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# Renal replacement therapy for acute kidney injury in burn patients, an international survey and a qualitative review of current controversies

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ABSTRACT

*Background of the study:* Acute kidney injury (AKI) is a common complication in critically ill burn patients and is associated with a number of serious adverse outcomes. The clinical decision-making process related to the management of AKI in burn patients is complex and has not been sufficiently standardized. The main aim of this study was to explore the diagnostic approach and clinician's attitudes toward the management of AKI and RRT in burn patients around the world.

*Methods:* The questionnaire was widely distributed among the members of International Society for Burn Injury (ISBI), who were invited to complete the survey. Data collection and report was compliant with the the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) Web-survey guidelines. The survey form with multiple-choice questions was divided into 3 parts: a. physician and institutional demographics, b. AKI diagnostic information, c. technical aspects of RRT.

*Results:* A total of 44 respondents worldwide submitted valuable data in the 2-month period. Of all respondents, 43.2% were from Europe, 30% from North America, 7% from South-East Asia 2.3% from Africa and 18.2% from other regions. 93.1% of participants declare that they use specific definitions to detect AKI, while 11.4% declare the use of renal ultrasonography for AKI diagnosis. CRRT appeared to be the most preferred option by 43.2% of participants, followed by intermittent hemodialysis (25%), and prolonged intermittent RRT (6.8%). The expertise to deliver a modality and the availability of resources were considered important factors when selecting the optimal RRT modality by 20.5% and 29.6% of respondents. The use of specific serum biomarkers for AKI diagnosis are stated by 16% of respondents; 25% of specialists refer to the use of biomarkers of AKI as a criterium for discontinuing the RRT.

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Femoral vena and right jugular vena were the most frequently used location for RRT temporary catheter placement, 54.6% of respondents declared using ultrasound guidance for catheter placement.

*Conclusions:* The majority of burn specialists use specific consensus classifications to detect acute kidney injury. Continuous renal replacement therapy appeared to be the most preferred option, while the expertise to deliver a particular modality and resources availability play a significant role in modality selection. The use of ultrasound and specific biomarkers for AKI evaluation is infrequent in routine clinical practice.



## 1. Background of the study

Acute kidney injury (AKI) is a common complication in critically ill burn patients admitted to the Intensive Care Unit (ICU) and is associated with a number of serious adverse outcomes including increased length of stay, development of chronic kidney disease, and increased mortality risk.

A recent systematic review and meta-analysis study revealed that AKI occurs in 38% of burn patients admitted to the burn ICU, with 12% of all patients receiving renal replacement therapy (RRT) [1]. Although the prognosis of patients with severe burns and AKI has improved significantly the mortality rate remains high (up to 45%) [2–6].

Acute kidney injury in burn patients is a heterogeneous condition ranging from mild impairment of kidney function to the need of renal replacement therapy [7,8]. Unifying the diagnostic standards of AKI in order to provide consistency to prevention and treatment measures is a current priority in critical care nephrology research agenda. Consensus definitions of AKI, including the risk, injury, failure, loss of function, end-stage renal disease (RIFLE), the AKI Network (AKIN), and the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, all rely on an acute rise in serum creatinine (SCr) levels and/or a decline in urinary output over a given time interval [9–11]. In the recent years, significant progress has been made in the validation of acute kidney injury biomarkers involved in the early detection of AKI, stratification into risk groups for AKI progression, and need for renal replacement therapy [13].

However, the clinical decision-making process related to RRT management for critically ill burn patients with AKI is complex and has not been sufficiently standardized. This is certainly related to the complicated multifactorial pathogenesis of the syndrome, inconsistencies in the diagnosis, and high variability in management of acute kidney injury across different ICU departments [14]. Currently, management of AKI is considered to be supportive, mainly focusing on maintaining hemodynamic stability, optimizing fluid balance, maintaining acid/base and electrolyte control, and avoiding the use of nephrotoxic drugs [15]. Acute kidney injury in critically ill patients often precipitates the use of renal replacement therapy (RRT); however, several unresolved issues remain in terms of RRT dose and timing [15,16]. Specific choice of renal replacement therapy modality for critically ill patients with AKI remains highly controversial, influenced by not only a patient's clinical condition but also the knowledge, experience, and equipment availability of both the prescribing clinician and institution [15–17]. To be able to develop a standard of care for AKI in burn injury, the first step is to understand the current state of practice, including limitations and biases.

The main aim of this study was to explore the diagnostic approach and clinician's attitudes on the management of AKI and RRT in burn patients around the world. For patients treated with RRT, data related to indication, timing of treatment initiation, technical aspects, dose and duration of therapy were also analysed.

