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How and when do we use continuous renal replacement therapy for acute kidney injury in Serbia? – The multicentric survey

Kako i kada koristimo kontinuiranu zamenu funkcije bubrega za lečenje akutnog oštećenja bubrega u Srbiji

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Abstract

Background/Aim. The absence of clear guidance in the definition, diagnostics, and indications for renal replacement treatment (RRT) is present. The aim of this study was to help outlining future clinical work in improving the treatment outcome and reducing complications of acute kidney injury (AKI) based on the current clinical practice. **Methods.** The questionnaires were distributed among physicians of different specialties who participated voluntarily and anonymously. The questionnaire was drawn up in accordance with the standard clinical practice. **Results.** We conducted a multicentric web survey among nephrologists (46.8%) and other physicians in Serbia. The sample consisted of 119 participants, out of which 78.9% filled out the survey forms correctly and were, therefore, included in the analysis. Most of them responded that the nephrologist indicates (76.8%) and prescribes (74.5%) continuous renal replacement therapy (CRRT). The application of the Kidney Disease Improving Global Outcomes (KDIGO) 2 criterion for "early" start of CRRT used 74.5% of the respondents, and 91.5% of them started "late" initiation of CRRT in the presence of complications associated with AKI or poor response to conservative treatment. Regarding the clinical experience of the respondents, 74.5% of them marked the "early" start of CRRT within 12 hours, whereas 56.4% of them considered the start of CRRT after 48 h as "late". The most commonly used modality was continuous venous hemodiafiltration (37.6%). Most participants used heparin as an anticoagulant (95.7%) with an average life span of filters less than 24 h (71.3%) and 25 mL/kg/h efficiency target dialysis effluent dose (45.2%) during CRRT. The most common complications of CRRT were hypotension (55.3%) and catheter-related infections (29.8%). **Conclusion.** The "early" start of CRRT is considered favorite by the majority of the participants. According to the obtained data, standardization of the strategy in the diagnostics and treatment of AKI is necessary.

Key words:
acute kidney injury; nephrologists; renal replacement therapy; continuous renal replacement therapy; surveys and questionnaires.

Apstrakt

Uvod/Cilj. Nedostaju jasne smernice u definiciji, dijagnostici i indikacijama za lečenje metodama zamene funkcije bubrega (ZFB). Cilj ove studije bio je da pomogne u kreiranju budućeg kliničkog rada u pogledu poboljšanja ishoda lečenja i smanjenja komplikacija akutnog oštećenja bubrega (AOB) na osnovu aktuelne kliničke prakse. **Metode.** Sprovedene su anonimne ankete među lekarima različitih specijalnosti. Upitnik je sastavljen u skladu sa

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standardnom kliničkom praksom. **Rezultati.** Istraživanje je sprovedeno kao multicentrična *web* anketa među nefrolozima (46,8%) i lekarima drugih specijalnosti u Srbiji. Uzorak je činilo 119 učesnika, od kojih su 78,9% korektno popunili anketu i bili uključeni u analizu. Većina učesnika je odgovorila da nefrolog ukazuje na potrebu korišćenja (76,8%) i određuje (74,5%) korišćenje kontinurane ZFB (KZFB). Na osnovu kriterijuma *Kidney Disease Improving Global Outcomes* (KDIGO) 2 „rani" početak KZFB koristilo je 74,5% ispitanika, a 91,5% među njima „kasno" počinju KZFB kod komplikacija povezanih sa AOB ili slabijeg odgovora na konzervativnu terapiju. U odnosu na kliničko iskustvo ispitanika, 74,5% je smatralo da bi „rani" početak KZFB trebalo da bude unutar 12 h, a 56,4% je odgovorilo da je preko 48 h „kasni" početak. Najčešće je korišćena kontinuirana veno-venska hemodijafiltracija (37,6%). Većina ispitanika (95,7%) je tokom KZFB koristila heparin kao antikoagulans, sa prosečnim trajanjem filtera kraćim od 24 h (71,3%), dok je najzastupljenija doza dijaliznog efluenta bila 25 mL/kg/h (45,2%). Najčešće komplikacije KZFB bile su hipotenzija (55,3%) i infekcije povezane sa prisustvom katetera (29,8%). **Zaključak.** Većina ispitanika daje prednost „ranom" početku KZFB. Prema dobijenim podacima u dijagnostici i lečenju AOB neophodna je standardizacija strategije.

