables, the incidence of AKI was 2.7% and 2.5%, respectively, OR 1.06 (0.54-2.08), p=1.00; after matching of 10 variables, the incidence was 3.1% and 2.6%, respectively, OR 1.22 (0.60-2.50), p=0.72). With respect to both the OR confidence intervals and p-values, there was no significant difference in AKI incidence using standard AKI criteria. Using the more stringent AKIN criteria, the incidence of AKI was increased in



all groups. Interestingly, even after propensity matching of 10 variables, the incidence of AKI in the contrast group (4.1%) was significantly less than in the non-contrast group (7.4%) using AKIN criteria, OR 0.53 (0.31-0.91),  $p=0.03$ ). It should also be noted that patients were stratified by pre-contrast eGFR in this study, and there was no significant difference in the incidence of AKI after contrast administration using either criteria in the eGFR>90 group in which our patient would fall.

These results show that intravenous contrast is not associated with AKI. Even after matching, the incidence of AKI was greater in the non-contrast group compared to the contrast group using AKIN, but not standard AKI, criteria. A possible explanation for this surprising finding is that there were confounders that could not be matched for, leading to patients at higher risk for AKI in the non-contrast group. Another possibility is that relatively minor, benign fluctuations of creatinine may have been flagged as AKI using the stricter criteria. This may explain why prior studies, especially those without control groups, identified intravenous contrast as a risk factor for AKI.

Another limitation of this study is that all patients administered contrast received prophylactic oral hydration. While the AMACING trial found that prophylactic intravenous hydration has no effect on the development of AKI, oral hydration has not been rigorously tested and may confound the results.<sup>2</sup>

Despite its limitations, the strengths and specificity of this study made it extremely useful. The power was high, given the large sample size of all groups analyzed. Groups were matched to reduce indication bias, and all patients administered contrast were given similar media. Most importantly, this study was specific to our patient's condition.

## Clinical Application

In the span of just a few weeks, Lisa Moore went from being a healthy woman to a hospitalized patient with nephrotic syndrome and a probable PE. She was overwhelmed and frightened, and she naturally valued the opinion of her husband, a medical professional who likely had been taught that contrast is a risk factor for nephropathy. They both sought information to balance the benefit of accurate PE diagnosis with the risk of AKI. Discussing the article reviewed in this appraisal with Mrs. Moore and her husband would have likely addressed many of their concerns.

The Tao et al. article reviewed in this appraisal was internally valid with a large sample size, despite the paradoxical findings compared to what has been historically taught about iodinated contrast and AKI. More importantly, the study was externally valid and could have directly been applied to our patient, who met all inclusion criteria. Sharing the conclusions of the study to Mrs. Moore and her husband would have gone far in addressing their concern in this stressful and urgent situation. It also would have given evidence-based confidence to the clinicians in this scenario despite the understandable hesitancy that the patient and her husband had towards receiving contrast. Giving contrast in this clinical scenario allowed our patient to be diagnosed and treated for PE, and it was the correct decision. In the future, this appraisal may be used by physicians both for clinical decision making and patient/family education. Until a randomized controlled study on this subject is attempted, the retrospective cohort study by Tao et al. remains the best evidence against iodinated contrast being a risk factor for AKI in adult patients with nephrotic syndrome.

### Learning points:

1. Intravenous iodinated contrast administration has historically been linked with AKI based on early studies that lacked control groups.
2. Recently, more elaborate studies have shown that intravenous contrast is not associated with AKI in adults with nephrotic syndrome or in the general population.
3. The belief that intravenous contrast causes kidney damage continues to be prevalent, and concerned individuals should be compassionately educated using current evidence.



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