Meta-analysis of Bailing Capsule After Renal Transplantation

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Abstract

To objectively evaluate the effectivity and safety of Bailing Capsule After Renal Transplantation. Search Chinese Journal Full-text Database (CNKI), Chinese Science and Technology Periodical Full-text Database (VIP), Wanfang Database, PubMed, SCI, EMBase, The Cochrane Library database. Chinese uses "Bai Ling Capsule" "Kidney Transplant" as the search term, and English uses "Bailing Capsule","Bailing Jiaonang", "Corbrin Capsule", "CS-C-Q80", "Kidney transplant", "Renal transplant", etc. as search terms. Two people screened, extracted data, quality assessment and data analysis of the retrieved articles according to the inclusion criteria and exclusion criteria.A total of 10 studies were included, including 1580 patients. Meta analysis results:the experimental group was more effective than the control group in SCr level WMD = -28.40 95% CI -45.87 ~ -10.94 Z = 3.19 P =0.001 BUN levels WMD = -0.72 95% CI -1.18 ~ -0.25 Z = 3.02 P =0.003 ALT levels(WMD = -6.05 95% CI- 9.26 ~ -2.85 Z = 3.70 P = 0.0002 AST levels WMD = -11.96 95% CI -19.2 5~ -4.68 Z = 3.22 P = 0.001 .But the experimental group did not show significant effects in reducing the incidence of acute rejection. OR = 0.45 95% CI 0.19 ~ 1.11 Z = 1.74 P =0.08 Compared with the control group, Bailing Capsule treatment group has obvious advantages in Improvement of liver and kidney function after renal transplantation1,but did not show good clinical results in reducing the incidence of acute rejection.

Background

With the increasing number of kidney transplantation patients, how to prevent and treat the complications after kidney transplantation better and improve the postoperative life quality of patients have drawn highly attention in the field of kidney transplantation. As the commonly clinical used alternative to natural cordyceps sinensis, Bailing capsule has the function of tonifying kidney and strengthening essence.[1] While after kidney transplantation, the etiology and pathogenesis of various complications mainly attribute to the deficiency of kidney, so the clinical usually used the adjuvant therapy. In the meantime, studies have found that the capsule could decrease the occurrence of transplanted renal rejection and improve the function of liver and kidney in the application after renal transplantation[2]. This article collected the clinical study of bailing capsule applied in post-renal transplantation, and used the data for meta-analysis, in order to promote the treatment of bailing capsule transforming from empirical medicine to evidence-based medicine after kidney transplantation. In addition, it could provide the theoretical basis for the application of bailing capsule after kidney transplantation.

Methods

2.1 Literature search

China journal full-text database (CNKI), Chinese science and technology journal full-text database, wanfang database, PubMed, EMBase, Cochrane were comprehensively searched until January, 2019. “Bailing Capsule”, “Bailing Jiaonang”, “Corbrin Capsule”, “CS-C-Q80”, “Kidney transplant”, “Renal transplant” were for the search term. Relevant clinical literature was screened out for research. At the same time, in order to prevent the occurrence of missed detection, we additional check the corresponding article references.

2.2 Inclusion criteria

Research type

Bailing capsule was used for clinical study after kidney transplantation.

Research object

This study was performed on the basis of routine western medicine group added in plus bailing capsule after renal transplantation. The dose of bailing capsule was not limited, and the patient's race, nationality, age and gender were not limited.

Outcome indicators

Serum creatinine (SCr), Blood urea nitrogen (BUN), ALT, AST, acute rejection, etc.

The number of samples in the literature was sufficient, and the comparison of indicators between groups had statistical significance

2.3 exclusion criteria

Experimental research, data and related information were similar or studies with insufficient data for pooling were excluded. Combined application of 2 or more traditional Chinese medicines.

2.4 Data extraction and quality assessment

Two investigators extracted data from all potentially relevant studies independently. The following characteristics were recorded: first author's name, year of publication, ethnicity and number of included patients, number of male and female patients, divided into groups, results of efficacy and safety. Missing data were also examined by contacting the first or corresponding author. Conflicting evaluations were resolved by discussion.

