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ORIGINAL

Contrast-associated acute kidney injury in the critically ill: systematic review and Bayesian meta-analysis

Stephan Ehrmann[1,2*], Andrew Quartin[3,4], Brian P Hobbs[5], Vincent Robert-Edan[6], Cynthia Cely[3,4], Cynthia Bell[7], Genevieve Lyons[5], Tai Pham[8,9,10], Roland Schein[3,4], Yimin Geng[11], Karim Lakhal[6] and Chaan S. Ng[12]

Abstract

Purpose: Critically ill patients, among whom acute kidney injury is common, are often considered particularly vulnerable to iodinated contrast medium nephrotoxicity. However, the attributable incidence remains uncertain given the paucity of observational studies including a control group. This study assessed acute kidney injury incidence attributable to iodinated contrast media in critically ill patients based on new data accounting for sample and effect size and including a control group.

Methods: Systematic review of studies measuring incidence of acute kidney injury in critically ill patients following contrast medium exposure compared to matched unexposed patients. Patient-level meta-analysis implementing a Bayesian nested mixed effects multiple logistic regression model.

Results: Ten studies were identified; only four took into account the baseline acute kidney injury risk, three by patient matching (560 patients). Objective meta-analysis of these three studies (vague and impartial a priori hypothesis concerning attributable acute kidney injury risk) did not find that iodinated contrast media increased the incidence of acute kidney injury (odds ratio 0.95, 95% highest posterior density interval 0.45–1.62). Bayesian analysis demonstrated that, to conclude in favor of a statistically significant incidence of acute kidney injury attributable to contrast media despite this observed lack of association, one's a priori belief would have to be very strongly biased, assigning to previous uncontrolled reports 3–12 times the weight of evidence strength provided by the matched studies including a control group.

Conclusions: Meta-analysis of matched cohort studies of iodinated contrast medium exposure does not support a significant incidence of acute kidney injury attributable to iodinated contrast media in critically ill patients.

Keywords: Contrast media (MeSH: D003287), Intensive care units (MeSH D007362), Drug-related side effects and adverse reactions (MeSH D064420), Tomography scanners, X-ray computed (MeSH: D015898), Percutaneous coronary interventions (MeSH: D062645)

*Correspondence: stephanehrmann@gmail.com
[1] Médecine Intensive Réanimation, Centre Hospitalier Régional et Universitaire de Tours, 37044 Tours, France
Full author information is available at the end of the article

Take-home message: This Bayesian meta-analysis of matched cohort studies of iodinated contrast medium exposure does not support a significant association with acute kidney injury incidence in critically ill patients. The continued belief that critically ill patients are particularly vulnerable to iodinated contrast medium nephrotoxicity rests on heavily weighting evidence from studies without a control group.

Introduction

Cases of acute kidney injury (AKI) following exposure to iodinated contrast media (contrast) have long been noted. This potential toxicity stresses the need to weight the risks and benefits of exposing patients to contrast [1, 2].

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Much of the evidence for contrast media nephrotoxicity has been derived from invasive cardiology procedures [3–5]. This setting does not allow for a control group against which to quantitatively assess the risk of contrast itself; this would require control patients to be exposed to all of the aspects of coronary angiography and/or intervention, except contrast. Indeed, the spectrum of mechanisms which are known to have a causative role in AKI are wide-ranging and include atheroembolism, low cardiac output, shock, and other nephrotoxic medications.

Despite the lack of controlled studies in the coronary angiography setting, there is a widespread assumption that a causal relationship exists between contrast infusion and AKI (often termed "contrast-*induced* nephropathy") rather than an association (contrast-*associated* AKI). Furthermore, by extrapolation, it is commonly inferred that administration of contrast for other purposes (e.g., intravenous infusion for computed tomographic scan) exposes patients to the same risks. This concept has been recently challenged in ward and outpatients, with observational studies comparing patients undergoing computed tomographic imaging with and without contrast infusion, questioning whether contrast itself is nephrotoxic [6–8].

Populations at increased risk of AKI after contrast administration include patients with already impaired kidney function, diabetes mellitus, dehydration and hypovolemia, heart failure, hypotension, and advanced age [3–5]. Critically ill patients have also been considered to be particularly prone to renal injury from contrast exposure [2, 9–11]. Indeed, in critically ill patients, the multi-organ insult is in many ways analogous to the multi-hit experimental models of renal toxicity of contrast [12–16]. On the other hand, AKI from critical illness itself renders rigorous analysis with controls even more important to delineate any attributable risk from contrast [2, 16]. This is not simply an academic issue: potentially exaggerated concerns about *contrast-induced nephropathy* may discourage crucial imaging studies necessary to accurately diagnose patients with acute life-threatening conditions [17].

We performed a systematic review and meta-analysis of studies which matched patients exposed to contrast with unexposed control patients to quantify the incidence of AKI attributable to iodinated contrast media in critically ill patients. We further examined how these studies, given their effective sample size and results, should influence rational evidence based physicians conducting analyses under different a priori assumptions, potentially reflecting prior beliefs of the clinical community.

Methods

The study was registered (PROSPERO-CRD42015025067) and reporting follows the PRISMA statement [18]. The clinical question was expressed according to the Patient, Intervention, Comparison, Outcome (PICO) system [19] (Table 1).

We searched Ovid MEDLINE and Embase, PubMed, Cochrane Library, Scopus, and Web of Science databases until 31 December 2015. Methodology is detailed in the electronic supplementary material (ESM). Briefly, studies, of any design type, evaluating intravascular administration of contrast were independently screened by two researchers. Studies comprising a control group and evaluating intensive care unit (ICU) patients were included in the qualitative synthesis and matched studies were included in the meta-analysis.

