

Article Appraisal

**Article:** Association of Intravenous Radiocontrast With Kidney Function A Regression Discontinuity Analysis. April 2021. JAMA Intern Med.

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# Background and Study Objective(s):

The objective was to determine the association between intravenous contrast administration for CT pulmonary angiography and long-term renal function, with secondary outcomes of AKI (using the standard definition of increase of Cr by 50% or 26 µmol/L within 7 days), or need for renal replacement therapy and all-cause mortality within 6 months.

# Study Design:

This is a retrospective cohort study using a fuzzy regression discontinuity design (RDD). The data source was provincial Alberta health records. Inclusion criteria were patients at least 18 without recent renal replacement (last 6 months) who underwent ED-based D-dimer testing between 2013-2018. They excluded people who did not have a baseline eGFR taken within 2 hours of the D-dimer Their running variable was the D-dimer. People were also excluded if the D-dimer value fell directly on the cut off due to ambiguity. The cut off was sent at 500 ng/mL, or else at the individual site cutoff. The assumption is that the people clustered around the

D-dimer cut off are similar in characteristics except for the D-dimer value; therefore, a D-dimer just above or just below the cutoff value dramatically increases or decreases the probability of the exposure variable CTPA. In other words, this is analogous to the cohort “randomized” to receiving IV contrast for a CTPA.

 The outcome variable is long-term kidney function, measured by eGFR up to 6 months after the index ED visit. To measure the association of CTPA on eGFR, authors adjusted for age, baseline eGFR, sex, DM, HTN, cancer, CAD, ED triage score, and Charlson comorbidity score.

The “fuzzy” RDD accounts for the fact that not everyone above the D-dimer cut off underwent CTPA testing. For people with D-dimer above the cut off, the intention is to treat them: to order a CTPA. For those below the cut off, the intention is to not treat them: to not order a CTPA. In order to account for the discrepancy in CTPAs ordered above and below the D-dimer cut off, the complier average causal effect was calculated. Compliers are physicians who only order a CTPA if the D-dimer is above the cut off. The assumption is that if there are differences in outcomes above or below the cut off, it is due to the number of CTPAs being ordered in the groups. Causality is estimated by dividing the difference in outcomes in the entire cohort with D-dimer just above versus just below the cut off (the ITT analysis) by the difference in percentages of people just above versus below the cut off who had CTPAs.

They also performed subgroup analyses looking at people thought to be at high risk of CIN, including people with diabetes, hypertension, eGFR < 45 mL/min/1.73m2, and age > 60.

# Results:

156 028 people underwent D-dimer testing and met inclusion criteria. Mean age was 53 years, 44% were men and mean baseline eGFR was 86 mL/min/1.73m2. There was a clear 23% discontinuity in CTPA exposure at the D-dimer cut off. They found no evidence for discontinuity with potential confounders, meaning the groups were well balanced at the cut off. Follow-up data were available for 84 624 patients (54%) and the frequency of missing data was not related to changes at the cutoff.

Median time to last eGFR test was 3.7 months. The estimated ITT effect of the D-dimer cutoff on longterm eGFR was nonsignificant (discontinuity of −0.1 mL/min/1.73 m2 (95% CI, −1.2 to 1.1)).

Overall, 165 (0.11%, 161 dialysis, 4 transplant) patients underwent kidney replacement therapy in the 6 months following the index visit. There was no association between CTPA and need for kidney replacement therapy (RD, 0.07% [95% CI, −0.47% to 0.61%]). For patients who had repeat eGFR testing within 7 days, 4147 (9.7%) developed AKI. There was no evidence of association with CTPA (RD, 4.3% [95% CI,−2.7% to 12.9%]). Repeat eGFR measurements within 7 days were only available for 42 691 (27%) of patients. 6 656 (4.3%) patients died in the 6 months following the index visit, with no association with CTPA.

Subgroup analyses found no evidence of contrast exposure impacting longterm eGFR based on age, baseline eGFR, hypertension or diabetes. However, the diabetes subgroup analysis was potentially consistent with harm with eGFR change of −6.4 mL/min/1.73 m2 (95% CI, −15.4 to 0.2; *P* for heterogeneity = .12).

# Validity of Results:

This study addressed a focused clinical question with objective and patient-centered outcomes. No conflicts of interest were identified for the study authors. Their analysis demonstrated that there were no significant differences between the patients who received and did not receive CTPA. There were more patients with cancer who underwent CTPA than did not (8% versus 3%), but this makes sense clinically as patients with malignancy are at higher risk of PE (and have a baseline predisposition for having a high D-dimer).

Nearly half the patients lacked follow-up data. Outcomes were censored at 6 months and cannot project longer trajectories. The statistical methods are very complex, and thus an assumption of the validity of their methods and of their statistical software is required for these conclusions.

# Generalizability of Results:

This study was conducted using data from an Alberta database. The fuzzy RDD analysis limits treatment effect to those close to the cutoff who are compliers. The authors did complete a subanalysis and found no heterogeneity in treatment effect between compliers and non-compliers. The generalizability is limited to those people clustered around the D-dimer cut off and is less applicable to those whose characteristics place them further from the cut off.

The results appear generalizable given the characteristics of the cohort and appropriate subgroup analyses, in particular those with eGFR < 45 mL/min/1.73 m2 who are typically thought to be at higher risk of kidney impairment following an iatrogenic insult. Only 27% of patients underwent repeat eGFR testing within 7 days of the index visit, so data regarding AKI is limited. Patients who underwent repeat eGFR testing were likely selected by their clinicians based on perceived risk of AKI, thus there is potential for selection bias for higher risk patients in this analysis.

# The Bottom Line:

In this retrospective cohort study, there was no association found between IV contrast exposure from CTPA and 6-month renal impairment. There was also no association found between contrast exposure and AKI, need for renal replacement therapy or all-cause mortality.

This design is presented as being analogous to an RCT and their subsequent analyses of potential confounders supports this. However, their complex statistical design is difficult to interpret and requires reliance on the design integrity in making these conclusions. This study design is presented as being less biased and less methodologically flawed than previous studies which demonstrate similar conclusions.

Overall, this study again refutes the theoretical concern of contrast CT scans placing patients at risk of renal impairment.