Propensity Score Matching as a Substitute for Randomized Controlled Trials on Acute Kidney Injury After Contrast Media Administration: A Systematic Review

Ilona A. Dekkers[1]
Aart J. van der Molen

OBJECTIVE. Controversy exists regarding the causal relationship between contrast media administration and the development of acute kidney injury because prospective randomized controlled trials (RCTs) confirming this relationship are lacking. In this systematic review we address studies using propensity score matching with regard to contrast-induced acute kidney injury and possible implications for future practice guideline development.

CONCLUSION. Propensity score matching can overcome the main limitations of conventional observational studies and could serve as an alternative in the absence of RCTs.

Intravascular low-osmolality iodinated contrast media (CM) have been associated with the development of acute kidney injury (AKI) [1, 2]. Currently, the descriptive term "post-contrast acute kidney injury" (PC-AKI) is used to describe all effects associated with a procedure involving CM administration; the terms "contrast-induced acute kidney injury" (CI-AKI) or "contrast-induced nephropathy" are reserved for acute kidney injury caused by the CM [1]. Most studies on contrast-enhanced acute kidney injury to date have been studies after intra-arterial CM administration in coronary angiography, percutaneous coronary intervention (PCI), or both and have lacked an adequate control group and, therefore, have limited generalizability to IV CM administration [3, 4]. Independent elevations in serum creatinine due to competing nephrotoxic risk factors in hospitalized patients and temporal physiologic fluctuations further complicate studies focused on the assessment of PC-AKI [5–7]. Controversy exists regarding the causal relationship between exposure to IV CM and the development of AKI because prospective randomized controlled trials (RCTs) are lacking [8–10]. Although RCTs have the strongest research design for assessing treatment effects and are considered to provide the highest level of scientific evidence for single studies, for several reasons we cannot solely rely on RCTs for clinical guideline development. First, the large number of questions regarding the management of PC-AKI negatively affects the feasibility of answering them all with RCTs, nor can society afford the time and resources associated with obtaining evidence through RCTs. Second, RCTs may not always be straightforward and generalizable because of a potential lack of external validity and restrictive enrollment criteria. The controlled setting of an RCT is not likely to occur in a real-life or hospital setting, and patients included in RCTs may not always be representative of patients encountered in clinical practice [11]. The assessment of rare outcomes, such as the incidence of PC-AKI, makes it particularly challenging to design and conduct an RCT because sample sizes would need to number in the hundreds of thousands of patients. In addition, ethical concerns could be present if CM is essential for diagnosis or if the diagnostic accuracy of contrast-enhanced CT is higher than that for unenhanced CT. For these reasons, the demand will continue to grow for evidence from well-designed observational studies on PC-AKI to guide clinicians, policymakers, and patients. Observational study designs have the advantage of providing relatively quick and inexpensive analyses of real-world data on large numbers of patients from existing databases with longitudinal follow-up over several years. Although the robustness of the conclusions drawn from observational studies has numerous well-known challenges, advanced statistical methods and improvement of data registries are increasingly combined to address these challenges. Ad-

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[1]Both authors: Department of Radiology, C2-S, Leiden University Medical Center, Albinusdreef 2, Leiden NL-2333 ZA, The Netherlands. Address correspondence to I. A. Dekkers (i.a.dekkers@lumc.nl).

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vanced statistical methods such as propensity score (PS) matching, a statistical matching technique that deals with unmeasured residual confounding, is increasingly being used in large studies on PC-AKI using nonrandomized observational data. In this systematic review, we give an overview of recent advanced observational studies on PC-AKI using PS matching and possible implications for guideline development.

How Does Propensity Score Matching Work?