AKI was defined as a serum creatinine increase ≥0.3 mg/dL or ≥50% within 48 h of contrast administration in all datasets [1]. Meta-analysis was performed

Table 1 PICO formulation of the clinical question

PICO criteria	Studies to be included in the final sample	Studies not to be included in the final sample
Patient	Critically ill patients ICU patients	Ward patients Patients undergoing coronary angiography but not admitted to an ICU Patients admitted to coronary care units Isolated myocardial infarction patients
Intervention	Intravascular iodinated contrast administration (intra-arterial or intravenous)	Non-iodinated contrast, e.g., gadolinium Extravascular contrast, e.g., oral, rectal
Comparison	Matched contemporary patients not receiving intravascular iodinated contrast	Historical controls Unmatched studies
Outcome	AKI defined by Acute (within few days) increase of a renal function biomarker AND/OR acute need for renal replacement therapy	

The PICO (Patient, Intervention, Comparison, Outcome) formulation enables one to translate the primary objective of the study which consisted in "Assessing the attributable risk of acute kidney injury (AKI) related to intravascular iodinated contrast media (contrast) administration in critically ill patients admitted to an intensive care unit (ICU) based on studies matching patients exposed to contrast to unexposed patients" into operational criteria

on patient-level data using a hierarchical Bayesian nested mixed effects multiple logistic regression model, accounting for inter-study and within-study, inter-pair heterogeneity [20, 21]: see ESM.

According to Bayesian principles, the AKI risk attributable to contrast is measured by the a posteriori distribution of the odds ratio (OR). It represents the synthesis of data gathered in clinical studies and of a priori assumptions regarding the belief that contrast causes AKI (a priori distributions of the OR). Bayesian methodology enables evaluation of how evidence-based observers would assess the AKI risk attributable to contrast according to both their a priori belief and the presentation of the studies identified in the systematic review. According to Spiegelhalter et al., two types of meta-analyses were undertaken to model such a priori hypotheses [22].

Objective meta-analysis

To model a neutral state of a priori belief, i.e., having no hypothesis concerning an increased or decreased AKI incidence attributable to contrast, we used an a priori OR of 1 with an uninformative distribution. Given this neutral hypothesis, the resultant a posteriori OR distribution is predominantly representative of the data observed in the clinical studies. This a posteriori distribution would support the conclusion of a significant AKI incidence attributable to contrast, in case of an a posteriori OR above 1 with a 95% highest posterior density interval (HPD) not including 1.0. The amount of information the included studies convey was measured by their relative effective sample size (RESS) compared to the neutral a priori hypothesis (RESS = 1) [23].

Subjective meta-analysis

To model the commonly held belief that contrast increases the incidence of AKI, we used an a priori OR of 1.37 based on studies not comprising a control group, representative of the clinical community putative consensus [10, 11, 24, 25]. Whereas the a priori OR represents the magnitude of the AKI risk increase that the community attributes to contrast, its distribution and resulting RESS model the strength of belief in such an increased risk. Thus, the a priori RESS represents how confident physicians are in their prior belief.

As the a priori RESS is increased in the Bayesian model, the relative impact of newly added objective data on the a posteriori OR decreases. One may ultimately conclude in favor of a significant AKI incidence attributable to contrast owing to a predominant weight of this a priori hypothesis in regard to the data observed in the clinical studies. We determined the minimum a priori RESS value needed to attain such a significant a posteriori conclusion (a posteriori OR 95% HPD not including 1.0) in favor of a significant AKI incidence attributable to contrast [21].

Sensitivity to the above OR value of 1.37 was evaluated with analyses that assumed a 1.20 and 1.50 a priori OR value [22].

Results

Systematic review

The primary literature search yielded 5696 references, of which 1522 remained after removal of out-of-topic references (Fig. 1). Of these, 817 records were removed as they were exclusively coronary angiography studies. Of the remainder, 90 studies potentially comprised a control group, and of these, 10 assessed ICU patients for contrast-associated AKI and included an unexposed control group. These 10 studies provided the basis for the qualitative analysis (Table 2). The conclusions from these ten studies were variable: some reported increased rates of AKI in patients receiving contrast, while others reported higher rates of AKI in their unexposed controls [26–35]. Only four of these ten studies performed statistical risk adjustments for baseline prognostic risk factors of AKI (thus, the remaining six were considered at high risk of bias). Of these four studies, one used logistic regression to perform statistical risk adjustment [35] and three used patient matching [30, 31, 33]. None of these four studies, taken individually, identified a statistically significant incidence of AKI attributable to contrast.

The three studies with matched exposed and unexposed patients provided the basis for our quantitative Bayesian meta-analysis. The three studies, undertaken in France [33], Texas [30], and Florida [31], comprised a total of 1153 ICU patients; of these, 280 patients who received contrast were matched with 280 control patients. Detailed patient-level data are provided in the ESM. Overall, 47 patients (8%) developed AKI and 18 (3%) required renal replacement therapy. The overall hospital mortality rate was 23%.

Meta-analysis

Objective analysis

The a posteriori RESS, reflecting the amount of information contained in the individual patient-level datasets of the studies performed in France [33], Texas [30], and Florida [31] was, respectively, 5.84, 3.37, and 5.05 (Table 3). Synthesis of the three datasets in the objective meta-analysis yielded an a posteriori RESS of 14.6. All of the resulting HPD intervals of a posteriori distributions of OR included the null value of 1.0 (Fig. 2; Table 3).

Therefore, each individual study as well as the objective meta-analysis lacked evidence to support the conclusion that administration of contrast increased the incidence of AKI. Of note, beyond matching those

