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Continuous renal replacement therapy in Iran; current practice, indications and outcomes in hemodynamically unstable patients

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ABSTRACT

Introduction: Continuous renal replacement therapy (CRRT) is the gold standard renal replacement therapy (RRT) for hemodynamically unstable patients.
Objectives: To study the characteristics and survival of patients undergoing CRRT in Iran.
Patients and Methods: This is a retrospective study conducted on 58 patients indicated for CRRT at the Shahid-Modarres hospital of Tehran during 2016-2017. Gender, age, underlying diseases, comorbidities, history of surgery, dialysis indication, and survival were gathered by reviewing patients' medical records. The data was analyzed in SPSS version 21.
Results: Sepsis constituted the most common underlying condition at admission. Overall, continuous venovenous hemodialysis (CVVHD) was performed in 72.4% of the patients. Diabetes and hypertension were the most common causes leading to RRT. The most common indication for CRRT was unstable hemodynamic condition. The patients were most frequently referred from ICU (34.5%), emergency department (20.7%), and CCU (15.5%).
Conclusion: We here reviewed the characteristics of hemodynamically unstable patients undergoing CRRT. Our findings can help to understand the most important indications for CRRT and to standardize CRRT practice in Iran.

Implication for health policy/practice/research/medical education:
In a study on 58 patients who underwent CRRT at the Shahid Modarres hospital of Tehran, the most common modality was CVVHD and the most indication of doing CRRT was unstability of hemodynamic condition.
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Original

Introduction

Acute kidney injury (AKI) is a dire clinical condition associated with severe consequences and a high rate of mortality (1). The overall incidence of AKI has been reported as 4% to 60% (2). According to the reports of the Iranian Ministry of Health and Medical Education, more than 32000 patients undergo dialysis in Iran (3,4).

Continuous renal replacement therapy (CRRT) is the gold standard for management of hemodynamically unstable patients requiring renal replacement therapy (RRT). This approach is increasingly used in intensive care units (ICUs) and cardiovascular care units (CCUs), especially in patients with sepsis (5-10). In comparison with intermittent hemodialysis (IHD), CRRT delivers a slow-acting removal of the waste materials while retaining the hemodynamic stability and intravascular volume (11, 10). In studies investigating the clinical implications of CRRT, better outcomes, as well as higher survival and residual renal function have been reported in long-term follow-up (12-16). Also, CRRT has been associated with reduced risk of mortality in AKI patients after surgery (17, 18). However, some studies reported similar outcomes for CRRT and IHD.

The choice of dialysis method largely depends on the level of knowledge and skill of the staff, as well as the available facilities in the treatment center. Using CRRT as a viable RRT has increased over the past two decades (19-21). A recent study has suggested the CRRT as the

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preferred RRT in AKI patients (24-29). In patients with liver disease and intracranial hypertension, CRRT has provided better control on the fluid balance than IHD (30, 31). Nevertheless, the use of CRRT should be limited only to patients with significant hemodynamic instability (24). CRRT imposes a relatively high cost on the health care system. Furthermore, patients need to remain immobilized during the procedure which is a disadvantage (22,23). Hemodynamic instability is a major complication that may lead to early termination of IHD and increased likelihood of morbidity and mortality in patients undergoing dialysis (2,25,26). Different dialysis methods represent variable therapeutic costs, complications, and limitations.

Objectives

There is limited understanding on the characteristics and clinical outcomes of Iranian patients undergoing CRRT. Also, there is no adequate information on the CRRT practice in Iran. In this study, we investigated the characteristics and outcomes of Iranian patients undergoing CRRT.

Patients and Methods

Data collection

This retrospective study was carried out on the patients undergoing CRRT at the Shahid- Modarres hospital of Tehran (2016 to 2017). The medical archives were reviewed to record the diagnoses, underlying organ involvements, gender, age, admission ward, serum creatinine level at admission, relevant comorbidities, indication for CRRT, duration of CRRT, urine output, history of surgery and finally mortality rate.

Ethical approval

The tenets of the Declaration of Helsinki and its later amendments were followed. The objectives of the study were explained to all the participants before obtaining written informed consent from them. This study was the result of a thesis for acquiring M.D, degree of Nima Taheri from Shahid-Beheshti University of Medical Sciences (Thesis # 34).

