



HAL
open science

Early Recognition of Persistent Acute Kidney Injury

Michael Darmon, Anne-Sophie Truche, Moustapha Abdel-Nabey, David Schnell, Bertrand Souweine

► **To cite this version:**

Michael Darmon, Anne-Sophie Truche, Moustapha Abdel-Nabey, David Schnell, Bertrand Souweine. Early Recognition of Persistent Acute Kidney Injury. *Seminars in Nephrology*, 2019, 39 (5), pp.431-441. 10.1016/j.semnephrol.2019.06.003 . hal-02304879

HAL Id: hal-02304879

<https://hal.science/hal-02304879v1>

Submitted on 20 Jul 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Early Recognition of Persistent Acute Kidney Injury

Michaël DARMON,^{1,2,3} Anne-Sophie TRUCHE,⁴ Moustapha ABDEL-NABEY,¹ David SCHNELL,⁵ Bertrand SOUWEINE.⁶

1. Medical ICU, Saint-Louis University Hospital, AP-HP, Paris, France;
2. Faculté de Médecine, Université Paris-Diderot, Sorbonne-Paris-Cité, Paris, France;
3. ECSTRA team, Biostatistics and clinical epidemiology, UMR 1153 (center of epidemiology and biostatistic Sorbonne Paris Cité, CRESS), INSERM, Paris, France;
4. Medical ICU, Grenoble University Hospital, La Tronche, France;
5. Medical-Surgical Intensive Care Unit, Angoulême Hospital, Angoulême, France;
6. Medical ICU, Gabriel Montpied University Hospital, Clermont-Ferrand, France.

Corresponding author

Michael DARMON, MD, PhD

Saint-Louis University Hospital

Phone: +33 1 42 49 94 22

michael.darmon@aphp.fr

Key words: Acute kidney injury; Biomarkers; Doppler; Resistive index; Sensitivity; Specificity; Renal Replacement Therapy

Abbreviations

ADQI: Acute Disease Quality Initiative

AKD: acute kidney disease

AKI: Acute kidney injury

CEUS: Contrast-enhanced ultra-sonography

CKD: Chronic kidney disease

GFR: glomerular filtration rate

ICU: intensive care unit

IGFBP-7: insulinlike growth factor binding protein 7

IL-18: Interleukin-18

K-DIGO: Kidney Disease Improving global outcomes

KIM-1: kidney injury molecule-1

L-FABP: Liver-type fatty acid-binding protein

NAG: N-acetyl-b-glucosaminidase

NGAL: neutrophil gelatinase-associated lipocalin

RFR: renal functional reserve

RI: Doppler-based renal resistive index

US: ultrasonography

RRT: renal replacement therapy

TIMP-2: tissue inhibitor of metalloproteinases2

95%CI: 95% Confidence Interval

Summary (word count: 135)

Despite the vast amount of literature dedicated to acute kidney injury and its clinical consequences, short term renal recovery has been relatively neglected. Recent studies suggest timing of renal recovery is associated with longer term risk of death, residual renal function and end-stage renal failure risk. In addition, longer AKI duration is associated with an increased requirement for renal replacement therapy. Comorbidities, especially renal and cardiovascular, severity of AKI, criteria to reach AKI diagnosis, as well as severity of critical illness have been associated with longer AKI duration, and more specifically risk of persistent renal dysfunction.

Since, predicting short-term renal recovery is clinically relevant, several tests, imaging, and biomarkers have been tested in way to predict course of AKI and chances for early renal recovery. In this review, definition of recovery, consequences of persistent AKI, and tools proposed to predict recovery will be described. Performance of these tools and their limits will be discussed.

Introduction

Although a vast amount of literature has been dedicated to acute kidney injury (AKI) and its clinical consequences, consideration short term renal recovery has been largely neglected [1]. In fact, renal recovery has been only recently defined and these criteria are still poorly validated [2]. Nevertheless, recent studies suggest timing of renal recovery to be associated with outcome [3–6], residual renal function and end-stage renal failure risk [3]. In addition, AKI duration is associated with an increased renal replacement therapy requirement (RRT). Consequently, predicting short term reversibility of AKI may help in assessing likelihood of needing RRT and ultimately could help determine optimal timing of RRT initiation (Figure 1) [7–9].

Several factors have been demonstrated to be associated with AKI duration. First, comorbidities, especially preexisting renal dysfunction and cardiovascular comorbidities, are associated with longer AKI duration and higher risk of persistent AKI [2–5]. Severity of AKI, both assessed by AKI stage [10] but also by criteria to reach AKI definition have been associated with higher risk of persistent AKI [2–5]. In this line, patients with AKI defined by both oliguria and elevated serum creatinine have higher risk of persistent AKI [2–5]. Last, severity of critical illness, need for additional organ support and probably, although poorly assessed, course of clinical illness are strong predictors of persistent AKI [2–5].

In this review, we will focus on short term AKI recovery, its definition, tools that have been investigated to allow its detection, their performance and limits. We will conclude on a paragraph underlining limits of current knowledge.

Renal recovery and time to recovery: definitions and prognostic impact

Renal recovery epidemiology description is limited by significant heterogeneity in available literature regarding the population studied, the definition used (RRT-independency, fall in one AKI severity stage, complete disappearance of AKI criteria, or return to baseline creatinine) or the timing of its assessment (at intensive care unit (ICU) or hospital discharge, or at the 3-month time point required to diagnose chronic kidney disease (CKD)). In a recent large observational study enrolling 16,968 ICU patients with Kidney Disease Improving global outcomes (KDIGO) stage 2 or 3 AKI, Kellum et al. aimed at describing the different patterns of renal recovery [3]. Among the 9,976 (58.8%) patients with complete renal recovery at hospital discharge, approximately 45% of them had an early sustained reversal (within 7 days), whereas 38% had an evolution marked by a relapsing AKI which ultimately recovered before hospital discharge. Of the 6,992 (41.2%) patients who did not exhibit renal recovery at hospital discharge, one third reversed their AKI at some point before another episode without recovery [3]. The early reversal group had the best prognosis (approximately 90% age-adjusted one-year survival), whereas the group without reversal had the worst (approximately 40% age-adjusted one-year survival) [3]. Interestingly, late recovery was associated with better outcomes than no recovery (75% one year-survival). This study and others [4, 5, 11] pointed out that the occurrence and the timing of renal recovery are associated with patients' outcomes. Of note, renal recovery is not limited to hospital discharge and should be search for up until one-year after the acute episode [12, 13]. However, despite recovery, AKI survivors are still at higher-risk for various complications ranging from CKD [14, 15] to coronary events and dramatically increased long-term mortality [16].

The Acute Disease Quality Initiative (ADQI) conference in 2017 proposed a consensual definition in order to develop a common lexicon, differentiating AKI from acute and chronic kidney diseases with a 7-

day and a 3-month threshold respectively [2] (Figure 2). Renal recovery corresponds to the disappearance of serum creatinine and urine output KDIGO criteria [2]. A reversal is rapid when it occurs within the first 48h and sustained when it persists for 48h [2]. This conference had also the advantage to refine acute kidney disease (AKD) description in terms of definition and severity and to acknowledge that AKI and AKD are a continuum. It appears a crucial period to mitigate patient's evolution toward CKD. These definitions however require to be adequately validated.

