

# Risk of Acute Kidney Injury after Intravenous Contrast Media Administration in Patients with Suspected Pulmonary Embolism: A Propensity-Matched Study

Adi Elias<sup>1,2</sup> Doron Aronson<sup>1,2</sup>

<sup>1</sup>Department of Cardiology, Rambam Medical Center, Haifa, Israel

<sup>2</sup>B. Rappaport Faculty of Medicine, Technion Medical School, Haifa, Israel

Address for correspondence Doron Aronson, MD, Department of Cardiology, Rambam Medical Center, POB 9602, Haifa 31096, Israel (e-mail: daronson@technion.ac.il).

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## Abstract

**Background** Although computed tomography pulmonary angiography (CTPA) is the preferred diagnostic procedure in patients with suspected pulmonary embolism (PE), some patients undergo ventilation/perfusion (V/Q) lung scan due to concern of contrast-associated acute kidney injury (AKI).

**Methods** The study used a cohort of 4,565 patients with suspected PE. Patients who received contrast during CTPA were compared with propensity score-matched unexposed control patients who underwent V/Q lung scanning. AKI was defined as  $\geq 50\%$  increase in serum creatinine during the first 72 hours after either CTPA or V/Q lung scan.

**Results** Classification and regression tree analysis demonstrated that baseline creatinine was the strongest determinant of the decision to use CTPA. Propensity-score matching yielded 969 patient pairs. There were 44 AKI events (4.5%) in patients exposed to contrast media (CM) and 33 events (3.4%) in patients not exposed to CM (risk difference: 1.1%, 95% confidence interval [CI]:  $-0.6$  to  $2.9\%$ ; odds ratio [OR]: 1.39, 95% CI: 0.86–2.26;  $p = 0.18$ ). Using different definitions for AKI and extending the time window for AKI diagnosis gave similar results. In a sensitivity analysis with the inverse probability weighting method, the OR for AKI in the CTPA versus V/Q scan was 1.14 (95% CI: 0.72–1.78;  $p = 0.58$ ).

**Conclusion** Intravenous contrast material administration was not associated with an increased risk of AKI in patients with suspected PE. Given the diagnostic superiority of CTPA, these results are reassuring with regard to the use of CTPE in patients with suspected PE perceived to be at risk for AKI.

## Keywords

- ▶ acute kidney injury
- ▶ contrast media
- ▶ CTPA
- ▶ pulmonary embolism

## Introduction

Intravascular administration of iodinated contrast media (CM) is considered to be a major cause of acute kidney injury (AKI).<sup>1</sup> Although contrast-associated AKI (CA-AKI) is frequently a reversible phenomenon, clinicians often delay critical diagnostic tests and procedures that include CM exposure due to the concern of CA-AKI.<sup>1–3</sup>

Pulmonary embolism (PE) is a major cause of mortality, morbidity, and hospitalization where prompt diagnosis is essential.<sup>4</sup> Computed tomography pulmonary angiography (CTPA) is considered the method of choice for imaging the pulmonary vasculature in patients with suspected PE. In uncontrolled studies, the incidence of reported CA-AKI following CTPA ranges between 12 and 25%, depending on the definition used.<sup>5–7</sup>

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Recent studies, however, argued against a causal relationship between CM and AKI,<sup>8–13</sup> emphasizing coexisting alternative causes of AKI that can also be relevant to patients with suspected PE (e.g., hemodynamic instability, low cardiac output, bleeding, postsurgery state, or sepsis).<sup>8–10,12,14–16</sup>

Ventilation/perfusion (V/Q) lung scan is considered to be an alternative test for suspected PE especially in patients who suffer from chronic kidney disease (CKD) or AKI.<sup>17–19</sup> However, V/Q lung scan suffers from several limitations such as lower sensitivity and specificity, difficult interpretation criteria, and lack of overnight availability.<sup>20</sup>

Delay in diagnosis and treatment of PE is associated with increased mortality and lower quality of life,<sup>21</sup> especially in patients with CKD.<sup>22</sup> Few studies, however, have focused on patients with suspected PE,<sup>23–25</sup> who not only require rapid diagnosis but also frequently have significant disease burden that may raise concern over precipitating AKI. In the current study, we aimed to assess the risk of AKI following CM exposure from CTPA compared with a control group who underwent V/Q scintigraphy.