Statistical analysis

The frequency, mean, and standard deviation were used as descriptive statistics. The student *t* test and chi-square test were used to determine any significant difference in the means of continuous variables and any significant association between the categorical variables respectively. Multivariate analysis was used to determine any significant relationship between the studied variables and mortality. The statistical significance level was designated as *P* value < 0.05. The statistical procedures were conducted in SPSS, version 21.

Results

The mean age of the patients was 65.4 ± 13.16 years old. Eight patients (13.79%) had < 50 years old. Males and females constituted 36 (62.1%) and 22 (37.9%) subjects respectively. The most common underlying diseases were diabetes (23, 39.6%), hypertension (15, 25.8%) and chronic kidney disease (9, 15.5%). The baseline characteristics of the patients and the underlying diseases have been summarized in Table 1. The majority of the patients were admitted to the ICU (23, 39.65%), emergency department (12, 20.7%) and CCU (9, 15.5%). Overall, 20 (34.5%) patients had been admitted for surgery.

The most common underlying conditions at the time of admission were sepsis (10, 17.24%), malignancy (9, 15.5%), cardiovascular surgery (9, 15.5%), and the loss of consciousness (7, 12.06%) (Figure 1). The main indications for CRRT were unstable hemodynamics (46, 79.3%) following by high serum potassium (3, 5.2%), fluid overload (3, 5.2%) and a combination of these indications (6, 10.3%). The continuous venovenous hemodialysis (CVVHD) and continuous veno-venous hemofiltration methods had been used in 72.4% and 27.6% of the patients respectively.

The means of CRRT dosage and duration were 23.75±2.03 mL/kg/h and 1073 ± 203.6 minutes respectively. The mean serum creatinine level at admission in the hospital was 3.7±2.7 mg/dL. The mean values of serum urea and urine output before initiation of CRRT were 176±47.8 mg/dL and 191±138. 1 cc/24 h respectively.

The in-hospital mortality rate was 60.3% (35 patients) at follow up. On the other hand, 23 patients (39.7%) were discharged. Regression multivariate analysis revealed that serum urea level before initiation of CRRT was associated with increased risk of in-hospital mortality. Also, the presence of more than one comorbidity decreased the survival rate in the patients.

Discussion

CRRT is a multidimensional procedure with wide range variations on the clinical practice in different global and

Table 1. Demographic characteristics and clinical outcomes in 58 patients undergoing CRRT

Characteristics	No.	Percent
Gender		
Male	36	62. 1%
Female	22	37. 9%
Past medical history		
Lung disease (asthma and COPD)	5	9. 61%
Hypertension	15	28. 8%
Diabetes	23	44. 2%
Malignancy and metastasis	11	21. 1%
Heart failure	8	15. 3%
Renal disease	16	30. 7%
Liver disease	1	1. 9%
Systematic lupus erythematosus	2	3. 84%
Morbid obesity	2	3. 84%

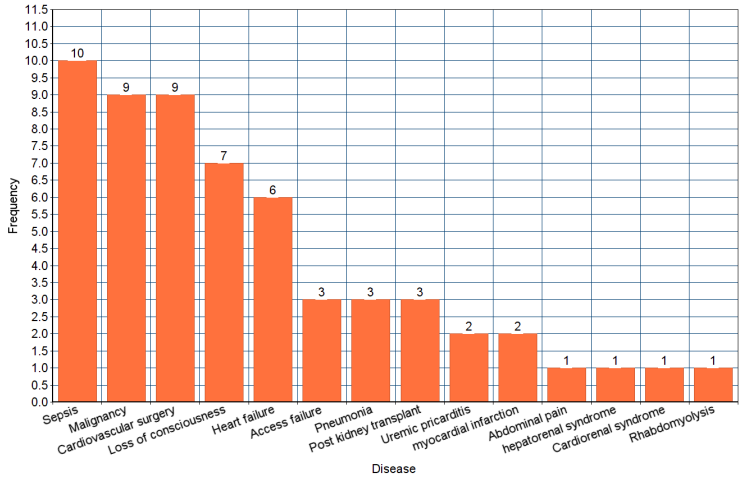

Figure 1. Diseases that cause initial admission by frequency.

regional centers (19-23). The application of CRRT in Iran is hindered because of limited facilities, high costs, inadequate experience of health providers, and finally the lack of sufficient data on the patient's specifications. Therefore, we here aimed to address the characteristics and clinical outcomes of Iranian patients undergoing CRRT. Providing such information can help optimizing resources to effectively implement CRRT in indicated patients. In this study, we examined 58 patients undergoing CRRT in one of the largest nephrology clinics in Iran (2016 to 2017).