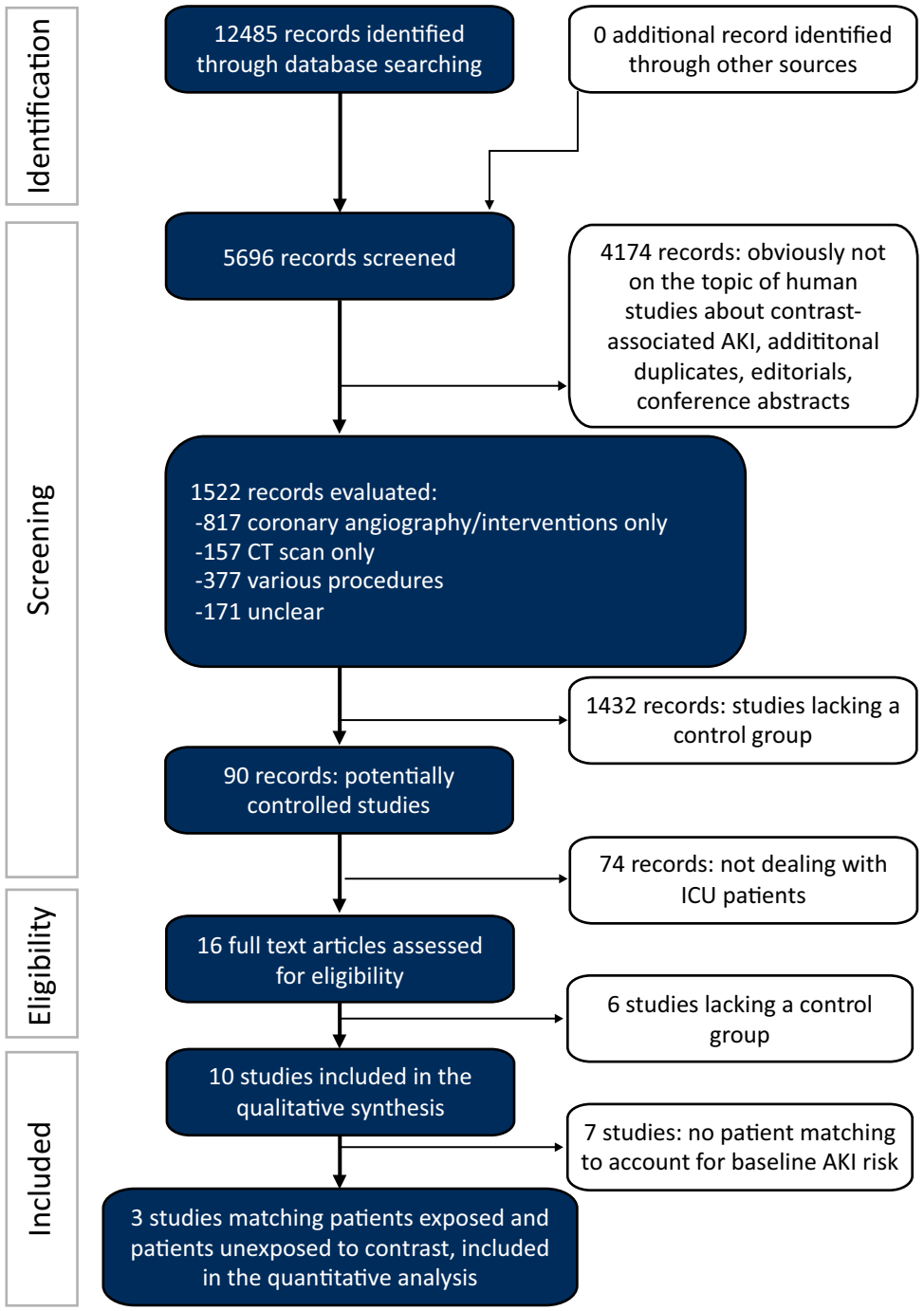

Fig. 1 PRISMA diagram. Beyond the 16 references reviewed in full text for eligibility, the full text of a further 80 references was reviewed during the screening process to enable robust classification. *Contrast* iodinated contrast media, *AKI* acute kidney injury

results were adjusted on age, volume of contrast (mL) for exposed patients, and creatinine at inclusion (µmol/L) which yielded 95% HPD intervals for the odds ratio of 0.976–1.02, 0.985–1.007, and 0.997–1.017, respectively.

Subjective analysis

Using an a priori OR of 1.37 (representing the putative consensus of the clinical community in favor of an AKI risk attributable to contrast) and modeling strength of belief within this hypothesis using an a priori RESS in

Table 2 Qualitative synthesis

References	Setting/design	Contrast group	Control group	Adjusted risk for contrast-associated AKI	Comments
Polena et al. 2005 [26]	ICU, retrospective cohort	*N* = 75 18.6% AKI	*N* = 75 2.0 % AKI	No statistical risk adjustment	
Tremblay et al. 2005 [27]	Trauma center, retrospective cohort	*N* = 56 9% AKI	*N* = 39 4% AKI	No statistical risk adjustment	Proportion of ICU patients unclear
Oleinik et al. 2009 [28]	Intracerebral hemorrhage, prospective cohort	*N* = 368 6% AKI	*N* = 130 14% AKI	No statistical risk adjustment	Main focus of study: computed tomographic angiography. Some control patients received contrast
McGillicuddy et al. 2010 [29]	Trauma center, retrospective cohort	*N* = 822 1.9% AKI	*N* = 249 2.4% AKI	No statistical risk adjustment	Proportion of ICU patients unclear
Ng et al. 2010 [30][a]	ICU, retrospective cohort	*N* = 81 17% AKI	*N* = 81 17% AKI	1-to-1 matching on baseline serum creatinine, SOFA score, and age	
Cely et al. 2012 [31][a]	ICU, prospective cohort	*N* = 53 9.4% AKI	*N* = 53 15% AKI	1-to-1 matching on baseline creatinine clearance, diabetes, mechanical ventilation, vasopressor use	
Kim et al. 2012 [32]	Trauma and surgical ICU, case–control	*N* = 389 30% AKI	*N* = 182 29% AKI	No statistical risk adjustment	Proportion of ICU patients unclear
Ehrmann et al. 2013 [33][a]	ICU, prospective cohort	*N* = 146 5.5% AKI	*N* = 146 5.5 AKI	1-to-1 propensity score-based matching	
Christ et al. 2015 [34]	Post-cardiac arrest, retrospective cohort	*N* = 89 15.7% AKI	*N* = 53 37.7% AKI	No statistical risk adjustment	
Gao et al. 2015 [35]	ICU, retrospective cohort	*N* = 474 14.8% AKI	*N* = 1896 12.4% AKI	Logistic regression OR 1.66 (0.72–3.90)	