Some drawbacks persist in evaluating the incidence of renal recovery. Indeed, in the ICU settings, serum creatinine can be lowered by fluid resuscitation, increased volume of distribution and decreased creatinine production in sepsis-context [17], as well as a reduced muscle mass due to prolonged critical illness [18]. Hence, taking into account the confounding effect of prolonged stay on measured creatinine, Prowle et al. demonstrated a potential 135% increase in potential CKD diagnosis [19]. Moreover, AKI diagnosis and as a consequence its potential reversal is dependent on the baseline creatinine. If a prior patient's creatinine is unknown, the different available methods to estimate it, such as creatinine nadir during ICU stay, creatinine value on admission or MDRD-derived value assuming a glomerular filtration rate (GFR) of 75 ml/min/1.73 m² [10], could both be associated with a biased estimation of AKI incidence and its recovery [20, 21]. It is well-known that serum creatinine increase is a delayed marker of renal function [22]. As a consequence, even if AKI criteria no longer exists, renal functional reserve (RFR), defined as the kidney ability to increase GFR following a physiological or pathological stimuli could still be impaired, and the patient thus more prompt to develop subsequent AKI in face of a new injury or to evolve toward CKD [23]. For now, neither a validated glomerular or tubular RFR measure in acute context, nor a better alternative to creatinine measurement exist. Last, competitive risk arising from patients' death should be taken into account in studies assessing renal recovery as the main outcome.

Urinary indices

Historically, non-obstructive acute kidney injury related from mere hypoperfusion (pre-renal AKI) and from organic renal injury (intrinsic AKI), were differentiated and ability of tubule to concentrate urines assessed [24, 25]. This assessment was performed using urinary indices demonstrating ability of the tubule to reabsorb sodium and water (fractional excretion of sodium, natriuresis, fractional excretion of urea, urinary urea/creatinine ratio) [24, 25]. Most of these indices were validated in studies in which gold standard to distinguish “pre-renal azotemia” from “intrinsic AKI” were poorly defined, arbitrarily defined, or where gold standard included all or part of the tested markers [25–27]. In ICU settings, several cohort studies underlined the wide overlap of urinary indices when trying to distinguish transient AKI (≤ 3 days) from persistent AKI (> 3 days) [28–32]. This overlap between urinary indices results resulted in poor to inconsistent discriminative ability of these indices in this setting [28–31]. Moreover, this poor discriminative ability was independent of the underlying context, was found similarly in septic and non-septic patients, and was independent from diuretic use [28, 29] (Table 1).

Although physiological rationale supporting use of urinary indices remains, several mechanisms may explain lack of discriminative ability in ICU settings. First, AKI pathophysiological mechanisms may coexist in ICU patients explaining lack of ability to discriminate a single mechanism in most of the patients [33]. In addition, renal macrocirculatory hypoperfusion may have been overestimated as a mechanism explaining renal injury [34, 35]. Hence, most of the recent models suggest renal blood flow to be normal or even increased even in sepsis models with AKI [34]. Moreover, large animal model suggests renal blood flow not only to be increased during sepsis, but also correlated with renal dysfunction, the higher the dysfunction, the higher the renal blood flow [34]. Thus, renal

hypoperfusion may be due to microcirculatory alteration, related to medullary perfusion regulatory dysfunction and to capillary obstruction rather than to a decreased renal blood flow [34, 35].

Concluding from these data that the classic distinction between “pre-renal azotemia” vs. “intrinsic AKI” should be abandoned is probably an error. Very recent experimental studies confirm that both mechanisms exist, leading to very different pathophysiological mechanisms and distinctive gene expression [36]. This finding is important, demonstrating that different injury pathways may exist and suggesting potential biomarkers to differentiate them [36]. On the other side, whether this finding may be relevant at bedside, and whether some patients may experience AKI mainly related to a single of these pathways remain however unknown.

Renal Doppler

Ultrasonography (US) is performed routinely to assess the morphology of kidneys, the collecting system and the renal arteries and veins [37]. Doppler-based renal resistive index (RI), so-called Pourcelot index, and contrast-enhanced ultrasonography (CEUS) are tools derived from Doppler suggested to assess renal perfusion and predict AKI in ICU patients [38, 39].

Renal RI measurement is rapid, easy to perform and to learn. A half-day course on renal Doppler allowed inexperienced juniors physician to assess renal perfusion with a good reproducibility when compared to senior operators, however the precision of the measure was limited, raising concern about the clinical significance of RI changes smaller than ± 0.1 [37].

The measure is usually performed using 2- to 5-MHz transducers [39]. A longitudinal view of the kidney is obtained in B-mode US in the postero-lateral approach then Colour-Doppler allows vessels' localization [39]. A semi-quantitative evaluation of renal perfusion using Colour-Doppler has been proposed (Table 2) and is closely correlated to RI values (Figure 3a) [37, 40]. Either the arcuate arteries or the interlobar arteries are then insonated with pulsed wave Doppler. Good quality measure is ensured by using a Doppler gate as small as possible and by obtaining optimized waveforms with the lowest pulse repetition frequency without aliasing, to maximize waveform size, the highest gain without obscuring background noise, and the lowest wall filter [39]. A spectrum is considered optimal when three to five consecutive similar-appearing waveforms are noted and RIs from these waveforms are averaged to compute the mean RI for each kidney (Figure 3b). This parameter is calculated as follows:

$$RI = \frac{\text{peak systolic shift} - \text{minimum diastolic shift}}{\text{peak systolic shift}}$$

RI can theoretically range from 0 to 1 and is normally lower than 0.70.

As suggested by its name, RI has long been considered as a valuable marker of renal vascular resistance and blood flow [39, 41]. However, both experimental and clinical studies revealed a weak correlation between RI and these parameters [42, 43]. Indeed, numerous physiological and pathological parameters are known to influence RI. As a matter of fact, if experimental studies confirmed RI correlation to renal vascular resistance, this correlation is weak and only supraphysiological variations of resistance are responsible for small, quite insignificant, RI variations [44]. Furthermore, numerous factors influence RI (Figure 4), the first of them being renal and central vascular compliance (vascular distensibility) [43, 44]. This factor may explain RI elevation observed during various physiological and pathological situations: aging [45], hypertension [46, 47], diabetes mellitus [46], and renal graft with previous vascular alteration [47]. In the same way, any elevation of intraabdominal, intrathoracic and renal interstitial pressures is responsible for RI elevation, by diminishing vascular distensibility [43, 48, 49]. In addition to these factors, both hypoxemia and hypercapnia may elevate RI [45, 50].

Renal RI has been proposed to monitor renal perfusion in ICU patients, considering its supposed link to renal vascular resistance and blood flow. If clinical studies showed variations of RI in response to dopamine infusion or mean arterial pressure increase induced by norepinephrine, it must be kept in mind that these variations were very small and their significance in term of renal perfusion unclear [51, 52]. Based on the same hypothesis, other studies tried to demonstrate the role of RI to evaluate renal response to vascular expansion [53, 54], or to detect occult haemorrhage shock in normotensive trauma patients [55]. Given the numerous factors influencing RI and its weak correlation to renal

blood flow, its potential interest to monitor renal perfusion seems questionable. An interventional study has been specifically designed to explore this topic (NCT01473498, DORESEP study).

Renal RI has been proposed for early AKI detection [56, 57] or to differentiate between transient from persistent AKI in ICU patients [58, 59]. Most of these studies were performed in expert center with limited patients' samples and were of high risk of bias. A recent multicenter prospective cohort study was performed to evaluate the exact performance of RI to predict short-term reversibility of AKI or the need for RRT in a large cohort of unselected ICU patients [40]. In this study, although statistically associated with AKI occurrence and severity, RI performed poorly in predicting renal recovery or need for RRT and was adequately powered to suggest no to little interest in measuring renal Doppler in this setting (Figure 5) [40].