Globally, RRT is mainly indicated in patients with sepsis and postoperative complications (7-9, 26). In a research conducted in china, sepsis was the most common indication of CRRT in 43% of patients admitted to ICUs. In other studies, sepsis has been reported to be responsible for 32% to 56% of CRRT procedures worldwide (34-36). Compared with other studies, sepsis accounted for a lower ratio of patients undergoing CRRT (17.24%) in the present report. This may be partly explainable by the lack of facilities for CRRT in the emergency ward (as a major unit for the referral of sepsis patients) in Iran.

Based on the clinical records, the most common underlying diseases leading to RRT in the current study were diabetes (36.9%) and hypertension (25.8%). These results were consistent with the reports of other studies indicating hypertension and diabetes as the underlying causes of RRT in 36.4% to 62.1% of the cases (11,32-34). In some multicenter studies in children, malignancy has been reported as the most common primary diagnosis in patients requiring RRT (11). Overall, special attention must be dedicated to diabetes and hypertension as the main comorbidities leading to RRT.

Other common reasons for RRT were volume overload (67.2%) and tumor lysis syndrome (18.8%) in another study. In other studies, low blood pressure, volume overload and electrolytic disturbances were the most common indications for RRT (37,40-42). Consistent with the mentioned studies, hemodynamic instability also constituted the most common indication for CRRT in the present report. Contrary to the previous studies, however, fluid overload constituted a lower percentage of our patients indicated for CRRT.

At one-year follow-up, the mortality rate was 60.3% in our patients. The mortality rate in patients undergoing CRRT has been reported as 32. 59% to 58% in previous studies (32-34). In addition to the in-hospital mortality, recent studies have reported 15% to 20% mortality rate at two-month follow-up which is somehow in contrast to our results. The mortality rate in patients undergoing CRRT varies between different centers. The factors affecting the mortality rate in these patients include the staff's experience, timing of dialysis initiation, and the presence of comorbidities. Nonetheless, the global rate of in-hospital mortality has been similar to our study (11,34,37).

Previous studies have asserted a direct correlation between pre-admission creatinine level and mortality rate in patients undergoing CRRT (38,39). However, neither pre-dialysis nor post-dialysis serum creatinine levels were significantly associated with mortality rate in this study. Moreover, we encountered no significant relationship between mortality rate and residual urine output, both pre-dialysis or peri-dialysis.

In pediatrics, the highest rate of recovery following CRRT has been observed in patients with renal insufficiency due to drug toxicity and tumor lysis syndrome (32). Future studies should address the impacts of underlying comorbidities on the survival and outcomes of patients undergoing CRRT. A meta-analysis found no differences in the renal recovery period, volume overload disturbance, mortality rate, and hospitalization period comparing the different methods of CRRT. In the current study, CVVHD was the main method applied in 72.4% of the cases. In other studies, CVVHD had been used in 48-82% of pediatric patients. Nevertheless, recent studies

have indicated a shift toward using CVVHDF as the main CRRT strategy (11,13,32,33), but our CRRT machine does not support this mode of treatment. As the CVVHDF mode of CRRT was not supported by our instrument, neither of our patients underwent this method.

The choice of RRT largely depends on the access to resources, cost-effectiveness, clinical outcomes and the staff's experience (22,20,37,40,44). The clinical effectiveness of each RRT approach should be further investigated by performing randomized clinical trials on patients with different clinical conditions (37,42).