2.5 Methods quality assessment

The quality of the included literature was evaluated with indicators including random sequence generation, allocation hiding, implementation and double blindness of participants, blindness in result evaluation, integrity of result data, selective reporting, and other biases. And the index data were graded (high risk, low risk, unclear).

2.6 Statistical analysis

The latest RevMan5.3 software provided by the Cochrane collaboration was used for meta-analysis. The pooled data were used to assess efficacy and safety by the standard mean difference (SMD) with 95% confidence intervals (95%CIs). $P < 0.05$ was considered statistically significant. Heterogeneity among trials was determined by I2, which was defined as $100\% \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df is the degrees of freedom, using a fixed-effect model set at low statistical inconsistency ($I2 < 50\%$); otherwise, we used a random-effects model, which is better adapted to clinical and statistical variations.

Subgroup analysis should be considered if there was statistical heterogeneity. Subgroup analysis should be conducted from the perspective of clinical medicine to analyze the factors that may cause heterogeneity, so as to explore the sources of heterogeneity as far as possible. The Z test was used to compare whether there was a statistical difference between the experimental group and the control group. The inverted funnel plot was used to test whether there was publication bias.[3]

Results

3.1 Literature search results

A total 143 articles were identified after the comprehensive literature research. 98 duplicates were removed and 45 articles remained. 42 studies were included after reviewing the titles and abstracts, of which 32 were excluded according to exclusion and inclusion criteria. An eventual ten full-text articles were eligible for the quantitative synthesis.[4-13] (Fig. 1)

3.2 Quality evaluation and basic information of included literature

The included studies were published between 1998 and 2016. A total of 1,580 patients participated in the 10 studies, including 990 in the bailing capsule treatment group and 590 in the control group. Among them, 1 document of "liang fangfang 2016" mentioned the use of random number table method, 1 document of "li. Y 2009" mentioned the use of lottery random method, and 3 documents of "Chen wu 2012, Zhang Zhihong 2008, Zhang Zhihong 2011" only mentioned random method, the rest did not list the random scheme. Table 3-1 for the quality evaluation of the included literature, Table 3-2 for the basic information of the included literature.

Table 3-1 Quality evaluation form

Included in the study	Time	Random sequence generation	Allocation concealment	Double blind	Blind method in result evaluation	Data integrity	Selective reporting	Other bias
Liang Fangfang	2016	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear
Wang Wei	2013	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear
Chen Wu	2012	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear
Zhang Zhihong	2011	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear
Ding Chenguang	2009	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear
Li.Y	2009	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear
Zhang Zhihong	2008	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear
He Xueling	2006	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear
Fang Li	1999	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear
Ren Jizhong	1999	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	Unclear

Table3-2 Basic characteristics of eligible studies

Abbreviations: G-CSF, granulocyte colony-stimulating factor; CsA, cyclosporine A; MMF, mycophenolate mofetil; Pred, prednisone; Aza, azathioprine;

Author	Time	Bailing capsule dose (g/day)	course of treatment	Number of cases (control group/test group)	Drug of control group	Drug of test group	Outcome indicators
Liang Fangfang	2016	6.0	Within 2 weeks	48(24/24)	FK506+Hormone+G-CSF+Batyl Alcohol	FK506+Hormone+G-CSF+Batyl Alcohol+Bailing Capsule	Scr、BUN、ALT、AST
Wang Wei	2013	3.6	3 years	180 (100/80)	CsA+MMF+Pred	CsA+MMF+Pred+Bailing	Scr、BUN、ALT、AST
Chen Wu	2012	3.0	6 months	56(26/30)	CsA/FK506+MMF+Pred+Irbesartan	CsA/FK506+MMF+Pred+Irbesartan+Bailing	Scr、BUN
Zhang Zhihong	2011	6.0	6 months	231 (109/122)	CsA+Aza/MMF+Pred	CsA+Aza/MMF+Pred+Bailing	Scr、BUN
Ding Chenguang	2009	3.0	48 weeks	67(42/25)	CsA+MMF/ FK506+Pred	CsA+MMF/FK506+Pred+Bailing	Scr、BUN、ALT、AST、Acute rejection
Li.Y	2009	3.0	1 year	202 (109/93)	CsA+MMF+Pred	CsA+MMF+Pred+Bailing	Scr、BUN、24h Upro、ALT
Zhang Zhihong	2008	6.0	9 months	42(21/21)	CsA/FK506+Aza/MMF+Pred	CsA/FK506+Aza/MMF+Pred+Bailing	Scr、BUN
He xuelin	2006	9.0	12 weeks	51(15/36)	CsA+MMF+Pred	CsA+MMF+Pred+Bailing	Scr、BUN
Fang Li	1999	3.0	3 months	323 (60/263)	CsA+Aza+Pred	CsA+Aza+Pred+Bailing	Acute rejection、Hepatic impairment
Ren Jizhong	1999	3.0	Unclear	380 (100/280)	CsA+Aza+Pred	CsA+Aza+Pred+Bailing	Acute rejection、Hepatic impairment