Ključne reči:
bubreg, akutna insuficijencija; nefrolozi; bubreg, zamena funkcije; bubreg, zamena funkcije, kontinuirana; ankete i upitnici.

Introduction

Acute kidney injury (AKI) has a particularly high incidence in admissions to the intensive care unit (ICU), with reports of an incidence range of 16–36% and a three- to five-fold increase of in-hospital mortality (compared to those without AKI). Despite the evolution of the guidelines for diagnosing AKI, we are still largely indebted to serum creatinine, as well as urinary output, to determine the stage of AKI. Thus, while the unification of criteria for AKI is useful for furthering clinical research, it still permits only a relatively late diagnosis. In any case, these biomarkers (as well as others undergoing clinical research) are still too innovative for clinical practice and too expensive for widespread utilization in many low and middle-income countries and lower resource areas of high-income countries. In general, outcomes for AKI are poor, with one systemic review of over 300 cohort studies revealing overall mortality of 23.9% among adult AKI patients [1]. With AKI not requiring dialysis and AKI requiring dialysis both rising, it remains unclear whether this is due to changes in International Classification of Diseases coding, changes in AKI definition, awareness of AKI, or clinical practice [2]. As no specific pharmacological therapy is effective in AKI patients, their care is limited to supportive management in which continuous renal replacement therapy (CRRT) plays a central role [3]. Although there are many aspects of CRRT that are still under debate, its life-saving potential in severe cases of AKI can not be questioned [4].

The aim of this study was to help outlining future clinical work in improving the treatment outcome and reducing complications of AKI.

Methods

The study was conducted using a questionnaire that was distributed among physicians of different specialties. Nephrologists, anesthetists, intensivists, cardiologists, and internists, mostly from tertiary and secondary health care institutions, were invited to participate voluntarily and anonymously. The questionnaire was drawn up in accordance with the standard clinical practice [1]. The 40-question survey form included 4 parts: 1) information on the type of specialty, type of institution and length of service of the physician; 2) information on AKI definition and classification, indications and contraindications of CRRT, optimal start (regarding time, biomarkers, biochemical parameters) and termination of CRRT treatment; 3) information on the choice of vascular approach, type of modality, the dose administered, and anticoagulation; and 4) information on complications of CRRT, renal function recovery, dialysis dependence, and mortality. All the data regarding statistical analysis were compiled from hardcopy sources and processed using a Microsoft Excel database/ datasheet. All the data are presented either as a percentages or as absolute numbers.

Results

Out of the 119 survey participants, 78.9% fully completed the survey form.

According to the reported answers, 46.8% of the participants were nephrologists, 39.4% were specialists in anesthesiology, reanimatology and intensive care, and 13.8% were internists of different branches of internal medicine (9%) and other physicians. Out of them, 72.3% were employed in tertiary care institutions, 23.4% were secondary health care workers, and 4.3% worked in other institutions. Out of all participants, 40.4% had more than 20 years of service, 16.0% had 5–10 years of service, 13.9% had more than 10 years of service, and 1.5% had less than 5 years of service.

The most common AKI classification responses were: Risk, Injury, Failure, Loss of Kidney Function, End-Stage Kidney Disease (RIFLE) criteria – 59.6% in total, followed by Kidney Disease Improving Global Outcomes (KDIGO) criteria – 30.9%. Regarding the use of diuretics in oliguric patients, 43.6% of the participants confirmed administering high doses of furosemide (≥ 250 mg/day), 48.9% used low doses of furosemide (≤ 250 mg/day), whereas 7.0% of the participants did not use diuretics. The respondents had an almost equal distribution of responses in the prevalence of