## 2. Methods

The questionnaire was designed by the authors and was assessed by two intensive care consultants who work in the specialised burn ICU of the first author. The reviewing consultants were not involved in conducting the survey, and their comments resulted in minor modifications to improve the clarity of the questionnaire. Data collection and report were compliant with the the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) Web-survey guidelines [18].

The questionnaire was widely distributed among the members of International Society for Burn Injury (ISBI). Nine hundred thirty-five members were invited to complete the survey. The survey was designed as an open survey for the site's visitors.

Participation in the survey was voluntary and anonymous. Collection time (time the survey remained open) was 2 months.

The participants were asked to answer based on their actual clinical practice. The survey form with multiple-choice questions was divided into 3 parts.

1 Physician and institutional demographics.
2 AKI diagnostic information, including incidence, definition and classification; role of novel biomarkers; diuretics used in oliguric patients; and preventive measures.
3 Technical aspects of RRT (choice of venous access, protocols, access).

### 2.1. *Statistical analysis*

All the data were examined using a Microsoft excel database/datasheet, which was compiled from hardcopy sources. All the data are presented either as a percentage or as absolute numbers of the questionnaires ($n$ = 44). Average with SD is presented where appropriate. Statistical analysis was performed using SPSS 17.0 software (SPSS Inc., Chicago, IL, USA).

## 3. Results

### 3.1. *Part 1. Physician and institutional demographics*

A total of 44 respondents worldwide submitted valuable data in 2-month period. Of the 935 members who received the newsletter, 4.7% clicked on a questionnaire link; all physicians who opened the link were completed the questionnaire (yielding a response rate of 100% of the viewers). No double participation was observed by checking electronic addresses.

Of all respondents, 43.2% were from Europe, 30% from North America, 7% from South-East Asia, 2.3% from Africa and 18.2% from other regions (including Western Pacific, Central and South Americas and Eastern Mediterranean). Respondents declared their profession as follows: intensive care specialists (47,7%), burn surgeons (22,7%), general surgeons (20.5%), other professionals taking care of burns in the ICU (10%). The majority of respondents were from burn centres with more than 100 admissions per year (33 centres, 75%), 9% of respondents were from burn centers with 50–100 admissions per year and 15.9% were from burn centers with less than 50 admissions per year. The mean percentage of TBSA (Total Body Surface Area) burned of the patients admitted to your Burn Center was between 20 and 50% in 45% of centers, less than 20% in 45.5% of centers and more than 50% in 9% of centers.

Almost thirty two percent of the respondents (31.8%) declare that nephrologists are responsible for the management of RRT (Renal Replacement Therapy) in their Burn Centers, 38.6% declare that attending medical doctors are responsible for the management and 29.6% of respondents state that a team of medical specialists including nephrologists and attending physicians are responsible for the management of AKI.

### 3.2. *Part 2. Approaches to the definition and management of RRT*

The majority of participants declare that they use specific definitions in their department to detect AKI (RIFLE criteria, KDIGO criteria and AKIN criteria); In addition to the specific diagnostic criteria specific biomarkers of AKI are used in 16% of centers and renal ultrasonography in 11.4% of centers. Diagnostic approaches to AKI and details of management are displayed in Table 1.

### 3.3. *Part 3. Technical aspects of RRT*

According to respondents, almost half of respondents (54.6%) use ultrasound guidance for temporary catheter placement for the initiation of RRT. Femoral vena and right jugular vena are the most frequently used location for RRT temporary catheter placement. Chlorhexidine impregnated dressing is used in 45.6% of centers and standard non antimicrobial polyurethane dressing is used in 22.7% of centers. Regional citrate anticoagulation is the preferable technique of anticoagulation in two thirds of centers (61.4%), however, low molecular weight heparins and unfractionated heparin are also used for anticoagulation in 38.6% and 36.4% of centers, respectively. Data on technical aspects of RRT management are presented in Table 2.

## 4. Discussion

Acute kidney injury is an increasingly common complication in burn patients admitted to the intensive care unit (ICU) associated with increased morbidity and mortality. A systematic review of Folkestad et al. included 33 observational studies comprising 8200 burn patients, reveals that AKI occurs in approximately 38% of critically ill burn patients admitted to the ICU, with use of RRT in 12% of all patients [1].

We found a marked paucity of data from Burn ICU's concerning the diagnostic and therapeutic approach to AKI, the optimal way that RRT should be delivered, particularly with respect to modality (convective versus diffusive methods), the timing of initiation and modality of RRT, as well as the prescribed dose and the criteria for discontinuation of renal replacement therapy. This report summarizes the results of a comprehensive physician survey designed to evaluate management of AKI patients in burn ICU setting, especially with respect to the practical issues of CRRT utilization. This was done by a questionnaire distributed to the members of ISBI. Although respondents from Europe and North America were the most frequent (43.2% and 30%, respectively), participation from the rest of the world (27.5%) was relevant for the purposes of such survey. Specialties were quite evenly distributed, since 43.2% of participants were surgeons and 47,7% were intensivists. The majority of centres participated to the study declared more than 100 admissions per year and almost half of them declared the mean TBSA of admitted patients being more than 20%. As such, we believe the survey is generally representative of RRT practices in referring burn centres with a high number of admissions per year.

