Delayed Nephrology Consultation and High Mortality on Acute Kidney Injury: A Meta-Analysis

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Key Words
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Abstract
Background: Acute kidney injury (AKI) is a complex syndrome associated with substantial morbidity, mortality and costs. Despite advancements in diagnosis and care practice, AKI remains a disorder usually under/late-recognized with high mortality. One of the hidden reasons for poor outcome might be delayed nephrology consultation, with the involvement of the specialist only in severe stages of AKI when renal replacement therapy (RRT) is required. Methods: We searched PubMed, EMBASE and Cochrane central register for related work on the subject. Six studies were identified for the meta-analysis, correlating time of nephrology consultation and mortality in AKI. Results: We found that delayed nephrology consultation is associated with higher mortality in AKI, with an OR 0.79 (95% CI 0.48–1.10, p < 0.05). Conclusion: Delayed nephrology consultation contributes to higher mortality in AKI. The early involvement of nephrologist may present an advantage in terms of early recognition, prevention and effective treatment of AKI. An early involvement of multidisciplinary task force may contribute to better treatment, before the preventable complications of AKI occur or an emergency RRT is required.

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Introduction
Acute kidney injury (AKI) reflects a broad spectrum of clinical presentations ranging from mild to severe injury that may result in dysfunction with recovery or non-recovery, leading to some or permanent and complete loss of renal function (RF). This is seen frequently in hospitalized, especially intensive care unit (ICU) patients, as a serious complication, which independently predicts poor outcomes. It is also associated with substantial morbidity, mortality and costs [1, 2].

There are several discussions about the timing of renal replacement therapy (RRT) on AKI in ICU and its relationship with prognosis [3]. Even though there are efforts put in the so-called early RRT in terms of its potential benefits on both survival and recovery of kidney function [3], it is still controversial [4, 5]. AKI remains the higher risk factor for mortality in ICU, leading to high rates of
deaths, long dependence of RRT and chronic kidney disease (CKD) [6]. This fact brings us to another perspective that maybe we are actually loosing time and AKI really needs more attention in its early stages.

One of the hidden reasons for persistent poor outcomes might be the delay in the timing for nephrology consultation. Unfortunately, nephrologists are usually involved when severe AKI has already settled, requiring RRT support [7]. We need to discuss based on a systematic review and meta-analysis, whether and how the early involvement of nephrologists in the management of these patients may represent an advantage in terms of early recognition of clinical/subclinical AKI, its risk factors and ways of prevention of severe AKI. For the correct management of early disturbances, most conditions that tend to be hidden under the cover of AKI, which are usually unnoticed or self-managed, need to be discussed as well (fig. 1).

**Systematic Review**

Timing to nephrology consultation on AKI in ICU is the object of studies that intend to find a relationship between delayed nephrology consultation and poor outcomes. We searched PubMed, EMBASE and Cochrane central register for this review. Six studies were identified for the meta-analysis, correlating the time of nephrology consultation and mortality in AKI.

First, Mehta et al. [8] discussed the timing of nephrology consultation. An observational study revealed that delayed nephrology consultation in patients admitted to the ICU with kidney failure (serum creatinine (SCr) >2 mg/dl or increment >1 mg/dl with pre-existing disease) was associated with higher mortality and morbidity. The definition of kidney failure used was before the era of the more recently advocated definitions that rely on minor changes in SCr levels [9, 10]. Delayed nephrology consultation was associated with increased mortality in the bivariate analysis [8], but this effect was not sustained when corrected by confounding variables.

Perez-Valdivieso et al. [11] in a prospective cohort study reported that an increase of ≥101% in SCr level from the baseline at the time of nephrology consultation was associated with higher mortality and impaired renal recovery on discharge. At the same degree of severity of kidney injury (RIFLE criteria) and comorbid illness, the relative increase of >101% from the SCr at the time of nephrology consultation was an indepen-
dent predictor of mortality and worse prognosis [11]. However, neither the adjustment for confounding variables nor further statistical analysis was performed. Thus, the influence of residual confounding factors remained uncertain.