Contrast-Enhanced UltraSonography associates low mechanical index (MI) ultrasonography and microbubble-based contrast agents and has been proposed to assess organ perfusion [38]. Use of the intravascular microbubbles distribution along with their sensitivity to high-power acoustic pulses are used to obtain destruction-refilling sequences, from which some parameters proportional to blood flow can be derived (Figure 3c) [38]. Rational of the technique is strong, correlation between CEUS and perfusion having been validated in several models [60], and the technique initially developed has been both simplified and improved [61]. Data in ICU and especially in assessing renal perfusion are however limited. In a feasibility study performed in healthy volunteers, Schneider and colleagues demonstrated CEUS to detect renal cortical changes following angiotensin II or captopril administration [62]. Observed changes were parallel to those of estimated renal plasma flow as estimated by para-aminohippurate clearance [62]. Two recent studies in critically-ill patients assessed changes in CEUS derived parameters following vasoactive drugs, namely terlipressin and

norepinephrine were however disappointing [63, 64]. Although CEUS was able to find significant changes in perfusion, responses across patients were heterogeneous, unpredictable and of unclear relationship with patients characteristics [63, 64]. More importantly, inter-observer variability was as high as 25% and discordant changes across perfusion parameters observed in 25% of tested patients [63, 64]. Thus, although this technique is certainly to be studied its clinical relevancy at bedside is for now uncertain. Last, although assessing renal perfusion is believed to be a potential predictor of renal recovery, use of CEUS in this setting has never been formally evaluated.

Predictive models

Only few predictive clinical models have been developed and tested specifically to assess probability of renal recovery. None of them has been adequately assessed and validated.

The “renal angina index” has been developed and validated to assess risk of AKI at day 3 mainly in pediatric settings and is the most studied model [65, 66]. This score is the results of serum creatinine or fluid overload increase multiplied by contextual variables (organ or stem cell transplantation) or organ support [65, 66]. In pediatric setting, this score proves to allow discrimination between patients that will develop severe AKI at day 3, needs for RRT or poor outcome [67, 68]. Discriminative performance of this score ranged from fair to good, area under ROC curve ranging from 0.7 to 0.8 in most of the studies [65, 67–69].

In adult patients, this score has been less well studied although renal angina index or similar score have been tested [65, 69, 70]. These predictive scores have several limitations, as is their validation. First, these score do not specifically detect renal recovery but intend to detect one of its surrogate, namely progression toward severe AKI over time [65, 67–69]. While these two endpoints are probably closely correlated, it may be misleading to use both events interchangeably [4, 5]. Although extensively studied, especially in pediatric settings, rate of event is usually low, translating into wide confidence interval and uncertainty as regard to actual performance of these scores [65, 67–69]. Calibration of these scores, i.e. relationship between predicted risk and actual risk, is usually not reported [71, 72]. The poor specificity in several studies may suggest calibration to be poor, the score to overestimate risk of severe AKI/lack of short term reversibility, and interest for individual prediction remains therefore to be confirmed [65, 67–69]. Last, formal superiority of the score when compared to usual predictors of poor outcome is lacking from most of the studies [67, 68].

Biomarkers

A biomarker is an indicator that can be objectively quantified or evaluated to indicate the status of a biological process or condition. Most AKI biomarkers are biochemical parameters that have been developed to detect early onset of AKI. However, their use has ranged from early AKI detection to assessment of chances of early renal recovery. Ideally, AKI biomarkers should have high sensitivity and specificity for kidney injury in the presence of concomitant injury involving other organs and across a range of different ICU populations. Their kinetics should be associated with known biological mechanisms, should correlate with the extent of damage, and should yield specific threshold values allowing risk stratification. Their measurement should be performed using a minimally invasive technique, by a rapid, reliable, inexpensive and standardized clinical assay, and unaffected by drugs or other endogenous substances. It is highly unlikely that a single biomarker of AKI fulfilling all these needs may exist.

Biomarkers specific to the kidney can be classified into two broad classes, either functional markers to estimate the glomerular filtration rate (e.g., serum cystatin C), or damage markers indicating kidney stress (kidney injury molecule-1 (Kim-1), neutrophil gelatinase-associated lipocalin (NGAL), Liver-type fatty acid-binding protein (L-FABP), Interleukin-18 (IL-18), N-acetyl-b-glucosaminidase (NAG), insulinlike growth factor binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases 2 (TIMP2)).

Although both classes have been investigated for prediction of renal recovery or persistent AKI, none has been sufficiently validated in this setting.

A few studies specifically assessed use of function or damage biomarkers in predicting short-term renal recovery [32, 73, 74] or an indirect assessment of recovery, namely progression to severe AKI or need for RRT [74–77]. Unsurprisingly NGAL is the most studied biomarker [32, 73–77], although

other markers have been tested including Cystatin C, KIM-1 and cell-cycle arrest ([TIMP-2].[IGFBP-7]), endostatine, or L-FABP [32, 73, 75, 77–81]. Results of the available studies are disappointing, most of the later demonstrating significant association between biomarkers and renal recovery but with poor to fair performance of biomarkers [32, 73–75, 77, 80], high rate of false positive results [73], limited input when compared to usual markers [76], clinical score [74], or kinetic change in serum creatinine [32]. Overall, results of these studies suggest a lack of obvious benefit of biomarkers to predict renal recovery and need for carefully designed phase 3 studies evaluating input of biomarkers when compared to clinical judgement at bedside.

Limits of current knowledge

Most of the studies performed to date are limited by imperfect definitions of renal recovery, various influence of time chosen to define transient/persistent AKI, and gold standard. The threshold of serum creatinine to define recovery is likely to influence rate of recovery as is rate of approximated renal dysfunction or of unknown preexisting renal dysfunction [20]. Moreover, patients without available baseline serum creatinine, differ significantly from patients with known baseline serum creatinine, suggesting selection of patients on this criterion may introduce a selection bias [18]. Last, influence of time dependency of renal recovery is poorly assessed or accounted for [5]. Hence, death or ICU/hospital discharge act as confounders in recovery assessment and this confusion factor has poorly been taken into account in previous studies and further limits reliability of recovery definition [5, 20]. Last, in patients with acute kidney disease, duration of ICU stay, muscle wasting and subsequent decrease in theoretical baseline serum creatinine may deserve to be taken into account in recovery definition [18]. These limits to detect and define recovery have been poorly assessed so far and may deserve to be more closely evaluated. Similarly, risk of transition from AKI to recovery at various time points are currently unknown and needs to be evaluated (Table 3).

Assessing reliability of tool aiming to predict an event require several information frequently missing from existing studies. First, uncertainty reported as confidence interval, is required and may deserve to be accounted for. In this line, uncertainty resulting from sampling in the studied population may influence findings [82]. Comparison to usual test, at similar period, is mandatory to assess input of marker, test or score when compared to usual severity criteria. In this line, comparison of discriminative ability (area under ROC curve) might require formal assessment rather than informal comparison of estimators [83]. Both discriminative ability and prognostic influence may deserve to be delineated respectively [84, 85]. In this line, adequate validation of predictive model is required

before drawing definite conclusion [72], both discriminative ability of the model and its calibration being required and informative [71, 72]. Last, although gaining popularity, new criteria to assess input of biomarker, such net reclassification index, are poorly reliable, may overstate incremental value of a biomarker, and should be interpreted only in light of usual discriminative and predictive ability of the tested marker [86, 87].

Last, clinically relevance of early detection of renal recovery or lack of this later deserves to be validated. Preliminary studies and theoretical framework suggest early detection of high risk patients may help in adapting treatment in way to avoid further renal deterioration [88] or to identify patients at high risk of requiring renal replacement therapy which may help determining optimal timing strategy for this later [7–9]. However, validation of these assumptions is needed in way to more clearly underline input of risk stratification strategies in real life and then assess their cost-effectiveness.