### 4.1. *Approaches to the definition of AKI*

Current definitions of AKI, including the risk, injury, failure, loss of function, end-stage renal disease (RIFLE), the AKI Network (AKIN), and the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, all rely on an acute rise in serum creatinine (SCr) levels and/or a decline in urinary output over a given time interval [11]. Our data show that the majority of respondents stated that they use a specific definition in their department to detect AKI. Interestingly participants declare the use of the most common consensus definitions at almost a similar rate: 31.8% declare the use of the RIFLE criteria, 31.8% declare the use of the KDIGO criteria and 29.6% stated the use of the AKIN criteria. In comparison with the results of published data from the previous decade in where majority of the participants opted only RIFLE and AKIN criteria for AKI classification [3,6,19], our results confirm the increased use of the KDIGO criteria, even if apparently RIFLE and AKIN are still

**Table 1 – Diagnostic and management approaches to AKI.**

| Question | % of Responses |
|---|---|
| What kind of criteria/tools do you use to define AKI in burn patients? | |
| RIFLE (Risk Injury Failure Loss End-stage renal disease) criteria | 31.8 |
| AKIN (Acute Kidney Injury Network) criteria | 29.5 |
| Kidney Disease Improving Global Outcomes (KDIGO) criteria | 31.8 |
| Urinary output and creatinine | 79.5 |
| Renal injury and functional loss biomarkers (Neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, KIM-1, etc) | 15.9 |
| Urinalysis and urinary biochemistry | 27.3 |
| Renal ultrasonography (US) | 11.4 |
| What kind of modalities do you use to treat AKI in burn patients? | |
| • Intermittent hemodialysis (IHD) | 25 |
| • Prolonged (extended) intermittent RRT, [PIRRT, sustained low efficiency dialysis (SLED), extended daily dialysis (EDD)] | 6.8 |
| • Continuous RRT (CRRT) | 43.2 |
| Both continuous and intermittent modalities | 47.7 |
| • Peritoneal dialysis (PD) | 4.6 |
| Which of the following do you consider when selecting the optimal RRT modality? | |
| • Patient's multi-morbidity | 45.5 |
| • Acuity of AKI | 47.7 |
| • Presence of multi-organ failure | 63.4 |
| • Expertise to deliver prescribed therapy | 20.5 |
| • Resources | 29.6 |
| On which parameters is the timing of starting RRT usually based? | |
| • Serum creatinine-based thresholds | 61.4 |
| • Serum urea nitrogen thresholds | 47.7 |
| • KDIGO stage 2 | 9 |
| • KDIGO stage 3 | 20.5 |
| • Fluid accumulation thresholds (> 10−20% fluid accumulation as a trigger for considering RRT) | 50 |
| • Severe electrolytes' disturbances | 81.8 |
| • Metabolic acidosis (pH below 7.15) | 70.5 |
| Which effluent flow rate do your patients usually receive when treated with CRRT? | |
| • 20−24 mL/kg/h | 29.6 |
| • 25−35 mL/kg/h | 56.8 |
| • >35−40 mL/kg/h | 13.6 |
| Which kind of strategies do you use to improve hemodynamic tolerance when utilizing intermittent RRT in critically ill patients with AKI? | |
| • Isovolemic initiation | 61.4 |
| • Reduced dialysate temperature | 4.6 |
| • Preferential use of bicarbonate buffer | 20.5 |
| • Dialysate sodium profiling | 20.5 |
| • Conservative initial ultrafltration | 45.5 |
| Which criteria for discontinuing the RRT do you use? | |
| • Restoration of spontaneous urine output | 79.6 |
| • Response to diuretics | 22.7 |
| • 24-h urine creatinine excretion | 18.2 |
| • Daily urea excretion | 6.8 |
| • 2-h creatinine clearance | 9 |
| • Serum creatinine | 65.9 |
| • Serum urea | 34.1 |
| • Serum biomarkers | 25 |

widely applied. Interestingly, 79.5% of participants declare the use of urinary output and creatinine to define AKI, while more than 90% stated the use of consensus classifications. It appeared that the definitions of AKI according to serum creatinine and urine output selected by respondents of the questionnaire are not necessarily fitting the criteria of the classification/staging of KDIGO, RIFLE, or AKIN. As far as it is possible to understand from the presented data, still some confusion might be existing regarding the issue of diagnostic criteria and the difference between AKI diagnosis and AKI severity classification.