ICU intensive care unit, *AKI* acute kidney injury, *Contrast* iodinated contrast media, *OR* odds ratio, *SOFA* sequential organ failure assessment

[a] Studies included in the quantitative meta-analysis

Table 3 Quantitative meta-analyses

Data source	Type	A priori hypotheses			A posteriori results		
		OR	95% HPD	RESS	OR	95% HPD	RESS
Individual studies							
Ehrmann et al., France [33]	Objective	1.0	(0.00, 4.33)	1.0	1.13	(0.36, 2.32)	5.8
Ng et al., Texas [30]	Objective	1.0	(0.00, 4.33)	1.0	1.13	(0.24, 2.76)	3.4
Cely et al., Florida [31]	Objective	1.0	(0.00, 4.33)	1.0	0.64	(0.11, 1.65)	5.1
Objective meta-analysis	Objective	1.0	(0.00, 4.33)	1.0	0.95	(0.45, 1.62)	14.6[a]
Subjective meta-analysis	Subjective	1.37	(1.06, 1.72)	70.0[b]	1.31	(1.00, 1.61)	79.1

A priori and a posteriori odds ratio (OR) and their distributions [evaluated by the 95% highest posterior density interval (HPD) of acute kidney injury (AKI) attributable to iodinated contrast media (contrast)]. Results of individual studies using the objective a priori hypothesis (no a priori opinion about AKI risk attributable to contrast, a priori OR = 1) are presented in the upper panel. Resulting a posteriori OR distributions did not reach statistical significance (1 included in the HPD interval). The a posteriori relative effective sample size (RESS) reflects the amount of information contained in the studies

Meta-analysis results are presented in the lower panel. Combining the objective a priori hypothesis (no a priori opinion about AKI risk attributable to contrast, a priori OR = 1) with the patient-level data observed in the three included studies in the objective meta-analysis, the a posteriori OR distribution did not reach statistical significance

[a] Significant information gain compared to the a priori objective hypothesis and the studies taken individually

[b] In the subjective meta-analysis, taking as an a priori hypothesis an OR value of 1.37 to reflect the commonly held belief of a significantly increase AKI risk attributable to contrast, a minimum a priori RESS value of 70 needed to be introduced in the model to observe an a posteriori OR distribution statistically supporting such an attributable risk (HPD interval not comprising 1); this RESS value was 4.8-fold higher than the one resulting of the objective meta-analysis

the range of the amount of information provided by the objective meta-analysis (RESS = 14.6 see above), the a posteriori distribution of the OR for AKI did not reach statistical significance (Fig. 2). In fact, the minimum a priori RESS value needed in the Bayesian model to observe an a posteriori OR distribution supporting the conclusion of a significant AKI incidence attributable to contrast was 70, i.e., an effective sample size 4.8 times higher than that of the objective meta-analysis (i.e., 14.6) and 70 times higher than the objective neutral reference a priori hypothesis (Table 3). Forest plots describing a posteriori OR estimations for increasing strengths of belief are depicted in Fig. 2.

Despite the presentation of the data gathered in the three included studies, observers still convinced that contrast causes AKI would need to start with an a priori strength of belief at least 4.8-fold greater than the information provided by those case-matched studies. Results were similar when performing the sensitivity analyses with a priori OR of 1.20 and 1.50. The minimum a priori RESS values needed to support the conclusion of a significant AKI incidence attributable to contrast were 3- to 12-fold the RESS of the objective meta-analysis (ESM).

Discussion

Our very sensitive systematic review showed that few studies used controls when evaluating the impact of iodinated contrast media on AKI occurrence. Actually, 95% of studies of contrast-associated AKI identified across all settings lacked a control group (Fig. 1). Six among ten studies performed in the ICU and comprising a control group did not adjust for baseline AKI risk. This is a major limitation as exposure to contrast is potentially linked to overall severity of disease, an important confounder for AKI risk. In fact, studies which observed the greatest increase in AKI incidence after contrast administration compared to the control group [26, 27] did not implement statistical risk adjustment (Table 2). The three studies identified that used case matching to account for baseline AKI risk, comprising a total of 560 ICU patients, did not identify a significant incidence of AKI attributable to iodinated contrast media. Bayesian meta-analysis, which explicitly accounts for sample size, results, and a priori beliefs, revealed that a rational evaluation of these matched studies could only coexist with a maintained confidence that contrast media causes AKI if one assigned a very high weight of evidence to the a priori belief supported by data lacking a control group.

Our results do not necessarily contradict experimental evidence for renal toxicity of iodinated contrast media, but rather question the clinical relevance of such findings. Numerous experimental studies documented renal toxicity of iodinated contrast media. Multi-hit animal models were frequently implemented to demonstrate consistent toxicity [12, 14, 15] and multiple patient aggressions during critical illness may constitute similar predisposing factors [16]. Conversely, contrast toxicity may be clinically negligible given the numerous already ongoing kidney aggression processes in the ICU. These laboratory results, along with widely held but less well founded preconceptions regarding risk in the clinical setting, led to our choosing a Bayesian approach, enabling integration of a priori knowledge and belief into the analysis. This point is important as, because of the paucity of