## Methods

Using Rambam Health Care Campus inpatient database, a tertiary academic medical center, we retrospectively identified all patients with suspected PE who underwent CTPA (typically, these patients received nonionic, low-osmolar, iodinated contrast agents at a dose of 80–90 mL) or V/Q lung scan for suspected PE between January 2000 and December 2019. The decision to use either diagnostic test was at the discretion of the treating physician. The study was approved by the local institutional review committee on human research (Approval ID: RMB-19-0454).

Exclusion criteria included dialysis, unavailable baseline creatinine, and patients without follow-up creatinine values. Baseline (prior to PE testing) estimated glomerular filtration rate (eGFR) was calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.<sup>26</sup>

## Endpoint Definitions

AKI was defined as  $\geq 50\%$  increase in serum creatinine during the first 72 hours after either CTPA or V/Q lung scan.<sup>3</sup> If AKI onset is likely to be a consequence of a specific insult, such as CM, the “baseline” can be assumed as the value most proximate to the precipitating event.<sup>27</sup> Therefore, the reference creatinine for the AKI definition was the closest creatinine measurement obtained prior to the diagnostic test. We also used alternative definitions including an increase in serum creatinine concentration  $\geq 0.5$  mg/dL (44  $\mu$ mol/L) or a  $>25\%$  relative rise in serum creatinine<sup>10</sup> and doubling of serum creatinine and/or requirement for acute dialysis during the index hospitalization.

## Statistical Analysis

Continuous variables are presented as mean  $\pm$  standard deviation or medians (with interquartile ranges), and categorical variables as numbers and percentages. Baseline characteristics of the unmatched groups were compared using unpaired *t*-test

for continuous variables and by the  $\chi^2$  statistic for noncontinuous variables. After propensity-score matching, the baseline covariates were compared between the two groups with a paired *t*-test or Wilcoxon signed-rank test for continuous variables and the McNemar’s test or marginal homogeneity test for categorical variables.

Classification and regression tree (CART) analyses were performed to gain insight into most predictive variables for selecting the imaging modality for PE diagnosis.<sup>28</sup> The analysis involves repeated partitioning of the sample (root node), selecting the most discriminative variable and optimal cut-points (according to an impurity function) to partition the data, and repeating this partition until the nodes are considered pure enough to be terminal.<sup>28–30</sup>

Because the clinical characteristics of patients submitted for CTPA differed markedly from those undergoing V/Q lung scan, propensity-score estimates representing the probability of CTPA being performed were generated using a nonparsimonious multiple logistic regression model derived from clinical and laboratory parameter covariates available prior to the diagnostic test assignment (► **Table 1**). Following propensity-score generation, patients were matched by using 1:1 nearest neighbor (Greedy type) matching without replacement and a caliper width of a 0.2 standard deviation of the propensity-score logit. Matching was performed without replacement, and nonmatched results were discarded.

We assessed the success of the matches by examining standardized differences (measured in percentage points) in the observed confounders between the matched groups. Small ( $<10\%$ ) standardized differences support the assumption of balance between groups based on observed confounders.<sup>31</sup>

The incidence of AKI was compared between CM and non-CM groups following propensity-score matching using methods that account for the matched nature of the sample. Accordingly, conditional logistic regression was used to assess the effect of CM exposure on the risk of AKI in the propensity-score-matched cohort.

Three sensitivity analyses were performed. First, a sensitivity analysis was performed where patients’ time window for diagnosis of AKI was extended to 7 days after CM exposure. Second, a separate propensity score matching was performed in the subgroup of patients with baseline eGFR  $\leq 45$  mL/min/1.73 m<sup>2</sup> (stage 3B CKD and higher) as this subgroup is considered to be at the highest risk.<sup>32</sup>

An additional sensitivity analysis was applied using inverse probability of treatment weights to our analyses to adjust for the probability of a patient receiving the diagnostic test conditional on observed covariates. We used a logistic regression model to estimate the propensity score as described above. We then assigned a weight to each patient based on the inverse of the estimated probability of choosing the diagnostic modality. The quality of weighting was verified using the absolute value of standardized difference between the groups after weighting, where a value  $<0.1$  was considered acceptable difference. After weighting, we again compared baseline characteristics of each treatment group to ascertain the balance between the groups. The estimated weights were incorporated into a logistic regression model that only included diagnostic procedure variable.<sup>33</sup>

