Incidence of Contrast-Associated Acute Kidney Injury in Renal-Competent COVID-19 Patients Undergoing Computed Chest Angiography

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Purpose: COVID-19 infection poses a significant risk of both renal injury and pulmonary embolism, producing a clinical challenge, as the criterion standard examination for pulmonary embolism, computed tomography angiography (CTA), requires the use of nephrotoxic iodinated contrast agents.

Our investigation evaluated whether symptomatic COVID-19–positive patients without laboratory evidence of renal impairment are at increased risk for developing contrast-associated acute kidney injury (CA-AKI). One notable exception is patients with abrupt decreases in renal function, as creatinine and estimated glomerular filtration rate (eGFR) are lagging indicators. In this scenario, patients may have significant renal impairment despite normal laboratory values, misconstruing the true risk of contrast administration.

Contrast-induced nephropathy (CIN) is a well-established cause of acute kidney injury (AKI), accounting for 11% of AKI in hospitalized patients, and represents the third most common cause of iatrogenic kidney injury. Although incompletely understood, CIN is thought to be multifactorial in etiology, related to direct nephrotoxicity mediated by free radicals, renal medullary hypoxia, and cellular apoptosis, among other causes. Although recent evidence indicates that CIN risks have been overstated, and the development of low- and iso-osmolar iodinated contrast agents has reduced its incidence, contrast-induced nephropathy remains a significant cause of patient morbidity and mortality, particularly in acutely ill patients with severe renal impairment.

Because of historical inconsistencies with the definition of CIN and the putative link between contrast usage and AKI, the American College of Radiology (ACR) and National Kidney Foundation have established the term “contrast-associated acute kidney injury” (CA-AKI), to describe renal injury after contrast administration that cannot definitively be linked to contrast administration because of the absence of a well-matched control population. Preexisting renal impairment is the most widely recognized risk factor for the development of CA-AKI, as such patients are routinely screened for chronic kidney disease risk factors before contrast administration, and when appropriate, creatinine and estimated glomerular filtration rate (eGFR) measurements are obtained. Although specific institutional guidelines vary, studies have shown a minimal risk of CA-AKI in patients with eGFR >30, above which contrast administration is generally thought to be safe. One notable exception is patients with abrupt decreases in renal function, as creatinine and eGFR are lagging indicators. In this scenario, patients may have significant renal impairment despite normal laboratory values, misconstruing the true risk of contrast administration.

COVID-19 was first identified in Wuhan, China, in December 2019. Initial reports described a respiratory illness, with a clinical course, ranging from mild upper respiratory tract infection–like symptoms to a severe pneumonia with accompanying acute respiratory distress syndrome (ARDS), leading to hospitalization and, in the most severe cases, death. As the illness spread, a complex pathophysiology has emerged, with patients with fulminant COVID experiencing a sepsis-like cytokine storm marked by hypercoagulability and end-organ damage. In this context, underdiagnosis of pulmonary embolism (PE) is a particular concern, because the symptoms of PE could be misattributed to COVID pneumonia and ARDS. At many institutions, computed tomography angiography (CTA) is routinely performed for acutely ill COVID patients, assessing for PE and establishing a baseline assessment of COVID pneumonia. The use of iodinated contrast, however, has been tempered because of a fear of worsening COVID-related AKI, theorized to be mediated by multiple factors including direct viral infection of the kidney, complement activation, and ischemia related to microangiopathy and thrombosis. This concern has been borne out in a small series of patients undergoing CTA and coronary catheterization, which demonstrate increased rates of AKI in this population.

Our investigation evaluated whether newly diagnosed COVID-positive patients without laboratory evidence of severe renal-impairment (eGFR >30) are at increased risk for CA-AKI. Although our study cohort was eligible to receive the contrast based
on contemporary guidelines, one could postulate that incipient COVID-related AKI may not manifest in measurable creatine increases at initial presentation, leading to an underestimation of CA-AKI risk. By comparing COVID-positive patients undergoing noncontrast computed tomography (CT) and CTA, we quantified the risk of renal injury attributable to intravenous iodine administration. To our knowledge, no prior studies have investigated the risk of CIN in renal-competent COVID-positive patients.

