The clinical efficacy of continuous renal replacement in the treatment of acute pancreatitis: a meta-analysis of randomized controlled trials

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Abstract

Abstract:Objective: The purpose of this study was to investigate the effect of continuous renal replacement therapy(CRRT) on patients with acute pancreatitis(AP). Methods: A comprehensive search of seven databases without language restrictions includes PubMed, Cochrane Library, Scopus, Embase, Web of Science, China National Knowledge Infrastructure(CNKI) and Wan fang database. Randomized controlled trials (RCTs) for the treatment of acute pancreatitis with CRRT were searched. All the included literatures were published before December 2020. Two review authors independently selected the study and extracted the data according to the inclusion criteria. A third review author will and discuss with the first two review authors and resolve the differences. Weighted mean difference(WMD), risk ratio (RR), and 95% confidence interval (CI) were used for estimating the clinical efficacy of AP in CRRT and control treatment. Results: Fifty-three RCTs met the inclusion criteria and were used in the meta-analysis, with a total of 3,382 effective samples. A comprehensive review of the system shows that the mortality rate of the CRRT group was significantly lower than that of the control group, and the difference was statistically significant(RR=0.44,95%CI0.34 to 0.57,P< 0.000001), the patients using CRRT had lower APACHE II scores level(WMD=-3.78, 95%CI-4.66 to -2.90,P<0.00001),higher CRP, PCT,TNF-αand IL-6 clearance effect. According to liver function, the patients using CRRT had lower ALT and AST levels. In the same way, according to renal function, the patients using CRRT had lower SCr (WMD=-94.28, 95%CI-125.47 to -63.10, P<0.00001). The patients using CRRT also had higher ALB levels(WMD=2.32, 95%CI-1.05 to 3.59 ,P=0.0003). Moreover, Results shown no statistical difference in Serum potassium level (WMD=-0.00, 95%CI-0.31 to 0.31,P=1.00)between the two groups. Conclusions: Our findings suggest that treatment with CRRT for acute pancreatitis may be more beneficial than conventional treatment. However, high-quality studies with a larger sample size are still needed to confirm our results.

The clinical efficacy of continuous renal replacement in the treatment of acute pancreatitis: a meta-analysis of randomized controlled trials

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Abstract: Objective: The purpose of this study was to investigate the effect of continuous renal replacement therapy(CRRT) on patients with acute pancreatitis(AP). **Methods:** A comprehensive search of seven databases without language restrictions includes PubMed, Cochrane Library, Scopus, Embase, Web of Science, China National Knowledge Infrastructure(CNKI) and Wan fang database. Randomized controlled

trials (RCTs) for the treatment of acute pancreatitis with CRRT were searched. All the included literatures were published before December 2020. Two review authors independently selected the study and extracted the data according to the inclusion criteria. A third review author will and discuss with the first two review authors and resolve the differences. Weighted mean difference(WMD), risk ratio (RR), and 95% confidence interval (CI) were used for estimating the clinical efficacy of AP in CRRT and control treatment. **Results:** Fifty-three RCTs met the inclusion criteria and were used in the meta-analysis, with a total of 3,382 effective samples. A comprehensive review of the system shows that the mortality rate of the CRRT group was significantly lower than that of the control group, and the difference was statistically significant(RR=0.44,95%CI0.34 to 0.57,P< 0.000001), the patients using CRRT had lower APACHE II scores level(WMD=-3.78, 95%CI-4.66 to -2.90,P<0.00001),higher CRP, PCT,TNF-αand IL-6 clearance effect. According to liver function, the patients using CRRT had lower ALT and AST levels. In the same way, according to renal function, the patients using CRRT had lower SCr (WMD=-94.28, 95%CI-125.47 to -63.10, P<0.00001). The patients using CRRT also had higher ALB levels(WMD=2.32, 95%CI-1.05 to 3.59 ,P=0.0003). Moreover, Results shown no statistical difference in Serum potassium level (WMD=-0.00, 95%CI-0.31 to 0.31,P=1.00)between the two groups. **Conclusions** : Our findings suggest that treatment with CRRT for acute pancreatitis may be more beneficial than conventional treatment. However, high-quality studies with a larger sample size are still needed to confirm our results.

Key words: Acute pancreatitis; Continuous renal replacement therapy; The prognosis; Meta-analysis; APACHE II scores; Serum markers; Inflammatory factors; Liver and kidney function

1.Introduction

Acute pancreatitis(AP), an inflammatory disorder of the pancreas, is the leading cause of admission to hospital for gastrointestinal disorders in many countries[1], it is one of the common acute abdominal diseases. The incidence rate of acute pancreatitis is rising globally, which sharp increasing its burden on healthcare services[2].Acute pancreatitis is an inflammatory response of pancreatic tissue to self-digestion, edema, bleeding and even necrosis after pancreatin activation in the pancreas due to various etiologies. The most likely causes of pancreatitis are Alcoholism, gallstones[3].Because the severity of acute pancreatitis is different, clinical acute pancreatitis is divided into three types: mild, medium and severe, while according to the type of inflammation, acute pancreatitis can be divided into interstitial edema pancreatitis or necrotizing pancreatitis.[4]About 80% to 85% of patients will develop only mild acute pancreatitis, while about 15% to 20% of patients will develop severe acute pancreatitis with severe organ failure and local complications, which may even lead to death[5].

The main clinical manifestations of acute pancreatitis are abdominal pain, nausea, vomiting, high fever, jaundice, peritoneal irritation and so on[6]. AP is a digestive system disease which caused by a variety of factors and characterized by acute inflammation of the pancreas and histologically acinar cell destruction. Two of the following three criterias can be defined as acute pancreatitis: abdominal pain, serum amylase and lipase thresholds typically three times the upper limit, and imaging criteria (computed tomography, magnetic resonance imaging, ultrasound)[7]. Lysosome function is disturbed, a series of digestive enzymes are activated abnormally, leading to digestive damage and local inflammation. It has been demonstrated that acini damage can stimulate inflammation in the pancreatic parenchyma due to the pancreas's own digestive process(like filtration of neutrophils and macrophages, and release of cytokines, tumor necrosis factor, and interleukin-1,6, and 8)[8]. Therefore, intervention for acute pancreatitis is very important. The conventional treatment of acute pancreatitis is mainly to reduce the secretion of pancreatic fluid and reduce the pancreas's self-digestion as much as possible. This usually involve fasting and water prohibition, gastrointestinal decompression, use of somatostatin and its analogs, thus inhibition of gastric acid secretion. Fluid resuscitation, enteral nutrition, and antibiotics to treat infections, suppress inflammation, and prevent organ failure[9]. However, some evidence suggest that prophylactic antibiotic used in patients with acute pancreatitis is not associated with significant reductions in mortality or morbidity recently. Therefore, routine prophylactic antibiotics are no longer recommended for all patients with acute pancreatitis[10]. Antibiotics are the first choice for the treatment of infectious severe acute pancreatitis. Whereas, diagnosis is a challenge because the clinical