Conclusion

Although definition of renal recovery has been standardized and its clinical relevancy demonstrated, several uncertainties remain. First, exact rate of recovery, accounting for competing risk is unknown as well as optimal definition to conclude to renal recovery. Moreover, although predicting short term recovery might help in optimizing patients' management and anticipate outcome, available imaging tests, biomarkers and scores have not yet been validated and, at the best were found to be poorly efficient in preliminary studies. Focus on recovery is however surprisingly recent and additional studies will hopefully help in more clearly delineating optimal definition and identify patients at high risk of non-recovery using either single, or more likely, association of scores and biomarker strategies.

DISCLOSURES

Dr. Darmon report having received consulting fees from Sanofi and Gilead-Kite, research support from Astute Medical and MSD, and speaker fees from MSD, Gilead-Kite and Astellas.

Other authors declare having no conflict of interest to declare.

FUNDING

None

REFERENCES

1. Ronco C, Ferrari F, Ricci Z (2017) Recovery after Acute Kidney Injury: A New Prognostic Dimension of the Syndrome. *Am J Respir Crit Care Med* 195:711–714. <https://doi.org/10.1164/rccm.201610-1971ED>
2. Chawla LS, Bellomo R, Bihorac A, et al (2017) Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol* 13:241–257. <https://doi.org/10.1038/nrneph.2017.2>
3. Kellum JA, Sileanu FE, Bihorac A, et al (2016) Recovery After Acute Kidney Injury. *Am J Respir Crit Care Med*. <https://doi.org/10.1164/rccm.201604-0799OC>
4. Perinel S, Vincent F, Lautrette A, et al (2015) Transient and Persistent Acute Kidney Injury and the Risk of Hospital Mortality in Critically Ill Patients: Results of a Multicenter Cohort Study. *Crit Care Med* 43:e269-275. <https://doi.org/10.1097/CCM.0000000000001077>
5. Truche AS, Ragey SP, Souweine B, et al (2018) ICU survival and need of renal replacement therapy with respect to AKI duration in critically ill patients. *Ann Intensive Care* 8:127. <https://doi.org/10.1186/s13613-018-0467-6>
6. Uchino S, Bellomo R, Bagshaw SM, Goldsmith D (2010) Transient azotaemia is associated with a high risk of death in hospitalized patients. *Nephrol Dial Transplant* 25:1833–1839. <https://doi.org/10.1093/ndt/gfp624>
7. Gaudry S, Hajage D, Schortgen F, et al (2016) Initiation Strategies for Renal-Replacement Therapy in the Intensive Care Unit. *N Engl J Med* 375:122–133. <https://doi.org/10.1056/NEJMoa1603017>
8. Barbar SD, Clere-Jehl R, Bourredjem A, et al (2018) Timing of Renal-Replacement Therapy in Patients with Acute Kidney Injury and Sepsis. *N Engl J Med* 379:1431–1442. <https://doi.org/10.1056/NEJMoa1803213>
9. Zarbock A, Kellum JA, Schmidt C, et al (2016) Effect of Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients With Acute Kidney Injury: The ELAIN Randomized Clinical Trial. *JAMA* 315:2190–2199. <https://doi.org/10.1001/jama.2016.5828>
10. Kellum JA, Lameire N, Aspelin P, et al (2012) Kidney disease: Improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney International Supplements* 2:1–138. <https://doi.org/10.1038/kisup.2012.1>
11. Han SS, Kim S, Ahn SY, et al (2013) Duration of acute kidney injury and mortality in critically ill patients: a retrospective observational study. *BMC Nephrol* 14:133. <https://doi.org/10.1186/1471-2369-14-133>

12. Cerdá J, Liu KD, Cruz DN, et al (2015) Promoting Kidney Function Recovery in Patients with AKI Requiring RRT. *Clin J Am Soc Nephrol* 10:1859–1867. <https://doi.org/10.2215/CJN.01170215>
13. Ichai C, Vinsonneau C, Souweine B, et al (2016) Acute kidney injury in the perioperative period and in intensive care units (excluding renal replacement therapies). *Ann Intensive Care* 6:48. <https://doi.org/10.1186/s13613-016-0145-5>
14. Jones J, Holmen J, De Graauw J, et al (2012) Association of complete recovery from acute kidney injury with incident CKD stage 3 and all-cause mortality. *Am J Kidney Dis* 60:402–408. <https://doi.org/10.1053/j.ajkd.2012.03.014>
15. Coca SG, Singanamala S, Parikh CR (2012) Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int* 81:442–448. <https://doi.org/10.1038/ki.2011.379>
16. Heung M, Steffick DE, Zivin K, et al (2016) Acute Kidney Injury Recovery Pattern and Subsequent Risk of CKD: An Analysis of Veterans Health Administration Data. *Am J Kidney Dis* 67:742–752. <https://doi.org/10.1053/j.ajkd.2015.10.019>
17. Doi K, Yuen PST, Eisner C, et al (2009) Reduced production of creatinine limits its use as marker of kidney injury in sepsis. *J Am Soc Nephrol* 20:1217–1221. <https://doi.org/10.1681/ASN.2008060617>
18. Schetz M, Gunst J, Van den Berghe G (2014) The impact of using estimated GFR versus creatinine clearance on the evaluation of recovery from acute kidney injury in the ICU. *Intensive Care Med* 40:1709–1717. <https://doi.org/10.1007/s00134-014-3487-1>
19. Prowle JR, Kolic I, Purdell-Lewis J, et al (2014) Serum creatinine changes associated with critical illness and detection of persistent renal dysfunction after AKI. *Clin J Am Soc Nephrol* 9:1015–1023. <https://doi.org/10.2215/CJN.11141113>
20. Schetz M, Gunst J, De Vlieger G, Van den Berghe G (2015) Recovery from AKI in the critically ill: potential confounders in the evaluation. *Intensive Care Med* 41:1648–1657. <https://doi.org/10.1007/s00134-015-3946-3>
21. Bernardi MH, Schmidlin D, Ristl R, et al (2016) Serum Creatinine Back-Estimation in Cardiac Surgery Patients: Misclassification of AKI Using Existing Formulae and a Data-Driven Model. *Clin J Am Soc Nephrol* 11:395–404. <https://doi.org/10.2215/CJN.03560315>
22. Ronco C, Kellum JA, Haase M (2012) Subclinical AKI is still AKI. *Crit Care* 16:313. <https://doi.org/10.1186/cc11240>
23. Ronco C, Bellomo R, Kellum J (2017) Understanding renal functional reserve. *Intensive Care Med* 43:917–920. <https://doi.org/10.1007/s00134-017-4691-6>