**MATERIALS AND METHODS**

**Study Population**

Our institutional review board approved this retrospective, Health Insurance Portability and Accountability Act–compliant study. A query of the electronic medical record was performed to identify 587 COVID-positive patients undergoing noncontrast CT and CTA between March 1 and December 10, 2020. Inclusion criteria included renal-competent (eGFR >30) status and availability of preexamination (≤24 hours) and postexamination (48–72 hours) creatinine measurements. Exclusion criteria included prior or subsequent receipt of iodinated contrast (up to 1 week before, or 72 hours after examination) and presumed spurious laboratory values (creatinine <0.4 mg/dL).

Patient weight and demographics, including age, race, and sex, were obtained using the electronic medical record. Risk factors for CA-AKI were identified on the basis of the ACR guidelines for contrast administration. Variables of interest included diabetes, hypertension, congestive heart failure (CHF), obesity, and a history of renal failure.12

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**FIGURE 1.** Patient selection flowchart.
Definitions and Criteria

Patients were deemed COVID positive based on a positive polymerase chain reaction or rapid antibody test performed up to 14 days before CT imaging. Given the possibility of AKI due to COVID, preprocedural creatinine values were required, defined as laboratory tests obtained ≤24 hours before a CT examination. For patients with multiple preprocedural laboratories, the most recent value was used.

Because there are multiple accepted definitions for CA-AKI, we used both of the most common criteria: a 48- to 72-hour increase in serum creatinine ≥0.5 mg/dL or an increase in serum creatinine by 25% or greater. Although some authors have used creatinine values obtained at 24 to 48 hours, we chose to use the more restrictive definition to reduce potential confounding systemic effects related to acute COVID, which may predominate early in a patient’s course.

The presence of comorbidities was determined based on a retrospective review of the electronic medical record using relevant International Classification of Diseases, Tenth Revision codes.

CT Scan Technique

Noncontrast chest CT and CTA were performed using standard institutional protocols, available at http://www.ctisus.com/ protocols. All patients were scanned on SOMATOM Sensation 64-slice helical CT scanner or SOMATOM Definition Flash 128-slice helical CT scanner (Siemens Healthineers, Forchheim, Germany). Of the 191 contrast-enhanced scans, 189 (98.95%) were performed using standard nonionic low-osmolar contrast (iohexol [Omnipaque 350; GE Healthcare]), and 2 of 191 (1.05%) were performed using iso-osmolar contrast (iopamidol [Visipaque 320; GE Healthcare]). Dose volume was fixed at 100 mL. No preexamination CA-AKI prophylaxis was performed per institutional protocol for renal-competent patients, and no formal patient consent was required before contrast administration.

All chest CT scans were scanned from lung apices through the diaphragm to include the adrenal glands. Scans were performed using ALARA principles, with technical parameters of 120 kVp, 0.5-second rotation time, 0.8 pitch value, and craniocaudal scan direction in inspiration phase. Pulmonary embolism protocol CTA examinations were obtained by injecting a fixed 100-mL iodinated contrast bolus at a rate of 4 to 5 mL/s using a power injector. The examination was triggered using a 150-Hounsfield unit threshold at the pulmonary trunk and was acquired in the inspiratory phase.

Statistical Analysis

Statistical analysis was performed using STATA statistical software (version 15.1; StataCorp, College Station, TX). Initial summary statistics were completed, followed by x² and 2-sided t testing to evaluate differences in demographics and clinical characteristics between the CT and CTA cohorts. Univariable and multivariable logistic regressions were then performed to evaluate the relationship between contrast administration and AKI meeting the CA-AKI criteria.

RESULTS

Patient Demographics and Clinical Characteristics

Of the identified 587 COVID-positive patients undergoing chest CT, 168 patients underwent noncontrast CT and 419 patients underwent CTA. Of these initial patients, 128 were excluded for not having initial creatinine measurements, 150 for insufficient follow-up, 49 for baseline GFR <30, and 2 for initial creatinine <0.4, leaving 258 patients for the analytic sample, 191 of which received CTA and 67 CT without contrast (Fig. 1).

The presence of comorbidities was determined based on a retrospective review of the electronic medical record using relevant International Classification of Diseases, Tenth Revision codes.

Table 1. Patients undergoing CTA were slightly younger, heavier in weight, and more likely to be female, although no statistically significant difference was observed. African American race was more common among the CTA group, although, again, not statistically significant.