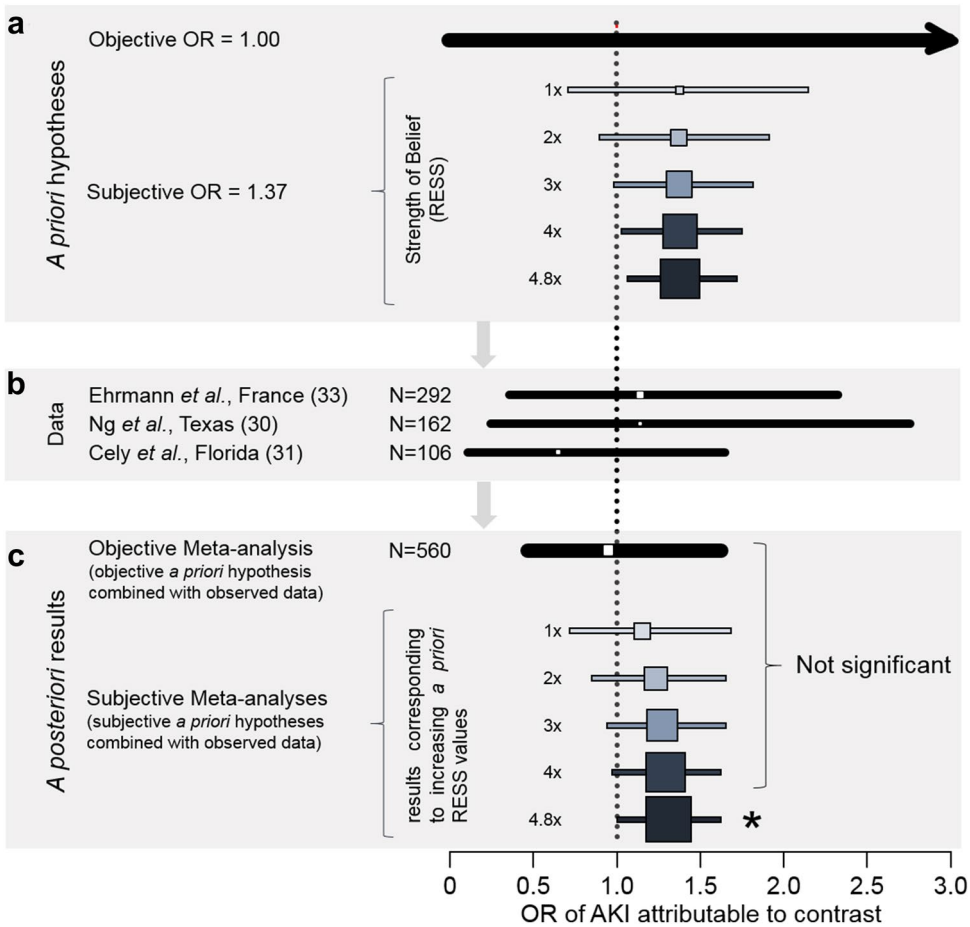

Fig. 2 Forest plot of the meta-analyses. **a** Depicts a priori hypotheses regarding both the magnitude of acute kidney injury (AKI) risk potentially attributable to iodinated contrast media (contrast), i.e., a priori odds ratio (OR) value and the strength of belief in this potential association, i.e., a priori relative effective sample size (RESS). For the objective analysis, those a priori hypotheses consisted in an OR = 1 with a reference RESS = 1 (*thick black bar*), thus making no hypothesis concerning an increased or decreased AKI incidence attributable to contrast. For the subjective meta-analysis, an OR = 1.37 was used to model the commonly held belief of a significant AKI risk attributable to contrast and five increasing RESS values were tested (*gray scale bars*). **b** Depicts actual data observed in the three studies included in the meta-analysis. **c** Depicts the a posteriori distributions of OR, resulting from the combination of the a priori hypotheses (**a**) with the observed data (**b**). For the objective meta-analysis, the a priori distribution (OR = 1, **a** *thick black bar*), when combined with the patient-level study data (**b**), did not yield statistically significant evidence for an AKI incidence attributable to contrast infusion as the a posteriori 95% highest posterior density (HPD) interval overlapped the null value of 1 (**c** *thick black bar*). Similarly, the subjective meta-analyses modeling an a priori belief in favor of a significant AKI risk attributable to contrast, when combined with the patient-level study data (**b**), did not yield statistically significant evidence for an AKI incidence attributable to contrast as a posteriori HPD intervals overlapped 1 (**c** *gray scale bars*), except when introducing a very high a priori RESS value* (i.e., 4.8 times the RESS of the objective meta-analysis). Thus, despite the presentation of the included studies, an evidence-based observer would need to hold an a priori strength of belief in an OR = 1.37 that is ≥4.8-fold the amount of information provided by the data of the matched clinical studies to remain convinced of a significant AKI incidence attributable to contrast. *Boxes* of a size proportional to the distribution's RESS were used to depict estimates of median OR, corresponding HPD intervals were represented by *horizontal bars*

studies comprising a control group, the a priori subjective belief plays an important role in the overall evidence assessment by the clinical community. Our results show that the value clinicians convinced of contrast toxicity place in studies not comprising a control group is exaggerated in terms of quantitative evidence. Spotlighting this imbalance of evidence prior and posterior to the studies comprising a control group requires Bayesian methodology. Taking into account the potential a priori belief of practitioners may thus possibly facilitate knowledge transfer and application of study findings to patient care.

However, Bayesian methodology may be less familiar than other meta-analysis methods to researchers and

clinicians. In summary, we first performed an objective (unbiased) analysis, modelling a naïve or neutral state in which no a priori information was introduced in the Bayesian model regarding the incidence of AKI attributable to contrast. This impartial meta-analysis, overcoming the potential low power limits of individual studies, showed no evidence of increased incidence of AKI attributable to contrast infusion.

We then undertook a subjective meta-analysis (referred to as a biased analysis in Bayesian terminology), modelling practitioners who have the commonly held belief that contrast increases the incidence of AKI. This belief was introduced in the analysis using an a priori OR for AKI attributable to contrast exposure of 1.37, a reasonable estimate from reports not comprising a control group [10, 11, 24, 25].

The subjective meta-analysis revealed that the incidence of AKI attributable to contrast was significant only if one assigned a very high strength to the a priori belief in such a risk (a priori RESS of 70), a weight of evidence some 4.8 times higher than that of all matched studies. This, in essence, reflects a state of a priori near certainty, to the extent that the observed data fail to inform one's opinion. In other words, the strength of belief an evidence-guided physician would have to have prior to being exposed to the information given by the case-matched studies identified by the systematic review needs to be extremely high to maintain a belief in an increased incidence of AKI attributable to contrast. To address variability when attempting to characterize the a priori belief of physicians, we undertook a sensitivity analysis of the subjective meta-analysis, expanding the range of a priori OR to 1.20 and 1.50. This additional sensitivity analysis demonstrated similar results, illustrating the robustness of our findings (ESM).

