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Effect of initiation of renal replacement therapy on mortality in acute pancreatitis patients

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Abstract

This study aims to explore effect of initiation of renal replacement therapy (RRT) on mortality in acute pancreatitis (AP) patients. In this study, a total of 92 patients from the surgical intensive care unit (SICU) of the Second Affiliated Hospital of Harbin Medical University who were diagnosed with AP and underwent RRT or not between January 2014 and December 2018 were included in this retrospective study. Demographic and clinical data were obtained on admission to SICU. Patients were divided into early initiation of RRT group ($n = 44$) and delayed initiation of RRT group ($n = 48$). Duration of mechanical ventilation (MV), intra-peritoneal pressure, vasopressors infusion, body temperature, procalcitonin, creatinine, platelet counts, length of hospital stay and prognosis were recorded during hospitalization, and then compared between groups. Patients with delayed initiation of RRT exhibited significantly higher APACHE II score, SOFA score and lower GCS score than those with early initiation of RRT ($P < 0.001$, < 0.001, $= 0.04$, respectively). No difference in the rest of the baseline data and vasopressors infusion was found. Dose of Norepinephrine, maximum and mean PCT, maximum and mean creatinine, maximum and mean intra-peritoneal pressure, length of hospital stay, prognosis of ICU and hospitalization showed significant difference between groups. Early initiation of RRT may be beneficial for AP patients, which can provide some insight and support for patients' treatment in clinic.

Abbreviations: AP = acute pancreatitis, APACHE II = acute physiology and chronic health evaluation II, CKD = chronic kidney dysfunction, IAH = intra-abdominal hypertension, PCT = procalcitonin, RRT = renal replacement therapy, SAP = severe acute pancreatitis, SICU = surgical intensive care unit, SIRS = systemic inflammatory response syndrome, SOFA = Sequential organ failure assessment.

Keywords: acute kidney injury, acute pancreatitis, intra-peritoneal pressure, procalcitonin, renal replacement therapy

1. Introduction

Acute pancreatitis (AP) is one of the most common acute abdominal diseases in surgical intensive care unit (SICU), in recent years its incidence is increasing worldwide.[1,2] AP may lead to many disease including local injury, gastrointestinal disorder, systemic inflammatory response syndrome (SIRS), capillary leak syndrome, microcirculatory disturbance, abdominal compartment syndrome, single or multiple organ failure, and even death.[3] AP could be categorized as mild, moderately severe, or severe according to Atlanta classification,[4] based on whether there is organ dysfunction and duration. The death peak of AP is biphasic, which was known as acute and infective stage. The overall mortality rate of AP ranged from about 1% to 5.6%,[5–8] whereas it could rise to 15% to 30% when severe acute pancreatitis (SAP) or infected pancreatic necrosis occurred.[9,10]

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XZ and YC contributed equally to this work.

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Undoubtedly, patients with SAP require more intensive organ support, longer length of ICU and hospital stay and more cost due to persistent organ dysfunction.

The kidneys are one of the most vulnerable organs in AP due to uncontrolled SIRS, microcirculatory disturbance and intra-abdominal hypertension (IAH) caused by abdominal cavity or retroperitoneal massive exudation. In ICU, AKI, as a "silent killer",[11] was a common and well-recognized complication of AP and an independent risk factor for mortality.[12] Over 50% SAP patients suffered from AKI[2,12] and a worse clinical prognosis was presented when both conditions existed.[13] In clinical practice, there are no specific therapies available for AKI, and the mainstay of treatment remains supportive care.[14] In the early stage of disease, inhibition of excessive and uncontrolled SIRS through renal replacement therapy (RRT) was beneficial to SAP accompanying multiple organ dysfunction syndromes.[15,16] However, recent trials varied widely in their definition of early and delayed RRT intervention,[17–19] that is to say there was no exactly unified definition of the terms "early" and "delayed" RRT. Huge variations existed in clinical RRT practice. Thus, optimal timing of RRT initiation is controversial, especially for AP patients.

As supportive treatment, RRT is one of the most important cornerstones of the management of AKI and non-AKI diseases during treatment of critically ill patients. RRT had evolved from simple kidney function replacement to multiple organ support therapy.[20] Timely initiation of RRT in AP patients will contribute to regulating the internal environment and electrolyte balance, alleviating edema, eliminating toxins, reducing intra-abdominal pressure, and further protecting organ function. In the early stage of disease, negative fluid balance through RRT may improve prognosis,[21] however, premature initiation of RRT may hinder the spontaneous recovery of renal function, lead to RRT-related anti-coagulation and technical complications, increase unnecessary RRT and cost. There is no doubt that too late to initiate RRT will miss optimal timing of treatment, worsen the condition, prolong hospital/ICU day and even increase the mortality.[22,23] Regarding AKI patients with RRT indications, no treatment would significantly increase risk for mortality.[24] To date few researches had formally focused on the effect of early vs delayed initiation of RRT on mortality in AP patients.