Ponce et al. [12], in an observational prospective study assessing AKI in critically ill patients (Acute Kidney Injury Network (AKIN) definition), reported that delayed nephrology consultation, using two-day interval – based on the previous work performed by Mehta et al. [8] was associated with increased mortality after adjustment in a multivariable analysis [12]. The criteria for nephrology consultation were based on the intensivist’s individual criteria, and after the intensivist called the nephrologist, it took less than 6 h until arrival of the nephrologist to ICU [12].

Balasubramanian et al. [13], in a prospective controlled non-randomized interventional study, showed that early nephrologist involvement, defined as first time nephrology consultation within 18 h of the onset of AKI (SCr level increase of 0.3 mg/dl over 48 h; AKIN definition) may reduce the risk of further progression. They hypothesized early renal service involvement as an intervention group, and this was the first prospective interventional study investigating the timing of nephrology consultation for AKI [13]. Also, the optimal timing of nephrology consultation was unknown before this study.

Costa e Silva et al. [14] reported through a prospective observational study that delayed nephrology consultation was associated with a higher mortality and increased dialysis dependence rates in critically ill patients with AKI (defined as an increase >50% from baseline SCr) at hospital discharge, even after adjustment for confounding factors. Early and delayed nephrology consultations were defined by an interval of 2 days before and after AKI diagnosis day [14].

Flores-Gama et al. [15], in a retrospective cohort study, revealed the potential preventive effects of a nephrologist integrated into the postoperative cardiac ICU vs. nephrology consultation depending on intensivist’s criteria in the ICU based on in-hospital outcomes. The results were favorable to a nephrologist ‘part of the team’, with a lower incidence of AKI, lower in-hospital mortality among patients with severe AKI and higher renal recovery rates. Integrating nephrologists into the postoperative cardiac ICU team was associated with a lower incidence of AKI, and even patients who developed severe AKI had lower in-hospital mortality and higher renal recovery [15].

Data Analysis and Results

Table 1 presents the main statistics from the 6 papers described above. Based on these statistics, we carried out a meta-analysis [16] to evaluate the statistical significance of the association between delayed nephrology consultation and mortality. The random-effects pooled estimate of the log OR (overall effect size) for delayed consultation vs. early consultation is 0.79 (95% CI 0.48–1.10, p < 0.05), as illustrated by the forest plot in figure 2. The log OR less than 0 suggests reduced mortality with delayed consultation, while log OR greater than 0 suggests increased mortality with delayed consultation. In addition, the overall effect size is the weighted average of the estimates from individual studies in which weights are proportional to the data markers in figure 2. Larger markers indicate less uncertainty from the results of individual studies.

All statistical calculations were performed with R [17] by the Metafor package [16]. In addition, the model was fitted by the DerSimonian-Laird estimator [18], before the test for heterogeneity rejected the null hypotheses of
homogeneity (p = 0.24 and I² statistic = 25.91%), as depicted graphically by the overlaps among the CIs in figure 2.

Despite the result being statistically significant, the indication that delayed nephrology consultation is associated with increased mortality should be viewed with caution, because of the sample size (6 studies) and the risk of bias [19].

Discussion

Delayed nephrology consultation is usually associated with severe stages of AKI and severe critical illness, what in general come with urgent indications of RRT, and higher mortality, reduced renal recovery, higher dependency of dialysis and higher costs. Early nephrology consultation may contribute to better outcomes, and may focus on prevention to more severe stages of AKI, and requirement of RRT.

Rather than just a rise in SCr or decrease in urine output (UO), AKI should be seen as a syndrome (fig. 3) that involves multiple factors, like fluid imbalance, electrolytes and acid-base disturbances, bleeding diathesis, anemia, nutrition, etc., and has an influence on diverse organs and systems, thus leading to a multisystem involvement. There are many reasons that justify the importance of an early-integrated approach with nephrologist’s involvement in AKI, to recognize and manage this complex syndrome early. Those aspects may justify better outcomes at the early approach as described above.

Delayed Diagnosis

The first challenge with AKI is actually its diagnosis, once AKIN and RIFLE criteria [9, 10] fail to diagnose AKI in a timely fashion. These criteria use the rise in SCr and/or decrease in UO, which represent a functional criterion for AKI and implies a glomerular filtration rate (GFR) alteration that may be a late phenomenon in the course of the syndrome [20]. Considering the changes in SCr, the diagnosis is made when AKI has already settled and dysfunction exists, rather than before the damage. It means that the opportunity to identify the risk factors and susceptibility is already skipped.