Our results are consistent with studies from outside the ICU setting which have already raised questions as to whether contrast, as used clinically for computed tomographic scanning, is nephrotoxic. McDonald et al. performed a single-center retrospective propensity score-matched study of patients undergoing computed tomography and observed a similar incidence of AKI, 4.8 and 5.1%, in 10,673 patients receiving and 10,673 not receiving contrast, respectively [7]. Those results were confirmed in another subset of 12,508 patients matched on baseline estimated glomerular filtration rate [8]. Stratified multiple regression analysis of a sample of about 6 million hospitalized patients showed similar results, i.e., lack of significant association between iodinated contrast media administration and AKI incidence [36]. The Bayesian methodology used in the present meta-analysis enables one to evaluate the potential impact of those large-scale studies performed outside the ICU. Indeed, while perhaps not directly germane to critically ill patients with a much higher baseline risk of AKI, such results would probably lower the a priori estimate of risk by physicians aware of them, correspondingly making it even more difficult to remain confident that contrast is nephrotoxic for ICU patients. For example, according to our sensitivity analysis, if the a priori OR fell to 1.20, after rational incorporation of the meta-analysis results, physicians should only be confident that contrast is nephrotoxic if they weighted their previous knowledge sources more than 10-fold as heavily as the evidence from the presently included studies (ESM).

In clinical research, it is difficult to attribute observation of a lack of statistically significant association to low power or true absence of association. In this regard the present meta-analysis adds significant information compared to the individual studies taken independently, the gain in information being quantified by the RESS of the objective meta-analysis (Table 3). It is unlikely that future studies will meaningfully challenge our results by identifying a high AKI incidence attributable to contrast. Indeed, such studies would have to be very large (to yield a RESS value at least 3- to 12-fold the RESS of the present objective meta-analysis) and/or find an effect of unprecedented magnitude (OR higher than the 1.50 value tested in the high attributable incidence hypothesis of our sensitivity analysis: ESM) to negate the present findings. Indeed, in small studies, lacking a control group, factors other than contrast exposure seem more likely to underlie AKI when it is observed [26, 27]. Similarly, preventive studies aiming at reducing the incidence of contrast-associated AKI are likely investigating other causes of renal injury. Despite two recent meta-analyses showing only low strengths of evidence in favor of such preventive strategies supporting this hypothesis, some currently ongoing trials may give a definite answer [37, 38].

Our study has limitations. Meta-analyses combine studies with some degree of heterogeneity. The three observational studies contributing to our meta-analyses used different matching strategies and were performed in different settings, prospectively and retrospectively, including patients of varying degrees of severity with various comorbidities. One study included exclusively patients with malignancies [30]. Inhomogeneity may, however, support the generalizability of the results. Our quantitative analysis excluded one study with a control group which did not use patient matching methodology to account for baseline AKI risk [35]. However, as this observational study similarly concluded towards the absence of an AKI incidence attributable to contrast in univariate and multivariate analysis, one may speculate with a high probability that overall results would

remain unaltered. The methodology used here to combine matched epidemiological studies (which constitute three out of four identified studies on the subject) is less common than techniques used for randomized clinical trials. However, randomized clinical trials are generally considered unethical when primarily testing for toxicity rather than efficacy. Furthermore, the Bayesian approach used enabled us to put results into the perspective of prior belief of the clinical community. This may potentially facilitate uptake of the results by clinicians at the bedside. Last, the definition of AKI used in our meta-analysis may be subject to some debate. We used a definition in common between the three matched studies and supported by current guidelines [1]. Previous definitions of contrast-associated AKI, relying on a 44 μmol/L absolute or 25% relative increase in serum creatinine concentration would yield, respectively, lower and higher incidences [11]. More sensitive or precise kidney monitoring based on functional and injury biomarkers may allow detection of an effect of iodinated contrast media on the kidney in the future [39, 40]. If such sensitive markers are required to detect an effect, however, it is likely of minimal clinical importance.

Our analysis may have important implications for critical care practitioners: when an ICU patient requires an imaging procedure, one should probably not refrain from using iodinated contrast if needed for diagnosis and management. The incidence of AKI attributable to contrast is, at most, very small. This low risk is likely outweighed by the benefits of more sensitive and specific imaging when undertaken with contrast [17]. Indeed, refraining from administering contrast may have serious consequences. However, the benefits in terms of imaging diagnostic performance have not been extensively studied in critically ill patients. The safety of contrast as observed in the present meta-analysis may enable development of such investigations in the future.

Despite animal experimental evidence and the common impression to the contrary, this systematic review of the literature and meta-analysis, with inherent methodological limitations, did not find evidence for an AKI incidence attributable to iodinated contrast media in critically ill patients. Physicians would have to give far more weight to the value of reports lacking a control group and subjective belief than from matched studies comparing exposed and unexposed patients to maintain confidence that iodinated contrast media are nephrotoxic in this patient population.

Electronic supplementary material
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Author details
[1] Médecine Intensive Réanimation, Centre Hospitalier Régional et Universitaire de Tours, 37044 Tours, France. [2] Faculté de Médecine, Université François Rabelais, Tours, France. [3] Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Department of Medicine, University of Miami Miller School of Medicine, Miami, FL, USA. [4] Department of Veterans Affairs Medical Center, Miami, FL, USA. [5] Department of Biostatistics, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA. [6] Réanimation Chirurgicale Polyvalente, Service d'Anesthésie-Réanimation, Hôpital Laënnec, Centre Hospitalier Universitaire, Nantes, France. [7] Division of Pediatric Nephrology and Hypertension, University of Texas Health Science Center-Houston, Houston, TX, USA. [8] Réanimation et USC Médico-chirurgicale, Hôpital Tenon, Assistance Publique, Hôpitaux de Paris, 75970 Paris, France. [9] INSERM UMR 1153, ECSTRA Team, Paris, France. [10] Saint Michael's Hospital, Interdepartmental Division of Critical Care, University of Toronto, Toronto, Canada. [11] Research Medical Library, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA. [12] Department of Radiology, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA.