presentation is indistinguishable from other infectious complications or inflammatory states associated with acute pancreatitis. How to choose more specific antibiotics for different patients has also become one of the difficult problems. With the development of science and technology, the continuous renal replacement therapy (CRRT) become one of the new methods of renal replacement therapy. Since it has to maintain electrolyte balance, regulate acid-base degree of fluid and waste from the blood metabolic, inflammatory mediator and endotoxin, thereby protect endothelial cells, help regulate the body's immune function, it not only can be widely used in acute and chronic renal failure, can also play an important role in the treatment of AP[11].Compared with conventional treatment, does CRRT have a more beneficial effect on the treatment of patients? Does it reduce inflammation more in patients with acute pancreatitis? What about the function of liver and kidney of patient and viscera maintenance respect? Up to now, no one has evaluated CRRT versus conventional treatment for acute pancreatitis in these areas. Through this study, the effect of CRRT on the treatment effect and prognosis of AP was systematically evaluated to explore whether CRRT was a necessary way to treat AP and provide evidence-based medicine basis for the treatment of AP.

2.Methods

This meta-analysis performed followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. The review protocol has been registered in PROSPERO (CRD42020220897), which is a systematic review of online international prospective registrations, planned by the National Institutes of Health Research.

2.1 Search Strategy

Electronic databases which including PubMed, Cochrane Library, Scopus, Embase, Web of Science, China National Knowledge Infrastructure(CNKI) and Wan fang database were searched. These following keywords were used individually or in a combined manner for the online literature: Continuous Renal Replacement Therapy OR Continuous RRT OR Continuous Renal Replacement Therapy OR Continuous Venovenous Hemodiafiltration OR CVVHDF OR Continuous Veno-Venous Hemodiafiltration OR Slow Continuous Ultrafiltration OR SCUF Technique OR CVVH Technique OR Continuous Veno-Venous Hemofiltration OR CAVHD OR Continuous Venovenous Hemodialysis OR CVVHD OR Continuous Veno-Venous Hemodialysis AND Acute Pancreatitis OR Acute Edematous Pancreatitides. Two reviewers (SJ Ma and MM Zhao) independently review the titles, keywords, and abstracts of the literature selected in these format, when they encounter differences of opinion, they discussed with the third reviewer(ZY Pan) then made arbitration and decision.

2.2 Types of studies

This study only included randomized controlled studies(RCTs), and there were no language restrictions. Animal studies, self-controlled studies, repeated studies, and studies where full texts were not available were excluded. Likewise, reviews articles, case reports, editorials, letters, and comments were not included.

2.3 Inclusion Criteria

(1)Research type: Randomized controlled trials (RCTS), whether blind or not, have no language limitations.(2)Research objects: Up to AP diagnostic criteria[4].(3)Intervention measures: The control group received routine treatment, including water abstinence, fasting, gastrointestinal decompression, acid inhibition, enzyme inhibition, catharsis, pain relief, anti-infection and nutritional support, as well as symptomatic treatment such as mechanical ventilation and anti-shock when necessary. The CRRT group was treated with continuous veno-venous hemofiltration on the basis of conventional treatment. None of the patients underwent surgery.(4)Outcome measurement index: mortality rate of AP patients, serum amylase, TNF-α, CRP,PCT, IL-6 clearance rate, liver and kidney function, APACHE II score after treatment.

2.4 Exclusion Criteria

Before the onset of the disease with other acute attack disease, serious cardiovascular disease, pregnancy and other serious chronic diseases or severe infection. It's not CRRT versus conventional treatment. Non-

randomized controlled trials. Self controlled experiment. Outcome indicators do not include the above main outcome indicators.

2.5 Data extraction

Three authors (Ma, Pan, and Fan) independent use standard form, the following data extracted from each article: the first author's last name, year of publication, sample size, age, sex, etiology, time recorded point, the outcome indicators (CRP, Serum amylase, TNF-α, CRP,PCT,IL-6 levels after treatment, liver and kidney function, APACHEII scores after treatment). If the raw data is not evident in the article, we will contact the author to ask whether the raw data is available. If the occasion should arise, we do not extract the data completely.

2.6 Data analysis

The Revman 5.3 software provided by Cochrane was used in this study. For continuous variable data, the random effects model or fixed effects model is used according to I^2 of the combined total results. $I^2$was used to evaluate heterogeneity. We considered that when I^2 is greater than 50%, there is a large inter-group heterogeneity, so the random effect model was applied; when I^2 is less than or equal to 50%, the inter-group heterogeneity is small, so the fixed effect model can be selected. For dichotomous results, a 95% confidence interval combined RR was used as a measure of efficacy. If the units of the variables were the same, WMD was used. Otherwise, we preferred to choice SMD.

2.7 Subgroup analysis and sensitivity analysis

Subgroup analysis and sensitivity analysis play an important role in order to explore the source of heterogeneity. Among them, methodology, statistics and clinical characteristics are all potential sources that may constitute heterogeneity. When there's a huge difference in the results of clinical trials and the heterogeneity is significant, we removed one trial that is significantly different from the other trials and then combined the remaining studies to compare the results before and after the trial.

3. Results

3.1 Literature Search

As shown in the flow chart in Figure 1, this study found a total of 846 relevant literatures through the database retrieval mentioned above.163 references were excluded due to duplication of content. After screening the title and abstract, 554 articles were excluded because they did not meet the eligible criteria. Then 76 articles were excluded according to the full text content, which combined with other interventions(n=30), review articles(n=6), non-RCT(n=4), with other early acute diseases(n=31), full text was not available(n=5). Finally, a total of 53 randomized controlled trials (RCTS) (3 English[11-13]and 50 Chinese[14-63]) that met the criteria were included for meta-analysis.