Risk Factors for AKI

Univariable analysis and multivariable analysis accounting for differences in demographics and comorbidities revealed no significant increase in the rate of AKI with contrast administration (univariable odds ratio [OR], 0.97 [95% confidence interval [CI], 0.43–2.20]; multivariable OR, 0.97 [95% CI, 0.40–2.36]; Table 2; note that HIV/AIDS was excluded from multivariable analysis because of its relatively low prevalence). All comorbidities increased the risk of CA-AKI on univariate analysis, with CHF demonstrating statistical significance (OR, 2.27; 95% CI, 1.09–4.73; P = 0.03).

Renal Function Trends of Both the Groups

Mean initial serum creatinine was significantly lower, and median eGFR was significantly higher among patients undergoing CTA (0.92 vs 1.07 [P < 0.01], 92 vs 83 [P = 0.01]). Figure 2, a box-and-whisker plot of eGFR, demonstrates stable eGFR levels in both groups over the analyzed 72-hour postexamination period. Twenty-five patients undergoing CTA and 9 patients undergoing noncontrast CT developed AKI meeting 1 or both of our diagnostic criteria for CA-AKI. The rate of AKI was similar among both populations, measuring 13.1% (CTA) and 13.4% (noncontrast CT).

Table 1. Patient Demographics and Clinical Characteristics

| Characteristics          | CT With Contrast | CT Without Contrast | P     |
|--------------------------|------------------|---------------------|-------|
| No. patients             | 191              | 67                  |       |
| Age, mean (SD), y        | 54.2 (15.5)      | 57.0 (15.1)         | 0.19  |
| Weight, mean (SD), kg    | 88.7 (21.2)      | 83.5 (25.2)         | 0.13  |
| Women, n (%)             | 94 (49.2)        | 31 (46.3)           | 0.68  |
| Race/Ethnicity, n (%)    |                  |                     |       |
| African American         | 103 (53.9)       | 29 (43.2)           | 0.26  |
| White                    | 43 (22.5)        | 21 (31.3)           |       |
| Other                    | 45 (23.6)        | 17 (25.4)           |       |
| Initial serum creatinine, mean (SD), mg/dL | 0.92 (0.33) | 1.07 (0.47) | <0.01* |
| Initial eGFR, median (IQR), ml/min per 1.73 m² | 92 (71–111) | 83 (52–107) | 0.01* |
| Comorbidities, n (%)     |                  |                     |       |
| Diabetes mellitus        | 68 (35.6)        | 35 (52.2)           | 0.02* |
| Hypertension             | 123 (64.4)       | 49 (73.1)           | 0.19  |
| CHF                      | 54 (28.3)        | 25 (37.3)           | 0.17  |
| Obesity                  | 94 (49.2)        | 29 (43.3)           | 0.40  |
| HIV/AIDS                 | 6 (3.1)          | 9 (13.4)            | <0.01* |
| Renal failure            | 39 (20.4)        | 21 (31.3)           | 0.07  |

*P < 0.05.
The association between contrast administration and AKI was not significant on multivariable logistic regression (OR, 0.97; 95% CI, 0.40–2.36).

**DISCUSSION**

Although initially perceived as a respiratory illness, COVID-19 is now widely recognized as a multisystem illness, with significant morbidity stemming from hypercoagulability and end-organ injury (including renal injury). One of the most significant complications of COVID-19 is pulmonary embolus, with a reported incidence of 23% to 30% in an early series of acutely ill COVID-19 patients. The possibility of coexisting acute PE and COVID-19 pneumonia poses a quandary for clinicians, as the criterion standard examination for PE, CTA, requires the use of iodinated contrast, a known nephrotoxic agent. In our investigation we sought to determine whether the use of iodinated contrast in renal-competent COVID-19 patients increased the risk of AKI. To our knowledge, our investigation is the first analysis of CA-AKI risk in patients with COVID-19.