### 4.2. *Approaches to the management of RRT*

Almost two thirds of respondents (68.2%) referred to that they are actively involved with management of patients who develop AKI, however, half of them declare sharing the responsibilities with the nephrologists and almost one third of the respondents (31.8%) declare that nephrologists involve exclusively in the management of RRT in burn patients. Available data suggest that in many ICUs intensivists have final responsibility for all aspects of care in patients with AKI, including the initiation and management of renal replacement

**Table 2 – Assessment of technical aspects of Renal Replacement Therapy (RRT) management.**

| Question | % of Responses |
|---|---|
| Which method of temporary catheter placement for RRT do you use? | |
| • Anatomical landmark placement | 45.5 |
| • Ultrasound guided placement | 54.6 |
| Which location is mostly used for RRT temporary catheter placement? | |
| • Right jugular vein | 36.4 |
| • Left jugular vein | 0 |
| • Femoral vein | 61.4 |
| • Subclavian vein | 2.3 |
| Which kind of dressing do you use? | |
| • Chlorhexidine-impregnated dressing | 45.5 |
| • Standard non-antimicrobial polyurethane dressing | 22.7 |
| • Securement with gauze and tape | 31.8 |
| Anticoagulation | |
| • Regional citrate anticoagulation | 61.4 |
| • Low molecular weight heparins | 38.6 |
| • Unfractionated heparin | 36.4 |

therapy [20,21]. Opinions on whether to consult a nephrologist for every patient with AKI in the ICU may differ. The respective arguments concentrate on the specific role of the intensivist, the different organizational models of the ICU, the scale and diversity of the problem, and the post-discharge “legacy” of AKI [21,22]. Transfer of knowledge between the ICU and nephrology specialists, e.g., during daily rounds, will undoubtedly improve the quality of care [23]. In addition, as our results show, burn centers teams are composed of physicians with multidisciplinary backgrounds therefore interactions between specialties for the management of difficult cases is of crucial importance.

a *RRT modalities*

Worldwide, RRT can be provided as peritoneal dialysis, intermittent haemodialysis (IHD), prolonged intermittent hybrid forms of RRT, combining the advantages of CRRT and IHD (sustained low-efficiency dialysis (SLED), extended daily dialysis (EDD)), and continuous renal replacement therapy (CRRT), which includes continuous veno-venous haemofiltration (CVVH), continuous veno-venous haemodialysis (CVVHD) and continuous veno-venous haemodiafiltration (CVVHDF) [11,24–29]. Coupled plasma filtration adsorption (CPFA) has been studied in recent years in the hope of maximizing the effect of renal replacement therapy in modulating the exaggerated host inflammatory response in sepsis [30,31]. Several ICUs adopted CPFA in septic burn patients with promising results [32,33]. However, these strategies are not widely utilized in practice and the evidence to support their use at this stage is considered of low level [34,35]. CRRT is considered as an important treatment modality for critically ill patients [11,36,37]. Consistent with the previous reports [38], CRRT appeared to be the most preferred option by a majority of the participants (43.2%), followed by intermittent hemodialysis (25%), and prolonged intermittent RRT (6.82%). Almost half of participants state that they use both continuous and intermittent modalities. Peritoneal dialysis was considered by 4.5% of the respondents. Numerous publications have provided conclusions that the modality of RRT, either continuous or intermittent, do not affect survival and recovery of kidney function [39–42].

Consistent with the KDIGO AKI Clinical Practice Guideline [11], the survey respondents declare the multiorgan failure, including hemodynamic instability status, as a major consideration when they make a choice of RRT modalities. However, the specific choice of renal replacement modality for critically ill patients with AKI remains controversial [15–17,43]; the decision is often influenced by not only a patient's clinical condition but also by the knowledge and experience of both the clinician involving in the decision making process and the availability of resources [44]. The existing variation in clinical utilization/application of RRT is believed to be more pronounced in the developing world, in which resource constraints, costs, and physician acceptance are important considerations [44,45]. Our survey evidences that resources play a significant role in modality selection, possibly providing a barrier to CRRT utilization: resources availability has been considered also important factors when selecting the optimal RRT modality by one third of respondents. Additionally, our survey suggests that the expertise to deliver a particular modality and resources availability play a significant role in modality selection. The expertise to deliver a modality and the availability of resources were considered important factors when selecting the optimal RRT modality by 20.5% and 29.6% of respondents. These cost-related and expertise factors might represent a divergence of the developing countries from the developed countries, in which varying combinations of health care policies render these considerations relatively unimportant.

b *Indications, timing, and dosing for RRT*

Although the indications for RRT (volume overload, severe metabolic acidosis and electrolyte abnormalities, uremic symptoms) are well established, they are subject to wide interpretation. In many patients, RRT is initiated in the setting of persistent or progressive AKI in the absence of these criteria [46]. The optimal timing for initiation of RRT in AKI remains also uncertain [47–50]. A small retrospective analysis of Burns