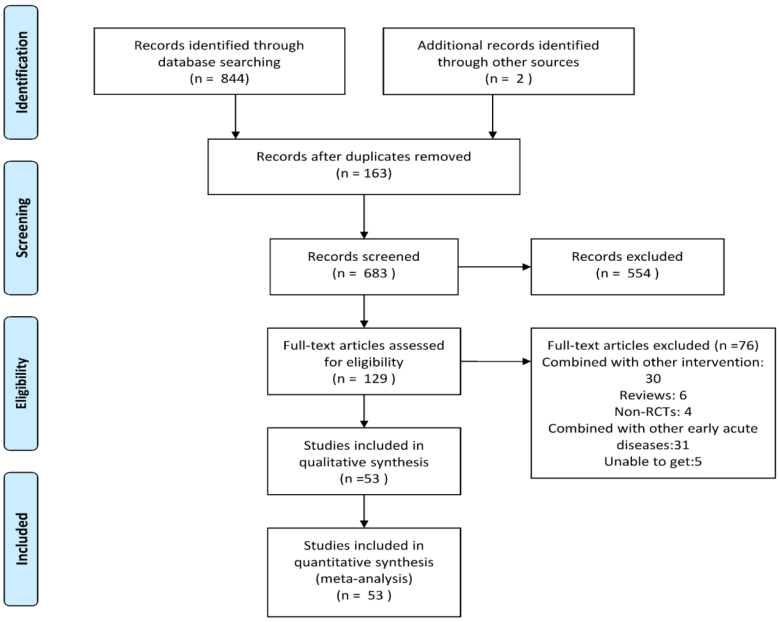

Fig. 1 Filter article flow diagram according to inclusion criteria

3.2 Risk of bias assessment

The quality of RCT was assessed according to the Cochrane Evaluation Manual, including six aspects: randomization, allocation concealment, blindness, incomplete data bias, selective reporting of results, and other factors that may potentially affect authenticity. If the number of people lost to follow-up exceeded 10% in the included study, the possible causes of loss of follow-up were further analyzed and intention-to-treat (ITT) analysis was performed. For each included study, 3 evaluations were made for the above 6 items, namely, low bias risk, high bias risk and unclear risk (Fig. 2).

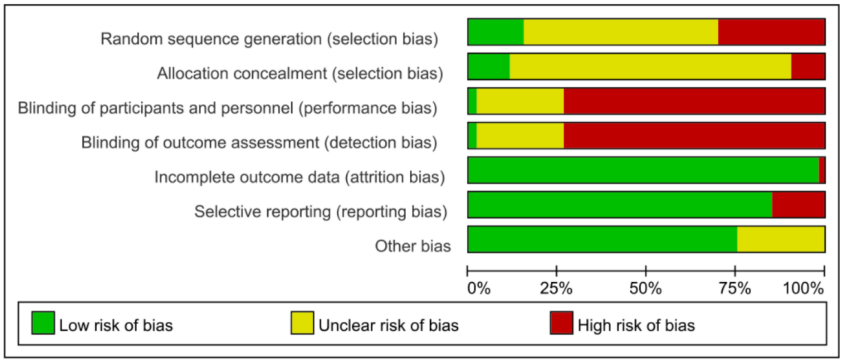

Fig.2 Assessment of the methodological quality of the included studies

3.3 Study Characteristics

The patient characteristics and main outcome indicators included in the included study are shown in Table 1. All the studies were published between 2001 and 2020. A total of 3382 patients were included in this study.

Table 1.Characteristics of patients with acute pancreatitis and disease causes and outcome indicators.

Studies	N (T/C)	Gender (male/female)	Mean age ± SD (years)	Cause of acute panScreatitis	time recorded point	outcome indicators
Xu GB et al. 2013	35/35	37/33	50. 3 ±7.9	biliary tract diseases:37 excessive drinking and eating:5 traumatic injury:5 unknown cause:5	NR	APACHE-II score,CRP,Length of ICU stay and mortality rate
Liu XS et al. 2017	22/53	T:14/8 C:31/22	T:(52.1±11.2) C:(50.7+-13.4)	NR	24h 72h	HR, urine volume, K+,BUN,Scr,CRP, α, IL-6
Wang XQ et al. 2019	35/25	T:22/13 C:18/7	T:(40.5±9.5) C:(41.1+-9.5)	hyperlipidemia	NR	Treatment effect,TG, CRP,blood amylase and urine amylase
Hui WJ et al. 2017	60/60	T:32/28 C:30/30	T:(37.6±5.4) C:(38.1+-5.6)	NR	NR	Treatment effect, blood amylase, TNF-α, IL-1
Zou YD et al. 2017	31/31	T:18/13 C:16/15	T:(43.02±4.51) C:(43.85+-3.91)	NR	NR	Treatment effect, blood amylase, CRP, IL-6,PO_2

Studies	N (T/C)	Gender (male/female)	Mean age ± SD (years)	Cause of acute panScreatitis	time recorded point	outcome indicators
Deng ZY et al. 2014	32/32	46/18	41.7	biliary pan-Screatitis:47 alcoholic pan-Screatitis:12 unknown cause:5	NR	APACHE-II score,TNF-α, endotoxin, IL-6, IL-18, mortality rate
Peng Y et al. 2019	22/20	25/27	37	biliary tract diseases:18 excessive drinking and eating:11 mixed cause:10 idiopathic cause:3	NR	IL-6,TNF-α, blood amylase
Zhong X et al. 2017	37/37	T:23/14 C:21/16	T:(56.5±4.3) C:(55.8+-4.4)	T: biliary tract diseases:14 excessive drinking and eating:8 alcoholism:9 other cause:6 C: biliary tract diseases:15 excessive drinking and eating:7 alcoholism:8 other cause:7	72h	Treatment effect, APACHE-II score,ALB,ALT, 24h urine output ,BUN,Scr
Peng B et al. 2019	41/41	T:27/14 C:26/15	T:(43.7±8.6) C:(44.3+-8.5)	T: biliary tract diseases:19 hyperlipidemia:8 alcoholism:10 other cause:4 C: biliary tract diseases:17 hyperlipidemia:9 alcoholism:10 other cause:5	6h 12h 24h	PCT,CRP, D-dimer, blood lipase,blood amylase,PLT
Zou H.2018	22/15	T:20/2 C:4/11	T:(39.23±6.36) C:(38.27+-6.77)	hyperlipidemia	48h	Treatment effect,TG,TCH, blood lipase,blood amylase,CRP,Scr

