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Meta-Analysis on Safety of Dapagliflozin in Patients with Type 2 Diabetes Mellitus

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Abstract

Objective: To evaluate the safety of dapagliflozin for Type 2 Diabetes Mellitus (T2DM). **Methods:** A systematic search of Pubmed, Embase, Cochrane Library, Web of Science, CNKI, Wanfang Data and VIP database for randomized controlled trials (RCTs) comparing dapagliflozin with placebo was performed up to February 2018. The index words included dapagliflozin, type 2 diabetes mellitus and randomized controlled trial. **Results:** A total of 19 RCTs involving 7704 participants were incorporated into the study. Compared with placebo, dapagliflozin did not increase the risk of hypoglycemia [OR = 1.14, 95%CI (0.95, 1.36), P = 0.17] and hypotension [OR = 1.43, 95%CI (0.94, 2.17), P = 0.10], but significantly increased the incidences of renal adverse events [OR = 1.57, 95%CI (1.17, 2.09), P = 0.002], genital tract infection [OR = 3.65, 95%CI (2.93, 4.56), P < 0.00001] and urinary tract infection [OR = 1.36, 95%CI (1.15, 1.61), P = 0.0004] and related doses. **Conclusions:** Generally, dapagliflozin had no risk of hypoglycemia and hypotension in patients with T2DM, but there were risks of renal adverse events and urogenital tract infection. Due to the limitations of this study, larger samples and RCTs with long-term follow-up are needed for further verification.

Keywords

Dapagliflozin, Type 2 Diabetes Mellitus, Randomized Controlled Trial, Meta-Analysis

1. Introduction

As a common disease in China, the incidence of T2DM has been increasing year by year, and drug therapy is the main method of treatment. Sodium glucose co-transporter 2 (SGLT-2), as the most important glucose transporter in the kidney, is responsible for the reabsorption of 90% glucose in the kidney [1]. The

SGLT-2 inhibitor, dapagliflozin is a novel oral hypoglycemic drug for the treatment of T2DM, which is independent from islet β -cell function and insulin sensitivity. It functions by increasing renal clearance of glucose, attenuating renal reabsorption of glucose and excreting excess glucose from the urine, thereby reducing blood glucose [2]. Studies have shown that dapagliflozin has multiple benefits such as reduction in blood glucose, weight and blood pressure. However, there is also risk for urogenital tract infections [3]. In this study, the safety is further analyzed by retrieving RCTs of dapagliflozin versus placebo through meta-analysis.

2. Data and Methods

2.1. Criteria for Inclusion and Exclusion of Literature

Inclusion criteria:

- 1) Research type: Included in the study were clinical RCTs of different doses of dapagliflozin versus placebo in the treatment of T2DM officially published before February 2018; full text is available; languages are limited to Chinese and English.
- 2) Research object: Age > 18 years, in accordance with the diagnostic criteria for T2DM (WHO Committee of Experts on Diabetes 1999 diagnosis and classification criteria), in accordance with the dapagliflozin guidelines.
- 3) Interventions: The experimental group was treated with dapagliflozin alone, regardless of dose size; placebo in the control group; or on the basis of other similar interventions.

Exclusion criteria:

Treatment observation time < 12 weeks, type 1 and special types of diabetes, review, non-RCT and so on.

2.2. Evaluation Index

Safety related indicators: hypoglycemia events, hypotension events, adverse renal reactions, genital tract infections, urinary tract infections.

2.3. Search Strategy

The search strategy follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [4]. Relevant studies for the analysis were selected by searching PubMed, Embase, Cochrance Library, Web of Science, CNKI, Wanfang Data and VIP database up to the end of February 2018. Taking Pubmed database as an example, subject words and free words are combined to search, and the retrieval scheme is as follows: #1 AND #2 AND #3.