patients requiring CRRT: < 5.0% (28.7% of the respondents); 5.0–10.0% (22.3% of the respondents); 11.0–20% (16.0% of the respondents); 21.0–30% (18.1% of the respondents) and > 30.0% (14.9% of the respondents). The majority of participants (74.5%) used the KDIGO 2 criterion when deciding on the "early" CRRT initiation, and 91.5% started "late" CRRT for AKI complications (oliguria/anuria, elevated creatinine, hyperkalaemia, metabolic acidosis, and/or refractory hypervolaemia) or a lower response to conservative therapy. In addition to the above criteria, regarding the clinical experience of the subjects, 46.8% thought that the "early" onset of CRRT should be within 6 h (Figure 1), whereas 22.3% said that the "late" onset was > 24 h, a similar percentage of respondents (21.3%) thought it was from 24–48 h, and the majority (56.4%) thought the "late" onset of CRRT was > 48 h. The prediction for the onset of renal replacement therapy (RRT) could be increased by functional tests (furosemide stress test), considered relevant by most of the participants (63.8%). Regarding the use of biomarkers as predictors of the onset of RRT, 43.6% of them indicated cystatin C in urine, 36.2% referred to neutrophil gelatinase-associated lipocalin in urine, and 20.3% indicated a combination of urine tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor (IGF) binding protein 7, whereas 3.2% were related to other biomarkers. As high as 77.7% stated that the severity and course of the disease were the determining factors for initiation of RRT, but that the decision was also influenced by the availability (apparatus, equipment, staff), the day of the week as well as the time of the day, the response to diuretic therapy, and comorbidities (Figure 2). Relative contraindications for the onset of CRRT in 56.4% of the responses were advanced malignant disease (except for multiple myeloma), followed by hypotension without vasopressor response (35.1%), older age, as well as other reasons in 4.3% of the cases. CRRT was indicated in 76.6% of the patients by a nephrologist, in 12.8% of the patients by a nephrologist in consultation with a specialist of anesthesiology, reanimatology, and intensive care, and in 7.4% specialists employed in the ICU/ semi-intensive care. A similar percentage was reported for the CRRT prescription (a nephrologist 74.5%; a nephrologist in consultation with anesthesia, reanimatology, and intensive care specialist 16%; a specialist employed at the intensive care unit 8.5% and an internist of another branch of internal medicine 1.1%). Moreover, 37.2% of the participants reported less than 6 h from the time the indication was given until the CRRT treatment began (Figure 3). Most of the respondents (51.1%) discontinued CRRT if diuresis was > 450 mL/day, 35.1% if creatinine clearance was > 20 mL/min while the others remain neutral.

In most institutions (87.2%), a specialist employed in Intensive Care Unit (ICU)/semi-ICU placed a dialysis catheter, whereas, in others, it was done by a nephrologist in consultation with a specialist of anesthesia, reanimatology, and intensive care. The catheter was mostly inserted using the Seldinger blind technique (in 69.1% of patients). The most often choice was the left/right internal jugular vein (77.7%), followed by ultrasonography (US) assessment in 12.8%, femoral in 5.3%, subclavian in 3.2%, and the jugular internal vein in obese and the femoral vein in non-obese in

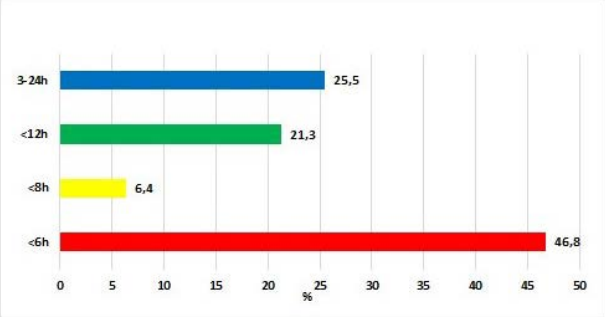

Fig. 1 – Opinion of respondents about timing of "early" continuous renal replacement therapy initiation in acute kidney injury.

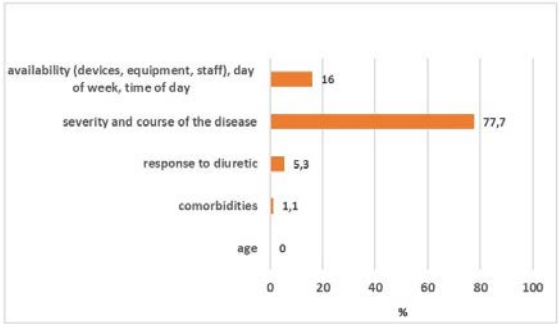

Fig. 2 – Opinion of respondents about factors influencing the decision to start continuous renal replacement therapy.