3.3 Results of meta-analysis

3.3.1 Effect of bailing capsule on serum creatinine level after kidney transplantation

Eight studies reported changes in SCr levels after treatment, and performed the meta-analysis on the SCr levels of bailing capsules after renal transplantation.[4-11] The results showed that there was statistical heterogeneity between the two groups（P < 0.00001，I^2 = 97%） (figure 3-2). The random effects model was used to combine the effect size, and subgroup analysis was considered. The results showed that there was still statistical heterogeneity in the 6.0g/day group（P < 0.00001，I^2 = 99%）. There was no statistical heterogeneity in the 3.0g/day group（P = 0.85，I^2 = 0%）. The dose 3.6g/day, 9.0g/day was only one literature and was meaningless. So it was considered that different doses of oral bailing capsules might be one of the sources of heterogeneity (figure 3-3). It can be considered that bailing capsule treatment group is better than control group in reducing SCr level, and the difference is statistically significant.(WMD= -28.40，95%CI[-45.87，-10.94]，Z= 3.19，P=0.001)(figure 3-2)

3.3.2 Effect of bailing capsule on blood urea nitrogen level after kidney transplantation

Eight studies reported the data of BUN level changes after treatment, conducted the meta-analysis on the BUN levels of bailing capsules after renal transplantation, and adopted WMD for statistical analysis.[4-11] The results showed that there was statistical heterogeneity between the two groups（P = 0.02，I^2 = 57%）(figure 3-4). The random effects model was adopted and subgroup analysis was considered. The results showed that there was no statistical heterogeneity between the 3.0g/day group（P = 0.41，I^2 = 0%） and the 6.0g/day group（P = 0.56，I^2 = 0%）. The dose 3.6g/day, 9.0g/day was only one literature and was meaningless. Thus, it was considered that different doses of oral bailing capsules might be one of the sources of heterogeneity (figure 3-5). It could be considered that bailing capsule treatment group is better than control group in reducing BUN level, the difference had statistical significance. (WMD= -0.72，95%CI[-1.18，-0.25]，Z= 3.02，P=0.003).，Figure 3-4，

3.3.3 Effect of bailing capsule on the level of alanine transaminase after kidney transplantation

Six studies reported changes in ALT levels after treatment.[4,5,8,9,12,13] Two papers ,Ren jizhong 1999 and Fang li 1999, only mentioned the number of liver function changes, so they were not included in the analysis. The data of ALT level changes after the use of Bailing capsule for patients post-renal transplantation of 4 articles were studied for Meta-analysis, and WMD was used for statistical analysis. The results showed that there was statistical heterogeneity between the two groups （P=0.04 ，I^2 = 63%）(figure 3-6). The random effects model was adopted and subgroup analysis was considered. The results showed that there was still statistical heterogeneity between the 3.0g/day group（P = 0.15，I^2 = 52%）. The dose 3.6g/day, 6.0g/day was only one literature and was meaningless(figure 3-7). It could be considered that bailing capsule treatment group is better than the control group in reducing the level of ALT, the difference is statistically significant. (WMD= -6.05，95%CI[-9.26，-2.85]，Z= 3.70，P= 0.0002)，，Figure 3-6，