#1 ((dapagliflozin) OR forxiga). #2 (((((((((((((((((((((((((((((((Diabetes Mellitus, Noninsulin-Dependent) OR Diabetes Mellitus, Ketosis-Resistant) OR Diabetes Mellitus, Ketosis Resistant) OR Ketosis-Resistant Diabetes Mellitus) OR Diabetes Mellitus, Non Insulin Dependent) OR Diabetes Mellitus, Non-Insulin-Dependent) OR Non-Insulin-Dependent Diabetes Mellitus) OR Diabetes Mellitus, Stable)

OR Stable Diabetes Mellitus) OR Diabetes Mellitus, Type II) OR NIDDM) OR Diabetes Mellitus, Noninsulin Dependent) OR Diabetes Mellitus, Maturity-Onset) OR Diabetes Mellitus, Maturity Onset) OR Maturity-Onset Diabetes Mellitus) OR Maturity Onset Diabetes Mellitus) OR MODY) OR Diabetes Mellitus, Slow-Onset) OR Diabetes Mellitus, Slow Onset) OR Slow-Onset Diabetes Mellitus) OR Type 2 Diabetes Mellitus) OR Noninsulin-Dependent Diabetes Mellitus) OR Noninsulin Dependent Diabetes Mellitus) OR Maturity-Onset Diabetes) OR Diabetes, Maturity-Onset) OR Maturity Onset Diabetes) OR Type 2 Diabetes) OR Diabetes, Type 2) OR Diabetes Mellitus, Adult-Onset) OR Adult-Onset Diabetes Mellitus) OR Diabetes Mellitus, Adult Onset). #3 (((randomized controlled trial) OR randomized) OR placebo).

2.4. Data Extraction

Data were independently abstracted by the two principal reviewers and any discrepancies were resolved by consensus. The data extracted included title, author, and year of publication, country, intervention measures, sample size, patient age, treatment time, main outcome indicators and intentionality analysis.

2.5. Quality Assessment

Jadad scoring criteria were used [5], including 4 items: random method, assignment concealment, blind method and withdrawal. The RCT score was 1 - 7, 1 - 3 as low quality and 4 - 7 as high quality.

2.6. Data Analysis

Outcomes were pooled using Review Manager 5.3 software. Dichotomous data were presented as odds ratio (OR) or risk ratio (RR). All results were estimated from each study with 95% confidence intervals (CIs). Heterogeneity was assessed using the I^2 statistic. If $P > 0.1$, $I^2 < 50\%$, a fixed-effect model with the Mantel-Haenszel method was used; otherwise, the random-effect model was adopted. Subgroup analysis was performed according to the different doses of dapagliflozin (1 mg, 2.5 mg, 5 mg, 10 mg and 20 mg). Funnel plot was adopted to evaluate the publication bias. The bilaterally symmetric graph indicates a low risk of publication bias. Otherwise, the risk of publication bias may exist.

3. Results

3.1. The Basic Characteristics and Process of Inclusion Study

A total of 19 RCTs involving 7704 participants was incorporated into the study, including 5304 cases of dapagliflozin group and 2400 cases of the placebo group. All 19 RCTs were performed from 2009 to 2016, and the follow-up duration was ≥ 12 weeks. Baseline data for both groups were described in all trials, and there was no statistical difference in general between the dapagliflozin and placebo groups before treatment ($P > 0.05$). The screening process is displayed in **Figure 1**. The basic information contained in the study is shown in **Table 1**.

Table 1. Basic information on the inclusion of the study.