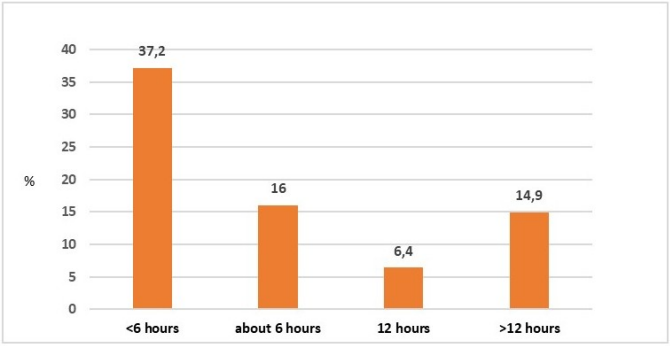

Fig. 3 – Opinion of respondents about "timing" from setting the indication to initiation of continuous renal replacement therapy.

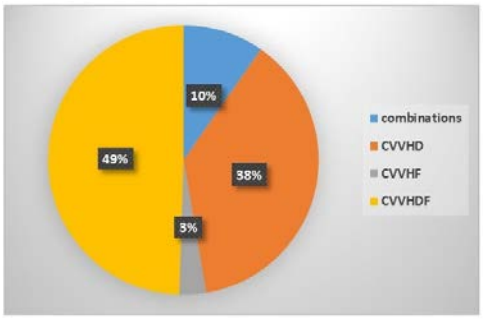

Fig. 4 – Most commonly used modalities of continuous renal replacement therapy.
CVVHD – continuous veno-venous hemodialysis;
CVVHF – continuous veno-venous hemofiltration;
CVVHDF– continuous veno-venous hemodiafiltration.

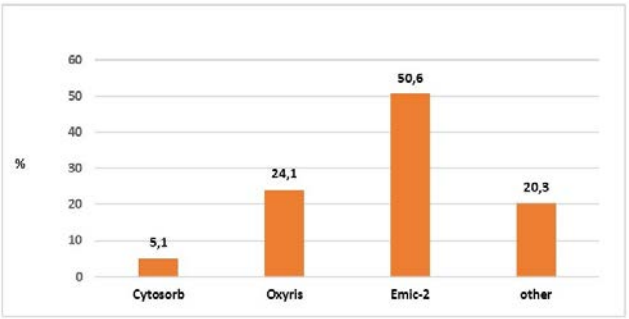

Fig. 5 – Adsorptive membranes use in the treatment of septic patients with acute kidney injury.

1.1% of the patients. The continuous veno-venous hemodiafiltration (CVVHDF) being most commonly used (49%) (Figure 4). The choice of modality depended on the clinical indication (38.7%), the decision of the nephrologist (34.4%), availability of modalities, logistics, personnel (20.4%), and other factors (6.5%). The most common target dose of CRRT was 25 mL/kg/h (45.2%), followed by 35 mL/kg/h (40.9%), 45 mL/kg/h (5.4%), and other values (8.6%). Systemic heparin-anticoagulation was prevalent – 95.7%, followed by regional anticoagulation (citrate) 3.2%, and another anticoagulation in 1.1% of the patients. The average filter life was in most respondents less than 24 h (71.3%). Adsorptive membranes in the treatment of sepsis in AKI were used by 60.6%, the most prevalent being Emic-2 in 50.6% of the cases (Figure 5).

The most common complications of CRRT were hypotension – 55.3% and catheter-associated infection – 29.8%, followed by electrolyte imbalance (8.5%), bleeding (2.1%), and other complications (4.3%). The incidence of catheter-related infections (1–3/1,000 catheter days) was reported by 43.6% of the participants, (4–6/1,000 catheter days) by 37.2% and (< 6/1,000 catheter days) by 19.1%. In patients who required CRRT, 41.9% of the respondents stated that 5–20% of the patients recovered their renal function by the period of 3 months, 35.1% reported that 5–20% of the patients had died, 47.9% said that the same percentage of patients lacked some of the stages of chronic renal failure, and 44.7% reported that 6–10% of the patients remained dialysis-dependent. Over the past year, 33% reported that 21–40% of the patients had "early" onset CRRT recovery in renal function, and 46.8% said that less than 5.0% of the patients had died, as opposed to "late" CRRT onset which reported an increase in renal function < 5.0% out of 44.7% of the participants, whereas 40.4% reported death in 5.0–20% of the patients (Table 1).

Discussion

The lack of clear guidelines in the definition, diagnosis, and treatment of AKI, but also the fact that standard biochemical and clinical parameters, as well as new biomarkers, did not optimize treatment outcomes, indicates the need for further research. The main aim of this multicentric research was to summarize CRRT clinical practice information for one year in order to gain insight into the most important issues, especially treatment timing, and to guide clinicians in their daily work.