Studies	N (T/C)	Gender (male/female)	Mean age ± SD (years)	Cause of acute panScreatitis	time recorded point	outcome indicators
Wang Y et al. 2018	36/36	T:24/12 C:25/11	T:(47.4±13.6) C:(46.7+-13.2)	T: biliary tract diseases:19 excessive drinking and eating:7 alcoholism:10 other cause:4 C: biliary tract diseases:11 excessive drinking and eating:10 alcoholism:6 other cause:7	24h 72h	CRP, PCT, Scr, BUN, Ca, APACHE-II score
Ni ZH.2013	29/22	T:21/8 C:10/12	T:(47.3±14) C:(47.18+-12.24)	T: biliary tract diseases:8 excessive drinking and eating:8 alcoholism:8 unknown cause:5 C: biliary tract diseases:7 excessive drinking and eating:3 alcoholism:5 unknown cause:7	24h 48h 72h	24h urine output,PH,PO2,PCO BUN,SCr,Na,K,C Treatment effect
Li YN et al. 2002	20/17	25/12	43.3	biliary tract diseases:7 excessive eating:6 alcoholism:10 unknown cause:3 Trauma:2	7days	Treatment effect, blood amylase,SCr,TP,A
Chen DJ et al.2018	49/49	T:26/23 C:24/25	T:(45.72±6.34) C:(46.52+-7.35)	NR	12h 24h 36h	HR, 24h urine output,PO_2,PCO
Tian JX et al.2015	60/60	T:35/25 C:36/24	T:(42.9±12.5) C:(43.8+-11.7)	NR	72h	APACHE-II score, blood amylase,ALB,TP

Studies	N (T/C)	Gender (male/female)	Mean age ± SD (years)	Cause of acute panScreatitis	time recorded point	outcome indicators
Li Q.2020	27/27	T:15/12 C:14/13	T:(45.39±5.56) C:(45.66+-5.79)	T: biliary calculi:4 alcoholism:7 sphincter dysfunction of hepatopancreatic ampulla:3 hyperlipidemia:3 excessive drinking and eating:10 C: biliary calculi:3 alcoholism:8 sphincter dysfunction of hepatopancreatic ampulla:4 hyperlipidemia:3 excessive drinking and eating:9	72h	APACHE-II score, Treatment effect
Xiao XP.2014	17/13	18/12	48±5	NR	24h 48h 72h	Treatment effect,TNF-α
Zhu JG et al.2007	17/14	T:10/7 C:9/5	T:(49.93±10.3) C:(51.05+-11.10)	NR	NR	HR,PCT,CRP, Treatment effect
Wang LY.2017	45/45	T:28/17 C:25/20	T:(46.25±5.63) C:(48.53+-6.24)	NR	NR	APACHE-II score,CRP,PCT, TNF-α
Yang H.2013	25/25	27/23	43.25	NR	NR	APACHE-II score,SCr,TG, blood amylase ,PO_2,ALT
Li KY.2016	30/30	T:20/10 C:16/14	NR	NR	24h 72h 7days	HR,APACHE-II score,CRP,PCT, TNF-α,BUN,SCr,ALT,

Studies	N (T/C)	Gender (male/female)	Mean age ± SD (years)	Cause of acute panScreatitis	time recorded point	outcome indicators
Cui WY et al.2017	16/11	T:10/6 C:4/7	T:(49.91±24.23) C:(50.63+-14.30)	T: biliary tract diseases:8 alcoholism:2 hyperlipidemia:5 other cause:1 C: biliary tract diseases:7 alcoholism:2 hyperlipidemia:2 other cause:0	24h 72h	SCr,WBC,CRP
Chen FS.2020	45/45	45/45	45±6.7	NR	48h	SCr,PCT,TG,TB blood amylase
Xu F et al.2019	32/32	T:19/13 C:18/14	T:(42.05±3.93) C:(42.68+-2.95)	T: biliary tract diseases:14 alcoholism:13 hyperlipidemia:5 C: biliary tract diseases:15 alcoholism:12 hyperlipidemia:5	72h	HR,BUN,SCr,AL blood amylase
Zhu CZ.2016	40/40	T:25/15 C:28/12	T:(45.2±8.5) C:(44.9+-7.9)	NR	72h	PO_2,PCO_2,WBC
Gao N. et al.2018	46/46	T:24/22 C:22/24	T:(38.87±6.47) C:(39.13+-6.56)	T: alcoholism:16 hyperlipidemia:20 cholelithiasis:7 other cause:3 C: alcoholism:14 hyperlipidemia:18 cholelithiasis:9 other cause:5	6h 12h 24h	PCT,CRP,IL-17,IL-6,HMGB1,D-dimer
Xu JM. et al.2017	25/11	T:24/22 C:22/24	NR	NR	7days	blood amylase,ALT,SCr
Chen X et al.2019	32/28	T:20/12 C:18/10	T:(54.32±10.65) C:(58.94+-9.02)	NR	7days	ALT,AST, TBIL,ALB,WBC blood and urine amylase
Zhang X.et al.2016	8/14	14/8	54±14	NR	48h	APACHE-II score,TG,CRP, Treatment effect

Studies	N (T/C)	Gender (male/female)	Mean age ± SD (years)	Cause of acute panScreatitis	time recorded point	outcome indicators
Wang LF.2020	15/15	T:8/7 C:7/8	T:(46.7±11.4) C:(46.8+-11.5)	NR	72h	Na,Ca,K,BUN,Sc 24h urine output
Liu MX.et al.2011	15/15	10/16	53±16	NR	48h	APACHE-II score,TG,CRP, blood and urine amylase, Treatment effect
Xu JY.2013	12/20	23/9	47.5	hyperlipidemia	48h	Treatment effect, APACHE-II score,TG,CRP,bl and urine amylase
Wu SK.2015	28/30	T:18/10 C:19/11	T:(67.5±10.3) C:(69.5+-11.3)	T: alcoholism:8 cholelithia-sis:10 other cause:10 C: alcoholism:10 cholelithia-sis:12 other cause:8	NR	Treatment effect, the time taken for clinical indicators to return to normal
Xu Y.et al.2009	30/30	T:20/10 C:19/11	T:(30±10.5) C:(43.1+-10.5)	T: alcoholism:6 high-fat diet:6 history of biliary tract infection:5 excessive drinking and eating:12 unknown cause:1 C: alcoholism:6 high-fat diet:5 history of biliary tract infection:8 excessive drinking and eating:9 unknown cause:2	24h 48h 72h	APACHE-II score
Wei R.2016	40/40	NR	60.3±1.8	alcoholism:37 cholelithiasis:43	NR	APACHE-II score,HR,MAP,C