3.3.4 Effect of bailing capsule on aspartate aminotransferase level after kidney transplantation

Five studies reported changes in AST levels after treatment.[4,5,8,12,13] Two papers ,Ren jizhong 1999 and Fang li 1999, only mentioned the number of liver function changes, so they were not included in the analysis. The data of AST level changes after the use of Bailing capsule for patients post-renal transplantation of 3 articles were studied for Meta-analysis, and WMD was used for statistical analysis. The results showed that there was statistical heterogeneity between the two groups（P< 0.00001 ，I² =94 %）. Subgroup analysis should have been considered. However, the number of included articles were only 3, which were meaningless for subgroup analysis. It could be considered that the treatment group of bailing capsules was better than the control group in reducing the level of AST, and the difference is statistically significant. (WMD= -11.96，95%CI[-19.25，-4.68]，Z= 3.22，P= 0.001)，Figure 3-8）

3.3.5 Effect of bailing capsule on the incidence of acute rejection after kidney transplantation

Three studies reported the incidence of acute rejection after kidney transplantation.[8,12,13] The following three articles of the incidence changes of acute rejection after the use of Bailing capsule for patients post-renal transplantation were meta-analyzed, and OR was used for statistical analysis. The results showed that there was statistical heterogeneity between the two groups（P=0.03 ，I² =70 %）. Subgroup analysis should have been considered, but the number of included literature were only 3, so subgroup analysis was meaningless. It could be concluded that there was no significant difference in the incidence of acute rejection comparing the two groups. (OR= 0.45，95%CI[0.19，1.11]，Z= 1.74，P=0.08)，，Figure 3-9）

3.4. Publication bias analysis

The inverted funnel plot was drawn for the analysis of 6 or more included literature. The inverted funnel plot was used to show whether the results of meta-analysis were affected by publication bias and to check whether they were symmetrical. The influence of bailing capsule treatment on SCr and BUN was shown on (figure 3-10) and (figure 3-11), respectively. Observing the symmetry of inverted funnel plot, it was considered that there might have the problem of publication bias or low methodological quality.

Discussion

Patients with end-stage nephropathy, whether undergoing dialysis or renal transplantation, the duration of the disease from onset to end-stage nephropathy is prolonged. It would be leading to the decline of viscera function eventually if failed to nurse. After kidney transplantation, the etiology can be attributed to long time illness and loss of condition and drug invasion generally, the pathogenesis is kidney deficiency, develop for viscera declining.[1]

The constituents of the bailing capsule mainly include D-mannitol (cordyceps acid), ergosterol, polysaccharide, carrier alkaloids, 18 amino acids, vitamins and trace elements[14,15]. Among them, D-mannitol has the effect of diuretic, dehydration, free radical scavenging, anti-oxidation, antiasthmatic and expectorant. It can treat edema and urinary retention caused by kidney diseases, and can prevent organ and tissue fibrosis. Ergosterol can inhibit the proliferation of mesangial cells, delay renal interstitial and glomerular fibrosis.Nucleosides (alkaloids) has the effect of inhibiting the increase of serum cholesterol and prevent atherosclerosis. Adenosine (one of alkaloids) is the main quality control index, which can regulate renin release, glomerular filtration rate, mesangial and vascular smooth muscle growth. Bailing capsule contains 8 essential amino acids and 10 non-essential amino acids, which can improve glomerular function, prevent glomerular sclerosis, and remove free radicals and antioxidants[16].

3.1 Effect and mechanism of bailing capsule in protecting renal function after kidney transplantation.

How to better protect renal function is the key to success after renal transplantation. Bailing capsule has the function of tonifying kidney and strengthening essence. Firstly, Bailing capsule can dilate renal arteries, increase renal blood flow, and thereby improve glomerular filtration rate, which is conducive to reduce the re-absorption of SCr and BUN by renal tubules[17]. Our study also revealed that Bailing capsule has statistical significance in reducing SCr and BUN. Secondly, Bailing capsule can inhibit renal tubulointerstitial lesion and apoptosis of renal tubular epithelial cells and reduce the destruction of renal tubule tissue, so as to protect the integrity of its structure and function, reduce the damage of renal parenchymal cells, and thus improve renal function[17].