Noncontrast CT is the mainstay of COVID-19 imaging, as the typical respiratory manifestations of COVID-19 (peripherally predominant ground-glass opacities) are well assessed without the administration of intravenous contrast. However, in acutely ill patients and patients with abrupt declines in respiratory status and/or elevated D-dimer levels, CTA has increasingly been used. Computed tomography angiography is helpful in these instances not only to identify pulmonary emboli occult on noncontrast CT but also to delineate imaging findings resulting from concurrent COVID-19 pneumonia and PE. For instance, subacute/chronic PE may result in dense consolidations related to pulmonary infarcts, mimicking superimposed bacterial pneumonia on noncontrast CT, or mosaic attenuation, which may resemble COVID pneumonia. With widespread recognition of thromboembolic events in the COVID-19 population and the establishment of high-dose therapeutic anticoagulation regimens, CTA has become the first-line examination for most patients with acute respiratory distress and newly diagnosed COVID-19 pneumonia at our institution.

A key factor limiting the use of CTA is fear of exacerbating COVID-related renal injury. In a meta-analysis of hospitalized COVID-19 patients, Silver et al found almost 1 in 3 patients hospitalized with COVID-19 experienced AKI (pooled prevalence, 28% 95% CI, 22%–34%). The mechanism of COVID-related renal injury, although incompletely understood, is presumed to be multifactorial, related to direct viral infection, cytokine release, and iatrogenic causes, including fluid restrictive ARDS treatments and administration of nephrotoxic medications. Given the complex nature of COVID-19-related renal injury, we theorized that traditional approaches to stratifying CA-AKI risk based on initial eGFR may not reflect the true CA-AKI risk in COVID-19-positive patients, especially those early in their disease course. Our investigation, in keeping with recent ACR/AKI guidelines, indicates that this is not the case.

### TABLE 2. Risk Factors for CA-AKI

| Characteristics | Univariable Odds of CA-AKI (95% CI) | Multivariable Odds of CA-AKI (95% CI) |
|-----------------|------------------------------------|--------------------------------------|
| Contrast         | 0.97 (0.43–2.20)                   | 0.97 (0.40–2.36)                     |
| Administration  |                                    |                                      |
| Age, y          | 1.01 (0.98–1.03)                   | 1.00 (0.97–1.03)                     |
| Female          | 1.23 (0.60–2.53)                   | 1.24 (0.55–2.79)                     |
| Race/Ethnicity  |                                    |                                      |
| Black           | 1.02 (0.45–2.32)                   | 1.07 (0.43–2.65)                     |
| White           | Reference                          | Reference                            |
| Other           | 0.27 (0.07–1.05)                   | 0.34 (0.09–1.39)                     |
| Initial eGFR, mean (SD), mL/min per 1.73 m² | | |
| 30–59           | 0.77 (0.28–2.11)                   | 0.40 (0.13–1.22)                     |
| 60+             | Reference                          | Reference                            |
| Comorbidities (%) |                                    |                                      |
| Diabetes mellitus | 1.84 (0.89–3.80)               | 1.48 (0.62–3.55)                     |
| Hypertension    | 1.46 (0.65–3.27)                   | 0.87 (0.33–2.30)                     |
| CHF             | 2.27 (1.09–4.73)*                  | 1.92 (0.83–4.42)                     |
| Obesity         | 1.46 (0.71–3.02)                   | 1.08 (0.47–2.49)                     |
| HIV/AIDS        | 0.45 (0.06–3.57)                   |                                      |
| Renal failure   | 2.00 (0.92–4.33)                   | 1.82 (0.73–4.50)                     |

CA-AKI: increase in serum creatinine of 0.5 mg/dL or 25% increase in patients with baseline of 0.4 to 4.0 and follow-up of at least 48 h.

*p < 0.05.

The association between contrast administration and AKI was not significant on multivariable logistic regression (OR, 0.97; 95% CI, 0.40–2.36).

**FIGURE 2.** Box-and-whisker plot of eGFR at baseline and at 24, 28, and 72 hours. Center line represents median, upper and lower boundaries of the rectangle represent 25th and 75th percentiles, and crosshatches represent maximum and minimum values. Number of patients with at each respective follow-up interval defined by n.
A box-and-whisker plot (Fig. 2) tracking eGFR at baseline and at 24, 48, and 72 hours after CT examination demonstrates stable renal function in both the CTN and noncontrast cohorts. In both univariate and multivariate analyses (accounting for comorbidities), patients receiving contrast were at no increased risk of AKI (Table 2). Conversely, well-established AKI/CA-AKI risk factors including diabetes mellitus, CHF, and history of renal failure demonstrated a strong positive correlation with the development of AKI (although only CHF was statistically significant). The noncontrast CT cohort exhibited a higher prevalence of CA-AKI risk factors, an expected finding given clinicians’ desire to minimize contrast use in high-risk patients. These differences are accounted for in our multivariable analysis, where the effects of contrast usage were isolated from other AKI/CA-AKI risk factors.