Thus, in this current study, we would like to make a thorough inquiry about the impact of RRT timing on mortality in AP patients, and try to verify an optimal timing of RRT initiation.

2. Materials and methods

2.1. Study design

This retrospective study included patients from the SICU of the Second Affiliated Hospital of Harbin Medical University (Harbin, China) between January 2014 and December 2018. Demographic and clinical data were obtained on patients' admission to SICU. The patients' related personal information was kept confidential. The study protocol was approved by the ethics committee of the Second Affiliated Hospital of Harbin Medical University.

2.2. Study population

Patients who met the following criteria were included:

(1) ICU admission;
(2) patients were diagnosed with AP;
(3) patients aged $>$ 18 years.

Patients who met the following criteria were excluded:

(1) pregnant or breastfeeding women;
(2) chronic kidney dysfunction (CKD);
(3) chronic or recurrent pancreatitis;
(4) patients with uncompleted medical records.

A total of 92 patients were included in this study. Patients were divided into early initiation of RRT group (no AKI, KDIGO stage I or within 8 hours of diagnosis of KDIGO stage II; n = 44) and delayed initiation of RRT group (after 8 hours of diagnosis of KDIGO stage II, KDIGO stage III or no initiation of RRT; n = 48). All enrolled patients were treated by the same group of experienced ICU physicians.

2.3. Diagnosis of AP

AP diagnosis was made through combination of medical history, clinical situation, and physical examination, laboratory tests, and imaging examination. Definite diagnosis for a small number of patients were finally made by laparotomy.

2.4. Diagnosis and classification of AKI

In this study, the diagnosis and classification of AKI were based on the 2012 KDIGO criteria,[25] in which creatinine criteria was defined as an absolute increase in serum creatinine of greater than or equal to 0.3 mg/dL ($\geq$26.4 μmol/L) and a percentage increase in serum creatinine of greater than or equal to 50% (1.5 fold from baseline value) within 48 hours. Baseline creatinine value was defined as the lowest value of serum creatinine obtained within 2 days prior to ICU admission. If no serum creatinine value was available, the first available creatinine value within 2 days after ICU admission was considered as the baseline creatinine value.

2.5. Definition of early or delayed initiation of RRT

All enrolled patients were divided into early initiation of RRT group (no AKI, KDIGO stage I or within 8 hours of diagnosis of KDIGO stage II) and delayed initiation of RRT group (after 8 hours of diagnosis of KDIGO stage II, KDIGO stage III or no initiation of RRT), which was similar to previous study.[17]

2.6. RRT treatment

All RRT patients included in this study were treated with CVVH mode, and heparin was used for anti-coagulation, 50% of the pre- and post-dilution, respectively. Blood flow rate and dehydration volume were individually adjusted according to the patients' condition.

2.7. Serum PCT level and intra-peritoneal pressure measurement

Serum PCT level was intermittently measured following ICU admission. Mini VIDAS (Hain Lifescience GmbH; Nehren, Germany) was applied to measure serum PCT level. Bladder pressure was measured by Freund's catheter to reflect intra-peritoneal pressure indirectly.

2.8. Data collection

Baseline data including age, gender, height, weight, body mass index (BMI), acute physiology and chronic health evaluation

Table 1

Baseline data of patients.

	Early n = 44	Delayed n = 48	t/z/χ^2 value	*P* value
Age	44.05 (15.62)	48.44 (13.97)	−1.42	.16
BMI	24.62 (1.96)	24.19 (2.44)	0.93	.36
APACHE II	13.52 (6.01)	18.85 (6.67)	−4.02	<.001
SOFA	6.66 (3.89)	9.917 (4.69)	−3.61	<.001
GCS	14.25 (0)	11 (0)	−2.11	.04
Gender				
Male	27	32	0.28	.60
Female	17	16		
Mechanical ventilation			2.63	.11
Yes	22	32		
No	22	16		
Abdominal puncture drainage	23	21	0.67	.41
Yes	21	27		
No				
Gallbladder puncture drainage			0.95	.33
Yes	12	9		
No	32	39		

APACHE II = Acute physiology and chronic health evaluation II, SOFA = Sequential organ failure assessment.

(APACHE) II score, sequential organ failure assessment (SOFA) score, GCS score, abdominal puncture drainage, gallbladder puncture drainage, duration of MV, intra-peritoneal pressure, vasopressors infusion, body temperature, procalcitonin (PCT), creatinine, platelet counts, length of hospital stay, and prognosis were obtained from medical records during hospitalization. APACHE II score and SOFA score were calculated using clinical data collected from the first 24 hours after ICU admission.