Conclusion

As the CRRT procedure is currently unavailable in many centers in in Iran, our results may not be generalizable to all Iranian medical centers. Finally, due to the nature of the disease and the patients being at high-risk of mortality, it was not applicable to compare the clinical outcomes of CRRT with other methods such as CRRT. In future studies, it is recommended to address variables such as the length of the admission to follow-up (as an indicator for dialysis initiation), as well as the interval between the disease diagnosis and initiation and completion of CRRT. These should be addressed as factors influencing the clinical outcomes of patients in future studies. We here provided a comprehensive view on the characteristics of patients indicated for CRRT at the Shahid-Modarres hospital of Tehran. The patients' specifications were similar to those in the global reports. It is essential to develop a standard practice for implementing CRRT in Iran.

Limitations of the study

Our study has some limitations. The studied population was relatively small and heterogeneous. This was because some patients were excluded from the study due to incomplete clinical records limiting the number of eligible patients. Nevertheless, the heterogeneity rendered the study as a comprehensive research encompassing various etiologies of renal insufficiency.

Authors' contribution

AA designed the study. NT performed the statistical analysis. EZ and NM drafted the manuscript. All authors approved the final version.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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References

1. De Corte W, Dhondt A, Vanholder R.Long-term outcome in ICU patients with acute kidney injury treated with renal replacement therapy: a prospective cohort study. Crit Care. 2016; 20:256. doi: 10.1186/s13054-016-1409-z
2. Bhatt GC, Das RR. Early versus late initiation of renal replacement therapy in patients with acute kidney injury-a systematic review & meta-analysis of randomized controlled trials. BMC Nephrol. 2017; 18:78. doi: 10.1186/s12882-017-0486-9
3. Mousavi SS, Soleimani A, Mousavi MB. Epidemiology of end-stage renal disease in Iran: A review article. Saudi J Kidney Dis Transpl 2014; 25:697-702. doi: 10.4103/1319-2442.1322.
4. Aghighi M, Mahdavi-Mazdeh M, Zamyadi M, Heidary Rouchi A, Rajolani H, Nourozi S. Changing epidemiology of end-stage renal disease in last 10 years in Iran. Iran J Kidney Dis 2009; 3:192-6.
5. Nusshag C, Weigand MA, Zeier M, Morath C, Brenner T. Issues of Acute Kidney Injury Staging and Management in Sepsis and Critical Illness: A Narrative Review. Int J Mol Sci. 2017; 18(7):1387. Doi: 10.3390/ijms18071387
6. Uchino S, Kellum JA, Bellomo R. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005; 294:813-8. doi:10.1001/jama.294.7.813.
7. García-Fernández N, Pérez-Valdivieso JR, Bes-Rastrollo M, et al. Timing of renal replacement therapy after cardiac surgery: a retrospective multicenter Spanish cohort study. Blood Purif. 2011;32:104-11. doi:10.1159/000324195
8. Demirkiliç U, Kuralay E, Yenicesu M. Timing of replacement therapy for acute renal failure after cardiac surgery. J Card Surg. 2004;19:17-20. doi: 10.1111/j.0886-0440.2004.04004.x
9. Morabito S, Pistolesi V, Cibelli L, Pierucci A. A favore delle CRRT: le terapie sostitutive renali continue rimarranno le metodiche prevalenti nelle unita' di terapia intensiva[Continuous renal replacement therapies (CRRT) will remain the most widely adopted dialysis modality in the critically ill]. G Ital Nefrol. 2009;26:13-21
10. Nash DM, Przech S, Wald R, O'Reilly D. Systematic review and meta-analysis of renal replacement therapy modalities for acute kidney injury in the intensive care unit. J Crit Care. 2017;41:138-44. doi: 10.1016/j.jcrc.2017.05.002
11. Al-Ayed T, Rahman NU, Alturki A, Aljofan F. Outcome of continuous renal replacement therapy in critically ill children: a retrospective cohort study. Ann Saudi Med. 2018;38:260-8. doi: 10.5144/0256-4947.2018.260
12. Rewa OG, Villeneuve PM, Lachance P. Quality indicators of continuous renal replacement therapy (CRRT) care in critically ill patients: a systematic review. Intensive Care Med. 2016;43:750-763. doi: 10.1007/s00134-016-4579-x
13. Zhang L, Yang J, Eastwood GM, Zhu G, Tanaka A, Bellomo R. Extended Daily Dialysis Versus Continuous Renal Replacement Therapy for Acute Kidney Injury: A Meta-analysis. Am J Kidney Dis. 2015;66:322-30. doi: 10.1053/j.ajkd.2015.02.328
14. Rauf AA, Long KH, Gajic O, Anderson SS, Swaminathan L, Albright RC. Intermittent hemodialysis versus continuous renal replacement therapy for acute renal

