Science Journal of Clinical Medicine
2023; 12(3): 31-36
http://www.sciencepublishinggroup.com/j/sjcm
doi: 10.11648/j.sjcm.20231203.11
ISSN: 2327-2724 (Print); ISSN: 2327-2732 (Online)

Delay in the Initiation of Extra Renal Purification on the Morbi-Mortality of Patients with Acute Renal Aggression in the Surgical Resuscitation of Mulhouse Hospital

José Mavinga[1, *], Christian Meyer[4], Eric Mafuta[3], Gibency Mfulani[1], Sylvie Ndjoko[1], Julie Pembe[1], Roddy Bengono[4], Eric Amisi[1], John Nsiala[1, 2], Medard Bula Bula[1], Berthe Barhayiga[1]

[1]Department of Anesthesia and Resuscitation, University Clinics of Kinshasa, Kinshasa, DRC

[2]Department of Anesthesia and Resuscitation, Clinique Caron, Paris, France

[3]Department of Statistics, School of Public Health, Kinshasa, DRC

[4]Surgical Resuscitation Department, Emile Muller Hospital, Mulhouse, France

Email address:

joicemav@yahoo.fr (José Mavinga)

[*]Corresponding author

To cite this article:

José Mavinga, Christian Meyer, Eric Mafuta, Gibency Mfulani, Sylvie Ndjoko, Julie Pembe, Roddy Bengono, Eric Amisi, John Nsiala, Medard Bula Bula, Berthe Barhayiga. Delay in the Initiation of Extra Renal Purification on the Morbi-Mortality of Patients with Acute Renal Aggression in the Surgical Resuscitation of Mulhouse Hospital. *Science Journal of Clinical Medicine*. Vol. 12, No. 3, 2023, pp. 31-36.
doi: 10.11648/j.sjcm.20231203.11

Received: July 10, 2023; **Accepted**: August 2, 2023; **Published**: September 20, 2023

Abstract: *Introduction:* Acute renal failure (ARI) is a sudden onset of the partial or total inability of the kidney to eliminate the products of nitrogen catabolism and to maintain the hydro-electrolyte balance. It results in the installation of an acute uremic syndrome, made up of a constellation of biological and clinical abnormalities, the intensity of which directly defines the therapeutic urgency. The ideal moment to start an ERA remains debated, with studies with sometimes contradictory results. *Objective:* to determine the effect of the delay in initiation of the RE on the morbidity and mortality of patients in intensive care surgery in Mulhouse, in the context of severe ARI with multi-visceral involvement. *Materials and methods:* This is a retrospective single-center study, of the professional practice evaluation type, carried out in the surgical intensive care unit of the Groupe Hospitalier de la Région de Mulhouse Sud Alsace (GHRMSA) over a period of 12 months (March 2019 to February 2020). All patients aged at least 18 years and presenting with ARF were included in the study. Diagnosis and severity of renal injury was determined using the DIGO K score. The primary endpoint was mortality. *Results:* In 122 patients, the diagnosis of ARF was retained. Twenty-six of them benefited from an RRT and among which 18 for an early RRT and 8 for a late RRT. Baseline patient characteristics were similar in the 2 groups. Mortality was 50.0% in the two early RRT groups and 50.0% in the late RRT group, among the patients who received dialytic treatment with a statistically non-significant difference. *Conclusion:* This study did not show a difference in terms of mortality between the early RRT group and the late RRT group in patients with severe acute renal injury in intensive care. On the other hand, it notes a reduction in the duration of stay in intensive care as well as the duration of the EER in the early group.

Keywords: IRA, Early EER, Late EER, Resuscitation, K DIGO, Mortality

1. Introduction

Acute renal failure (ARI) is a sudden onset of partial or total inability of the kidney to eliminate the products of nitrogen catabolism and to maintain the water-electrolyte balance [1-3]. It results in the installation of an acute uremic syndrome, made up of a constellation of biological and clinical abnormalities, the intensity of which directly defines the therapeutic urgency.

It occurs in 4–15% of patients after cardiothoracic surgery and in 40–60% of patients admitted to intensive care including 20% will require extrarenal purification (ERT) [4,

5]. The latter remains the only method of replacement of renal function.

The ideal moment to start an RRT remains debated, with studies with sometimes contradictory results [6].