2.9. Statistical analysis

Continuous data conforming to normal distribution were described as mean ± SD, while continuous data not conforming to normal distribution were expressed by median (range), and SPSS 22.0 (SPSS Inc., Chicago, IL) was used for statistical analyses. Mann–Whitney *U* test was used to compare GCS score which did not conform to normal distribution, while independent sample *t* test was employed for age, BMI, APACHE II score, and SOFA score which conformed to normal distribution. χ^2 test was used to compare gender, duration of MV, abdominal puncture drainage, gallbladder puncture drainage, and vasopressors infusion between the 2 groups. In the intergroup analysis of prognostic indicators, duration of MV, dose of norepinephrine and adrenaline, maximum and mean PCT, maximum and mean creatinine were compared by Mann–Whitney *U* test due to non-normal distribution. Comparison of prognosis of ICU and hospitalization was performed by bivariate logistic regression analysis, while the other indicators were compared by independent sample *t* test. *P*-values < .05 were considered to be statistically significant.

3. Results

3.1. Baseline data of patients

This retrospective study contained a total of 92 patients who were confirmed to be with AP and underwent RRT or not. Most patients were diagnosed as AP by combination of medical history, clinical situation, and physical examination, laboratory tests and imaging examination, whereas a minority of patients were finally given a definite diagnosis by laparotomy. Forty-four patients were included in early initiation of RRT group, while the rest patients in delayed initiation of RRT group. As shown in Table 1, AP patients with delayed initiation of RRT exhibited significantly higher APACHE II score, SOFA score, and lower GCS score than those with early initiation of RRT ($P < .001$, $P < .001$, $P = .04$, respectively). There was no difference in the rest of the baseline data including age, BMI, gender, MV, abdominal puncture drainage, and gallbladder puncture drainage.

3.2. Vasopressors infusion

No significant differences were observed in vasopressors infusion between the 2 groups (shown in Table 2).

3.3. Analysis of prognostic indicators between the 2 groups

Analysis showed a significant change in dose of norepinephrine, maximum and mean PCT, maximum and mean creatinine, maximum and mean intra-peritoneal pressure, length of hospital stay, prognosis of ICU, and hospitalization between the 2 groups

Table 2

Vasopressors infusion.

	Early n = 44	Delayed n = 48	χ^2 value	*P* value
Types of Vasopressors			1.92	.38
No	18	15		
1	19	20		
≥2	7	13		
Norepinephrine infusion			2.62	.11
Yes	23	33		
No	21	15		
Adrenaline infusion			0.83	.36
Yes	6	10		
No	38	38		
Vasopressors infusion			0.93	.34
Yes	26	33		
No	18	15		

Table 3

Analysis of prognostic indicators between the groups.

	Early n = 44	Delayed n = 48	t/z/wald value	*P* value	OR
Prognosis of ICU			6.004	.014	3.46
Cure	37	29			
Other	7	19			
Prognosis of hospitalization			7.85	.005	4.11
Cure	37	27			
Other	7	21			
Duration of MV	0 (74)	0 (51.5)	−1.11	.27	
Dose of Norepinephrine	0 (24)	0 (45)	−2.32	.02	
Dose of Adrenaline	0 (0)	0 (0)	−1.04	.3	
Maximum PCT	2.55 (10.96)	7.89 (9.12)	−2.53	.01	
Mean PCT	1.45 (6.49)	3.94 (4.19)	−2.99	<.001	
Maximum creatinine	102.28 (70.58)	255.75 (242.48)	−6.67	<.001	
Mean creatinine	75.53 (43.08)	159.38 (136.58)	−6.33	<.001	
Maximum intra-peritoneal pressure	20.59 (6.37)	26.48 (6.44)	−4.41	<.001	
Mean intra-peritoneal pressure	16.88 (5.06)	22.98 (6.94)	−4.78	<.001	
Maximum body temperature	38.02 (0.69)	37.92 (0.89)	0.6	.55	
Mean body temperature	37.03 (0.32)	37.09 (0.47)	−0.81	.42	
Minimum platelet counts	101.977 (60.49)	118.229 (61.75)	−1.273	.21	
Mean platelet counts	182.418 (74.63)	179.654 (87.13)	0.163	.87	
Hospital day	14.523 (10.57)	9.167 (7.93)	2.764	.01	

MV = mechanical ventilation, PCT = Procalcitonin.

(shown in Table 3). In AP patients with delayed initiation of RRT, the ICU and hospital mortality risk increased by 3.46 and 4.11 times, respectively.