The concept of AKI implies injury or damage, potentially reversible, but not necessarily a dysfunction, which only becomes clinically evident when more than 50% of renal mass is compromised [20]. Several studies have shown evidence that there is an additional value of new biomarkers [21] not only because they allow a kidney injury to be diagnosed earlier, but also because they allow a kidney injury to be diagnosed even in the absence of subsequent physiological dysfunction [20].

Recently, tubular damage without glomerular function loss was demonstrated to be associated with worse renal and overall outcomes [20]. The term ‘subclinical AKI’ was introduced, challenging the traditional view that a renal issue is clinically relevant only when a loss of filtration function becomes apparent. Variations in GFR may occur after the initial injury, but before the clinical evidence of rising SCr, which explains why a minimal rise in SCr is often a sign of severe kidney damage [20, 22, 23].
Renal Angina

The second problem about time is: how we can recognize risk factors for AKI, and if there is something that we can do for prevention? Goldstein and Chawla [22] first described ‘renal angina syndrome’ in the context of the dilemma of subclinical AKI in critically ill patients [18]. Like the well-established risk factors for coronary artery disease, the authors suggest that there are known risk factors for AKI that clinicians should consider as they risk-stratify patients for AKI, including age >65 years, diabetes, liver failure, congestive heart failure (CHF), CKD and cardiopulmonary bypass, among others. The presence of any of these angina equivalents in a patient should trigger the clinician to be more vigilant for the risk of early and easy AKI.

Cruz et al. [23] hypothesized a high-risk combination group, in which clinical factors combining small changes in SCr (0.1–0.4 mg/dl) could predict the risk for severe AKI in cases where AKI biomarker testing may be used effectively. In a large heterogeneous multicenter cohort of critically ill adults, they showed that early SCr elevation and risk grouping is a good predictor of severe AKI [23]. It can be used as a screening test to identify patients at low risk for severe AKI, in whom AKI biomarker could be expected to have a low yield [23].

Fig. 3. The timeline of syndrome of AKI. AKI should be seen as a syndrome in terms of early recognition of clinical and subclinical AKI, and its risk factors, once the damage induced even by unnoticed subclinical episodes of AKI may, in fact, produce an irreversible loss of a variable amount of renal mass with deleterious effect on the overall RF. It can be seen even when the baseline GFR returns to normal value, once RF is impaired, leading to the concept of renal recovery or non-recovery.

If nephrologists are involved on-time in the management of critically ill patients, they are capable of helping in the early management of risk factors, susceptibility and prevention, mainly in mild to moderate forms of AKI, and in avoiding further preventable injuries and adoption of safe and renoprotective strategies and therapeutics, respectively [13, 24, 25].

RF Reserve

It is already known that pre-existing renal dysfunction is a risk factor for AKI, and the reasons for this is understandable [26]. To understand how AKI is a proven risk factor for CKD [26], and to estimate the risk of AKI in patients with a normal baseline GFR, the concept of RF reserve (RFR) is introduced [27, 28]. Baseline GFR does not necessarily represent the anatomical and functional conditions of a kidney, but a normal baseline GFR can be present despite significant renal impairment [28].

Critically ill patients, even with a normal baseline GFR, could potentially be at an increased risk of AKI. It could be due to slow and progressive loss of RFR caused by multiple associated physiological and pathological factors leading to progressive nephron loss. The damage induced even by unnoticed subclinical episodes of AKI may, in fact, produce an irreversible loss of a variable amount of renal mass with deleterious effect on the overall RF. It can
be seen even when the baseline GFR returns to normal value, once RFR is impaired, leading to the concept of renal recovery or non-recovery [28].

RFR measure may help in identifying critically ill patients who are prone to develop an AKI in response to a less severe injury, recognizing those that are at a higher risk of developing severe AKI and deserve a more conservatory and renoprotective therapeutic strategies, and also a close follow-up by a nephrologist on discharge.

**Multidisciplinary Approach**

The interaction between intensive care and nephrology has been growing through the last decades, with focused research and strong investments in modalities and therapies for AKI [29]. With persistent high incidence and mortality, association with multiple organ dysfunctions, intricacies of pharmacokinetics in such setting, the evolving nature of approach, and finally the demand of a complex human care and financial costs justify the undoubted necessity of a multidisciplinary approach for AKI [29].