Database in Singapore General Hospital demonstrated that early initiation of RRT leads to improved outcome and survival among burned patients with acute kidney injury [51]. Recently published studies involving critically ill patients with severe acute kidney injury found no significant difference with regard to mortality between an accelerated and a standard or delayed strategy for the initiation of renal replacement therapy [47,52–54]. Earlier initiation of AKI allows for early optimization of volume status, early correction of acid-base and electrolyte abnormalities, control of uremia; however, these potential benefits of early starting need to be balanced with considerable risks and burdens associated with RRT, including vascular access, hemodynamic consequences of RRT, resource utilization as well as with the concerns that early RRT may impair subsequent recovery of kidney function [55]. Data from our survey related to RRT indications and initiation were conflicting in several respects. Along with severe electrolyte/acid-base disturbances, multi-organ failure, and fluid overload, AKI stage 2 and 3 were reported as the initiation criteria. However, recently published data show that when severe acute kidney injury is not accompanied by one of the clinical complications the benefits of renal replacement therapy remain unclear [15,17,47]. Statements from the recent Kidney Disease: Improving Global Outcomes (KDIGO) conference on controversies confirm the need to better define and classify acute kidney disease [17]. Expert panel states that biopsy, kidney damage biomarkers and imaging methods may be useful tools for classification of risk factors, cause, prognosis, and treatment of AKI and pose the question whether the markers of kidney damage should be incorporated into the AKI definition. Moreover, the participants of the controversy conference outline the need for a new, revised definition and classification of AKI which could be better tied to clinical management. KDIGO group members declare that the decision on the appropriate time to start RRT is naturally complex, integrating numerous variables, and should largely be individualized until results of ongoing and future large randomized trials will provide additional evidence and will help to reduce current variations in the practices of renal replacement therapy prescription [48,56–58]. Creatinine levels were prioritized by a substantial percentage of our survey's respondents in their decision-making; almost two thirds of participants initiate RRT based on serum creatinine thresholds. Our results are surprising in the light of the rapidly accumulating evidence that in complex clinical situations the decision to start RRT and the choice of RRT modality are often more dependent on the underlying pathology than on the actual level of kidney function [11,59].

Our survey indicates that RRT practices in Burn centers in many respects are similar to those in the other critically ill patients. Indeed, the survey responses reporting a wide variety of prescribed CRRT modalities, a prescribed hourly dose in the range of 20–30 mL/kg/h, and a measures to improve hemodynamic tolerance (conservative initial ultrafiltration and isovolemic initiation) are all consistent with worldwide RRT practice [11,37,60–62]. Overall, 56.8% of participants responded that rate of 20–24 mL/kg/h is the efficiency target during CRRT, 30% said that they target 25–35 mL/kg/h, 13.6% said rate higher than 35 mL/kg/h is their efficiency target. A multicenter, prospective, randomized trial of Chung et al. evaluating the efficacy of high-volume hemofiltration (HVHF) in burn patients with septic shock and acute kidney injury concluded that HVHF was safe and effective in reversing shock and improving organ function [63]. Although several studies published almost two decades ago [64,65] suggested that higher effluent flow rates were associated with improved outcome, the results were inconsistent [66] and this relationship was not confirmed in multicenter, randomized, controlled trials. Recently published data demonstrated that using intensive renal support in critically ill patients with acute kidney injury were not associated with improved recovery of kidney function, decreased mortality, or reduced rate of nonrenal organ failure as compared with less-intensive therapy [60,66,67].

The respondents of our survey stated that the main strategies used to improve hemodynamic tolerance to RRT in critically ill patients with AKI include isovolemic initiation and conservative initial ultrafiltration strategy, approaches that are consistent with the available guideline recommendations [11]. Practices including the use of lower temperature, the use of higher dialysate sodium levels and individualized ultrafiltration rate profiles have also the potential to improve hemodynamic tolerance of hemodialysis, however, there is a paucity of high-quality data on this issue to date [62,68–70].

c *Discontinuation of RRT*

We found a wide variation in clinical practice regarding timing of discontinuation of renal replacement therapy in patients with acute kidney injury [37,71–73]. Our data show that more than two third of centers use the restoration of spontaneous urine output and serum creatinine as the main criteria for discontinuing the RRT; 22,7% of respondents also estimate the response to diuretics when deciding the discontinuation of RRT. Whether diuretics influence renal recovery has not been sufficiently elucidated until now. The current KDIGO guidelines recommend discontinuing RRT when it is no longer indicated, either because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs, or because RRT is no longer consistent with the goals of care [11]. Experts suggest not using diuretics to enhance kidney function recovery, or to reduce the duration or frequency of RRT (grade of recommendation 2B) [11]. Prolonged, unnecessary RRT treatment can contribute to length of stay, overall hospital costs, and risk of complications associated with RRT. In addition, prolonged RRT can paradoxically lengthen the time for which the patient remains dialysis dependent. The importance of frequent and careful clinical assessment while considering discontinuation of RRT for AKI patients has been emphasized by many investigators [11,67,74,75].