4. Discussion

AP is a common gastrointestinal disorder caused by the digestion of trypsin itself, which can lead to dysregulated systemic inflammatory response, further resulting in local and distant organ damage or failure. The most important risk factors associated with AP in adults were gallstones and excessive alcohol consumption,[2,26] which contributed approximately 80% of all causes. In recent years, despite increasing AP-related morbidity, AP-associated mortality and hospital stay had decreased;[27] however, the cost was substantial, especially in ICU. AP had become a huge medical cost burden for patients' families as well as the health care system in China. The overall mortality rate is as expected higher for more severe condition,[26,28] under which patients need to be admitted to ICU for earlier identification and intensive care support as soon as possible.[29,30] When surgical intervention was needed, minimally invasive strategy and step-up approach were advocated.[28,31]

The protection of important organs (such as heart, brain, and liver) was always put in the first place, kidney was prone to be damaged in AP. Therefore, AKI was common in critically ill patients and was always associated with adverse outcomes in any disease. Higher incidences of AKI were observed in ICU,[32] which might be still substantially underestimated. AKI was mainly manifested as the accumulation of products of metabolism or decreased urine output, or both. Deteriorated kidney function could lead to further damnification and aggravation of other important organs. Although continuous improvement for the early identification and intervention of AKI was made, the mortality associated with AKI and risk of developing chronic renal failure (CKD) remained high in recent years. Undoubtedly, the mortality of AKI increased with the stages increase of AKI[33] and was inversely associated with percentage of gross domestic product spent on total health expenditure.[34] The underlying cause was the lack of effective measures for the treatment of AKI in clinical practice, with an exception of RRT. Routine use of diuretics was no longer recommended in KDIGO guidelines, although there was a considerable proportion of application in clinical practice.[35]

AP-induced AKI was different from AKI caused by other pathogenic factors. IAH and AKI could aggravate each other, and further form a vicious circle without early intervention. Aggressive fluid resuscitation and fluid accumulation can be associated with harms in AP patients, including respiratory and renal insufficiency,[36] and IAH,[37] which may occur in approximately 60% to 80% of SAP patients. Fluid balance abnormalities, which are customarily tolerated and neglected by clinicians, can occur before the diagnosis of AKI,[38] thus correcting them in time will contribute to preventing or mitigating AKI. Approximately, 20% of patients with AKI required RRT,[33] and this demand continued to rise in clinical practice because of improved performance and safety of RRT. Regarding the timing of RRT initiation, going beyond the limit is as bad as falling short. The decision when to initiate RRT is not merely academic issue but an important determinant of prognosis.[21] Thus, in this study we worked to explore the optimal timing of RRT initiation in AP patients in order to avoid complications associated with catheter and extracorporeal circulation caused by unnecessary early RRT or more severe condition induced by delayed treatment.

Due to more predictive value for mortality,[39] KDIGO criteria was the most commonly utilized classification system for the identification of AKI. APACHE II score and SOFA score are common scoring systems in clinical practice to reflect the severity of illness and predict the prognosis. PCT, as a marker of infection, is related to the severity of sepsis,[40] and even prognosis.[41] Increased intra-peritoneal pressure is also associated with the severity and clinical outcome of AP.

In this study, early initiation of RRT is associated with lower dose of norepinephrine, PCT, intra-peritoneal pressure and

creatinine counts, and improved prognosis of ICU and hospitalization, compared with delayed initiation of RRT. A possible explanation was that early initiation of RRT contributed to stabilizing internal environmental, eliminating toxins, alleviating systemic inflammatory response, and avoiding fluid overload speed.[42] Compared with previous experiments, the definition of early or delayed RRT was the most important difference in our study, which was more suitable for clinical practice. Another explanation was that the patients enrolled in this study were all surgical patients, and CKD was excluded. In addition, all RRT patients received homogeneous CVVH as the sole method, rather than interval hemodialysis or diuretics. An analysis of secondary outcomes showed no significant difference in duration of MV, dose of adrenaline, maximum and mean body temperature, and minimum and mean platelet counts between early and delayed RRT groups.

There are several limitations in our study. First, the etiology of AP has not been further distinguished. Secondly, this is a single-central retrospective study which reduces the reliability of the conclusion. Thirdly, a relatively small sample size needs to be explained with caution. More well-designed and large-scale trials are needed to confirm our findings and determine the optimal timing of RRT initiation in AP patients. These findings can only be explained and applied to AP patients with caution. Lastly, the AP patients in delayed RRT group obviously had more severe condition than those in early RRT group, which would inevitably have an impact on the prognosis. However, to the best of our knowledge, this study is one of the few studies to explore the effect of early vs delayed initiation of RRT in AP patients.

In conclusion, among AP patients, survival was significantly better in the early initiation of RRT group as well as other relevant clinical outcomes, including dose of norepinephrine, PCT, intra-peritoneal pressure and creatinine, which may provide some insight for AP patients treatment in clinical practice.

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