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Compliance with ethical standards

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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References

1. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group (2012) KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2:S1–S138. doi:10.1038/kisup.2012.1
2. Brochard L, Abroug F, Brenner M, Broccard AF, Danner RL, Ferrer M, Laghi F, Magder S, Papazian L, Pelosi P, Polderman KH, ATS, ERS, ESICM, SCCM, SRLF Ad Hoc Committee on Acute Renal Failure (2010) An Official ATS/ERS/ESICM/SCCM/SRLF statement: prevention and management of acute renal failure in the ICU patient: an international consensus conference in intensive care medicine. Am J Respir Crit Care Med 181:1128–1155. doi:10.1164/rccm.200711-1664ST
3. Lautin EM, Freeman NJ, Schoenfeld AH, Bakal CW, Haramati N, Friedman AC, Lautin JL, Braha S, Kadish EG, Sprayregen S (1991) Radiocontrast-associated renal dysfunction: incidence and risk factors. AJR Am J Roentgenol 157:49–58. doi:10.2214/ajr.157.1.2048539
4. Mehran R, Aymong ED, Nikolsky E, Lasic Z, Iakovou I, Fahy M, Mintz GS, Lansky AJ, Moses JW, Stone GW, Leon MB, Dangas G (2004) A simple risk score for prediction of contrast-induced nephropathy after percutaneous coronary intervention: development and initial validation. J Am Coll Cardiol 44:1393–1399. doi:10.1016/j.jacc.2004.06.068
5. Brown JR, DeVries JT, Piper WD, Robb JF, Hearne MJ, Ver Lee PM, Kellet MA, Watkins MW, Ryan TJ, Silver MT, Ross CS, MacKenzie TA, O'Connor GT, Malenka DJ, Northern New England Cardiovascular Disease Study Group (2008) Serious renal dysfunction after percutaneous coronary interventions can be predicted. Am Heart J 155:260–266. doi:10.1016/j.ahj.2007.10.007
6. McDonald JS, McDonald RJ, Comin J, Williamson EE, Katzberg RW, Murad MH, Kallmes DF (2013) Frequency of acute kidney injury following intravenous contrast medium administration: a systematic review and meta-analysis. Radiology 267:119–128. doi:10.1148/radiol.12121460
7. McDonald JS, McDonald RJ, Carter RE, Katzberg RW, Kallmes DF, Williamson EE (2014) Risk of intravenous contrast material-mediated acute kidney injury: a propensity score-matched study stratified by