**Table 1** Baseline clinical characteristics in unmatched and propensity-matched patients

Characteristics	Before propensity-matching			After propensity-matching		
	V/Q scan (n = 1,446)	CTPA (n = 3,119)	p-Value	V/Q scan (n = 969)	CTPA (n = 969)	p-Value
Age (y)	67 ± 17	63 ± 18	<0.0001	65 ± 18	64 ± 18	0.37
Female	751 (52)	1,692 (54)	0.13	498 (51)	481 (50)	0.44
Hypertension	933 (65)	1,356 (43)	<0.0001	539 (56)	541 (56)	0.10
Diabetes	534 (37)	733 (24)	<0.0001	290 (30)	285 (29)	0.79
Smoking	318 (22)	638 (20)	0.24	216 (22)	224 (23)	0.67
Congestive heart failure	330 (23)	365 (12)	<0.0001	172 (18)	169 (17)	0.85
Heart rate (beats/min)	85 ± 19	92 ± 21	<0.0001	87 ± 15	86 ± 19	0.31
Systolic blood pressure (mm Hg)	131 ± 24	129 ± 24	0.01	130 ± 19	129 ± 24	0.69
Serum creatinine						0.99
(mg/dL)	1.4 [0.9–2.0]	0.8 [0.7–1.1]	<0.0001	1.1 [0.8–1.5]	1.1 [0.8–1.4]	
(μmol/L)	124 [80–177]	71 [62–97]		97 [71–133]	97 [71–124]	
GFR > 60 mL min <sup>-1</sup> /1.73 m <sup>-2</sup>	468 (32)	2,359 (76)	<0.0001	468 (48)	497 (50)	0.32
GFR 45–60 mL min <sup>-1</sup> /1.73 m <sup>-2</sup>	212 (15)	411 (13)	0.17	197 (20)	188 (19)	0.56
GFR 30–44 mL min <sup>-1</sup> /1.73 m <sup>-2</sup>	329 (23)	222 (7)	<0.0001	202 (21)	185 (19)	0.21
GFR < 30 mL min <sup>-1</sup> /1.73 m <sup>-2</sup>	437 (30)	127 (4)	<0.0001	102 (11)	117 (12)	0.16
Serum BUN (mg/dL)	29 [17–44]	17 [12–24]	<0.0001	23 [14–33]	21 [15–32]	0.19
Baseline hemoglobin (g/dL)	11.3 ± 2.1	11.6 ± 2.2	0.006	11.6 ± 2.2	11.7 ± 2.3	0.16
Charlson score	3.4 ± 2.3	3.1 ± 2.2	<0.0001	3.0 ± 2.0	2.9 ± 2.0	0.55
Ischemic heart disease	332 (23)	336 (12)	<0.0001	163 (17)	168 (17)	0.75
Background medical therapy						
ACE inhibitors/A-II blockers	825 (57)	1,196 (38)	<0.0001	488 (50)	479 (49)	0.60
Diuretics	508 (35)	516 (17)	<0.0001	252 (26)	251 (26)	0.96
MRA	80 (6)	119 (4)	0.008	46 (5)	42 (4)	0.66
Beta blockers	777 (54)	1,013 (32)	<0.0001	441 (46)	445 (46)	0.85
Insulin	248 (17)	247 (18)	<0.0001	109 (11)	112 (12)	0.83

Abbreviations: ACE, angiotensin-converting enzyme; BUN, blood urea nitrogen; CTPA, computed tomography pulmonary angiography; GFR, glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; V/Q, ventilation/perfusion.

Note: Data are number (%) or mean ± SD. For the matched group, comparisons were done with paired *t*-tests, Wilcoxon matched-pairs signed-rank test, or the McNemar's test.

When weighted regression analyses were performed, a robust sandwich variance was used to account for the weighted nature of the sample.<sup>34</sup>

Differences were considered statistically significant at the two-sided *p* < 0.05 level. Statistical analyses were performed using STATA version 16.1 (College Station, Texas, United States).