24. Lameire N, Van Biesen W, Vanholder R (2005) Acute renal failure. *Lancet* 365:417–430. [https://doi.org/10.1016/S0140-6736\(05\)17831-3](https://doi.org/10.1016/S0140-6736(05)17831-3)
25. Espinel CH (1976) The FENa test. Use in the differential diagnosis of acute renal failure. *JAMA* 236:579–581
26. Miller TR, Anderson RJ, Linas SL, et al (1978) Urinary diagnostic indices in acute renal failure: a prospective study. *Ann Intern Med* 89:47–50
27. Carvounis CP, Nisar S, Guro-Razuman S (2002) Significance of the fractional excretion of urea in the differential diagnosis of acute renal failure. *Kidney Int* 62:2223–2229. <https://doi.org/10.1046/j.1523-1755.2002.00683.x>
28. Darmon M, Vincent F, Dellamonica J, et al (2011) Diagnostic performance of fractional excretion of urea in the evaluation of critically ill patients with acute kidney injury: a multicenter cohort study. *Crit Care* 15:R178. <https://doi.org/10.1186/cc10327>
29. Pons B, Lautrette A, Oziel J, et al (2013) Diagnostic accuracy of early urinary index changes in differentiating transient from persistent acute kidney injury in critically ill patients: multicenter cohort study. *Crit Care* 17:R56. <https://doi.org/10.1186/cc12582>
30. Dewitte A, Biais M, Petit L, et al (2012) Fractional excretion of urea as a diagnostic index in acute kidney injury in intensive care patients. *J Crit Care* 27:505–510. <https://doi.org/10.1016/j.jcrc.2012.02.018>
31. Vanmassenhove J, Glorieux G, Hoste E, et al (2013) Urinary output and fractional excretion of sodium and urea as indicators of transient versus intrinsic acute kidney injury during early sepsis. *Crit Care* 17:R234. <https://doi.org/10.1186/cc13057>
32. Dewitte A, Joannès-Boyau O, Sidobre C, et al (2015) Kinetic eGFR and Novel AKI Biomarkers to Predict Renal Recovery. *Clin J Am Soc Nephrol* 10:1900–1910. <https://doi.org/10.2215/CJN.12651214>
33. Bellomo R, Bagshaw S, Langenberg C, Ronco C (2007) Pre-renal azotemia: a flawed paradigm in critically ill septic patients? *Contrib Nephrol* 156:1–9. <https://doi.org/10.1159/000102008>
34. Langenberg C, Wan L, Egi M, et al (2007) Renal blood flow and function during recovery from experimental septic acute kidney injury. *Intensive Care Med* 33:1614–1618. <https://doi.org/10.1007/s00134-007-0734-8>
35. Molitoris BA (2014) Therapeutic translation in acute kidney injury: the epithelial/endothelial axis. *J Clin Invest* 124:2355–2363. <https://doi.org/10.1172/JCI72269>

36. Xu K, Rosenstiel P, Paragas N, et al (2016) Unique Transcriptional Programs Identify Subtypes of AKI. *J Am Soc Nephrol*. <https://doi.org/10.1681/ASN.2016090974>
37. Schnell D, Reynaud M, Venot M, et al (2014) Resistive Index or color-Doppler semi-quantitative evaluation of renal perfusion by inexperienced physicians: results of a pilot study. *Minerva Anesthesiol* 80:1273–1281
38. Schneider A, Johnson L, Goodwin M, et al (2011) Bench-to-bedside review: contrast enhanced ultrasonography--a promising technique to assess renal perfusion in the ICU. *Crit Care* 15:157. <https://doi.org/10.1186/cc10058>
39. Schnell D, Darmon M (2012) Renal Doppler to assess renal perfusion in the critically ill: a reappraisal. *Intensive Care Med* 38:1751–1760. <https://doi.org/10.1007/s00134-012-2692-z>
40. Darmon M, Bourmaud A, Reynaud M, et al (2018) Performance of Doppler-based resistive index and semi-quantitative renal perfusion in predicting persistent AKI: results of a prospective multicenter study. *Intensive Care Med* 44:1904–1913. <https://doi.org/10.1007/s00134-018-5386-3>
41. Lerolle N (2012) Please don't call me RI anymore; I may not be the one you think I am! *Crit Care* 16:174. <https://doi.org/10.1186/cc11831>
42. Tublin ME, Bude RO, Platt JF (2003) Review. The resistive index in renal Doppler sonography: where do we stand? *AJR Am J Roentgenol* 180:885–892. <https://doi.org/10.2214/ajr.180.4.1800885>
43. Murphy ME, Tublin ME (2000) Understanding the Doppler RI: impact of renal arterial distensibility on the RI in a hydronephrotic ex vivo rabbit kidney model. *J Ultrasound Med* 19:303–314
44. Tublin ME, Tessler FN, Murphy ME (1999) Correlation between renal vascular resistance, pulse pressure, and the resistive index in isolated perfused rabbit kidneys. *Radiology* 213:258–264. <https://doi.org/10.1148/radiology.213.1.r99oc19258>
45. Darmon M, Schortgen F, Leon R, et al (2009) Impact of mild hypoxemia on renal function and renal resistive index during mechanical ventilation. *Intensive Care Med* 35:1031–1038. <https://doi.org/10.1007/s00134-008-1372-5>
46. Ohta Y, Fujii K, Arima H, et al (2005) Increased renal resistive index in atherosclerosis and diabetic nephropathy assessed by Doppler sonography. *J Hypertens* 23:1905–1911
47. Naesens M, Heylen L, Lerut E, et al (2013) Intrarenal resistive index after renal transplantation. *N Engl J Med* 369:1797–1806. <https://doi.org/10.1056/NEJMoa1301064>

48. Umgelter A, Reindl W, Franzen M, et al (2009) Renal resistive index and renal function before and after paracentesis in patients with hepatorenal syndrome and tense ascites. *Intensive Care Med* 35:152–156. <https://doi.org/10.1007/s00134-008-1253-y>
49. Kirkpatrick AW, Colistro R, Laupland KB, et al (2007) Renal arterial resistive index response to intraabdominal hypertension in a porcine model. *Crit Care Med* 35:207–213. <https://doi.org/10.1097/01.CCM.0000249824.48222.B7>
50. Sharkey RA, Mulloy EM, O'Neill SJ (1999) The acute effects of oxygen and carbon dioxide on renal vascular resistance in patients with an acute exacerbation of COPD. *Chest* 115:1588–1592
51. Lauschke A, Teichgräber UKM, Frei U, Eckardt K-U (2006) “Low-dose” dopamine worsens renal perfusion in patients with acute renal failure. *Kidney Int* 69:1669–1674. <https://doi.org/10.1038/sj.ki.5000310>
52. Deruddre S, Cheisson G, Mazoit J-X, et al (2007) Renal arterial resistance in septic shock: effects of increasing mean arterial pressure with norepinephrine on the renal resistive index assessed with Doppler ultrasonography. *Intensive Care Med* 33:1557–1562. <https://doi.org/10.1007/s00134-007-0665-4>
53. Schnell D, Camous L, Guyomarc'h S, et al (2013) Renal perfusion assessment by renal Doppler during fluid challenge in sepsis. *Crit Care Med* 41:1214–1220. <https://doi.org/10.1097/CCM.0b013e31827c0a36>
54. Moussa MD, Scolletta S, Fagnoul D, et al (2015) Effects of fluid administration on renal perfusion in critically ill patients. *Crit Care* 19:250. <https://doi.org/10.1186/s13054-015-0963-0>
55. Corradi F, Brusasco C, Vezzani A, et al (2011) Hemorrhagic shock in polytrauma patients: early detection with renal Doppler resistive index measurements. *Radiology* 260:112–118. <https://doi.org/10.1148/radiol.11102338>
56. Lerolle N, Guérot E, Faisy C, et al (2006) Renal failure in septic shock: predictive value of Doppler-based renal arterial resistive index. *Intensive Care Med* 32:1553–1559. <https://doi.org/10.1007/s00134-006-0360-x>
57. Schnell D, Deruddre S, Harrois A, et al (2012) Renal resistive index better predicts the occurrence of acute kidney injury than cystatin C. *Shock* 38:592–597. <https://doi.org/10.1097/SHK.0b013e318271a39c>
58. Darmon M, Schortgen F, Vargas F, et al (2011) Diagnostic accuracy of Doppler renal resistive index for reversibility of acute kidney injury in critically ill patients. *Intensive Care Med* 37:68–76. <https://doi.org/10.1007/s00134-010-2050-y>