Studies	N (T/C)	Gender (male/female)	Mean age ± SD (years)	Cause of acute panScreatitis	time recorded point	outcome indicators
Tian GX.2016	60/60	T:32/28 C:30/30	T:(37.6±5.4) C:(38.1+-5.6)	NR	NR	Treatment effect,IL-1,TNF-α,blood amylase
Wan CS.2017	60/60	NR	NR	T: alcoholism:18 cholelithiasis:13 excessive drinking and eating:24 unknown cause:5 C: alcoholism:20 cholelithiasis:15 excessive drinking and eating:21 unknown cause:4	72h	Na,K,Ca,BUN,SC 24h urine output
Wang YF.et al.2017	12/20	T:7/5 C:14/6	T:42 C:41	hyperlipidemia	NR	HR,SCr,TG,CRP 1,TNF-α,GLU, APACHE-II score
Ji HL.et al.2011	36/38	T:23/13 C:25/13	T:57 C:54	NR	NR	CRP,APN, Treatment effect
Li LL.2018	40/40	T:23/17 C:25/15	T:(43.26±8.87) C:(42.17+-8.67)	NR	72h	IL-6,TNFα,SCr,BUN Treatment effect
Li YP.2014	13/13	T:9/4 C:9/4	T:51.8 C:56.5	alcoholism:8 cholelithiasis:3 excessive drinking and eating:10 hyperlipidemia:2 surgery:1 hepatopancreatic ampulla sphincter dysfunction:2	7days	IL-6,TNF-α,WBC,HR,CRP, ,Treatment effect

Studies	N (T/C)	Gender (male/female)	Mean age ± SD (years)	Cause of acute panScreatitis	time recorded point	outcome indicators
Li QB.et al.2009	19/19	T:12/7 C:14/5	T:(44.3±19.5) C:(45.4+-18.7)	T: cholelithiasis:10 excessive drinking and eating:5 trauma:2 unknown cause:2 C: cholelithiasis:13 excessive drinking and eating:6	72h	IL-6,TNF-α, APACHE-II score,PO_2,PH, Treatment effect
Hu W.et al.2001	10/10	T:7/3 C:7/3	T:(56.8±15.4) C:(59.7+-13.2)	NR	7days	IL-6,TNF-α,IL-1β,APACHE-II score,Treatment effect
Shen Q.et al.2016	43/35	47/31	47.3±14.8	cholelithiasis:23 excessive drinking and eating:13 alcoholism:18 hyperlipidemia:15 unknown cause:9	72h	APACHE-II score, TNF-α,CRP, Treatment effect, blood amylase
Sun JH.et al.2018	39/39	T:22/17 C:24/15	T:(40.4±5.9) C:(43.6+-6.9)	NR	24h	HR,BUN,SCr,AL blood amylase
Wu LM.et al.2013	40/18	T:17/23 C:11/7	T:(50.5±9.4) C:(51.4+-7.8)	cholelithiasis:43 hyperlipidemia:13 other cause:2	72h	APACHE-II score,TBIL,SCr,C
Liu JQ.2019	50/50	T:27/23 C:26/24	T:(42.3±6.5) C:(42.1+-7.1)	T: cholelithiasis:11 hyperlipidemia:17 alcohol abuse:14 other cause:8 C: cholelithiasis:13 hyperlipidemia:15 alcohol abuse:16 other cause:6	72h	PO_2,WBC,MAP,
Hou QC.et al.2018	36/36	T:20/18 C:22/16	T:(42.3±6.5) C:(45.6+-3.6)	NR	NR	APACHE-II score,CRP,PCT,T α

Studies	N (T/C)	Gender (male/female)	Mean age ± SD (years)	Cause of acute panScreatitis	time recorded point	outcome indicators
Zhou JY.2015	23/23	T:13/10 C:12/11	T:(46.7±8.7) C:(47.2+-9.1)	T: cholelithiasis:12 hyperlipidemia:4 alcohol abuse:6 other cause:1 C: cholelithiasis:10 hyperlipidemia:4 alcohol abuse:7 other cause:2	NR	CRP,PCT,SCr,B
Yu ZD.et al.2015	25/25	T:18/7 C:12/13	NR	biliary tract :25 cholelithiasis with cholecystitis:10 high-fat diet:7 alcohol abuse:3 overeating:3 unknown cause:2	NR	APACHE-II score,CRP
Wang XM.2016	50/50	T:28/22 C:26/24	T:(48.5±8.4) C:(45.4+-6.2)	NR	NR	PO_2,PH
Tang W.et al.2017	35/35	T:21/14 C:20/15	T:(45.6±13.1) C:(46.7+-12.9)	T: alcoholism:8 cholelithiasis:7 excessive drinking and eating:6 hyperlipidemia:6 hepatopancreatic ampulla sphincter dysfunction:8 C: alcoholism:5 cholelithiasis:9 excessive drinking and eating:6 hyperlipidemia:7 hepatopancreatic ampulla sphincter dysfunction:8	48h	TG,TB,SCr,PCT

Studies	N (T/C)	Gender (male/female)	Mean age ± SD (years)	Cause of acute panScreatitis	time recorded point	outcome indicators
Peng Y.et al.2017	40/40	48/32	34	NR	NR	Il-1β,TNF-α,PCT,AMS,HR, APACHE-II score, Treatment effect

3.4 Meta-Analysis of Outcomes Measured

3.4.1 Mortality rate

Nineteen studies were included, which including 1070 patients, with 542 in the CRRT group and 528 in the control group. There was no statistical heterogeneity among the studies. The fixed effect model was used to combine the effect sizes. The results showed that the mortality rate of the CRRT group was significantly lower than that of the control group, and the difference was statistically significant(RR=0.44,95%CI0.34 to 0.57,P< 0.000001)(Fig.3).