	Year	Country	Interventions	Include number	Age (year)	Treatment time (week)	Key outcome indicators	Intentional analysis	Radad-score
List JF	2009	U.S.A	dapagliflozin (2.5, 5, 10, 20, 50 mg) vs. placebo vs. Metformin (750 mg - 1500 mg)	389	18 - 79	12	HbA1C, FPG, BW (body weight)	YES	4
Bailey CJ	2010	UK	dapagliflozin (2.5, 5, 10 mg) + Metformin (1500 mg) vs. placebo + Metformin (1500 mg)	546	18 - 77	24	HbA1C	YES	7
Ferrannini E	2010 (1) (2)	Italy	dapagliflozin (2.5, 5, 10 mg) vs. placebo	485	18 - 77	24	HbA1C	YES	4
Bolinder J	2012	Sweden	dapagliflozin (10 mg) + Metformin vs. placebo + Metformin	182	30 - 75	24	BW, Waist circumference, Body fat	YES	7
Strojek K	2011	Poland	dapagliflozin (2.5, 5, 10 mg) + Glimepiride (4 mg) vs. placebo + Glimepiride (4 mg)	597	≥18	24	HbA1C	YES	7
Bailey CJ	2012	UK	dapagliflozin (1, 2.5, 5 mg) vs. placebo	282	18 - 77	24	HbA1C	YES	7
Rosenstock J	2012	U.S.A	dapagliflozin (5, 10 mg) + Pioglitazone (30 mg) vs. placebo + Pioglitazone (30 mg)	420	≥18	24	HbA1C	YES	4
Wilding JP	2013	UK	dapagliflozin (2.5, 5, 10 mg) + insulin ± OAD vs. placebo + insulin ± OAD	808	18 - 80	48	HbA1C	YES	7
Kaku K	2013	Japan	dapagliflozin (1, 2.5, 5, 10 mg) vs. placebo	279	18 - 79	12	HbA1C	YES	7
Bailey CJ	2013	UK	dapagliflozin (2.5, 5, 10 mg) + Metformin (≥1500 mg) vs. placebo + Metformin (≥1500 mg)	546	18 - 77	102	HbA1C, FPG, BW	YES	7
Bolinder J	2014	Sweden	dapagliflozin (10 mg) + Metformin vs. placebo + Metformin	182	60.7	102	HbA1C, BW, Waist circumference, Body fat	YES	7
Ji L	2014	China	dapagliflozin (5, 10 mg) vs. placebo	393	≥18	24	HbA1C	YES	7
Kaku K	2014	Japan	dapagliflozin (5, 10 mg) vs. placebo	261	≥20	24	HbA1C	YES	4
Schumm-Draeger PM	2015	Germany	dapagliflozin (2.5, 5, 10 mg) + Metformin (≥1500 mg) vs. placebo + Metformin (≥1500 mg)	400	18 - 77	16	HbA1C	YES	7
Matthaei S	2015	Germany	dapagliflozin (10 mg) + Metformin + Sulfonylureas vs. placebo + Metformin + Sulfonylureas	218	≥18	24	HbA1C, FPG	YES	7
Cefalu WT	2015	Canada	dapagliflozin (10 mg) vs. placebo	922	-	52	HbA1C	YES	4
Wilding JP	2009	UK	dapagliflozin (10, 20 mg) + insulin vs. placebo + insulin	71	18-75	12	HbA1C	YES	4
Bailey CJ	2015	UK	dapagliflozin (2.5, 5, 10 mg) vs. placebo	274	18 - 77	102	HbA1C, FPG, BW	YES	7
Weber MA	2016	U.S.A	dapagliflozin (10 mg) vs. placebo	449	48.5 - 64	12	HbA1C, SBP	YES	7

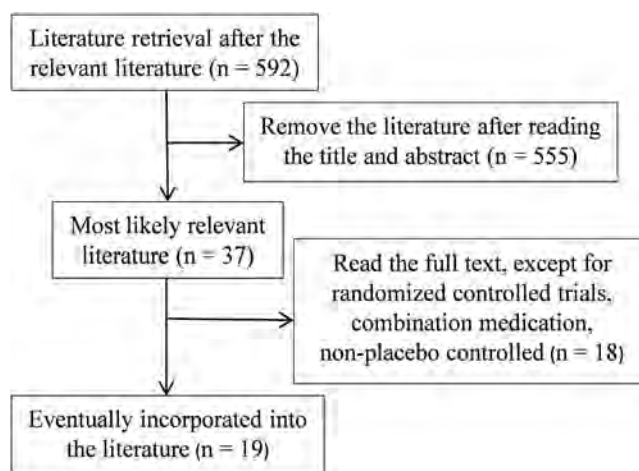


Figure 1. Screening flow chart for inclusion studies.

3.2. Risk Assessment of Bias Included in the Study

Two reviewers independently applied the Cochrane Risk of Bias tool to assess the risk of bias in the RCTs. The following methodological features relevant to the minimization of bias were assessed: randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The following judgments were used: low risk, high risk, or unclear risk (either lack of information or uncertainty regarding the potential for bias). The bias risk assessment is shown in **Figure 2**.