3.2 Effect and mechanism of bailing capsule in protecting liver function after kidney transplantation.

After renal transplantation patients need a lot of oral immunosuppressive drugs, and most of these drugs metabolized through the liver, increase the burden of the liver. Several studies have shown that after the treatment of the preparation of cordyceps sinensis, inflammatory cell of liver infiltration and Hepatocyte necrosis were lighter than the model group. Moreover, the function of kupffer cells enhanced obviously, and the immune complexes deposition in the liver reduced significantly. It illustrated that Bailing capsule as artificial cordyceps preparation may have protective effect on liver cells. The hepatotoxicity of other immunosuppressive drugs can be alleviated by using

bailing capsules in patients after renal transplantation. It could accelerate the harmful material removal, reduce liver cell damage, and promote the recovery of damaged liver cells. Thus the reducing of ALT and AST was reacted on the index. This meta-analysis also illustrated the condition of the lower ALT, AST after renal transplantation.[18]

3.3 Effect and mechanism of bailing capsule on anti-rejection after renal transplantation

There is no unified opinion as to whether bailing capsule is an immunosuppressant or an immunoregulator. Ding Chenguang et al. believed that bailing capsule is more suitable as an immune regulator, which has a two-way regulating effect on the body's immune system[8]. It would not reduce the body's systemic immune defense while suppressed the parenchymal organs selectively. It also has a regulatory effect on humoral immunity, which can increase serum IgG and reduce the incidence of infection. However, our study showed that there was no statistical significance of bailing capsule in alleviating acute rejection after renal transplantation.

3.4 The characteristics and limitations of this study

This meta analysis combined the bailing capsule with conventional western medicine group therapy for patients after renal transplantation, collecting all eligible controlled trials published at home and abroad, expanding the clinical sample size, to obtain further test results, guide clinical medication usage better and more objective, and then provide objective and meaningful theoretical basis for the application of bailing capsule in the treatment of kidney transplantation. The study found that took the capsule combined with conventional western medicine compared with the group using western medicine only was much more effective in protection of the renal and liver function after renal transplantation, but there was no statistical significance in reducing acute rejection. We hope this research can avoid misunderstanding of clinical workers in this respect, at the same time we hope that more scholars conducted mutual discussion and syndrome differentiation.

This study has some limitations, such as the number of the standard literatures included is relatively small, experimental study population is lack, the study time is short In addition, some documents have been published for so long time that the probability of publication bias and the statistical heterogeneity was higher, thus the accuracy of the research results may be affected. If we expanded the sample content, unified the dosage and time, extend the test time, or have more high-quality literatures in recent years, we will get more stable and reliable test results. Therefore, more large-sample, multicenter, high-quality studies should be conducted in the future to guide clinical treatment better.

Abbreviations

China journal full-text database (CNKI)

Serum creatinine (SCr)

Blood urea nitrogen (BUN)

Alanine transaminase (ALT)

Aspartate aminotransferase (AST)

Standard mean difference (SMD)

Granulocyte colony-stimulating factor (G-CSF)

Cyclosporine A (CsA)

Mycophenolate mofetil (MMF)

Prednisone (Pred)

Azathioprine (Aza)

Declarations

The authors declared that there was no conflict interest exsited.