Despite technological advances and a better therapeutic approach, the mortality of AKI acquired in intensive care remains high at 45 to 70 percent [3, 7-10]. This is largely linked to a profound change in the epidemiology of ARI. ARF is multifactorial, often of septic, postoperative or post-traumatic origin and easily fits into a context of multi-visceral failure. The increasingly complex and delicate treatment, essentially RRT, determines the prognosis [3].

For about ten years, research has been carried out on the criteria and the ideal moment of initiation of RE in the management of severe ARF [11, 12] and there are currently no recommendations on the optimal time to initiate the so-called EER [12-16].

The objective of our study was to assess the impact an early RRT on mortality and recovery of renal function in patients admitted and presenting with AKI in intensive care.

2. Methods

It is a retrospective single-centre study, of the professional practice evaluation type. It was carried out in the surgical intensive care unit of the Emile Muller hospital of the Groupe Hospitalier de la Région de Mulhouse Sud Alsace (GHRMSA) over a period of 12 months (March 2019 to February 2020). The protocol of this study received the authorization of the head of intensive care unit; in addition, we also obtained permission from the patients or family to use the data from their records in the context of the research.

All patients aged at least 18 admitted to the department during the study period and presenting with acute renal injury were included. Patients whose data necessary for the study were incomplete in the medical file were excluded.

The present study concerns the files of patients who were hospitalized in the intensive care unit during the study period considered.

The data had been collected using a sheet designed for this purpose, which was validated after pre-testing. A screening of the files of the included patients was carried out to note the parameters of interest. Patients were selected on the basis of renal involvement, the diagnosis and classification of which were retained according to the K DIGO criteria [17], as shown in Table 1.

The patients selected were divided into two groups (early and late) taking into account the recommendations of experts in extra renal purification in intensive care [4]. The early group included patients who underwent early RRT and the late group included patients who underwent late RRT.

Was considered to be early, the RE started within 24 hours following the diagnosis of an ARF at stage K DIGO 3 with respiratory and/or haemodynamic complication requiring the use of mechanical ventilation and/or vasopressors. Was considered late, the RRT started beyond 24 hours of the diagnosis of AKI with or without complications.

The following data were collected: patient characteristics on admission (age, sex, comorbidities, reason for admission, and IGS II severity score of patients on admission); data on the evolution of patients in the department (length of stay in intensive care, duration of EER, delay in EER, improvement in renal function and patient outcome.

The primary endpoint was mortality in intensive care and the secondary endpoints were: improvement in renal function, length of stay in intensive care unit, time to initiation of REE, type of REE.

Data were analyzed using SPSS 23.0 software. The quantitative variables were described by their mean ± standard deviation or by their median with their extreme values and the qualitative variables by their frequency and in percentage. Comparisons were made using Pearson's chi-square test or Fisher's exact test, depending on the application conditions for qualitative (categorical) variables and Student's t test for quantitative variables. For non-normally distributed numeric variables, medians were calculated and compared using the nonparametric test.

Table 1. *Classification KDIGO.*

Internship	Serum creatinine	Urine output
1	1.5–1.9 times baseline v GOLD ≥0.3 mg/dl (≥26.5 mmol/l) increase	< 0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	< 0.5 ml/kg/h for ≥ 12 hours
3	3.0 times baseline GOLD Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 mmol/l) GOLD Initiation of renal replacement therapy OR, In patients < 18 years, decrease in eGFR to < 35 ml/min per 1.73 m2	< 0.3 ml/kg/h for ≥ 24 hours GOLD Anuria for ≥ 12 hours

KDIGO Guideline 2012

Table 2. *Basic patient characteristics.*

	Early EER (n=18)	Late ERA (n=8)	P
Demography			
Age/ years. Mean ± SD	70.28±10.3	66.88±19.6	0.536
Median (min-max)	69 (50-85)	68 (51-86)	
Gender Male (%)	10 (56.6)	7 (87.5)	0.289
IGS II score (%). Mean ±SD	75.50± 22.19	53.88± 11.06	0.536