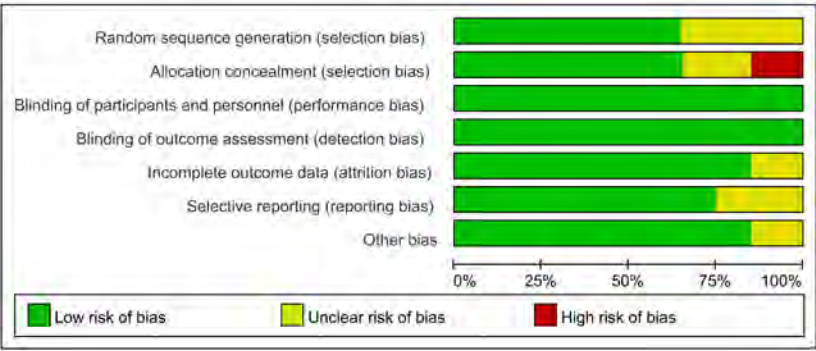
4. Results of Meta-Analysis

4.1. Hypoglycemia Event

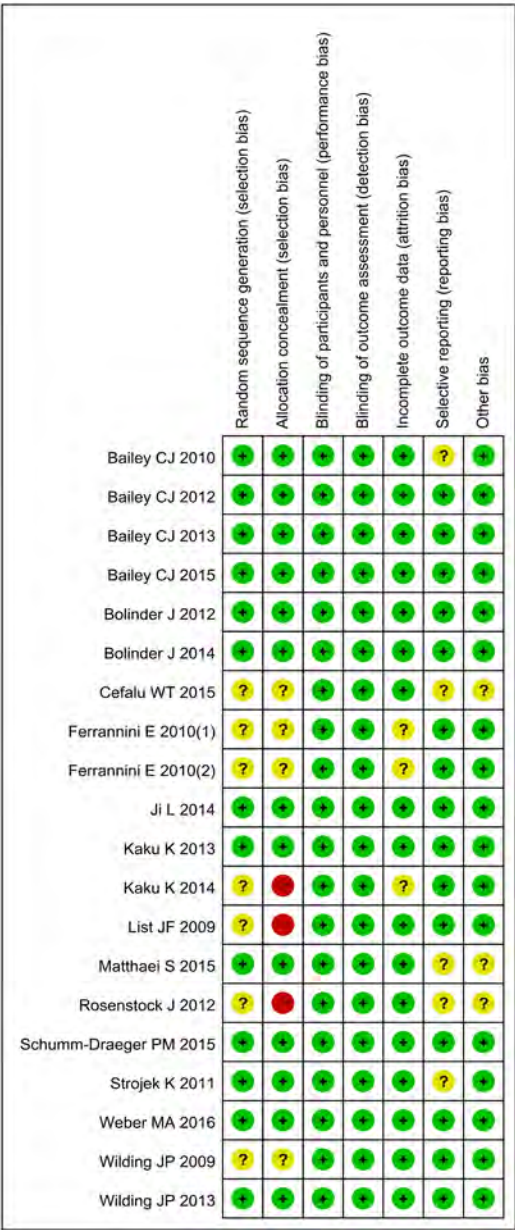
A total of 19 studies were implemented [3] [6]-[23] to compare hypoglycemia events. Heterogeneity was detected in study subgroups (2.5 mg, 5 mg, 10 mg, 20 mg), indicating that there was no statistically significant heterogeneity ($I^2 = 0\%$, $P = 0.96$), ($I^2 = 0\%$, $P = 0.67$), ($I^2 = 0\%$, $P = 0.70$), ($I^2 = 0\%$, $P = 0.89$) between studies included in the analysis (**Figure 3**). Therefore, the M-H fixation effect model was used for meta-analysis. Funnel plot of publication bias evaluation is presented in **Figure 4**. There was no risk of publication bias among subgroups in the study. No significant differences were observed in the comparison results of dapagliflozin with placebo in the incidence of hypoglycemia event [OR = 1.14, 95%CI (0.95, 1.36), $P = 0.17$], as shown in **Figure 3**.

4.2. Hypotension Event

A total of 13 studies were implemented [6]-[11] [13] [15] [16] [18] [19] [20] [22] to compare hypotension events. Heterogeneity was detected in the study subgroups (2.5 mg, 5 mg, 10 mg), indicating that there was no statistically significant heterogeneity ($I^2 = 0\%$, $P = 0.60$), ($I^2 = 0\%$, $P = 0.85$), ($I^2 = 0\%$, $P = 0.79$) between studies included in the analysis (**Figure 5**). Therefore, the M-H fixation



(a)



(b)

Figure 2. Bias risk assessment charts.