Ronco and Bellomo [29] in 1998 described the formal development of the specialty area called Critical Care Nephrology, and were the first to recognize that the management of AKI in ICU demands a multidisciplinary approach. Vincent [30] in 2007 published a review in favor of the multidisciplinary approach to ICU patients with AKI: an intensivist-led care supported by specialist consultation associated with improved patient outcomes [31].

AKI in ICU is rarely an isolated event and frequently occurs within a broader spectrum of diseases, and often progresses to multiorgan dysfunction syndrome, with profound effects on mortality rates [32]. At times, the approach of critically ill patients is very complex, and it is often difficult to identify if AKI has preceded or resulted from other organic dysfunctions. This complex interactional pathophysiology that involves diverse mechanisms is called organ crosstalk, and has been described between kidney and others organs (e.g. heart, lung, brain, liver and intestines) [33].

The multifactorial nature of AKI in ICU [34] demands a multidisciplinary approach, where nephrologists can help in identifying early risk factors and adopting preventable strategies for the progression to severity forms, and offering support renal therapy, not only RRT, when indicated, based on the multiple organ support therapy concept of blood purification therapies in ICU [35–37]. Also, we should consider a nephrologist-intensivist crosstalk, where both are subjected to various co-interventions [35] that may influence directly or indirectly the development of AKI in the ICU and its progression to severity (fig. 4).

**It Is Not All About RRT**

**Volume Status**

The volume assessment of critically ill patients is quite difficult, especially in older, and remains a challenge in ICU. Misunderstood volume assessment can lead to both inadvertent use of loop diuretics or massive crystalloid administration, and parameters beyond clinical edema must receive greater attention in such patients. Volume overload is a complication of the impaired sodium and water excretion in oliguric AKI, and it can be observed during the initial evaluation or develop due to excessive fluid administration in the setting of impaired RF [38]. Volume overload leads not only to extracellular fluid expansion, but also to organ edema, with mostly cardiopulmonary complications such as CHF and pulmonary edema requiring mechanical ventilation [39].

In ICU patients, volume overload can occur instead of preserved UO, and avoiding volume overload can be difficult, since their daily fluid balance is usually positive, a result of the administration of venous antibiotic, medications and nutritional support. The lung injury commonly observed in these patients is also a reason for poorly tolerated pulmonary edema, and left ventricular dysfunction that can occur in the context of AKI or CRS [40]. Net fluid balance should be carefully assessed in the ICU, with special care taken to not pursue the negative fluid balance and disregarding parameters of hypovolemia and tissue hypoperfusion that could precipitate AKI, and also early avoidance of large fluid administration in patients with AKI.

**Electrolyte Disturbance**

Electrolyte disturbances are very common in AKI, especially in critically ill patients, once innumerous conditions and therapeutic options on ICU lead to disturbed electrolyte imbalance. Nephrologists can contribute for adequate management, identification, and adoption of necessary adjustment if it is reversible, in mild to moderate electrolyte disturbances. And also, can help in preventing life-threatening complications of severe disturbances with on-time RRT, and in maintaining the homeostasis with adequacy of dialysis in those patients with severe AKI who require RRT [41, 42].

Hypomagnesaemia deserves a special consideration because recent studies reported this disturbance as an independent risk factor for the development of AKI and
non-recovery of RF in critically ill patients with AKI [43]. In animal experiments, hypomagnesaemia decreases the GFR and RBF, and enhances post-ischemic renal injury [44]. Conversely, the administration of magnesium in an animal model of ischemic AKI resulted in GFR and RBF increases [45].

**Metabolic Acidosis**

Critically ill patients with AKI are at high risk of metabolic acidosis due mostly to impaired excretion of acid product of daily metabolism, bicarbonate loss from diarrhea, and also related conditions with increased production of lactic acid or ketoacids [46]. Treatment of severe metabolic acidosis (pH < 7.1) in critically ill patients should never be delayed; it is related to reduced left ventricular contractility and hemodynamic instability, arrhythmias, arterial vasodilation and vasoconstriction, and impaired responsiveness to catecholamine vasopressors [47]. Early treatment of severe organic acidosis (i.e. lactic or ketoacidosis) to prevent further renal injury due to rhabdomyolysis also deserves attention [48]; in oligoanuric patients, the RRT might be the best choice [46].