PS matching was introduced in 1983 and is defined as the probability that a subject will receive a specific treatment conditional on the observed covariates [12, 13]. In the setting of PC-AKI, the PS represents the probability of having IV CM administered on the basis of the presence of certain predefined medical conditions. For each individual in the treatment and control group, propensity scores are calculated; they have a hypothetic distribution ranging from 0 (0% probability that a patient will be given a specific treatment) to 1.0 (100% probability that a patient will be given a specific treatment). Patients with a high PS for CM administration will tend to be older and have more comorbidities, which influences their likelihood of being offered IV CM in usual practice. Because propensity scores are an estimate of probabilities and not actual proportions, the treatment and control groups can overlap, which is needed for the two groups to be comparable. In practice, the two groups often partially overlap, and the validity of the analysis depends on the extent of these overlapping ranges. Careful selection of the covariates in the PS model is of great importance and must be done before the decision is made whether to initiate treatment [14]. These covariates should represent all relevant variables that could affect both the decision to treat and the outcome of interest. In PS analyses, it is only possible to adjust for known and measured variables, in comparison with true randomization in RCTs. After selection of these covariates, the PS is calculated using logistic regression that weights each variable according to how that variable influences the treatment assignment. Because PS matching effectively adjusts for confounders, it facilitates comparability between patient groups in the final analysis, which makes PS matching a useful technique for assessing risk factors for PC-AKI and potential protective effects of preventive strategies. Although PS matching minimizes several limitations of conventional observational studies, there are important challenges. The accuracy of the PS depends directly on the quality of the available variables, and missing data will not be incorporated. In addition, propensity scores are almost exclusively used to compare only two study groups; comparison of more groups is considered inappropriate [15]. A more detailed overview can be found elsewhere [15, 16].

TABLE 1: Propensity Score–Based Studies Evaluating Risk of PC-AKI After IV and Intraarterial CM Administration

Administration Type, First Author	Year of Publication	Reference No.	No. of Patients	Principal Findings
IV administration				
Ehrmann	2013	[18]	380	AKI incidence was similar in pairs of CM and control inclusions, matched on propensity for IV CM administration
Davenport	2013	[19]	20,242	IV low-osmolar CM had a significant effect on the development of AKI after CT for patients with serum creatinine levels of ≥ 1.6 mg/dL before CT
McDonald	2013	[20]	53,439	AKI risk was not significantly different between patients who did and did not receive CM
Davenport	2013	[21]	17,652	IV low-osmolar CM was found to be a nephrotoxic risk factor in patients with a stable eGFR ≤ 30 mL/min/1.73 m^2 but not in patients with an eGFR ≥ 45 mL/min/1.73 m^2 before CT
McDonald	2014	[22]	12,508	Risk of AKI was independent of CM exposure, even in patients with eGFR ≤ 30 mL/min/1.73 m^2
McDonald	2014	[23]	21,346	IV CM administration was not associated with excess risk of AKI, dialysis, or death, even among high-risk patients
McDonald	2015	[24]	6902	Rates of AKI, emergent dialysis, and mortality were not significantly higher in the group receiving CM than in the group that did not for patients with diminished renal function
Hsieh	2016	[25]	7100	CM exposure was not associated with an increased risk of ESRD development in patients without advanced CKD
Hinson	2017	[26]	17,934[a]	No significant differences were found in AKI rates in patients who underwent contrast-enhanced, unenhanced, or no CT
McDonald	2017	[27]	6877	No significant differences were found for AKI, emergent dialysis, or short-term mortality after IV CM in ICU patients with eGFR > 45 mL/min/1.73 m^2 before CT, but an increased risk of dialysis was found in patients with an eGFR ≤ 45 mL/min/1.73 m^2 before CT
McDonald	2017	[28]	5758	Rates of AKI, dialysis, and mortality were not significantly higher in patients receiving CM vs those who did not for all CKD subgroups

(Table 1 continues on next page)

TABLE 1: Propensity Score–Based Studies Evaluating Risk of PC-AKI After IV and Intraarterial CM Administration (continued)