### 4.3. *Use of serum biomarkers*

Acute kidney injury biomarkers, complementing standard diagnostic tools such as serum creatinine (SCr) and urine output, are currently the focus of preclinical and clinical investigations. These biomarkers include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), liver-type fatty acid-binding protein, interleukin 18 (lL-18), insulin-like growth factor-binding protein 7, tissue inhibitor of metalloproteinase 2 (TIMP-2), calprotectin, urine angiotensinogen (AGT), and urine microRNA [76]. However, despite the evidence that several blood and urinary biomarkers (neutrophil gelatinase-associated lipocalin (NGAL), Kidney injury molecule-1 (KIM-1), cystatin C, the combination of tissue inhibitor of metalloproteinase-2 and insulin growth factor binding protein-7) showed promising diagnostic and prognostic value in critically ill patients with AKI, investigators highlight that the strength of evidence currently precludes their routine use to guide decision-making on when to initiate RRT, with the decision on this being almost totally dependent on clinical expectations [77]. A recent study of Hoste et al. revealed that a novel biomarker - urinary CC motif chemokine ligand 14 (CCL14) was predictive of persistent stage 3 AKI [78]. In our study the use of specific biomarkers for AKI diagnosis are stated by 16% of respondents; interestingly, 25% of specialists refer to the use of biomarkers of AKI as a criterium for discontinuing the RRT. Our results are consistent with the data from the recent study of Digvijay et al. [38] evaluated the clinical approach to AKI and RRT in a population of nephrologists and intensivists participating in the 36th International course on AKI and Continuous RRT (CRRT). According to the reported answers 19% of respondents referred to the use of cystatin C and 25% of participants declared that biomarkers should replace serum creatinine on routine laboratory screening.

Although the use of biomarkers remains largely experimental, biomarkers potentially could help clinicians to detect kidney injury at earlier stage, guide timing of therapy, assess response to therapy, provide prognostic information on the course of renal impairment, as well as provide a rationale for randomization of patients for clinical studies. Additionally, future use of sensitive, specific, and reliable biomarkers for early diagnosis and prognosis of AKI together with validation of innovative technologies that allow rapid detection and complex analysis of multiple markers at the bedside could facilitated development of new, effective therapies for AKI [79].

### 4.4. *Technical aspects of RRT*

a *Use of ultrasound*

Only a minority of burn specialists (11.4%) declare the use of renal ultrasonography for AKI diagnosis however, almost half of respondents use ultrasound guidance for catheter placement for RRT initiation. with femoral vena and right jugular vena are the most frequently used location for RRT temporary catheter placement. Ultrasonographic (US) evaluation is considered to be particularly useful for the evaluation of acute kidney injury [80–82]. A study of Liu et al. evaluated the ultrasonography characteristics of 111 patients with AKI. Compared with the control group, AKI patients had greater kidney length and kidney volume ($p < 0.05$). Patients with AKI also displayed thicker parenchyma than those in the control group [80]. Recent data suggest that renal resistive index (RRI) evaluated by Doppler US could also have a certain clinical value in the management and prognosis of clinical outcome in patients with acute kidney injury [83]. Although many factors may influence the interpretation of RRI [84] such as arrhythmia, intra-abdominal pressure, right heart function, renal resistive index changes have demonstrated high sensitivity in detecting acute renal ischemia induced by systemic occult hypoperfusion in patients with polytrauma [85]. Additionally, RRI > 0.7 may also identify even mild organ-specific supply and demand mismatch when arterial oxygenation is normal, thus reflecting an early vascular response to tissue hypoxia [86]. Further studies are indicated to validate the role of RRI and to establish a correlation between changes in this index and markers of renal function and outcome in burn patients.