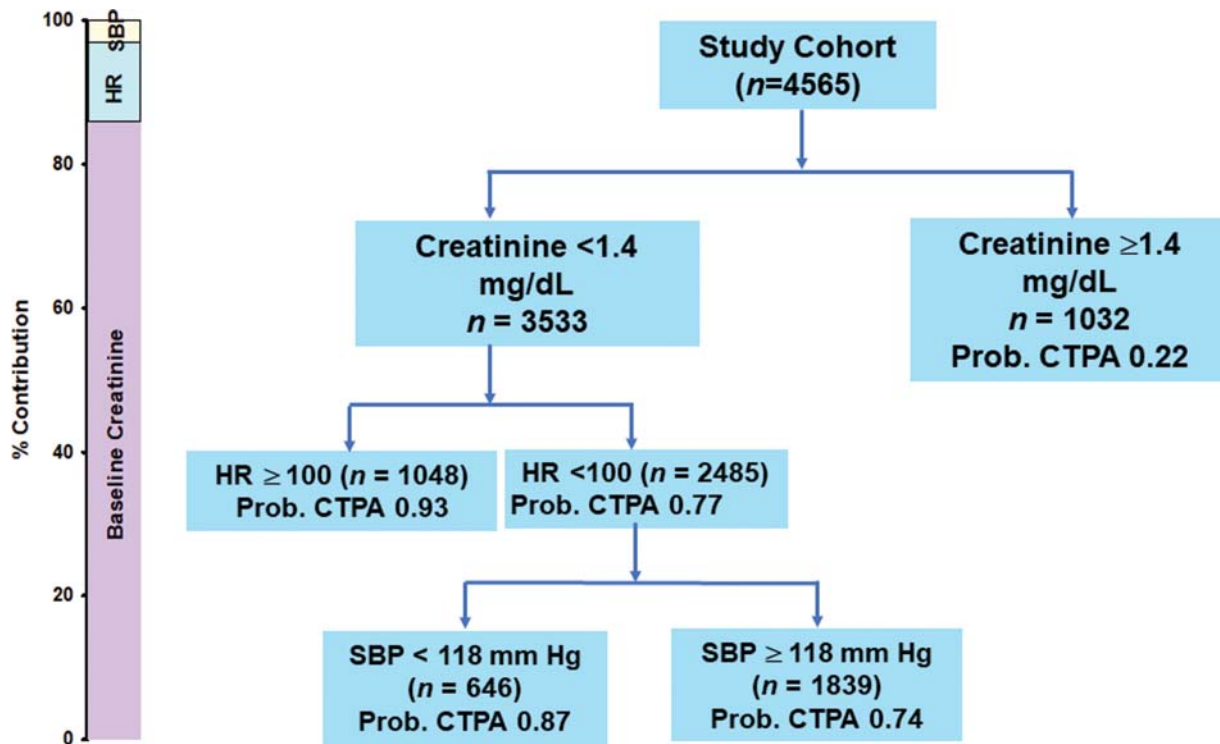
## Results

A total of 7,619 cases with suspected PE were screened for the study. Missing baseline creatinine (*n* = 322) and missing creatinine after the diagnostic test (*n* = 2,732; typically, patients evaluated in the emergency department and discharged from hospital) resulted in the exclusion of 3,054 patients. Of the remaining 4,565 patients, 3,119 (68.3%) were exposed to CM. The baseline clinical characteristics of the

study population prior to matching are shown in **Table 1** (left panel). Patients receiving V/Q lung scans were older, had worse renal function (higher baseline creatinine and blood urea nitrogen and lower eGFR), and more comorbidities, including higher rates of hypertension, diabetes, congestive heart failure, anemia, and ischemic heart disease. They also received more agents that may affect renal function such as angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers and diuretics.