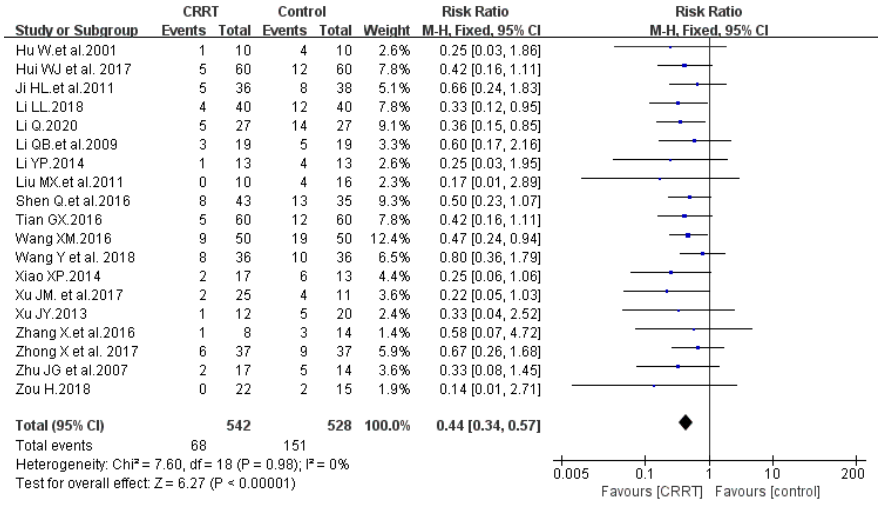

Fig.3 Comparison of forest plot of overall mortality rate between CRRT and control groups

3.4.2 APACHEIIscores

Twenty-one studies compared the impact of CRRT group and control group on APACHE II scores. Due to large heterogeneity (I^2=91%), random effects model was used for analysis, and the results showed that the difference was statistically significant(WMD=-4.20, 95%CI-4.81 to -3.58,P<0.00001)(Fig.4). Patients treated with CRRT had lower APACHE II scores than those in the control treatment group. Because APACHE II is a score that reflects the severity of a patient's illness, patients with a score greater than 15 are often considered as critical in ICU. Therefore, we conducted a subgroup analysis of the included studies based on the size of APACHE II after intervention, with the boundary of 15. Based on sensitivity analysis, the results of Wang Y, Yu DZ and Li Q crossed the invalid line and were obviously inconsistent with other research trends, therefore the three studies were excluded. I^2 went from 91% to 76%.

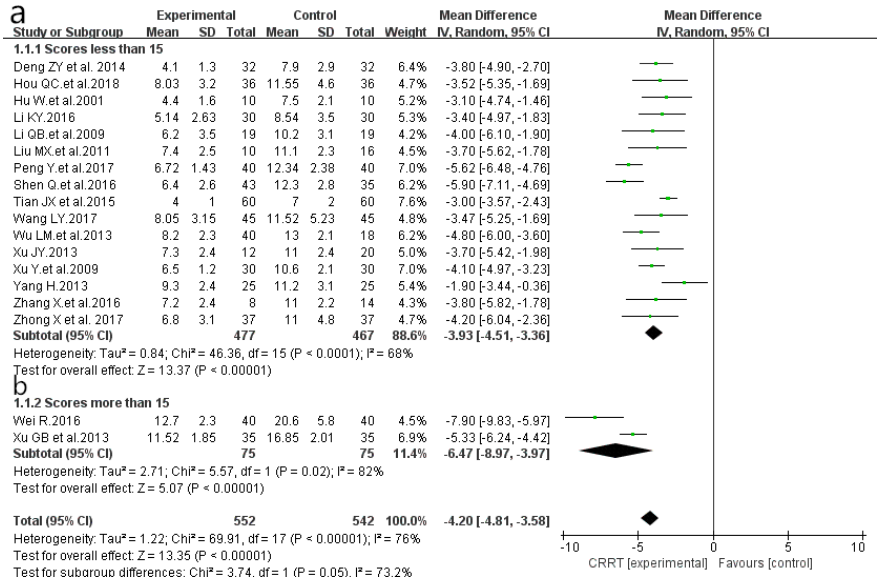

Fig.4 Comparison of forest plot of APACHEII score between CRRT and control groups. (a)The scores of the first group were less than 15 in two groups. (b)The scores of the contorl group were more than 15.

3.4.3 CRP clearance effect

Twenty-one studies compared the impact of CRRT group and control group on CRP clearance effect. Due to large heterogeneity (I^2=96.4%), random effects model was used for analysis, and the results showed that the difference was statistically significant, that compared with the control treatment group, patients treated with CRRT had significantly higher CRP clearance effect. (WMD=-8.25, 95%CI-9.74 to -6.76, P<0.00001)(Fig.5). We conducted a subgroup analysis according to the clinical CRP value, and divided the CRP value 1-5 into a group, which was the normal value. CRP values of 5-50 were divided into a group, indicating the presence of mild and moderate inflammation in the body. CRP above 50 was divided into a group, suggesting severe inflammation in the body.