	Early EER (n=18)	Late ERA (n=8)	P
Median (min-max)	71.50 (30-113)	13.8 (0.9-99.4)	
Co-morbidity n (%)			
Alcohol	4 (22.2)	1 (12.5)	0.462
Smoking	5 (27.8)	4 (50.0)	0.506
COPD	2 (11.1)	1 (12.5)	0.686
hypertension	13 (72.2)	6 (75.0)	0.132
Diabetes	11 (61.1)	3 (37.5)	0.002
Cardiovascular pathologies	10 (55.6)	4 (50.0)	0.466
Cancer	2 (11.1)	1 (12.5)	0.812
Others	7 (38.9)	2 (25.0)	0.781
Admissions n (%)			
Medical	13 (72.2)	4 (50.0)	0.212
Planned surgery	0 (0.0)	1 (12.5)	
Urgent surgery	5 (27.8)	3 (37.5)	
Main diagnoses at admission n (%)			
IRA	5 (27.8)	0 (0.0)	0.000
Respiratory distress	7 (38.9)	2 (22.1)	0.165
Neurological impairment	2 (11.1)	0 (0.0)	0.243
States of shock	9 (50.0)	5 (62.5)	0.068
Vascular surgery	2 (11.1)	0 (0.0)	0.624
Visceral surgery	1 (5.6)	1 (12.5)	0.175
infections	1 (5.6)	1 (12.5)	0.790
Others	3 (16.7)	0 (0.0)	0.429

Table 3. *Effect of RRT Type on Patient Outcome.*

Indicator	Early REE	Late EER	p
Renal function improvement (%)	2 (40.0)	3 (60.0)	0.115
Mortality (%)	2 (50.0)	2 (50.0)	0.359

Table 4. *Elements of the secondary judgment criterion.*

Indicator	Early REE	Late ERA	p.
Stay Réa (days) Mean ± SD	15.06±13.61	60.75±37.20	0.219
Median (min-max)	13 (1-41)	60.5 (13-104)	
EER duration (days) Mean ± SD	10.33±10.11	25.13±25.67	0.456
Median (min-max)	9.5 (1-38)	17.5 (1-75)	

3. Results

A total of 422 patient files had been compiled in the department's archives. In 122 of them, the diagnosis of ARI had been retained. 26 patients underwent RRT, including 18 for early RRT and 8 for late RRT, as shown in Figure 1.

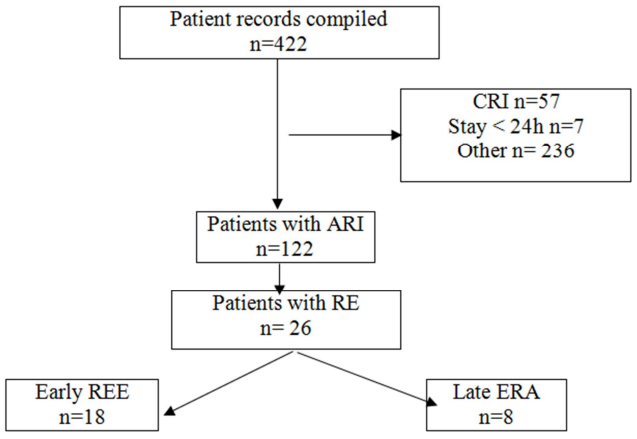

Figure 1. *Flow chart.*

The baseline characteristics of the patients are shown in Table 2.

It is found that the mortality is 50.0% in the early REE group and 50.0% in the late REE group, among the patients who received dialytic treatment with a statistically non-significant difference. (p=0.359).

Among those who underwent RRT and whose renal function was explored, it appeared that only 2, or 40% of patients with improved renal function, had benefited from early RRT. As presented in Table 3.

As for the secondary endpoints, we found no significant difference in terms of length of stay in intensive care or length of extra renal replacement therapy, as indicated in table 4.

4. Discussion

In the two study groups, the general characteristics of the patients were broadly similar which allows for comparability. The male gender was more represented in both groups with a marked increase in the late group 56.6% vs 87.5% (p=0.289); the same applies to cardiovascular pathologies, particularly hypertension, taking into account comorbidities. These results corroborate with the literature [15, 18].

Indeed, it has been observed in several studies that the male sex is twice as represented as the female sex in the development of an ARF requiring the use of an RRT [19-25]. This is explained by a protective role provided by female hormones on the cardio-renal system.