Administration Type, First Author	Year of Publication	Reference No.	No. of Patients	Principal Findings
Intraarterial administration				
Medalion	2010	[29]	395	Use of ≥ 1.4 mL/kg of CM was found to be an independent predictor of postoperative acute renal failure in patients who underwent coronary artery bypass grafting
Reed	2010	[30]	58,957	No differences were found in the adjusted risk of PC-AKI among patients treated with iodixanol compared with those treated with low-osmolar CM
LaBounty	2012	[31]	107,994	Compared with patients exposed to iohexol, no differences were observed for patients exposed to iopamidol or ioversol for in-hospital hemodialysis, in-hospital mortality, or 30-day readmission for PC-AKI
Wang	2016	[32]	6992	Overall long-term mortality was comparable in patients receiving low-osmolar versus isoosmolar CM, but low-osmolar CM tended to induce higher long-term mortality in CKD cohorts
Sigterman	2017	[33]	583	Endovascular procedures for peripheral artery disease were associated with long-term loss of kidney function compared with exercise therapy alone
Shah	2017	[34]	230	Staged PCI was associated with worse renal function 4–12 weeks after intervention in patients with baseline GFR ≤ 60 cm^3/min
Caspi	2017	[35]	3050	Risk for AKI was similar among patients with ST-segment-elevation myocardial infarction who did and did not receive CM

Note—PC-AKI = post-contrast acute kidney injury, CM - contrast media, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, CKD = chronic kidney disease, PCI = percutaneous coronary intervention, GFR = glomerular filtration rate.
[a]Number of emergency department visits.

Materials and Methods

We conducted a systematic literature review to obtain all studies evaluating the risk of PC-AKI after both IV and intraarterial CM administration [17]. The literature was systematically searched in PubMed, MEDLINE, Embase, Web of Science, Central, Cochrane Library, Science Direct, and Academic Search Premier databases. After removal of duplicates, the search found 203 studies. After title and abstract selection, 51 studies were selected for full-text evaluation. Studies that did not use PS matching or solely focused on specific risk factors (e.g., race, sex, access route) were excluded.

Results

Overview of Studies Using Propensity Score Matching in Post-Contrast Acute Kidney Injury

The first study in the field of contrast nephropathy applying PS matching for studying the effects of CM on AKI was performed in 2010 [18]. In total, 18 studies evaluating the risk of PC-AKI using PS matching have been published: 11 evaluated IV and seven intraarterial CM administration [18–28, 29–35] (Table 1). Of these studies, half (9) were published after January 2015, indicating the increased use of PS matching for retrospective cohort studies. PS matching was also found to be increasingly used for evaluating specific preventive strategies for PC-AKI or evaluating specific risk factors, but these studies are beyond the scope of the current review.

IV Contrast Media Administration

Several studies using PS matching were performed to evaluate adverse effects of IV iodinated CM on renal function in patients undergoing contrast-enhanced CT [18–28]. In these studies, PS matching was used to stratify subjects according to their baseline renal function (serum creatinine or estimated glomerular filtration rate [eGFR]) to evaluate whether lower renal function was associated with increased risk. After matching, no significantly increased excess risk of PC-AKI was found in patients with a renal function above 30 mL/min/1.73 m^2. However, one study by Davenport et al. [21] found borderline increased risk for PC-AKI (odds ratio [OR], 1.40; 95% CI, 0.997–1.97; p = 0.07) in patients with moderate renal impairment (eGFR, 30–44 mL/min/1.73 m^2) and substantially increased risk for PC-AKI (OR, 2.96; 95% CI, 1.22–7.17; p = 0.005) in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2). A similar study investigating the incidence of PC-AKI by McDonald et al. [20] was unable to detect an increased risk for PC-AKI in patients with moderate or severe renal impairment (OR, 0.97; 95% CI, 0.72–1.30; p = 0.89), and subsequent analyses including additional predictors (such as IV fluid administration, medication use, and year of CT scan) did not alter the results [24]. In addition, the incidence of hard clinical endpoints (e.g., death, dialysis) after CM administration has been studied using PS analysis techniques. These studies did not find any significant differences in incidences of emergent dialysis and short-term mortality in patients receiving CM versus the control group [24, 27, 28], and the risk of AKI was independent of CM administration (OR, 0.94; 95% CI, 0.83–1.07; p = 0.38) [23].