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Figures

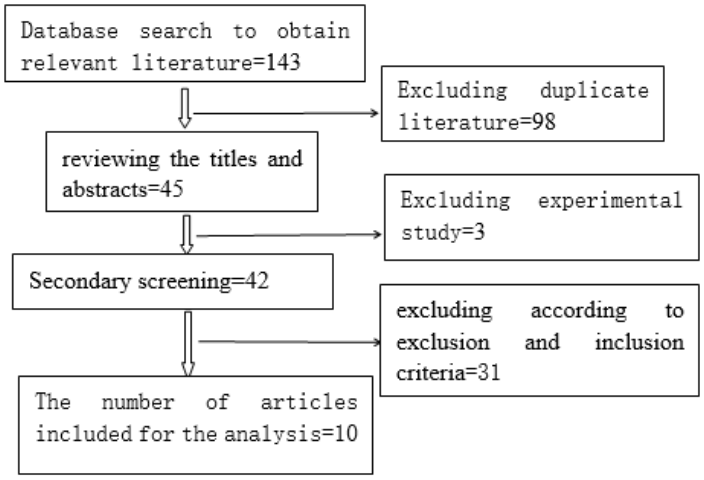

Figure 1

Literature screening flow chart

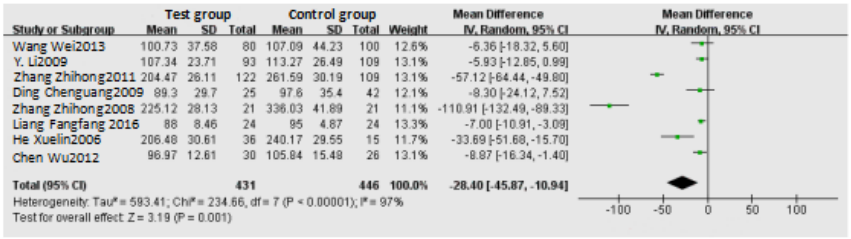

Figure 2

SCr forest graph

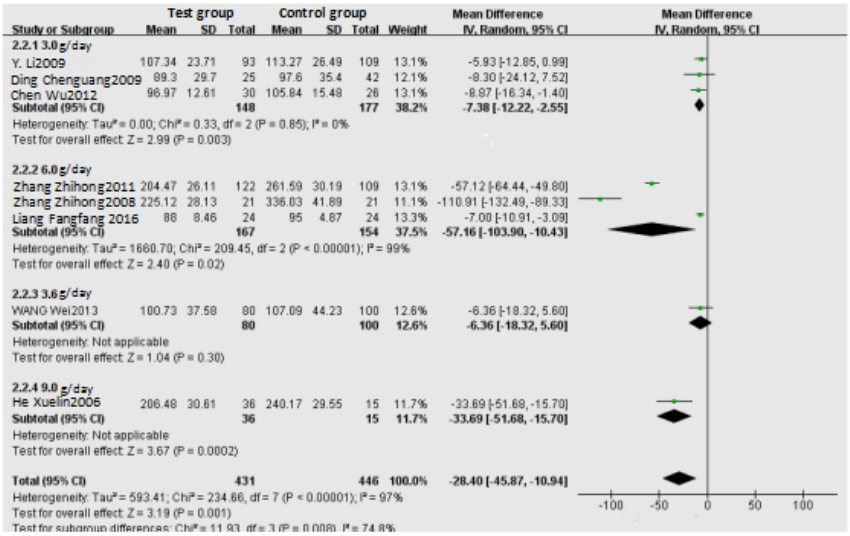

Figure 3

SCr subgroups analysis of different dose of bailing capsule

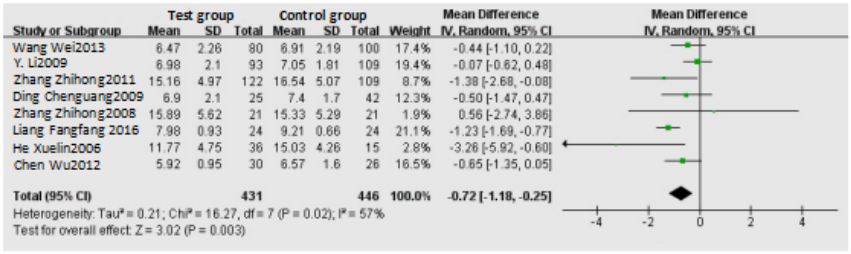