The question of the timing of the RRT in intensive care arose in our study where we have a homogeneous population and who were admitted in most cases in a table of states of (septic) shock. Indeed, in our study, we found respectively in the two groups (early and late) 50.0% vs. 62.5% (p=0.068) the states of shock. When the data relating to the other pathologies at admission are taken into account, it appears that the outcome of the patients is associated with the state of shock, in an environment of multi-visceral failure [26-28]. All these factors therefore reduce the probability of a favorable outcome for the patients, which could thus explain the mortality described in this study.

Indeed, we noted an absence of significant difference in terms of mortality between patients who underwent early RRT compared to those with late RRT with respectively 50.0% vs 50.0% (p=0.359). Several studies confirm these results [15, 29-32]. On the other hand, three recent randomized studies [15, 16, 33] have explored the issue of the timing of the initiation of REE in patients with ARF, but their results were contradictory. This contradiction lies in the severity of the patients included. Indeed, the study by Zarbock A et al [33] had included less severe patients (stage 2 K DIGO) whereas Barbar SD et al [15] and Gaudry S et al [16] had enrolled patients with severe kidney damage (stage 3 K DIGO).

Our results are similar to those reported by Barbar SD and Gaudry S, who enrolled a large sample of 488 and 600 patients respectively divided into the two study groups (early group and late group) with patients with severe renal impairment (stage 3 K DIGO) as in our study; unlike ours, was monocentric, retrospective with a small sample making the results not statistically significant.

A potential advantage of early initiation of RE in IRA is the possibility of managing the acid-base imbalance, the management of the hydro-electrolyte balance and perhaps the purification of toxins of inflammatory origin [15, 34]. This prevents the occurrence of severe complications of AKI and has an impact on reducing deaths. However, we could not demonstrate a lower death rate in the early EER group in our study. It should be noted that the management of water balance is not easy given that patients are often admitted in a context of states of shock with hemodynamic instability already upon admission to intensive care. This could explain the lack of reduction in the death rate in the early RRT group compared to the late group, whereas a significant drop is described in some studies [18].

It is also likely that our small sample can to some extent justify this state of affairs in our study.

The median length of stay in intensive care in our study was respectively 13 days with extremes of 1-41 days in the early group and 60.5 days with extremes of 13-104 days in the late group.

The median duration of the early RRT was 9.5 days with extremes of 1-38 days while that of the late group was 17.5 days with extremes ranging from 1-75 days. A reduction in the length of stay in intensive care as well as that of the EER is associated with the early EER, compared to the late EER.

Several meta-analyses having reported a reduction in mortality associated with early RE in patients with ARI in critical care [26, 35-37], have also reported a reduction in the length of stay in intensive care, a reduction in duration of the EER, a decrease in the duration of mechanical ventilation, as in our study. However, these studies are criticized for the lack of a control group. Thus, the possibility of spontaneous renal recovery (in the control group) which could be obtained by delaying an ERT, was not explored.

A Brazilian retrospective study published in 2013 [18] also found consistent results, although the diagnostic criteria for AKI were based on the AKIN/RIFFLE classification. In the latter, early RRT was defined only when it was performed in the early stages of AKI (RIFLE Classification 0 or R). At these stages, patients without ARI could be included. Since AKI is associated with a poor prognosis in critical patients first and secondarily, patients can reach the severe stage of AKI and mistakenly remain in the early group, this could be the basis of a interpretation bias that can influence the results, due to the lack of specificity of this classification [15].

In our study, renal function was less improved at 40.0% in the early group compared to the late group with 60.0% with a statistically non-significant difference (p = 0.115). These results are contradictory to those of the literature, as shown by Zarbock et al. [33] who demonstrated an increased rate of improvement in renal function in the early RRT group compared to the late group. But we must recognize the difference between us and this study. Indeed, while Zarbock's study was randomized, ours is retrospective with a small sample, which could justify this discrepancy.

The strength of our study lies in the fact that it is original in the sense that it is a first conducted in the Surgical Resuscitation department of Mulhouse, in the field of renal assistance in critical patients with acute renal damage. Our patients were not on dialysis and had no history of Chronic Kidney Failure (CRI) before their admission to the intensive care unit, which avoided confusion bias.