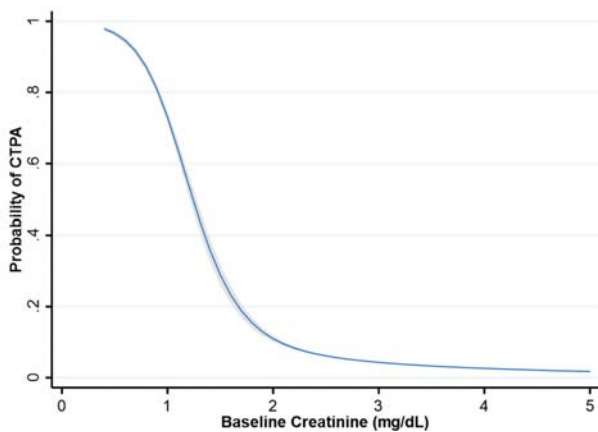
## CART Analysis

The results of the CART analysis for choosing the diagnostic modality in patients with suspected PE are shown in **Fig. 1**. The three variables found to provide optimal splits were baseline creatinine, heart rate, and systolic blood pressure, with the largest predictive information provided by baseline serum creatinine. The *c*-statistics of the three-variable CART



**Fig. 1** Decision-tree model for choosing the imaging modality for diagnosis of suspected PE. Values are expressed as the number of patients in each node and the probability of choosing CTPA in each of the terminal nodes. The stacked bar on the left displays the amount of information provided by each variable as a measure of variable importance. CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism.

model was 0.81. The tree also demonstrates that with elevated creatinine, the probability of performing CTPA was low regardless of other risk factors. Using baseline creatinine as a continuous variable, there was a rapid decline in the probability of choosing CTPA with creatinine above 1.0 mg/dL (►Fig. 2).



**Fig. 2** Predicted probability (95% confidence interval) of choosing CTPA as the diagnostic modality in patients with suspected PE according to baseline creatinine as a continuous variable in the whole study cohort. The probabilities were calculated from a logistic regression adjusting for other important predictors (heart rate and blood pressure). CTPA, computed tomography pulmonary angiography; PE, pulmonary embolism.

**Propensity-Score Matching**

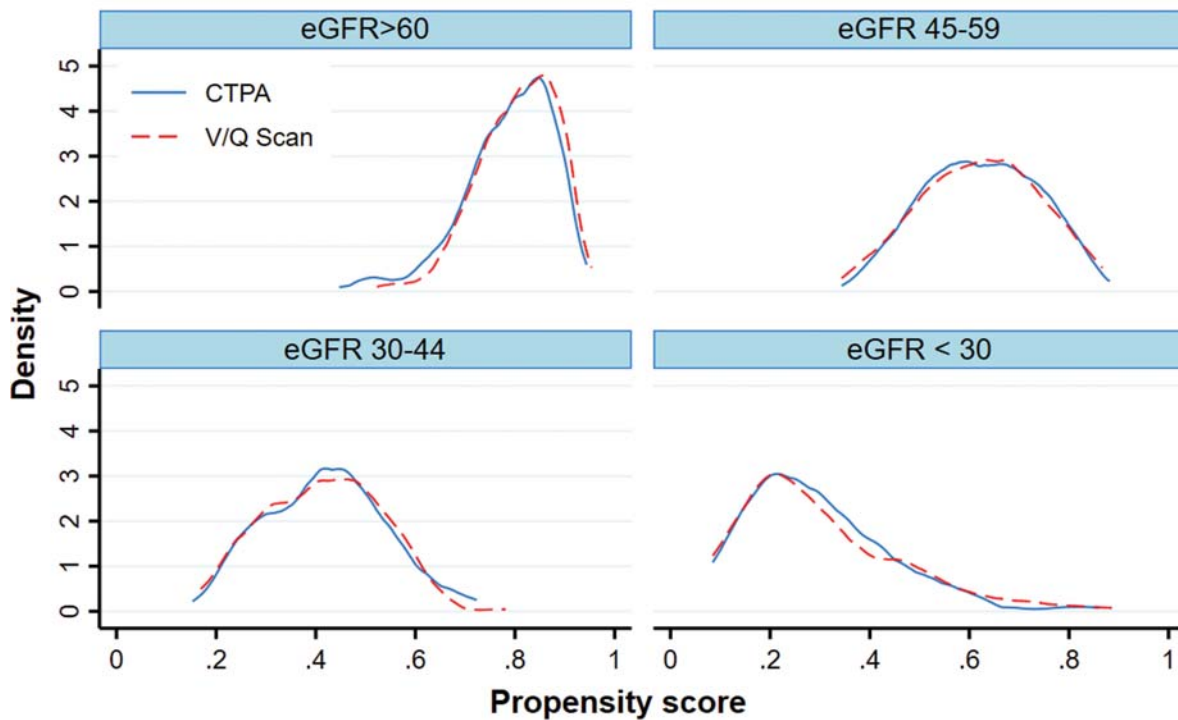
From the original cohort, 969 (31.1%) participants who received CTPA were matched on their propensity score to 969 (67.0%) patients who received V/Q lung scans. After propensity-score matching, the mean standardized difference in covariates between the two groups decreased from 31.8% (range: 3.8–76.9%) before matching to 2.3% (range: 0.1–6.6%) after matching.