failure in the intensive care unit: an observational outcomes analysis. J Intensive Care Med. 2008;23:195-203. doi:10.1177/0885066608315743.
15. Schefold JC, von Haehling S, Pschowski R. The effect of continuous versus intermittent renal replacement therapy on the outcome of critically ill patients with acute renal failure (CONVINT): a prospective randomized controlled trial. Crit Care. 2014; 18:R11. Doi: 10.1186/cc13188
16. Ávalos-López M, Pérez-López MJ, Aguilar-Martínez C, Díaz-Franco AMC, Esquivel-Chávez A, Baltazar-Torres JA. Pronóstico de lesión renal aguda en pacientes críticamente enfermos tratados con hemodiálisis intermitente frente a TRRC [Prediction of acute kidney injury in critically ill patients treated with intermittent hemodialysis versus CRRT]. Rev Med Inst Mex Seguro Soc. 2017;55:696-703.
17. Fayad AI, Buamscha DG, Ciapponi A. Intensity of continuous renal replacement therapy for acute kidney injury. Cochrane Database Syst Rev. 2016;10:CD010613. doi:10.1002/14651858.CD010613.pub2.
18. Li P, Qu LP, Qi D. High-dose versus low-dose haemofiltration for the treatment of critically ill patients with acute kidney injury: an updated systematic review and meta-analysis. BMJ Open. 2017;7(10):e014171. doi:10.1136/bmjopen-2016-014171.
19. Maoujoud O, Zajjari Y, Asseraji M, Aatif T, Ahid S, Oualim Z. Commentary: the practice of dialysis in the intensive care unit in a developing country. Ethn Dis. 2014;24:226-8.
20. Bouchard J, Lavergne V, Roberts DM, Cormier M, Morissette G, Ghannoum M. Availability and cost of extracorporeal treatments for poisonings and other emergency indications: a worldwide survey. Nephrol Dial Transplant. 2017;32:699-706. doi: 10.1093/ndt/gfw456.
21. Roderick P, Nicholson T, Armitage A, Mehta R, Mullee M, Gerard K.An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales. Health Technol Assess (Winchester, England). 2005;9:1-178. doi: 10.3310/hta9240.
22. Manns B, Doig CJ, Lee H. Cost of acute renal failure requiring dialysis in the intensive care unit: clinical and resource implications of renal recovery. Crit Care Med. 2003; 31:449-55. doi: 10.1097/01.CCM.0000045182.90302.B3.
23. Langford S, Slivar S, Tucker SM, Bourbonnais FF. Exploring CRRT practices in ICU: a survey of Canadian hospitals. Dynamics. 2008;19:18–23.
24. Kashani K, Mehta RL. We restrict CRRT to only the most hemodynamically unstable patients. Semin Dial. 2016; 29:268-71. doi: 10.1111/sdi.12507
25. Douvris A, Malhi G, Hiremath S. Interventions to prevent hemodynamic instability during renal replacement therapy in critically ill patients: a systematic review. Crit Care. 2018; 22:41. doi: 10.1186/s13054-018-1965-5.
26. Donauer J, Kölblin D, Bek M, Krause A, Böhler J. Ultrafiltration profiling and measurement of relative blood volume as strategies to reduce hemodialysis-related side effects. Am J Kidney Dis. 2000;36:115-23. doi: 10.1053/ajkd.2000.8280.
27. Uchino S, Bellomo R, Kellum JA, Morimatsu H, Morgera S, Schetz MR, et al. Patient and kidney survival by dialysis modality in critically ill patients with acute kidney injury. Int J Artif Organs 2007;30:281-92.
28. Vanholder R, Van Biesen W, Hoste E, Lameire N. Pro/con debate: continuous versus intermittent dialysis for acute kidney injury: a never-ending story yet approaching the finish?. Crit Care. 2011;15:204. doi:10.1186/cc9345.
29. Bell M; SWING, Granath F, Schön S, Ekbom A, Martling CR. Continuous renal replacement therapy is associated with less chronic renal failure than intermittent haemodialysis after acute renal failure. Intensive Care Med. 2007;33:773–80. doi:10.1007/s00134-007-0590-6.
30. Hoste EA, Dhondt A. Clinical review: Use of renal replacement therapies in special groups of ICU patients. Critical Care. 2012;16:201. doi: 10.1186/cc10499.
31. Ortega L, Ladino M. The use of continuous renal replacement therapy in sepsis, liver disease, acute neurological injuries and decompensated heart failure. Diálisis y Transplante. 2009;30:133-8. doi: 10.1016/S1886-2845(09)72697-9
32. Symons JM, Chua AN, Somers MJ, et al. Demographic characteristics of pediatric continuous renal replacement therapy: a report of the prospective pediatric continuous renal replacement therapy registry. Clin J Am Soc Nephrol. 2007;2:732-8. doi: 10.2215/CJN.03200906
33. AlEnezi F, Alhazzani W, Ma J. Continuous venovenous hemofiltration versus continuous venovenous hemodiafiltration in critically ill patients: a retrospective cohort study from a Canadian tertiary centre. Can Respir J. 2014;21:176-80. doi: 10.1155/2014/965479
34. Choi GY, Joynt GM, Gomersall CD, So HY. Utilization and outcome of renal replacement therapy in an Asian tertiary intensive care unit. Hong Kong Med J. 2011;17:446-52.
35. Hutchison CA, Crowe AV, Stevens PE, Harrison DA, Lipkin GW. Case mix, outcome and activity for patients admitted to intensive care units requiring chronic renal dialysis: a secondary analysis of the ICNARC Case Mix Programme Database. Crit Care. 2007;11:R50. doi: 10.1186/cc5785.
36. Bagshaw SM, George C, Bellomo R; ANZICS Database Management Committee. Early acute kidney injury and sepsis: a multicentre evaluation. Crit Care. 2008;12:R47. doi: 10.1186/cc6863.
37. Park S, Lee S, Jo HA. Epidemiology of continuous renal replacement therapy in Korea: Results from the National Health Insurance Service claims database from 2005 to 2016. Kidney Research and Clinical Practice. 2018;37:119-29. doi: 10.23876/j.krcp.2018.37.2.119.
38. Eckardt KU, Bansal N, Coresh J. Improving the prognosis of patients with severely decreased glomerular filtration rate (CKD G4+): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney Int. 2018;93:1281-92. doi: 10.1016/j.kint.2018.02.006.
39. de Souza SP, Matos RS, Barros LL, Rocha PN. Inverse association between serum creatinine and mortality in acute kidney injury. J Bras Nefrol. 2014;36:469-75. doi:

10.5935/0101-2800.20140067.
40. Rhee H, Jang GS, Han M. The role of the specialized team in the operation of continuous renal replacement therapy: a single-center experience. BMC Nephrol. 2017;18:332. doi: 10.1186/s12882-017-0746-8.
41. Wang XT, Wang C, Zhang HM, Liu DW. Clarifications on Continuous Renal Replacement Therapy and Hemodynamics. Chin Med J (Engl). 2017;130:1244-1248. doi: 10.4103/0366-6999.205863.
42. Heung M, Bagshaw SM, House AA, Juncos LA, Piazza R, and Goldstein SL. CRRTnet: a prospective, multi-national, observational study of continuous renal replacement therapy practices. BMC Nephrol. 2017;18:222. doi: 10.1186/s12882-017-0650-2.
43. de Souza Oliveira MA, Dos Santos TOC, Monte JCM. The impact of continuous renal replacement therapy on renal outcomes in dialysis-requiring acute kidney injury may be related to the baseline kidney function. BMC Nephrol. 2017;18:150. doi: 10.1186/s12882-017-0564-z
44. Connor MJ, Karakala N. Continuous Renal replacement therapy: reviewing current best practice to provide high-quality extracorporeal therapy to critically ill patients. Adv Chronic Kidney Dis. 2017;24:213-218. doi: 10.1053/j.ackd.2017.05.003.