Figure 4

BUN Forest graph

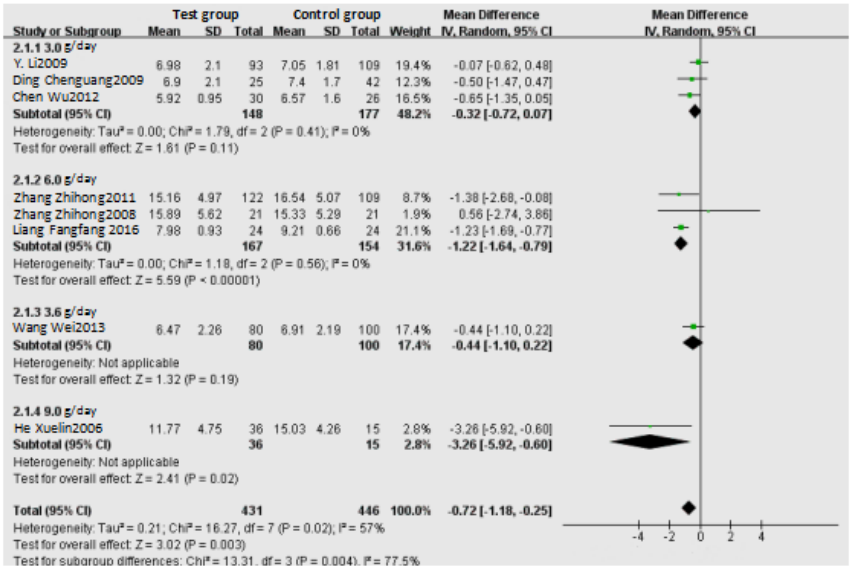

Figure 5

BUN subgroups analysis of different dose of bailing capsule

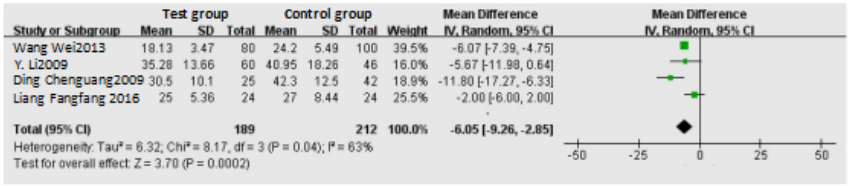

Figure 6

ALT Forest graph

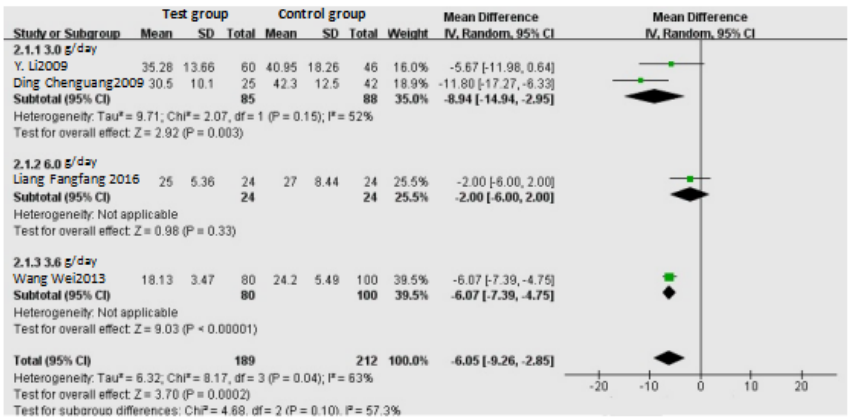

Figure 7

LT subgroups analysis of different dose of bailing capsule

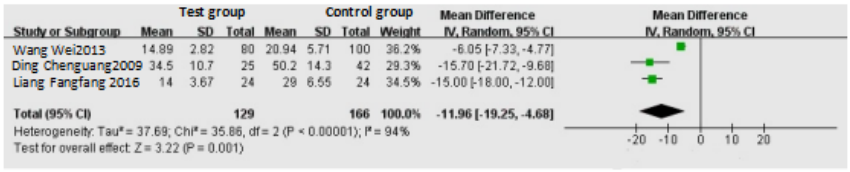