Propensity-score distributions for each eGFR category in the matched CTPE and V/Q lung scan groups are shown in ►Fig. 3. Patients with eGFR ≥60 mL/min/1.73 m<sup>2</sup> had the highest propensity scores, representing a high likelihood that the patients underwent CTPE. The eGFR of 30 to 44 and <30 mL/min/1.73 m<sup>2</sup> had lower propensity scores and therefore higher likelihood of receiving V/Q lung scan.

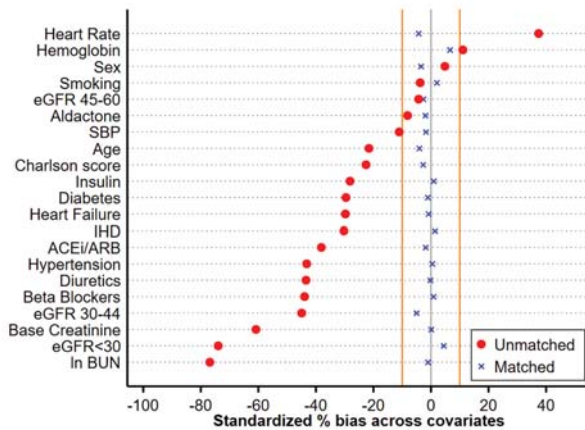
Patients were well balanced with respect to the individual variables included in the propensity model, with absolute standard differences between <10% for all variables (►Fig. 4). In the matched cohort, there were no significant differences between the groups for all clinical characteristics (►Table 1, right panel). The median time to performing the diagnostic test was similar in the CTPA (1 day [interquartile range: 0–5 days]) and V/Q scan (1 day [interquartile range: 0–4 days]) groups (p = 0.38).

**Effect of Contrast Media Exposure on AKI**

Following propensity-score matching, there were 44 AKI events (4.5%) in patients exposed to CM and 33 events (3.4%) in patients not exposed to CM (risk difference: 1.1%,



**Fig. 3** Kernel density distribution of propensity scores in study population according to baseline eGFR subgroups. eGFR, estimated glomerular filtration rate.



**Fig. 4** Covariable balance before (red circles) and after (blue crosses) matching. The standardized difference after propensity matching are all well within 10% (orange lines).

95% confidence interval [CI]:  $-0.6$  to  $2.9\%$ ). Compared with the control group, the odds ratio (OR) for the AKI in patients undergoing CTPA was  $1.39$  (95% CI:  $0.86$ – $2.26$ ;  $p = 0.18$ ). Similar results were obtained using AKI definitions of  $>25\%$  or  $\geq 0.5$  mg/dL ( $44 \mu\text{mol/L}$ ) increase in serum creatinine and doubling of creatinine (► **Table 2**).

Extending the time window for AKI diagnosis after CM exposure to 7 days as a sensitivity analysis yielded similar results. There were no significant differences in AKI events between patients exposed and unexposed to CM (► **Table 2**). The distribution of AKI events over the 7 days after the

diagnostic test was similar in the propensity-score-matched groups (► **Fig. 5**).

Propensity-score analysis of the subset of patients with baseline  $\text{eGFR} \leq 45 \text{ mL/min/1.73 m}^2$  yielded 293 patient pairs with mean standardized difference in covariates between the two groups of  $3.7\%$  (range:  $0.7$ – $8.0\%$ ) after matching. The rates of AKI were not statistically significantly different between the contrast ( $6.1\%$ ) and noncontrast ( $4.1\%$ ) groups (risk difference:  $2.0\%$ , 95% CI:  $-1.6$  to  $6.4\%$ ; OR:  $1.64$ , 95% CI:  $0.77$ – $3.83$ ).