Intraarterial Contrast Media Administration

Propensity score matching has also been used for evaluating the risk of PC-AKI after intraarterial CM administration. Intraarterial CM is frequently administered with second pass renal exposure (CM circulates first through a capillary bed, as in coronary artery injections during PCI) and may therefore pose a level of risk similar to that of IV CM administration [36, 37]. Initial PS studies evaluating intraarterial CM administration focused on identifying different risk factors that affect postinterventional recovery, rather than focusing solely on the effect

of contrast media on renal function [29, 30]. More recent studies evaluated the adverse effects of various classes of contrast media (low-osmolar versus isoosmolar) and cumulative contrast media dose in staged versus same-session PCI on renal function [31–33]. A recent study in 3050 patients with ST-segment elevation myocardial infarction was the first to our knowledge to evaluate patients who had been exposed to intraarterial CM administration (undergoing primary angioplasty) versus those who had not (undergoing fibrinolysis or no reperfusion) using PS matching. Among PS-matched patients, AKI rates were not significantly different in groups with or without intraarterial CM exposure (8.6% vs 10.9%, $p = 0.12$) [34].

Discussion

A previous meta-analysis of 13 conventional observational cohort studies with control populations was unable to find an increased incidence of PC-AKI after CM exposure [35]. However, these studies were hampered by the inclusion of patients with unrecognized and unaddressed nephrotoxic risk factors [38, 39]. PS-based studies add novel information because PS matching offers the possibility to deal with unmeasured residual confounding in the absence of RCTs. Since 2010, 18 studies that focused primarily on the increased risk of AKI after contrast administration have been published to our knowledge. Of them, 11 evaluated IV and seven intraarterial CM administration, and the overall findings suggest a substantially lower incidence of PC-AKI than previously estimated. It is important to note that these PS-matched studies made use of retrospective data. Because retrospective studies are limited to the number of available patients and amount of laboratory tests that were performed during clinical care, the quality of the studies largely depends on the quality of previously collected data. The lack of adjustment of competing predictor variables in previous conventional observational studies may explain the attributed increased risks to CM administration when compared with the recent studies using PS matching.

The results of recent large studies using PS matching do not permit strong inferences in the absence of standard care prophylactic measures, because many patients in these studies were preselected and possibly received prophylaxis to prevent PC-AKI. Further elucidation could be gained from prospective studies or retrospective studies using data of specific patient subgroups that did not receive CM prophylaxis irrespective of renal function, such as CT angiography and interventional angiography in the setting of acute events (e.g., pulmonary embolism, myocardial infarction, stroke) [40]. Besides ethical concerns of randomizing patients to a control arm without prophylaxis, another relevant critique regarding the use of unenhanced CT as a comparison group is the possible misallocation of confounders [41].

The results of these large PS matched studies have been used to design smaller prospective studies in patients with eGFR < 30 mL/min/1.73 m^2, but the latter failed and were terminated early (Davenport MS, McDonald RJ, personal communication). Therefore, future studies may have to rely more on well-designed, nonrandomized studies as a source of evidence in systematic reviews or meta-analyses [42], especially in a field such as pharmacovigilance or CM safety [42]. The value of PS matching in retrospective studies on PC-AKI indicates the importance of adding PS-adjusted effect estimates to original research articles, which could help to confirm or refute previous findings.

The increased use of PS matching for studies of patients with PC-AKI has implications for clinical guideline development because widely used initiatives for evaluating quality of evidence (such as Grading of Recommendations Assessment, Development and Evaluation [GRADE] and Appraisal of Guidelines for Research and Evaluation [AGREE]) have been primarily developed for interventional studies and do not differentiate between conventional observational studies and observational studies using PS matching [43]. Recently published methods on evaluating the risk of bias of nonrandomized interventions and adverse drug events may add value when assessing PS-based studies for new CM safety guidelines [44, 45]. In addition, the use of PS matching should be encouraged in studies using intraarterial CM administration in coronary angiography, PCI, or both, because the risk of true PC-AKI is also likely to have been overestimated for intraarterial CM administration [29, 30].

In conclusion, it is clear that the demand for evidence from observational studies for the prevention of CI-AKI will continue to grow. PS analysis methods are increasingly used in PC-AKI and will have a crucial role in large observational studies. Novel initiatives on the evaluation of evidence have been developed for observational studies that could be of use for the evaluation of the new PS-based studies for practice guideline development and guideline implementations in patient care.

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