Like any study, this one also had weaknesses. Indeed, it is a monocentric study, whereas most of the studies on the subject are multicentric. Its small sample justifies that the results are not statistically significant and therefore does not allow us to draw definitive conclusions. Also, we were confronted with another bias which is that of retrospective studies [12, 38] which consisted in comparing only patients having benefited from an RRT (early and late), whereas in randomized studies it is It is a question of comparing strategies of initiation of the REE (early versus waiting). The comparison of strategies actually allows certain patients not to be purified in a waiting strategy. We were unable to study the duration of mechanical ventilation (MV). Indeed, the latter would also have a certain negative influence on kidney function.

5. Conclusion

This study did not show a significant difference in terms of mortality between the early RRT group and the late RRT group in patients with severe acute kidney injury in intensive care. But she notes a reduction in the length of stay in intensive care as well as the duration of the EER between the early group, compared to the late group.

Also, we did not show an improvement in renal function in the early EER group.

Conflict of Interests

All the authors do not have any possible conflicts of interest.

References

[1] Corwin HL, Bonventre JV (1988). Acute renal failure in the intensive care unit (Part1). Intensive Care Med 14: 10–6.

[2] Corwin HL, Bonventre JV (1988). Acute renal failure in the intensive care unit (Part2). Intensive Care Med 14: 86–96.

[3] K. Klouche·D. Sandapa · H. Barrau·O. Jonquet. Acute renal failure during intensive care— Prevention and treatment © SRLF and Springer-Verlag France 2011.

[4] Christophe Vinsonneau, Emma Allain - Launay, Clarisse Blayau, Michael Darmon, Damien du Cheyron, Théophile Gaillot, Patrick Honoré, Étienne Javouhey, Thierry Krummel, Annie Lahoche et al. Extrarenal purification in adult and pediatric intensive care. Formalized recommendations from experts under the aegis of the French-speaking Resuscitation Society (SRLF), with the participation of the French Society of Resuscitation Anesthesia (Sfar), the French-speaking Resuscitation and Pediatric Emergencies Group (GFRUP) and the French-speaking Dialysis Society (SFD). REFERENCE / *GUIDELINES*. Resuscitation Lavoisier SAS 2014.

[5] Clec'h C, Gonzalez F, Lautrette A, et al (2011) Multiple -center evaluation of mortality associated with acute kidney injury in critically ill patients: a competing risks analysis. Critical Care 15: R128.

[6] Olivier JOANNES-BOYAU et al, News in extrarenal purification. 2019 SFAR Update Conference.

[7] Hoste EA, Schurgers M (2008) Epidemiology of acute kidney injury: how big is the problem? Crit Care Med 36: S146–S51.

[8] S. Gaudry, N. Zucman, D. Dreyfuss. Criteria for starting and stopping extrarenal purification in intensive care. Resuscitation (2015) 24: S400-S405.

[9] Schortgen F, Soubrier N, Delclaux C, et al (2000) Hemodynamic tolerance of intermittent hemodialysis in critically ill patients: usefulness of practice guidelines. Am J Respir Crit Care Med 162: 197-202.

[10] Ympa YP, Sakr Y, Reinhart K, Vincent JL, et al (2005) Has mortality from acute renal failure decreased? Asystematic review of the literature. Am J Med 118: 827-32.

[11] Pikkers P, Ostermann M, Joannidis M, Zarbock A, Hoste E, Bellomo R, Prowle J, Darmon M, Bonventre et al. 2017 The intensive care medicine agenda on acute kidney injury. Intensive Care Med 43: 1198-1209.

[12] K. Chaibi, SD Barbar, JP Quenot, D. Dreyfuss, S. Gaudry. Delaying extrarenal purification in acute renal failure: the night belongs to us. Med Intensive Réa (2019) 28: 164-171.

[13] Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Practice 2012; 120: 179-184.

[14] Smith OM, Wald R, Adhikari NKJ, Pope K, Weir MA, Bagshaw SM, Canadian critical care Trials group. Standard versus accelerated initiation of renal replacement therapy in acute kidney injury (STARRT-AKI): study protocol for a randomized controlled trial. Trials 2013; 2: 320 p. m.

[15] Barbar SD, Clere-Jehl R, Bourredjem A, Hernu R, Montini F, Bruyère R, et al, Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. N Engl J Med 2018; 379: 1431-1442.