Finally, after inverse probability weighting adjustment, the covariates were well balanced (standardized difference range:  $0.1$ – $9.7\%$ ). With the inverse probability weighting method, the  $\text{OR}_{\text{IPW}}$  for AKI in the CTPA versus V/Q scan was  $1.14$  (95% CI:  $0.72$ – $1.78$ ;  $p = 0.58$ ).

### Discussion

The current analysis of patients with suspected PE demonstrates that serum creatinine is a major determinant in the decision to perform CTPA in patients with suspected PE and that CTPA is frequently avoided in patients with renal dysfunction. In an analysis of 969 propensity-score-matched pairs of patients with suspected PE, AKI rates (using several common definitions) were not significantly different between patients who were exposed to CM during CTPA and V/Q lung scan recipients who were not exposed to CM.

Acute PE is the third leading cause of cardiovascular-related death and is responsible for the hospitalization of more than 250,000 patients in the United States annually. Prompt diagnosis is essential to reduce mortality.<sup>4</sup> CTPA is

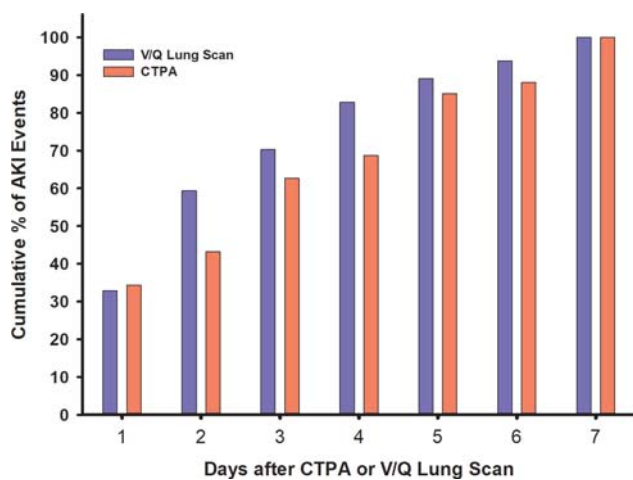
**Table 2** AKI endpoints

	AKI CTPE	AKI V/Q lung scan	Risk difference <sup>a</sup> (95% CI)	OR (95% CI) <sup>a</sup>	p-Value
<b>AKI at 72 hours</b>					
≥ 50% creatinine increase	44 (4.5%)	33 (3.4%)	1.1% (−0.6–2.9%)	1.39 (0.86–2.26)	0.18
> 25%/≥ 0.5 mg/dL creatinine increase <sup>b</sup>	105 (10.8%)	113 (11.7%)	−0.9% (−3.7–2.0%)	0.92 (0.69–1.22)	0.56
Creatinine doubling/dialysis	9 (0.9%)	12 (1.2%)	−0.3% (−1.3–0.7%)	0.75 (0.32–1.78)	0.51
<b>AKI at 7 days</b>					
≥ 50% creatinine increase	67 (6.9%)	64 (6.6%)	0.3% (−2.0–2.7%)	1.05 (0.74–1.50)	0.79
> 25%/≥ 0.5 mg/dL creatinine increase	112 (11.6%)	123 (12.7%)	−1.1% (−4.1–1.8%)	0.90 (0.68–1.18)	0.44
Creatinine doubling/dialysis	42 (4.3%)	49 (5.1%)	−0.8% (−2.7–1.2%)	0.85 (0.55–1.29)	0.45

Abbreviations: AKI, acute kidney injury; CI, confidence interval; CTPA, computed tomography pulmonary angiography; V/Q, ventilation/perfusion.

<sup>a</sup>Odds ratio or risk difference of CTPE versus V/Q lung scan.

<sup>b</sup>Creatinine 0.5 mg/L = 44 μmol/L.



**Fig. 5** Time to onset of AKI as cumulative proportions 7 days after the diagnostic test for PE. AKI, acute kidney injury; PE, pulmonary embolism.

the imaging modality of choice in the work-up of patients with suspected acute PE<sup>35</sup> and is an essential component of the clinical diagnostic algorithm.<sup>18</sup> However, there are various clinical situations in which V/Q lung scan is deemed reasonable or even preferred, particularly in patients with renal failure due to the concern of CA-AKI.<sup>18,19,36</sup> This was also evident in the current study as renal function was the strongest predictor choosing CTPA as the diagnostic modality in patients with suspected PE. However, V/Q scans are associated with a higher proportion of nondiagnostic results, particularly in older patients (partly owing to the presence of significant underlying cardiopulmonary disease)<sup>37,38</sup> who also suffer more from renal impairment.