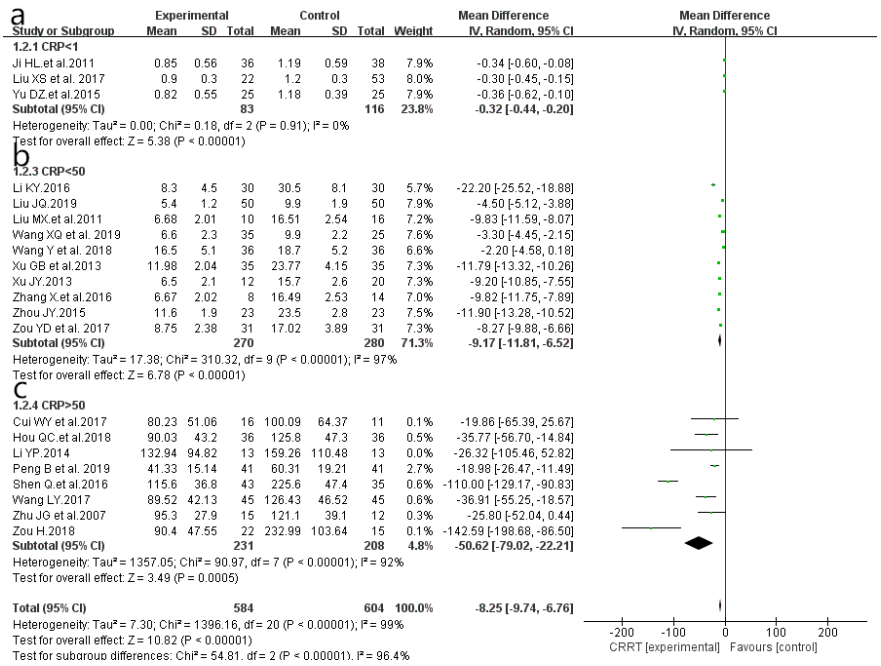

Fig.5 Comparison of forest plot of CRP clearance effect between CRRT and control groups. (a) After intervention, CRP clearance effect was below 5 in both groups. (b)CRP clearance effect was between 5 and 50 in two groups. (c)CRP clearance effect was greater than 50 in two groups.

3.4.4 ALB level

Six studies reported changes in ALB, there was no heterogeneity between the two groups, so the fixed-effect model was adopted. The results showed that there was a statistically significant difference between the two groups. (WMD=2.32, 95%CI-1.05 to 3.59 ,P=0.0003) (Fig.6)

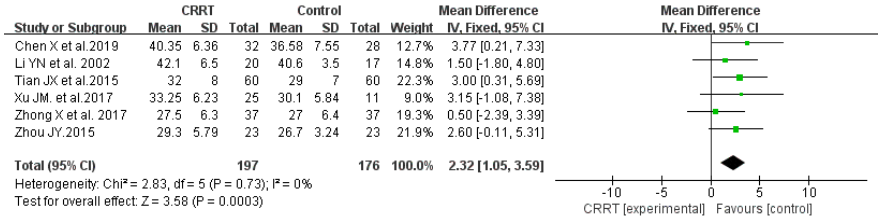

Fig.6 Comparison of forest plot of ALB level between CRRT and control groups.

3.4.5 Renal function

There were 19 studies comparing serum creatinine level(Fig.7) in the CRRT combination control group. Due to heterogeneity (I^2>90%), random effect model analysis was used, and the difference between the two groups was statistically significant(WMD=-95.59, 95%CI-126.71 to -64.46, P<0.00001). Based on the subgroup analysis of whether the Scr was greater than 95 clinically, we concluded that the CRRT group presented a more significant degree of decreased creatinine value regardless of whether the patients' creatinine value was normal after treatment. However, there was great heterogeneity. After analyzing factors such as age, gender and treatment time, I^2 was more than 70%. So the inter-group heterogeneity of the two indicators was considered to be clinically possible.

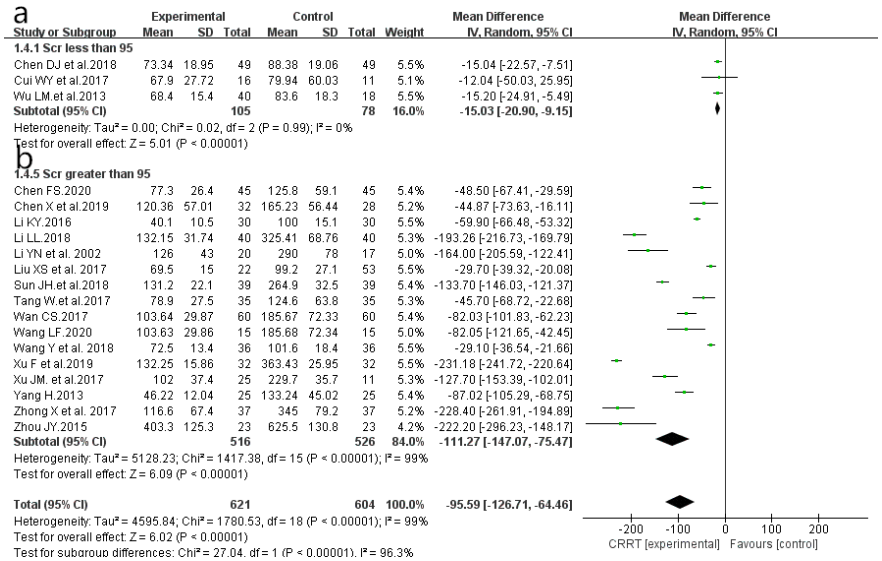

Fig.7 Comparison of forest plot of SCr level between CRRT and control groups. (a)The SCr level of two groups was less than 95. (b)The SCr level of control groups was greater than 100.

3.4.6Serum potassium level

Six studies reported changes in serum potassium, but the results showed no statistically significant difference between the two groups.(WMD=-0.00, 95%CI-0.31 to 0.31, I^2=89%,P=1.00)(Fig.8)

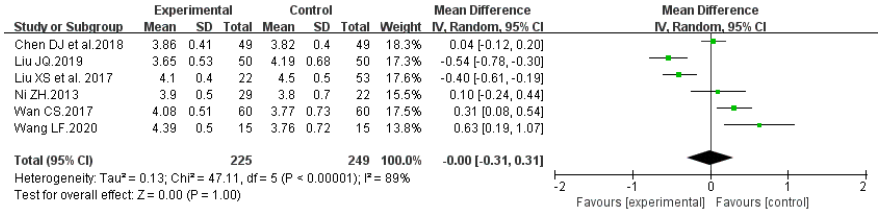

Fig.8 Comparison of forest plot of Serum potassium level between CRRT and control groups.

3.4.7 Other outcome measures

Nineteen studies analyzed the clearance effect of serum amylase in the CRRT group and the control group, and the heterogeneity was large(I^2>95%). There were respectively 9 and 15 studies compared the impact of CRRT group and control group on IL-6 and TNF-α clearance effect. In the same way, both outcomes have the large heterogeneity (I^2>95%). We attempted to conduct a subgroup analysis of each study by age, population and the treatment time, but the results showed that there was great heterogeneity between groups, all of which exceeded 90%. Therefore, we considered that the main source of heterogeneity may was clinical heterogeneity. For this reason, we conducted a systematic evaluation of the above outcome indicators, the results showed that the application of CRRT was superior to the conventional treatment in reducing the level of inflammatory factors in patients. Among them, in terms of IL-6 clearance, all the studies after CRRT were controlled below 140, while 5 studies with conventional treatment were above 200. In terms of TNF-α clearance effect, 6 studies were reduced to less than 50 and 12 to less than 100 after CRRT treatment, while only 2 were reduced to less than 50 and 6 were reduced to less than 100 in the conventional group. The difference between the two groups was statistically significant(P<0.00001).