Point-of-care ultrasound (PoCUS) is gaining wide recognition during the last decades and more physicians are using it to effectively diagnose and adequately manage patients moreover, PoCUS is considered a core competency skill for residents in various training programs [87–90]. Interestingly, according to our results, more than half of respondents (54.6%) use ultrasound guidance for temporary catheter placement for the initiation of RRT with femoral vein and right jugular vein being the most frequently used locations for catheter placement. Our data support the existing evidence on the use of ultrasonography for central venous cannulation [91,92]. A systematic review included 13 studies involving 2360 procedures reveals that two-dimensional ultrasound offers advantages in safety and quality when compared with an anatomical landmark technique for subclavian (arterial puncture, hematoma formation) or femoral vein (success on the first attempt) cannulation for central vein catheterization [91]. A meta-analysis evaluating the clinical effectiveness of ultrasound guided central venous cannulation shows a clear benefit from two dimensional ultrasound guidance for central venous access compared with the landmark method [92]. This is manifest in a lower technical failure rate (overall and on first attempt), a reduction in complications, and faster access. Remarkably, when asking about the selection of the vascular access site, more than half of participants obtain central venous access via the femoral vein. Data from the literature highlight caution in the use of femoral access for RRT catheter placement as it could associated with a lower delivered dose of dialysis especially during intermittent treatment modality [93]. The femoral veins are generally easier to access and provide dependable access for less experienced operators in case of emergency. Earlier studies reported that compared with internal jugular or subclavian access femoral access was associated with a higher risk of catheter-related bloodstream infections (CRBSIs), especially when the catheters were inserted directly in the burn wound or in the surrounding unwounded skin [94]. However, subsequent studies and meta-analysis examining femoral access found similar rates of CRBSIs when comparing femoral, subclavian, and jugular sites [95–97].

b *Anticoagulation during RRT*

Appropriate anticoagulation during renal replacement therapy is usually maintained with unfractionated heparin, which is the most widely used anticoagulant worldwide for the prevention of blood clotting in the dialysis circuit [98]. Alternative methods of regional and systemic anticoagulation, include low molecular weight heparin, heparin coated membranes, and regional citrate anticoagulation [98–100]. Our survey demonstrates that almost two third of centers use regional citrate anticoagulation; however, systemic unfractionated heparin and low molecular weight heparin are also administrated at almost the similar rates as anticoagulants in many centers (39% and 36%, respectively). Recent data from a study of Arnold et al. [101] demonstrated that administration of unfractionated heparin fails to prevent early clotting events in the dialysis circuit with regional citrate being the most effective anticoagulation strategy for patients who have no indication for systemic anticoagulation; for patients with systemic anticoagulation indication, the use of low molecular weight heparin results in the longest dialysis circuit life spans and, consequently, in the longest treatment times. A randomized multicenter clinical trial in 26 centers across Germany, comparing the effects of regional citrate anticoagulation with systemic heparin anticoagulation, demonstrated that anticoagulation with regional citrate resulted in significantly longer filter life span and had significantly fewer bleeding complications [102]. Given that burn injury is frequently accompanied by coagulation abnormalities [103,104] and undergo frequent surgical operations, the use of citrate would provide an additional advantage by reducing blood loss and reducing mortality associated with transfusion. Low-molecular weight heparins have been proposed as an alternative to unfractionated heparin due to their more consistent anticoagulant response, higher anti-Xa activity and lower incidence of heparin-induced thrombocytopenia [105,106]. A prospective randomized controlled study of Joannidis et al. showed that the use of enoxaparin for anticoagulation during CVVH resulted in higher filter lifespan compared with unfractionated heparin; however, obvious superiority of low-molecular weight heparins compared with UFH had not been demonstrated [106]. Current guidelines suggest the use of regional citrate anticoagulation as the first-line anticoagulation method for continuous RRT in critically ill patients [11].

c *Catheter dressing*

Bloodstream infection is one of the major complications of dialysis catheter use, which is associated with an increased morbidity and mortality [107,108]. Interventions to reduce infections in the hemodialysis setting include adherence to strict aseptic techniques in accordance with the Centers for Disease Control and Prevention's Core Interventions for catheter care, the improvement of stuff education, screening for pathogens colonization, appropriate catheter exit site cate and lumen care as well as the development of novel devices for preventing catheter colonization [109,110]. Our study results show that chlorhexidine-based products are widely used in the Burn ICU setting for prevention of central catheter –associated bloodstream infections in RRT patients. On being asked which kind of dressing of catheters is used in participants units, most of the participants responded to use the chlorhexidine impregnated dressing (45.5%), followed by the securement with gauze and tape (31.8%) and non - antimicrobial polyurethane dressing (22.7%). The application of chlorhexidine as a preferred skin antiseptic agent for routine catheter exit site care is an important additional recommendation to the updated 2016 CDC core interventions [107,109,111]. Triple antibiotic ointment and povidone-iodine ointment are also the recommended antimicrobial agents, and both are associated with marked reductions in bloodstream infections; the application of mupirocin to prevent catheter exit site colonization, although effective, may have the potential for development of microbial resistance and, therefore, its routine use is not recommended [109,110]. More recently, a novel catheter hub device (ClearGuard HD Antimicrobial Barrier Cap, Pursuit Vascular, Inc.) has been shown to reduce central catheter–associated bloodstream infections in hemodialysis patients despite the high cost of this novel product the advantages from their use attributable to lower rate of infectious complications might be substantial [112,113]. Our data reveal that a substantial percentage of respondents-almost one third - use dry gauze dressing in their routine practice. However, a recent publication of Apata et al. evaluating a quality improvement project in hemodialysis patients shows a significant reduction in bloodstream infection (50%) when using chlorhexidine-impregnated transparent dressings compared with the use of dry gauze dressings applied to the catheter exit site [114]. A well-designed study is needed to evaluate chlorhexidine-based exit site applications versus various topical antimicrobial agents and devices which target the extraluminal route of microbial entry for the prevention of CRBSI in burn patients who are undergoing hemodialysis.