Recent studies argued against a causal relationship between CM exposure and AKI.<sup>8–13</sup> These investigations have shown that the nephrotoxic risk of CM contrast is much lower than has been commonly thought and may not exist at all.<sup>8–13,39</sup> The major reason for the overestimation of CM-associated risk is ignoring the possibility that AKI can occur for reasons other than CM administration, and consequently, failure to use appropriate control (nonexposed) populations

in clinical series.<sup>10,12,39</sup> In uncontrolled studies, the incidence of reported CA-AKI following CTPA in patients with suspected PE ranges between 12 and 25%, depending on the definition used.<sup>5–7,23</sup> In the present study, AKI rates in patients exposed to CM were similar to those found in uncontrolled studies (10.8% using one definition), but were comparable to patients who were not exposed to CM.

Kooiman et al reported similar CA-AKI rates in patients undergoing CTPA who were randomized to no hydration versus sodium bicarbonate hydration.<sup>25</sup> Turedi et al reported no statistically significant differences between N-acetylcysteine, sodium bicarbonate, and normal saline prophylaxis in patients undergoing CTPA on suspicion of pulmonary PE.<sup>23</sup> These negative findings are consistent with the lack of causative relationship between CM and AKI.<sup>12</sup>

To our knowledge, our study represents the first study to include a control group of patients who were not exposed to CM in the setting of suspected PE. In keeping with previous controlled studies, we were unable to demonstrate a clinically meaningful (or statistically significant) difference in AKI event rates between patients undergoing CTPA or V/Q scan.

In choosing the diagnostic modality in patients with suspected PE, several factors can be used to determine whether intravenous CM should be administered. These include probability and necessity of an accurate diagnosis, alternative methods of diagnosis, risks of misdiagnosis, as well as risk for AKI. Because PE is a life-threatening diagnosis, there is an emergent indication for CTPA and insufficient time for preprocedural volume expansion. Therefore, choosing V/Q scanning may seem an attractive alternative. However, the current study results suggest that AKI risk should not be a key consideration, as contrast exposure does not meaningfully alter AKI risk.

## Limitations

It is important to consider several limitations pertinent to the methods of this study. First, this was a single-center posthoc analysis of our cardiac CTA data, and thus, the results must be regarded as hypothesis-generating and exploratory and require validation in other studies. Propensity-score-based

studies can provide excellent covariate balance but have inherent limitations including reduced sample size, resulting in a loss of both precision and generalizability.<sup>40</sup> Propensity-score methods cannot control for unmeasured confounding, which may be highly unbalanced in the treated and untreated groups and may arise when clinicians use their expert knowledge to make clinical decision regarding PE work-up. AKI events were categorized based on creatinine measurement obtained at variable time points after the diagnostic test based on the discretion of the treating physicians. Therefore, some of the AKI events may have been missed. Finally, our analysis of CM in risk patients with CKD stage IV or V (eGFR < 30 mL/min/1.73 m<sup>-2</sup>) is limited given the small number of patients in this category. Therefore, uncertainty remains with regard to the risk associated with CM use within this group.

## Conclusion

Intravenous CM administration was not associated with an increased risk of AKI in patients with suspected PE. Given the diagnostic superiority of CTPA, these results are reassuring with regard to the use of CTPE in patients with suspected PE perceived to be at risk for AKI.

### What is known about this topic?

- In uncontrolled studies, the incidence of contrast-associated acute kidney injury (AKI) following CT pulmonary angiography (CTPA) for suspected pulmonary embolism (PE) ranges between 12 and 25%.
- Some patients with suspected pulmonary embolism (PE) may undergo V/Q lung scan due to concern of contrast-associated AKI.

### What does this paper add?

- Serum creatinine is a major determinant in the decision to perform CTPA in patients with suspected PE and CTPA is frequently avoided in patients with renal dysfunction.
- In 969 propensity-score-matched pairs of patients with suspected PE, AKI rates (using several common definitions) were not significantly different between patients who were exposed to contrast media during CTPA and V/Q lung-scan recipients who were not exposed to CM.

**Conflict of Interest**  
None declared.

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