**Bleeding Diathesis**

Major clinical manifestations of platelet dysfunction in AKI are cutaneous and mucosa bleeding, but gastrointestinal bleeding, with increased sensitivity to aspirin and hematuria are other possibilities [49]. Possible causes of platelet impairment include intrinsic platelet defects, abnormal platelet-endothelial interaction, uremic toxins and anemia, while coagulation parameters are generally intact [49].

Raising the hemoglobin to approximately 10 mg/dl by transfusion or administration of recombinant erythropoietic-stimulating agents can improve the platelet function and reduce the bleeding time [39]. Desmopressin provides the most rapid acute treatment for bleeding in uremic patients, although the response to subsequent doses is generally diminished (tachyphylaxis) [49]. Also,
desmopressin, a cryoprecipitate improves bleeding in the first hour, but potential infectious complications limit its use to life-threatening conditions [49].

Nutritional Support
Several trials reported that AKI results in a negative nitrogen balance, insulin resistance, gluconeogenesis and imbalance in plasma amino acid concentrations [50]. The major goal of nutritional support for critically ill patients with AKI is to provide adequate energy, protein and nutrients [51, 52], even if it increases the urea concentration or leads to fluid overload, sometimes acting as a trigger for RRT. Nutrition support should not differ from patients with multiorgan failure (MOF), once the level of nitrogen catabolism induced by MOF with AKI overwhelms any catabolic effects of AKI per se, except to keep watch on the phosphorus and potassium levels and modify the diet plan accordingly [51, 52].

Despite the lack of specific data on underfeeding in AKI, some trials recommend 25–30 kcal/kg/day, based on the underlying catabolic state, while others recommend a more permissive underfeeding as a preferred approach [50–52]. The protein energy wasting is common and represents a major negative prognostic factor, contributing to mortality. The protein requirement increases with the severity of the underlying illness, and the requirement of RRT (1.2–1.5 g/kg/day at least) [52].

Accumulating evidence also suggest that immune-enhancing enteral preparations decrease the duration of hospital stay, the number of infections and perhaps mortality. Not only those preparations, but also adequate vitamin and trace element supplementation are recommended to counterbalance the decrease in antioxidants and the loss of some vitamins, mainly during CCRT [46, 50].

Breaking Some Myths
Clinical practice is full of some ‘vicious’ and usually ‘not based on evidence’ and/or ‘wrong interventions’ in the management of AKI, which certainly contributes to poor outcomes.

Try to Transform an Oliguric AKI in a Non-Oliguric AKI
The first one, and maybe the most controversial, is the indiscriminate use of loop diuretics. In patients with AKI, oliguria is associated with mortality [53], and any delay in recognition can lead to severe progression of AKI [38]. Otherwise non-oliguric AKI seems to have a better prognosis, which partially explains why many ICU practitioners want to preserve or increase urine flow by using loop diuretics [54]. If tubules are injured in AKI, maximal concentrating ability is impaired, and the urine volume may be normal [53, 54]. Intact tubular function should not definitely be interpreted as ‘benign’ or even as ‘pre-renal azotemia’ since it may also be seen in various forms of diseases (e.g. sepsis).

Use Large Volume Fluid Administration
It has been demonstrated that a restrictive strategy in fluid administration, obviously after complete resuscitation in ICU patients, is related to better outcomes [39, 55]. Not only with benefits in reduced postoperative complications and reduced time of mechanical ventilation, but also because of the demonstration of a high positive cumulative fluid balance as an independent risk factor for in-hospital mortality. Restrictive strategy in fluid administration improved the lung function, increased ventilator-free days, reduced ICU stay, did not increase the rate of non-pulmonary organ failure or shock, and has a trend for reduced need of RRT [56].

Dialysis for Volume Management
Although several observational studies have demonstrated an association between the severity of volume overload and the time of initiation dialysis [55, 56], no study has demonstrated a benefit of early initiation of dialysis for volume management. Early dialysis for volume management is still controversial and regular examination of patient, assessment of UO in response to diuretics and other aspects (e.g. mechanical ventilation, nutritional support, fluid balance) give a clue for challenging the decision for RRT in ICU. The management of hypervolemia and positive fluid balance in patients with AKI may require the use of intravenous diuretics, but it is important to restrict its use to responders, and not indiscriminate its use for prolonged periods to postpone the initiation of RRT [38].