[16] Gaudry S, Hajage D, Schortgen F, Martin-lefèvre L, Pons B, Boulet E, Boyer A et al, Initiation strategies for renal replacement therapy in the intensive care unit. N Engl J Med 2016; 375: 122-133.

[17] Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney inter. Supplement 2012; 2: 1–138. http://www.kidney-international.org & 2012 KDIGO.

[18] Tacyano T Leite, Etienne Macedo, Samuel M Pereira, Sandro RC Bandeira, Pedro HS Pontes, André S Garcia, Fernanda R Militão et al. Timing of renal replacement therapy initiation by AKIN classification system. Critical Care 2013, 17: R62.

[19] Joel Neugarten, Ladan Golestaneh and Nitin V. Kolhe Sex differences in acute kidney injury requiring dialysis. BMC Nephrology (2018) 19: 131.

[20] Neugarten J. Gender and the progression of renal disease. J Am Soc Nephrol. 2002; 13 (11): 2807–9.

[21] Neugarten J, Acharya A, Silbiger SR. Effect of gender on the progression of nondiabetic renal disease: a meta-analysis. J Am Soc Nephrol. 2000; 11 (2): 319–29.

[22] Neugarten J, Golestaneh L. Gender and the prevalence and progression of renal disease. Adv Chronic Kidney Dis. 2013; 20 (5): 390–5.

[23] Neugarten J, Silbiger SR. Effects of sex hormones on mesangial cells. Am J Kidney Dis. 1995; 26 (1): 147–51.

[24] Dubey RK, Jackson EK. Estrogen-induced cardiorenal protection: potential cellular, biochemical, and molecular mechanisms. Am J Physiol Renal Physiol. 2001; 280 (3): F365–88.

[25] Metcalfe PD, Meldrum KK. Sex differences and the role of sex steroids in renal injury. J Urol. 2006; 176 (1): 15–21.

[26] Kaiping Luo, Shufang Fu, Weidong Fang and Gaosi Xu. The optimal time of initiation of renal replacement therapy in acute kidney injury: A meta-analysis Oncotarget, Advance Publications 2017.

[27] Chung KK, Lundy JB, Matson JR, Renz EM, White CE, King BT, Barillo DJ, Jones JA, Cancio LC, Blackbourne LH, Wolf SE. Continuous venovenous hemofiltration in severely burned patients with acute kidney injury: a cohort study. CritCare. 2009; 13: R62.

[28] Vinsonneau C, Camus C, Combes A, Costa de Beauregard MA, Klouche K, Boulain T, Pallot JL, Chiche JD, Taupin P, Landais P, Dhainaut JF, and Hemodiafe Study Group. Continuous venovenous haemodiafiltration versus intermittent haemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicentre randomized trial. Lancet. 2006; 368: 379–85.

[29] Bagshaw SM, George C, Bellomo R. Early acute kidney injury and sepsis: a multicentre evaluation. CritCare 2008; 12: R47.

[30] The RENAL Replacement Therapy Study Investigators. Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 2009; 361: 1627-38.

[31] The VA/NIH Acute Renal Failure Trial Network. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2008; 359: 7-20.

[32] Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 2005; 294: 813-8.

[33] Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. JAMA 2016; 315: 2190-9.

[34] Wald R, Bagshaw SM. The timing of renal replacement therapy initiation in acute kidney injury: is earlier truly better? Crit Care Med 2014; 42: 1933-4.

[35] Sebra VF, Balk EM, Liangos O, Sosa MA, Cendoroglo M, Jaber BL. Timing of renal replacement therapy initiation in acute renal failure: a meta-analysis. AM J Kidney Dis 2008; 52: 272-84.

[36] Kavellas CJ, Farhat MR, Sajjad I, et al. A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systemetic review and meta-analysis. CritCare 2011; 15: R72.

[37] Caixia wang, Lin-sheng lv, Hui huang, Jjianqiang guan, Zengchun ye, Shaomin li, Yanni wang, Tanqi lou and Xun liu. Initiation time of renal replacement therapy on patients with acute kidney injury: A systematic review and meta-analysis of 8179 participants Review Article. Nephrology 22 (2017) 7–18.

[38] Palevsky PM, (2008). Indications and timing of renal replacement therapy in acute kidney injury. Crit Care Med 36: S224.