Figure 8

AST Forest graph

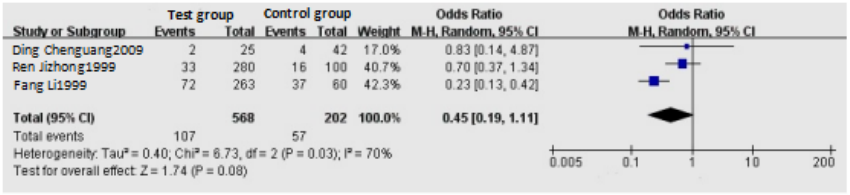

Figure 9

acute rejection Forest graph

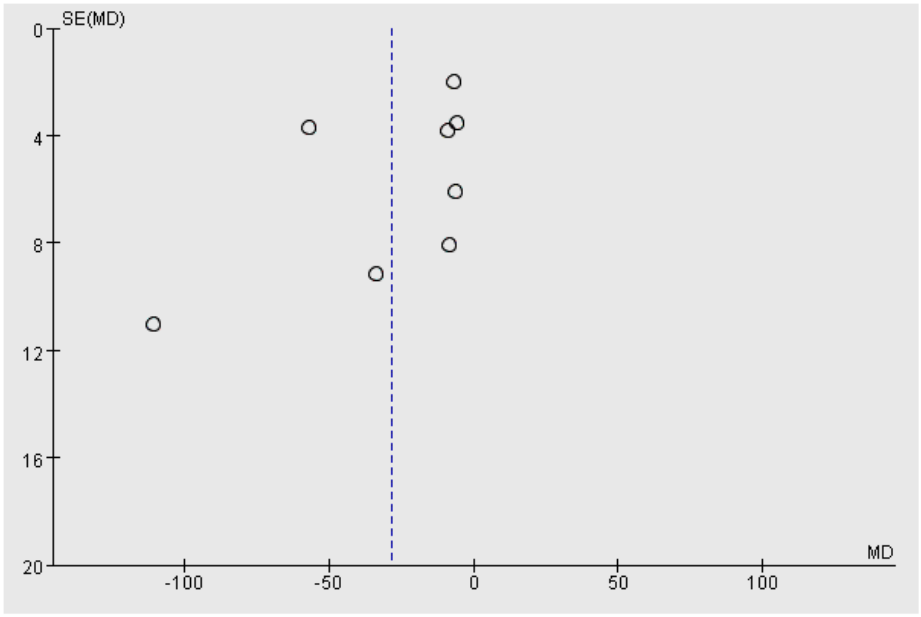

Figure 10

SCr inverted funnel plot

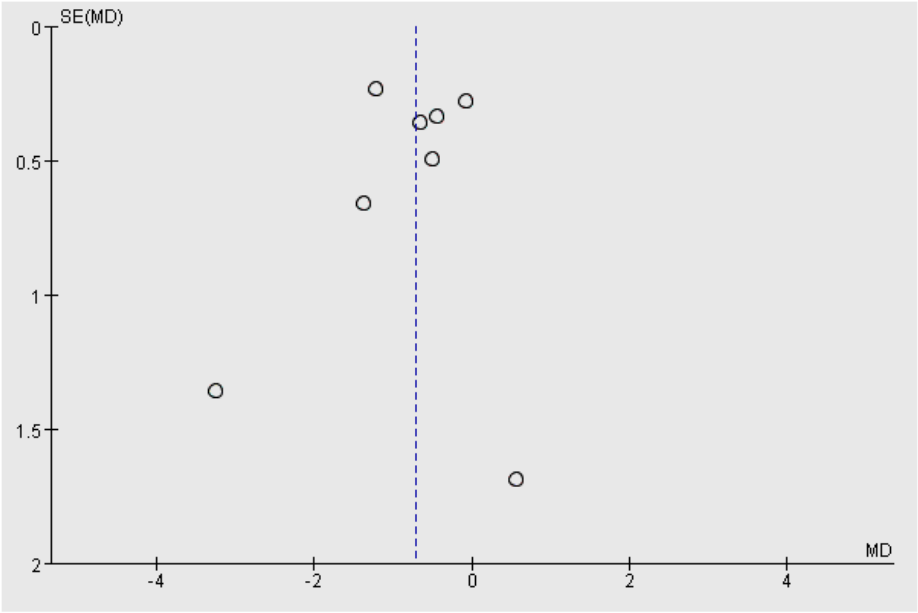

Figure 11

BUN inverted funnel plot

Supplementary Files

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