By limiting our analysis to the 48–72 hours, we hoped to delineate CA-AKI from COVID-19-related renal injury,38 which may predominate immediately after contrast administration. Our objective was to quantify the risk of kidney injury related to contrast usage, an acute phenomenon that is transient in most renal-competent patients.3,39 Although our results indicate that CA-AKI is an unlikely contributor to long-term renal impairment in renal-competent COVID-19 patients, we did not analyze the effects of contrast usage throughout a patient’s course. This is notable because greater than 1 in 3 patients in a large series of hospitalized COVID-19 patients with AKI had persistent declines in renal function at discharge.39 Moreover, a recent Veterans Affairs analysis of 30-day COVID-19 survivors demonstrated statistically significant eGFR declines, not only in patients who were hospitalized with acute COVID-19 but also in those with milder disease treated as outpatients.40 These data suggest that postacute COVID (long COVID) is a distinct clinical entity, and the relationship of other potential exacerbating factors, including contrast usage, bears further investigation.

Although our investigation suggests that current approaches to COVID-19 imaging adequately account for CA-AKI risk, our results cannot be generalized to all renal-competent patients. Our data reveal that patients undergoing CTA had lower creatine, higher initial eGFR, and lower rates of diabetes mellitus, hypertension, CHF, HIV/AIDS, and renal failure compared with the noncontrast cohort. This indicates judicious contrast use by clinicians at our institution, and without randomization and a control population, our results cannot be extrapolated to a general patient population. In addition, the safety of contrast usage in patients with marginal renal function remains uncertain, as only 3 of 191 patients undergoing CTA had an initial eGFR <45, and 2 of 3 received isomolar contrast (iodoxanol), the possible benefit of which is beyond the scope of this investigation. Furthermore, many of the most severely ill COVID patients required multiple contrast-enhanced examinations41 and were thus excluded from our analysis. Finally, our investigation preceded the development of therapeutics and vaccinations, and the emergence of new COVID-19 strains, including the Delta variant, which currently represented 99.9% of new cases in the United States in the fall of 2021,42 the subsequent Omicron variant, and the BA.2 Omicron subvariant, which currently predominates.43 Although therapeutics and vaccination reduce the risk of systemic effects from COVID-19, initial studies of the Delta variant indicate increased vascular virulence compared with the original COVID-19 strain, and potentially increased the risk of renal injury.44 Conversely, early evidence from South Africa suggests that Omicron has reduced virulence,45 potentially meaning a decreased risk of systemic effects, including both PE and AKI.

Our investigation has several limitations. The study was conducted retrospectively, and contrast administration was nonrandomized, determined by clinician and radiologist discretion, likely based on both patient risk of CA-AKI (resulting in higher rates of CA-AKI risk factors in the CTA cohort) and the degree of concern for PE. Because our investigation is based on early clinical data, the inherent variation in clinical practice and imaging guidelines resulted in some randomization of the respective cohorts. Nonetheless, comorbidities were higher in the noncontrast group. Although this was accounted for in the multivariable analysis, only the most commonly recognized CA-AKI risk factors were identified, as many patients had limited initial evaluations and clinical follow-up, and other potentially nephrotoxic medications, including investigational COVID therapies, were not accounted for. Moreover, we were unable to generate a representative control group because of limitations in procuring representative-matched COVID-negative controls. In addition, statistical power was reduced by small study size, with a significant proportion of patients excluded because of lack of creatine measurements and prior/ subsequent contrast administration. Despite these limitations, the similar rate of AKI in the CTA cohort remains a compelling finding, suggesting that the judicious use of iodinated contrast in renal-competent COVID-19 patients is safe.

In conclusion, our investigation revealed no increased risk of AKI in renal-competent COVID-positive patients undergoing CTA. Although our investigation is confounded by the higher incidence of CA-AKI risk factors in our control population, our experience suggests that adherence to existing guidelines for iodinated contrast media use is sufficient to minimize CIN risk in this population. Additional studies with larger sample sizes and representative control populations are needed to confirm this preliminary finding.

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