Mostly nephrologists, followed by specialists in anesthesiology, reanimatology, and intensive care and physicians with other specialties, of whom 40.4% had work experience of over 20 years and most of them were employed in tertiary care institutions, participated in our questionnaire.

Table 1

Outcomes in patients with acute kidney injury who required renal replacement therapy (RRT) regarding "early" vs. "late" start of continuous RRT (CRRT) according to responses of participants

Patients (%)	Recovery (one year)	Mortality (one year)
Early start CRRT		
< 5	7.4	46.8
5–20	29.8	31.9
21–40	33.0	10.6
41–60	23.4	9.6
> 60	6.4	1.1
Late start CRRT		
< 5	44.7	19.1
5–20	26.6	40.4
21–40	19.1	21.3
41–60	8.5	10.6
> 60	1.1	8.5

According to the results, slightly more than half of the participants still use the RIFLE criteria to define the AKI, while in terms of representation, the following use the KDIGO criteria, which is different from the previous results, in which the KDIGO criteria are dominant [5]. The higher prevalence of the RIFLE classification has been reported in previous studies, and in our sample, it can be explained by the participation of non-nephrological specialty respondents and possibly by a high percentage of physicians with many years of experience who are somewhat skeptical about accepting novelties [6, 7].

Our subjects use almost equally high (≥ 250 mg/day) and low doses of furosemide (≤ 250 mg/day) in the conservative treatment of AKI, and a relatively equal representation in the range of up to 30.0% of AKI patients requiring CRRT is reported. These results are different from earlier study in which it was stated that most use high doses in oliguria patients and that 13.0% of patients require CRRT [5]. In our institutions, most respondents stated that they use the KDIGO 2 criterion for the "early" start of CRRT, and for already present complications associated with AKI or poor response to conservative therapy, participants start CRRT "late". Compared to comprehensive clinical work so far, almost 50.0% believe that the timeline for "early" start of CRRT should be within 12 h, which corresponds to the KDIGO 2 criterion, and slightly more than 50.0% believe that over 48 h is "late" start. These "early" start CRRT results rule out urgent indications and leave time for patient monitoring and clinical evaluation for the late start. However, Thakar et al. [8] reported in their survey that 53.0% of respondents felt that there was no benefit from "early"-start CRRT. Moreover, 35.0% of respondents believed that the risk of "early" CRRT outweighed the benefit. However, 46.0% of respondents indicated that they often initiate "early" CRRT in patients with AKI in ICU. The most influential parameters in determining dialysis initiation were complications of AKI, such as hyperkalemia and hypoxemia due to volume overload, whereas the degree of severity of kidney injury or markers of azotemia played a less important role in the "early" dialysis decision. In their work, Clark et al. [9] have shown that potassium levels and pulmonary edema are the most common indicators of "early" CRRT. The aforementioned surveys were conducted in 2012 when different biochemical and clinical parameters were used in deciding to initiate CRRT. By defining the KDIGO guidelines in the same year in the AKI classification, the use of the same was made possible in the following years, and the above-mentioned surveys are not comparable with ours. Most believe that the Furosemide Stress Test, cystatin C, and neutrophil gelatinase-associated lipocalin (NGAL) in the urine could increase the prediction for the start of CRRT. Our centers have no experience in using biomarkers other than cystatin C, and this may be the reason why only 20.3% of respondents said that (TIMP-2)•(IGFBP7) and other biomarkers would be good predictors. In a previous survey, 60.0% of participants indicated that they were implementing new biomarkers in their practice and research [9]. It is interesting to note that 77.7% still consider the severity and course of the disease to be the deciding factors for the start of CRRT, which indicates the importance of the "clinical scenario" as the most important part of the strategy in the treatment of AKI and also meets the current "watchful waiting" recommendations. However, the responses of the rest of the participants stating comorbidities, response to diuretic therapy, availability (appliances, equipment, staff), day of the week, and time of day are not negligible. It should be noted that none of the subjects indicated a decisive factor for the start of CRRT, but 4.3% indicated that older age was a relative contraindication for the start of CRRT. Just over 50.0% of participants cited advanced malignancy (except for multiple myeloma), and about a third of respondents reported hypotension with no response to vasopressors as relative contraindications for the start of CRRT. So far, many studies have been conducted towards the decision to initiate treatment, and there are fewer data about the patients with a very low probability of surviving where the used CRRT would be a source of inadequate information, as it would probably suggest that CRRT itself increases the risk of poor outcomes. The complexity of the clinician's decision-making in comprehensive consideration of the indications, prognosis, and outcome of the disease is sometimes hampered by subjectivity relative to the preferences of the patient or family, so CRRT is applied, although it is unlikely to modify the outcome. Therefore, the future consensus of the decision to start CRRT should include irrelative contraindications. Most participants stated that the nephrologist indicates the start and writes the CRRT prescription. Please note that in our region, due to the distance of CRRT institutions and some without employed nephrologists, training was conducted by nephrologists in previous years and consultative cooperation continued. About 50.0% of the respondents believe that from the diagnosis to the indication for RRT it takes up to 6 h and from the indication to the beginning of RRT around 6 h, although a quarter of them stated that the stated time depends on the availability of the apparatus, logistics, and staff.