59. Ninet S, Schnell D, Dewitte A, et al (2015) Doppler-based renal resistive index for prediction of renal dysfunction reversibility: A systematic review and meta-analysis. *J Crit Care* 30:629–635. <https://doi.org/10.1016/j.jcrc.2015.02.008>
60. Schneider AG, Calzavacca P, Schelleman A, et al (2014) Contrast-enhanced ultrasound evaluation of renal microcirculation in sheep. *Intensive Care Med Exp* 2:33. <https://doi.org/10.1186/s40635-014-0033-y>
61. Fischer K, Meral FC, Zhang Y, et al (2016) High-resolution renal perfusion mapping using contrast-enhanced ultrasonography in ischemia-reperfusion injury monitors changes in renal microperfusion. *Kidney Int* 89:1388–1398. <https://doi.org/10.1016/j.kint.2016.02.004>
62. Schneider AG, Hofmann L, Wuerzner G, et al (2012) Renal perfusion evaluation with contrast-enhanced ultrasonography. *Nephrol Dial Transplant* 27:674–681. <https://doi.org/10.1093/ndt/gfr345>
63. Schneider AG, Schelleman A, Goodwin MD, et al (2015) Contrast-enhanced ultrasound evaluation of the renal microcirculation response to terlipressin in hepato-renal syndrome: a preliminary report. *Ren Fail* 37:175–179. <https://doi.org/10.3109/0886022X.2014.977140>
64. Schneider AG, Goodwin MD, Schelleman A, et al (2014) Contrast-enhanced ultrasonography to evaluate changes in renal cortical microcirculation induced by noradrenaline: a pilot study. *Crit Care* 18:653. <https://doi.org/10.1186/s13054-014-0653-3>
65. Chawla LS, Goldstein SL, Kellum JA, Ronco C (2015) Renal angina: concept and development of pretest probability assessment in acute kidney injury. *Crit Care* 19:93. <https://doi.org/10.1186/s13054-015-0779-y>
66. Basu RK, Zappitelli M, Brunner L, et al (2014) Derivation and validation of the renal angina index to improve the prediction of acute kidney injury in critically ill children. *Kidney Int* 85:659–667. <https://doi.org/10.1038/ki.2013.349>
67. Basu RK, Wang Y, Wong HR, et al (2014) Incorporation of biomarkers with the renal angina index for prediction of severe AKI in critically ill children. *Clin J Am Soc Nephrol* 9:654–662. <https://doi.org/10.2215/CJN.09720913>
68. Basu RK, Kaddourah A, Goldstein SL, AWARE Study Investigators (2018) Assessment of a renal angina index for prediction of severe acute kidney injury in critically ill children: a multicentre, multinational, prospective observational study. *Lancet Child Adolesc Health* 2:112–120. [https://doi.org/10.1016/S2352-4642\(17\)30181-5](https://doi.org/10.1016/S2352-4642(17)30181-5)

69. Matsuura R, Komaru Y, Miyamoto Y, et al (2018) Response to different furosemide doses predicts AKI progression in ICU patients with elevated plasma NGAL levels. *Ann Intensive Care* 8:8. <https://doi.org/10.1186/s13613-018-0355-0>
70. Cruz DN, Ferrer-Nadal A, Piccinni P, et al (2014) Utilization of small changes in serum creatinine with clinical risk factors to assess the risk of AKI in critically ill adults. *Clin J Am Soc Nephrol* 9:663–672. <https://doi.org/10.2215/CJN.05190513>
71. Nattino G, Finazzi S, Bertolini G (2014) A new calibration test and a reappraisal of the calibration belt for the assessment of prediction models based on dichotomous outcomes. *Stat Med* 33:2390–2407. <https://doi.org/10.1002/sim.6100>
72. Labarère J, Renaud B, Bertrand R, Fine MJ (2014) How to derive and validate clinical prediction models for use in intensive care medicine. *Intensive Care Med* 40:513–527. <https://doi.org/10.1007/s00134-014-3227-6>
73. Doi K, Katagiri D, Negishi K, et al (2012) Mild elevation of urinary biomarkers in prerenal acute kidney injury. *Kidney Int* 82:1114–1120. <https://doi.org/10.1038/ki.2012.266>
74. Srisawat N, Wen X, Lee M, et al (2011) Urinary biomarkers and renal recovery in critically ill patients with renal support. *Clin J Am Soc Nephrol* 6:1815–1823. <https://doi.org/10.2215/CJN.11261210>
75. Kashani K, Al-Khafaji A, Ardiles T, et al (2013) Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care* 17:R25. <https://doi.org/10.1186/cc12503>
76. de Geus HRH, Bakker J, Lesaffre EMEH, le Noble JLML (2011) Neutrophil gelatinase-associated lipocalin at ICU admission predicts for acute kidney injury in adult patients. *Am J Respir Crit Care Med* 183:907–914. <https://doi.org/10.1164/rccm.200908-1214OC>
77. Hjortrup PB, Haase N, Treschow F, et al (2015) Predictive value of NGAL for use of renal replacement therapy in patients with severe sepsis. *Acta Anaesthesiol Scand* 59:25–34. <https://doi.org/10.1111/aas.12427>
78. Zeng X-F, Li J-M, Tan Y, et al (2014) Performance of urinary NGAL and L-FABP in predicting acute kidney injury and subsequent renal recovery: a cohort study based on major surgeries. *Clin Chem Lab Med* 52:671–678. <https://doi.org/10.1515/cclm-2013-0823>
79. Gharaibeh KA, Hamadah AM, El-Zoghby ZM, et al (2018) Cystatin C Predicts Renal Recovery Earlier Than Creatinine Among Patients With Acute Kidney Injury. *Kidney Int Rep* 3:337–342. <https://doi.org/10.1016/j.ekir.2017.10.012>

80. Daubin D, Cristol JP, Dupuy AM, et al (2017) Urinary Biomarkers IGFBP7 and TIMP-2 for the Diagnostic Assessment of Transient and Persistent Acute Kidney Injury in Critically Ill Patients. *PLoS ONE* 12:e0169674. <https://doi.org/10.1371/journal.pone.0169674>
81. Jia H-M, Zheng Y, Huang L-F, et al (2018) Derivation and validation of plasma endostatin for predicting renal recovery from acute kidney injury: a prospective validation study. *Crit Care* 22:305. <https://doi.org/10.1186/s13054-018-2232-5>
82. Shen C, Li X (2016) On the uncertainty of individual prediction because of sampling predictors. *Stat Med* 35:2016–2030. <https://doi.org/10.1002/sim.6849>
83. Hsieh H-N, Su H-Y, Zhou X-H (2009) Interval estimation for the difference in paired areas under the ROC curves in the absence of a gold standard test. *Stat Med* 28:3108–3123. <https://doi.org/10.1002/sim.3661>
84. Cook NR (2007) Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation* 115:928–935. <https://doi.org/10.1161/CIRCULATIONAHA.106.672402>
85. de Grooth H-J, Parienti J-J, Schetz M (2018) AKI biomarkers are poor discriminants for subsequent need for renal replacement therapy, but do not disqualify them yet. *Intensive Care Med* 44:1156–1158. <https://doi.org/10.1007/s00134-018-5151-7>
86. Kerr KF, Wang Z, Janes H, et al (2014) Net Reclassification Indices for Evaluating Risk-Prediction Instruments: A Critical Review. *Epidemiology* 25:114–121. <https://doi.org/10.1097/EDE.000000000000018>
87. Hilden J, Gerds TA (2014) A note on the evaluation of novel biomarkers: do not rely on integrated discrimination improvement and net reclassification index. *Stat Med* 33:3405–3414. <https://doi.org/10.1002/sim.5804>
88. Meersch M, Schmidt C, Hoffmeier A, et al (2017) Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. *Intensive Care Med*. <https://doi.org/10.1007/s00134-016-4670-3>
89. Wlodzimirow KA, Abu-Hanna A, Royackers A a. NM, et al (2014) Transient versus persistent acute kidney injury and the diagnostic performance of fractional excretion of urea in critically ill patients. *Nephron Clin Pract* 126:8–13. <https://doi.org/10.1159/000357678>
90. Legrand M, Le Cam B, Perbet S, et al (2016) Urine sodium concentration to predict fluid responsiveness in oliguric ICU patients: a prospective multicenter observational study. *Crit Care* 20:165. <https://doi.org/10.1186/s13054-016-1343-0>