### 4.5. *Study limitations*

Our study has some limitations.

Firstly, the response rate was unfortunately low, the small number of responses did not allow us to analyse differences between geographic regions and countries in depth.

Secondly, the participants who respond to the survey were obviously a self-selected burn specialists' group and consequently, their responses potentially do not completely reflect the actual practice in AKI and renal replacement therapy management in burn settings worldwide.

Thirdly, the study was limited to burn specialists and did not address a multidisciplinary group of specialists involved in burn care, including nephrologists, which could be an interesting target group for analogous future investigations.

In conclusion:

- The majority of burn specialists use specific consensus classifications to detect acute kidney injury; our results confirm the increased use of the KDIGO criteria, even if apparently RIFLE and AKIN are still widely applied.
- Continuous renal replacement therapy appeared to be the most preferred option, while the expertise to deliver a particular modality and resources availability play a significant role in modality selection.
- Regarding timing of starting and discontinuation of renal replacement therapy in patients with acute kidney injury our data show that the majority of burn specialists use the urine output and serum creatinine criteria as the main criteria for starting and discontinuing the RRT.
- Only a minority of burn specialists use renal ultrasonography for evaluation of acute kidney injury; however,

**Table 3 – Gaps in knowledge and research recommendations in burn related acute kidney injury.**

| Knowledge gaps | Research recommendations |
|---|---|
| **Epidemiology** | Standardize reporting of AKI in burn patients. |
| What is the incidence of AKI in burn patients? | Evaluate the impact of AKI diagnosis on outcome. |
| How does AKI diagnosis affect outcome? | Determine long-term outcomes after AKI and RRT. |
| **Risk stratification** | Conduct multicenter studies for validation of AKI risk models. |
| Is there utility for a risk-based screening approach? | Identify “pre-clinical” AKI signs and symptoms. |
| | Investigate whether biomarkers for risk prediction, surveillance, or diagnostic evaluation (to discriminate between kidney dysfunction and injury) can affect choice of treatment strategy. |
| **Diagnosis** | Investigate the use of optimal diagnostic system to confirm kidney injury. |
| Are the general classification systems valid in burn patients? | Determine the value of biomarkers and renal resistive index in addition to laboratory and clinical findings for AKI diagnosis in burn patients. |
| **General management** | Investigate the most promising strategies in ameliorating risk of AKI in burn patients. |
| What are the most promising strategies in ameliorating risk of AKI in burn patients? | Investigate the optimal targets and the optimal method of administering fluids and vasoactive drugs for preventing or mitigating AKI in burn patients and explore whether the optimal methods vary in different contexts where different levels of monitoring are available, including pre-hospital settings and resource-limited settings. |
| How can we define recovery of kidney function after AKI? | Define the role of kidney ultrasound and biomarkers in managing AKI. |
| | Identify the impact of nephrotoxic drugs and contrast. |
| | Identify endpoints for trials in burn patients (mortality, recovery of kidney function, chronic kidney disease, dialysis dependency). |
| **Renal replacement therapy** | Investigate the optimal timing, dose, and modality of RRT. |
| What are the most promising treatment options? | Identify the indicators that predict successful discontinuation of RRT. |
| When renal replacement therapy should be stopped? | Compare anticoagulation strategies used during RRT. |
| Which is the optimal anticoagulation strategy for RRT? | Develop a registry focused on patients receiving RRT. |

Abbreviations: AKI, acute kidney injury; RRT, renal replacement therapy.

almost half of respondents use ultrasound guidance for catheter placement for RRT initiation.

- Very few burn physicians declare the use of specific biomarkers for AKI evaluation.
- Acute kidney injury management standardization and education of specialists involving in the management of kidney injury should be considered as the fundamental aspects of harmonizing treatment approaches and improve outcome of burn patients worldwide.
- Additional clinical trials should aim to extend our knowledge about diagnostic and therapeutic approach to acute kidney injury in burn patients. Gaps in knowledge and fields in need of further research are enumerated in Table 3.

## Conflict of interest

The authors declare no conflicts of interest.

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