baseline-estimated glomerular filtration rate. Radiology 271:65–73. doi:10.1148/radiol.13130775
8. McDonald RJ, McDonald JS, Carter RE, Hartman RP, Katzberg RW, Kallmes DF, Williamson EE (2014) Intravenous contrast material exposure is not an independent risk factor for dialysis or mortality. Radiology 273:714–725. doi:10.1148/radiol.14132418
9. Rashid AH, Brieva JL, Stokes B (2009) Incidence of contrast-induced nephropathy in intensive care patients undergoing computerized tomography and prevalence of risk factors. Anaesth Intensive Care 37:968–975
10. Hoste EA, Doom S, De Waele J, Delrue LJ, Defreyne L, Benoit DD, Decruyenaere J (2011) Epidemiology of contrast-associated acute kidney injury in ICU patients: a retrospective cohort analysis. Intensive Care Med 37:1921–1931. doi:10.1007/s00134-011-2389-8
11. Lakhal K, Ehrmann S, Chaari A, Laissy JP, Régnier B, Wolff M, Pajot O (2011) Acute Kidney Injury Network definition of contrast-induced nephropathy in the critically ill: incidence and outcome. J Crit Care 26:593–599. doi:10.1016/j.jcrc.2011.05.010
12. Persson PB, Hansell P, Liss P (2005) Pathophysiology of contrast medium-induced nephropathy. Kidney Int 68:14–22. doi:10.1038/sj.ki.5001887
13. Andreucci M, Solomon R, Tasanarong A (2014) Side effects of radiographic contrast media: pathogenesis, risk factors, and prevention. Biomed Res Int 214:741018. doi:10.1155/2014/741018
14. Fernandes SM, Martins DM, da Fonseca CD, Watanabe M, de Vattimo MF (2016) Impact of iodinated contrast on renal function and hemodynamics in rats with chronic hyperglycemia and chronic kidney disease. Biomed Res Int 2016:3019410. doi:10.1155/2016/3019410
15. Rouse RL, Stewart SR, Thompson KL, Zhang J (2013) Kidney injury biomarkers in hypertensive, diabetic, and nephropathy rat models treated with contrast media. Toxicol Pathol 41:662–680. doi:10.1177/0192623312464122
16. Heyman SN, Rosen S, Rosenberger C (2008) Renal parenchymal hypoxia, hypoxia adaptation, and the pathogenesis of radiocontrast nephropathy. Clin J Am Soc Nephrol 3:288–296. doi:10.2215/CJN.02600607
17. Vandenberghe W, De Corte W, Hoste EA (2014) Contrast-associated AKI in the critically ill: relevant or irrelevant? Curr Opin Crit Care 20:596–605. doi:10.1097/MCC.0000000000000156
18. Stewart LA, Clarke M, Rovers M, Riley RD, Simmonds M, Stewart G, Tierney JF, PRISMA-IPD Development Group (2015) Preferred reporting items for a systematic review and meta-analysis of individual participant data. The PRISMA-IPD statement. JAMA 313:1657–1665. doi:10.1001/jama.2015.3656
19. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P (2007) Utilization of the PICO framework to improve searching PubMed for clinical questions. BMC Med Inform Decis Mak 7:16. doi:10.1186/1472-6947-7-16
20. Ruppert D, Wand MP, Carroll RJ (2003) Semiparametric regression. Cambridge University Press, New York
21. Hobbs BP, Thall PF, Lin SH (2016) Bayesian Group sequential clinical trial design using total toxicity burden and progression-free survival. J R Stat Soc Ser C Appl Stat 65:273–297. doi:10.1111/rssc.12117
22. Spiegelhalter DJ, Abrams KR, Myles JP (2003) Evidence synthesis. In: Spiegelhalter DJ, Abrams KR, Myles JP (eds) Bayesian approaches to clinical trials and health-care evaluation. Wiley, Chichester, pp 267–299
23. Morita S, Thall PF, Müller P (2008) Determining the effective sample size of a parametric prior. Biometrics 64:595–602. doi:10.1111/j.1541-0420.2007.00888.x
24. Huber W, Jeschke B, Page M, Weiss W, Salmhofer H, Schweigart U, Ilgmann K, Reichenberger J, Neu B, Classen M (2001) Reduced incidence of radiocontrast-induced nephropathy in ICU patients under theophylline prophylaxis: a prospective comparison to series of patients at similar risk. Intensive Care Med 27:1200–1209
25. Haveman JW, Gansevoort RT, Bongaerts AH, Nijsten MW (2006) Low incidence of nephropathy in surgical ICU patients receiving intravenous contrast: a retrospective analysis. Intensive Care Med 32:1199–1205. doi:10.1007/s00134-006-0198-2
26. Polena S, Yang S, Alam R, Gricius J, Gupta JR, Badalova N, Chuang P, Gintautas J, Conetta R (2005) Nephropathy in critically ill patients without preexisting renal disease. Proc West Pharmacol Soc 48:134–135
27. Tremblay LN, Tien H, Hamilton P, Brenneman FD, Rizoli SB, Sharkey PW, Chu P, Rozycki GS (2005) Risk and benefit of intravenous contrast in trauma patients with an elevated serum creatinine. J Trauma 59:1162–1166
28. Oleinik A, Romero JM, Schwab K, Lev MH, Jhawar N, Delgado Almandoz JE, Smith EE, Greenberg SM, Rosand J, Goldstein JN (2009) CT angiography for intracerebral hemorrhage does not increase risk of acute nephropathy. Stroke 40:2393–2397. doi:10.1161/STROKEAHA.108.546127
29. McGillicuddy EA, Schuster KM, Kaplan LJ, Maung AA, Lui FY, Maerz LL, Johnson DC, Davis KA (2010) Contrast-induced nephropathy in elderly trauma patients. J Trauma 68:294–297. doi:10.1097/TA.0b013e3181cf7e40
30. Ng CS, Shaw AD, Bell CS, Samuels JA (2010) Effect of IV contrast medium on renal function in oncologic patients undergoing CT in ICU. AJR Am J Roentgenol 195:414–422. doi:10.2214/AJR.09.4150
31. Cely CM, Schein RM, Quartin AA (2012) Risk of contrast induced nephropathy in the critically ill: a prospective, case matched study. Crit Care 16:R67. doi:10.1186/cc11317
32. Kim DY, Kobayashi L, Costantini TW, Chang D, Fortlage D, Curry T, Wynn S, Doucet J, Bansal V, Coimbra R (2012) Is contrast exposure safe among the highest risk trauma patients? J Trauma Acute Care Surg 72:61–66. doi:10.1097/TA.0b013e31823f36e0
33. Ehrmann S, Badin J, Savath L, Pajot O, Garot D, Pham T, Capdevila X, Perrotin D, Lakhal K (2013) Acute kidney injury in the critically ill: is iodinated contrast medium really harmful? Crit Care Med 41:1017–1026. doi:10.1097/CCM.0b013e318275871a
34. Christ M, Auenmüller KI, Amirie S, Brand M, Sasko BM, Trappe HJ (2016) Acute kidney injury and renal replacement therapy in victims from out-of-hospital cardiac arrest with administration of contrast agent. Herzschrittmarcherther Elektrophysiol 27:6–14. doi:10.1007/s00399-015-0410-6
35. Gao J, Zhang M, Fang G, Ye L, Tang W (2005) Risk and harm of contrast induced nephropathy in critically ill patients. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 27:366–370. doi:10.3760/cma.j.issn.2095-4352.2015.05.009
36. Wilhelm-Leen E, Montez-Rath ME, Chertow G (2016) Estimating the risk of radiocontrast-associated nephropathy. J Am Soc Nephrol 28. doi:10.1681/ASN.2016010021
37. Subramaniam RM, Suarez-Cuervo C, Wilson RF, Turban S, Zhang A, Sherrod C, Aboagye J, Eng J, Choi MJ, Hutfless S, Bass EB (2016) Effectiveness of prevention strategies for contrast-induced nephropathy: a systematic review and meta-analysis. Ann Intern Med 164:406–416. doi:10.7326/M15-1456
38. Eng J, Wilson RF, Subramaniam RM, Zhang A, Suarez-Cuervo C, Turban S, Choi MJ, Sherrod C, Hutfless S, Lyoha EE, Bass EB (2016) Comparative effect of contrast media type on the incidence of contrast-induced nephropathy: a systematic review and meta-analysis. Ann Intern Med 164:417–424. doi:10.7326/M15-1402
39. Salmon-Gandonnière C, Benz-de-Bretagne I, Mercier E, Joret A, Halimi JM, Ehrmann S, Barin-Le Guellec C (2016) Iohexol clearance in unstable critically ill patients: a tool to assess glomerular filtration rate. Clin Chem Lab Med 54:1777–1786. doi:10.1515/cclm-2015-1202
40. Bihorac A, Chawla LS, Shaw AD, Al-Khafaji A, Davison DL, Demuth GE, Gitzgerald R, Gong MN, Graham DD, Gunnerson K, Heung M, Jortani S, Kleerup E, Koyner JL, Krell K, Letourneau J, Lissauer M, Miner J, Nguyen HB, Ortega LM, Self WH, Sellman R, Shi J, Straseski J, Szalados JE, Wilber ST, Walker MG, Wilson J, Wunderink R, Zimmerman J, Kellum JA (2014) Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. Am J Respir Crit Care Med 189:932–999. doi:10.1164/rccm.201401-0077OC