Figure Legends

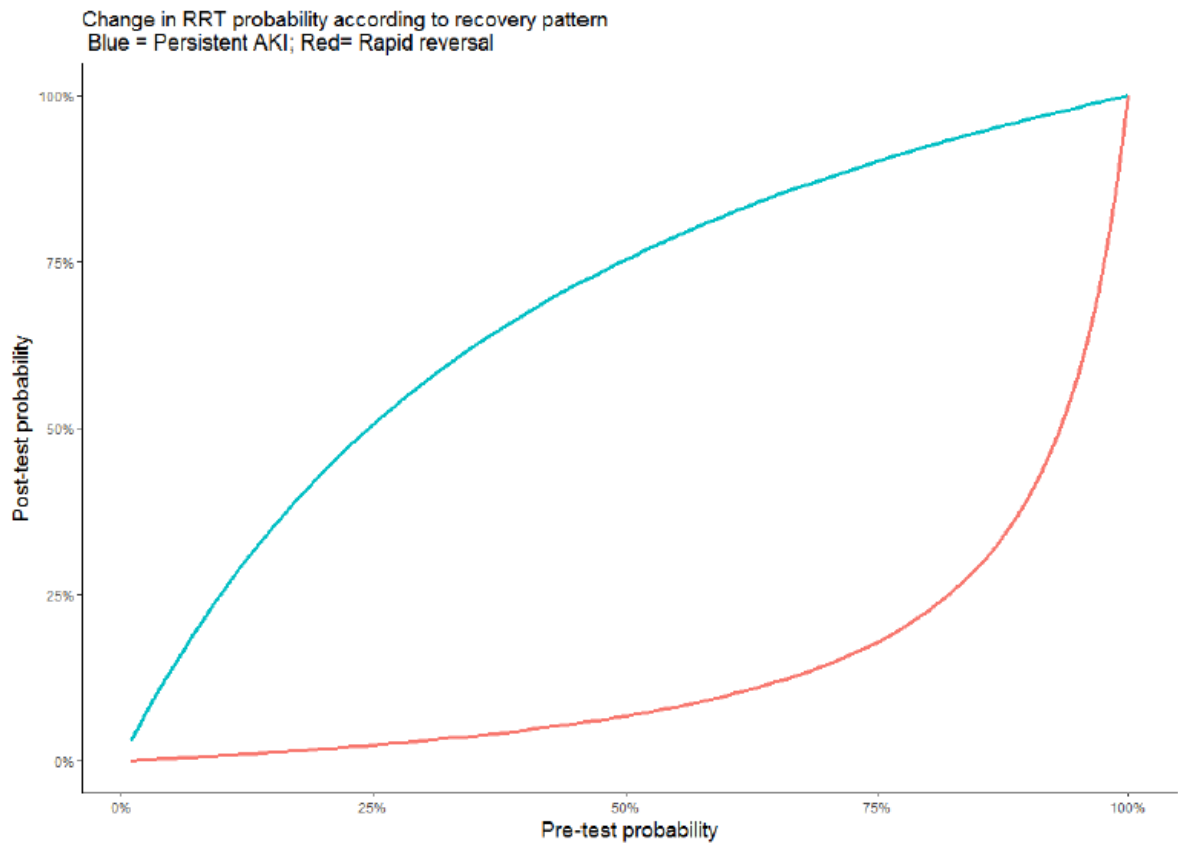


Figure 1. Probability of renal replacement therapy according to persistent AKI (redrawn from Perinel et al. Crit Care Med 2015 [4]).

Acute Kidney Injury According to KDIGO definition			
Reversibility within 48h	Reversibility within 7 days	Reversibility within day 90	Chronic Kidney Disease
Transient AKI	Persistent AKI	Acute Kidney Disease	

Figure 2. AKI terminology according to its reversibility over time. Modified from Chawla et al. Nature Review Nephrology 2017 [2].

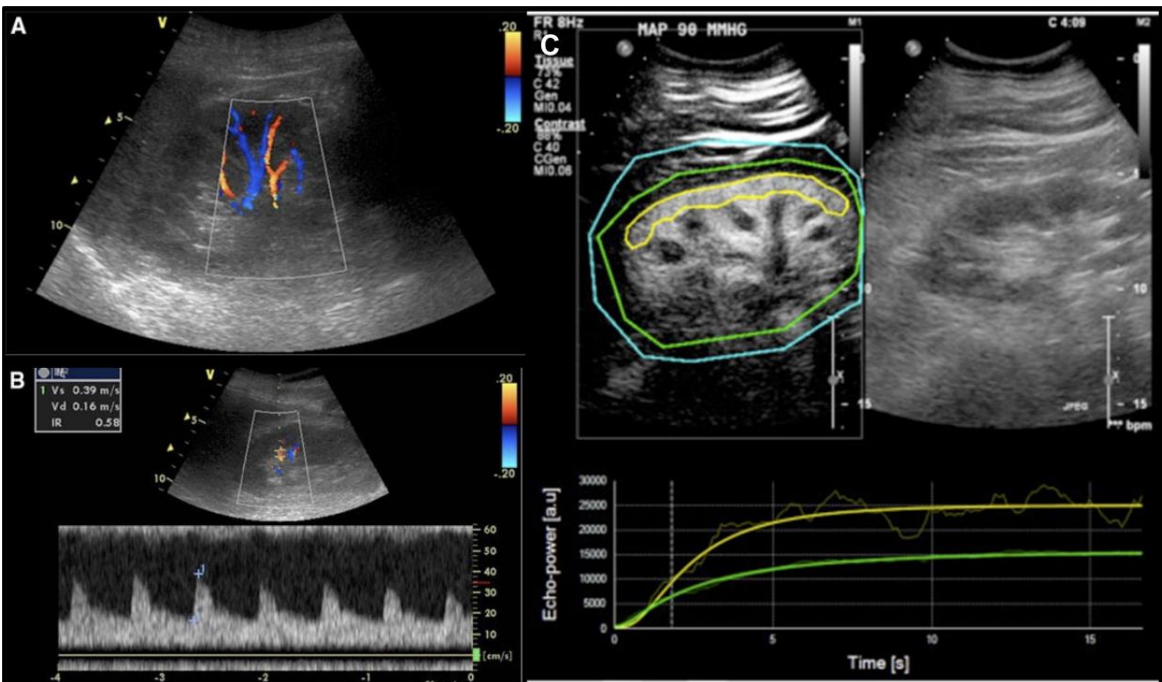


Figure 3. Panels showing respectively color Doppler allowing semi-quantitative perfusion (A), measurement of Resistive index (B) and destruction refilling sequence allowing perfusion assessment using Contrast-Enhanced Ultrasonography (Reproduced from Schnell et al. Intensive Care Med 2012 [39] and Schneider et al. Crit Care 2011 [38], with permission)