The ’Benign’ Alkalosis
A common misunderstood and neglected acid-base disorder in critically ill patients, especially in CHF [57], is metabolic alkalosis. In most cases, it is a result of excessive diuretic therapy, which contributes to bicarbonate retention and generation (contraction alkalosis) [57]. Although believed to be benign by most clinicians, when severe it can have significant adverse effects on cellular function and potential complications [58]. Identifying this acid-base disorder and initiating specific treatment is very important, once settled alkalemia may be associated with worse outcomes, especially in CHF, including increased rate of mortality [58].

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General management of metabolic alkalosis starts with the correction of generation and maintenance factors, but sometimes other interventions are required, as aldosterone antagonists, acetazolamide and hydrochloric acid (life-threatening conditions) [57, 58]. Dialysis with low (or zero) bicarbonate bath or CRRT [59] with fluid replacement without bicarbonate [60, 61] and citrate anticoagulation, are typically restricted in patients with impairment of RF or possibly refractory volume overload during CHF.

Bicarbonate for Everyone

There are many different and not standardized ways of using sodium bicarbonate for metabolic acidosis, with consequent indiscriminate use in ICU. Rapid infusions of sodium bicarbonate have potentially adverse effects, like hypocalcemia, hypernatremia and hypervolemia. In inadequately ventilated patients, it can worsen intracellular acidosis, even when arterial blood pH increases. And this dissociation between tissue and systemic arterial base parameters is magnified in patients with circulatory failure [62].

Also, the cerebrospinal fluid (CSF) pH may fall when bicarbonate is infused, but any systemic and/or local increase in PCO2 will be quickly reflected within the CSF, while an increased blood bicarbonate concentration is only slowly transmitted to the CSF. Because of this dissociation, 'paradoxical' CSF acidemia can develop, and may be associated with neurologic deterioration [63].

Sodium bicarbonate is a commonly erroneous first choice therapy for lactic acidosis, once the infusion of exogenous bicarbonate may increase the lactate generation [64]. The role of exogenous bicarbonate therapy and alternative buffering agents in patients with lactic acidosis is controversial. The majority of experts suggest its use in patients with severe lactic acidosis as an adjuvant therapy until the primary process can be reversed, thus unless reversed any beneficial effect of exogenous bicarbonate infusion will be transient.

Conclusion

We believe that this meta-analysis can influence the changing paradigm about the time on AKI. After severe stages of AKI and requirement of RRT, time of initiation of RRT (early vs. delayed) seems to not make any difference regarding mortality [4, 5]. But in earlier stages, nephrologists seem to make all the difference, when time definitely matters.

The delayed nephrology consultation dismisses varied contributions that nephrologists offer in the bedside management of critically ill patients. Certainty, nephrologists would rather help earlier than later, in the early management of risk factors and susceptibility, in recognizing subclinical AKI and avoiding further preventable injuries, adopting safe and renoprotective therapeutic strategies, recognizing and managing early disturbances, and choosing on-time the right patient for the RRT, and even the best modality for each patient.

A new challenge is to find a way to enlighten centers to consider AKI as a syndrome and consider the need for a nephrologist until the tip of the iceberg of AKI unfolds the hidden complications. The best approach seems to be a multidisciplinary task force for AKI, involving the nephrologist early on decisions regarding the management of such patients. This leads to the requirement of a universal scoring system or a guideline for the clinicians to recognize the time to involve a nephrologist in the management of patients with AKI.

AKI is also one of the leading causes for the development of CKD due to nephron loss and progressive loss of RFR after each insult. The early involvement of a nephrologist can prevent not only the progression of the severity of AKI and its complications, but also the significant nephron and RFR loss, and progression to CKD. This indirectly gives a big economic relief to the nation preventing longer hospital stays, RRT dependency and cost of treatment, just by the on-time call to a nephrologist.

Further strategies must be designed to ensure the early involvement of nephrologists in the management of AKI. Controlled and randomized trials are necessary to understand why delayed consultation is related to higher mortality, and also to analyze other outcomes like requirement of RRT, dependency of RRT and low renal recovery.

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