In most of our centers, the specialist employed in the ICU places a dialysis catheter, predominantly by the blind Seldinger technique, most commonly in the left/right internal jugular vein. About half of the respondents use CRRT in their institutions and all modalities (CRRT/hybrid), and the most commonly used modality is CVVHDF. Although there is an upward trend in extracorporeal methods, the results indicate an under-representation of CRRT [5–7]. Most participants indicated that the choice of CRRT modality depends on the clinical indication and the decision of the nephrologist. The most commonly used target dose of CRRT is 25 mL/kg/h, systemic anticoagulation with heparin (95.7%) with an average filter life of less than 24 h (71.3%) is prevalent. Digvijay et al. [5] reported similar results, except in the use of anticoagulation (mostly unfractionated heparin followed by citrate, low molecular weight heparin, and regional anticoagulant therapy). Overberger et al. [10] stated that in their study CRRT was also the most commonly used modality of therapy as well as the applied dialysis effluent dose of 25 mL/kg/h. In another earlier study, over 90.0% of

subjects used CRRT, however, the most commonly prescribed dose was 35 mL/kg/h [8]. In our study, adsorptive membranes were used by 60.6% of subjects to treat sepsis in AKI (Emic-2–50.6% were the most prevalent).

The most common complications of CRRT are hypotension (55.3%) followed by catheter-related infection with an incidence of 1–6/1,000 catheter days reported by most subjects, similar to the results of certain previous studies [11–13]. In presented patients who required CRRT, the majority of respondents stated that up to 20.0% of patients had renal function recovery by 3 months and that, in the same percentage, some patients had some stage of chronic renal failure/dialysis dependency/death in the first year. Those that survive the initially high mortality rate associated with dialysis-requiring AKI mostly become independent of RRT within a year, but some of them do go on to develop chronic kidney disease and even progress to end-stage renal disease [14].

It is unclear whether a preventive/"early" strategy of the initiation of RRT in order to avoid complications associated with AKI leads to better patient outcomes and the use of health services, or a more conservative strategy in which RRT is started as a response to the development of complications provides better results [15]. About 50.0% of the respondents stated that the least patients died with the "early" start of RRT, as opposed to the "late" start of RRT, which was confirmed in our single-center retrospective study of 385 patients with AKI who were admitted between 2014 and 2017 [16].

About half of the physicians reported that patients with "late" dialysis start had the recovery of renal function in the lowest number, while one in three respondents said that 20–40% of patients who started dialysis "early" recovered the renal function. Recent meta-analyses are also remarkably clear, noting that increased mortality and recovery of renal function by "early" dialysis stems from lower quality data (i.e., high heterogeneity and/or higher risk of bias). Meanwhile, an analysis of high-quality pooled data shows no significant difference in mortality [17–22].

Conclusion

Most subjects consider the severity and course of the disease to be the determining factors for initiation of CRRT and favored the "early" start of CRRT – KDIGO 2 criterion within 12 h of diagnosis with an increasing prediction of the Furosemide Stress Test. Although there is an increasing trend in the use of extracorporeal methods, our data indicate underutilization of CRRT and a lack of citrate dialysis. Further research is needed to form a clinical model that, in addition to a functional test, would include one of the biomarkers or a combination of biomarkers in order to increase the prediction of initiation of CRRT treatment.

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