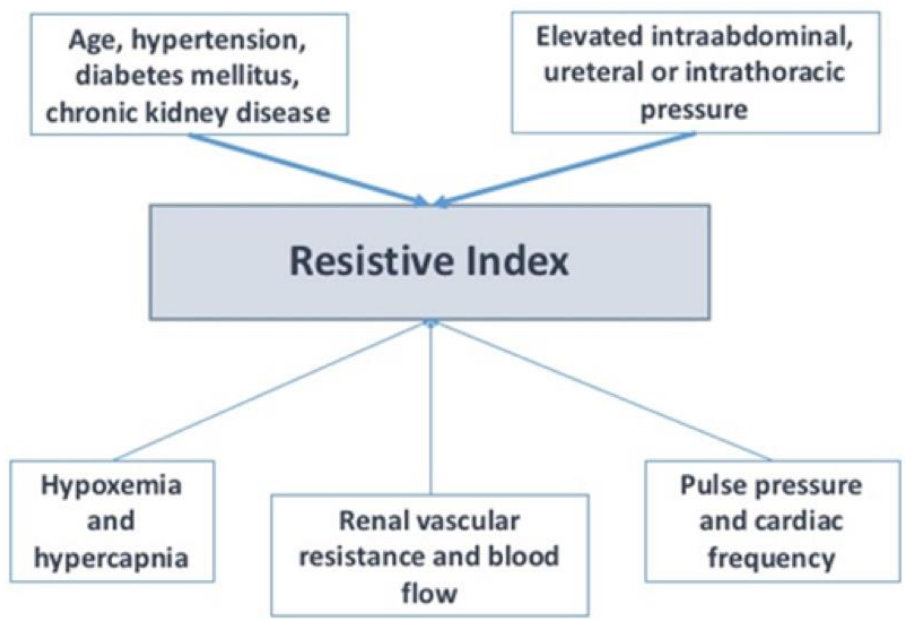


Figure 4. Factors influencing Doppler-based renal Resistive Index value. Modified from Schnell et al. Intensive Care Med 2012 [39].

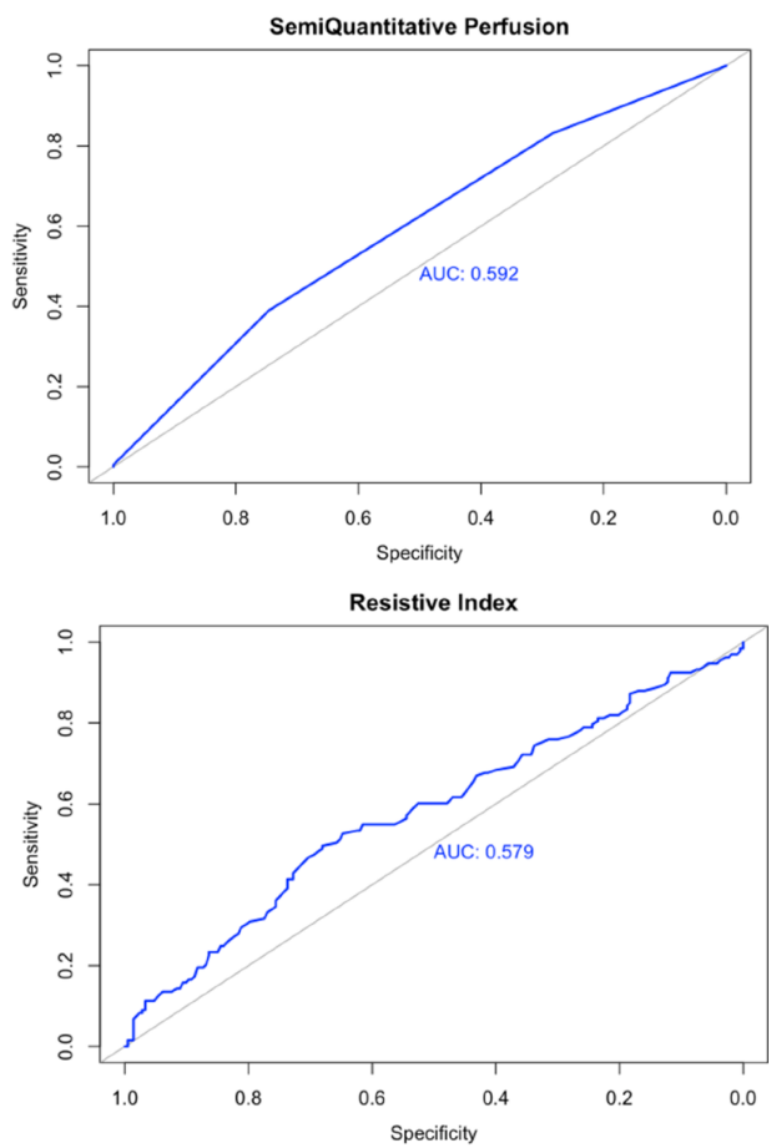


Figure 5. Semi-quantitative renal perfusion and Doppler-based resistive index performance in predicting short term renal recovery in the R2D2 study (Reproduced from Darmon et al. Intensive Care Med 2018 [40], with permission).

Table 1. Main studies assessing performance of urinary indices in predicting short-term renal recovery in ICU setting

	Vanmassenhove et al. [31]	Darmon et al. [28]	Dewitte et al. [30]	Pons et al. [29]	Wlodzimirow et al. [89]	Legrand et al. [90]
N patients	107 (81 with AKI)	203 (136 with AKI)	47 (47 with AKI)	244 (147 with AKI)	150 (92 with AKI)	54 (54 oliguric)
Population	Medical/Surgical	91.3% with medical condition	Surgical	91.9% with medical condition	Medical /Surgical	Medical/Surgical Oliguric patients
Natriuresis	Not Reported	Not Reported	0.44 [0.27-0.62]	Not Reported	Not Reported	0.51 [0.35-0.68]
FeNA	0.59 [95%CI?]	0.62 [0.52-0.72]	0.60 [0.43-0.77]	0.59 [0.49-0.69]	Not Reported	0.56 [0.39-0.73]
FeUrea	0.36 [95%CI?]	0.59 [0.49-0.70]	0.59 [0.42-	0.50 [0.41-	0.61 [0.49-0.73]	0.60 [0.54-0.67]

			0.77]	0.60]		
U/P Urea	Not Reported	0.71 [0.62-0.80]	0.78 [0.63-0.92]	0.57 [0.48-0.67]	Not Reported	Not Reported
Specificities	High negative predictive value of both criteria combined	Similar findings in patients with sepsis or without diuretics	Similar findings in patients with diuretics	Similar findings in patients with sepsis, without diuretics and at various time during first 24 hours	Similar findings in predicting occurrence of AKI	Fluid renal responsiveness

Table 2. Semi-quantitative Colour-Doppler scale for evaluating intrarenal perfusion (adapted from Schnell et al. Minerva 2014 [37])

Grade	Renal perfusion
0	Unidentifiable vessels
1	Few vessels visible in the vicinity of the hilum
2	Hilar and interlobar vessels visible in most of the renal parenchyma
3	Renal vessels identifiable until the arcuate arteries in the entire field of view

Table 3. Main unanswered question in assessing risk of persistent AKI

Unanswered question	
1	Competing risk adjusted rate of recovery
2	Change in recovery rate according to setting and ICU discharge
3	Transition risk and rate of Transient AKI/Persistent AKI/AKD according to ADQI definition
4	Risk factors for AKD and influence of timing to recovery on subsequent residual renal function
5	Validation of prognostic score and biomarkers of persistent AKI
6	Clinical relevancy and impact of adequate prediction on patients' management
7	Cost-benefit ratio of predictive measure to assess renal recovery