Similarly for serum amylase, 11 of the patients in the CRRT group had serum amylase levels below 200 after treatment, compared with only 1 in the conventional treatment group. In terms of safety, ALT levels were analyzed 11 studies, patients in the CRRT treatment group had AST over 40 in 6 studies and over 40 in 9 studies in the conventional group. The difference between the two groups was statistically significant($P<0.00001$).

4. Discussion

Due to pancreatic and extra-pancreatic necrosis, acute pancreatitis (AP) is largely secondary to infection and causes Multiple organ dysfunction syndrome (MODS), which is a inflammatory disease with high morbidity and mortality[64]. Researchs have shown that during the pathogenesis of AP, neutrophils, lymphocytes, monocytes, natural killer cells and endothelial cells can produce a variety of cytokines or inflammatory mediators such as TNF-α, IL-1 and IL-6, and then induce inflammatory response or reduce cellular immune response through various pathways[65]. Early treatment in intensive care units has been recognized to be of great benefit to patients with severe episodes. Patients with AP are generally divided into three subgroups: mild, moderate, and severe. It is necessary to adjust the treatment regimen according to their specific needs, but determining the severity of the disease remains a clinical challenge. Serum markers are generally regarded as important indicators to predict the severity of AP. Serum C-reactive protein (CRP) is an acute phase reactant synthesized by the liver. In response to inflammation and infection, its levels in the blood increase within hours. Especially in inflammatory diseases, it is often used in infection and inflammation follow-up due to its short half-life, easy measurement and close relationship with prognosis of the disease[66]. In many textbooks, CRP is still considered as a gold standard for disease severity assessment[67]. Studies have reported that low serum albumin is independently associated with an increased risk of persistent organ failure and death in acute pancreatitis and can be used to predict the severity of acute pancreatitis[68].

Continuous renal replacement therapy (CRRT) is defined as a blood purification treatment technique that continuously and slowly removes water and solutes by means of extracorporeal circulation blood purification to replace renal function. Compared with common hemodialysis, CRRT can prolong the treatment time of blood purification and reduce the treatment efficiency per unit time, so as to minimize the impact of changes in the concentration and volume of solute in blood on the body. Meanwhile, it adopts a filter with high permeability and good biocompatibility. It provides an important homeostasis balance for the treatment of severe patients. With the continuous development of science and technology, CRRT has new functions in addition to regulating water and electrolyte, maintaining acid-base balance and removing metabolic wastes[69]. Its application scope is no longer limited to kidney disease, and began to be used in the treatment of non-renal failure diseases such as pancreatitis[13].Early CRRT can reduce the fatality rate of AP patients, as early as 2006 JPN Guideline wrote CRRT into the treatment of AP[70]. Researches have shown that CRRT can effectively remove the components of damaged vascular endothelial cells, improve endothelial cell function, thus reducing the incidence of MODS, and can delay or even block the process of MODS[71].

This meta-analysis, which was based on 53 RCTs including 3382 participants, found that CRRT may indeed more beneficial to AP patients than conventional treatment. The study showed that after CRRT treatment, the mortality rate of the CRRT group was significantly lower than that of the control group, and there was no obvious heterogeneity between the groups, and the difference was statistically significant. CRRT also significantly reduced the APACHEIIscores and cleared serum amylase and markers of the patients, and was superior in inflammatory factor clearance rate, alleviate the liver and kidney injury and without significant adverse reactions. According to the data of each research scope is different, we carried out subgroup analysis for serum inflammatory markers, liver and kidney function, APACHE II scores. We found that there was less heterogeneity within the subgroup (less than 50%) after grouping according to data range, but greater heterogeneity (90%) between groups as a whole. However, there were statistically significant differences in the results, shown the efficacy of CRRT treatment was better. Therefore, we believe that the inter-group heterogeneity is mainly due to clinical heterogeneity, that is, the severity of AP patients in different studies is different, so that the datas of outcome indicators is different.

The difference between the meta-analysis in our study and the previous meta-analysis are the following : First

of all, our study covered a large number of RCT studies and was not limited by language. A total of 3,392 subjects were included, with a larger sample size. Secondly, despite the past research done on meta-analysis of CRRT treatment of acute pancreatitis, but does not involve that much serum markers of inflammation factors and discuss the effects on liver and kidney function. As an updated and more comprehensive meta-analysis, this study further strengthened previous meta-analysis results, focused on more representative and specific results, fully described the impact of CRRT on AP patients, and strengthened the persuadability of existing evidence. Third, we registered the agreement of this study with PROSPERO in order to enhance PROSPERO's transparency and quality of this meta-analysis.

From the perspective of the included literature content, the original research has several limitations due to the defects in design, measurement and evaluation. First of all, the randomized controlled trials included in this meta-analysis were conducted in different patient groups and in different clinical Settings. Therefore, potential heterogeneity risk exists. Secondly, although baseline status was compared between groups in each study, due to the different degree of AP patients included in the meta-analysis, the baseline status varied widely from study to study, various outcome indicators in different studies may also be different, which is also considered as the main source of heterogeneity in some outcome indicators. Thirdly, since CRRT treatment is significantly different from conventional treatment, doctors and patients cannot be blinded, which may cause performance bias and observation bias. Fourthly, due to the different conditions of different patients and the different time of CRRT treatment, the experimental results may be affected. Finally, the causes of these AP patients are different, and the description of whether they have diabetes, hypertension and other underlying diseases is not detailed.

5. Conclusions

In conclusion, our study shows that compared with traditional treatment methods, CRRT treatment can significantly reduce the level of blood amylase, clear inflammatory mediators more significantly, reduce the score of APACHEII, slow alleviate the liver and kidney injury of patients, increase serum albumin, and reduce the mortality of AP patients. In order to confirm the reliability of the results of this study, we hope that more high-quality randomized controlled studies would be conducted in the future.

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Conflicts of Interest: The authors declare no conflict of interest.

Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

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