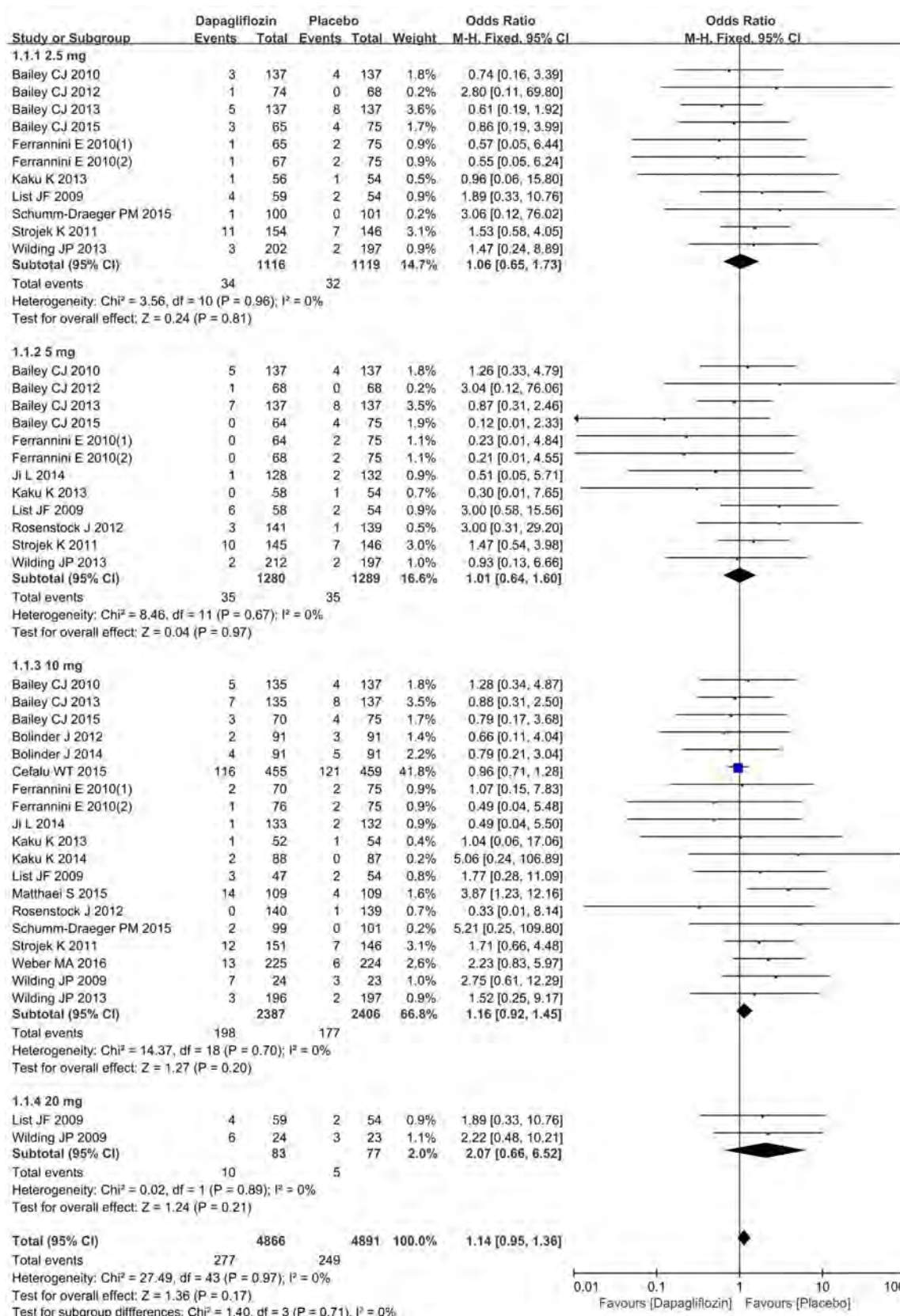


Figure 3. Comparison of dapagliflozin versus placebo for hypoglycaemic events in patients with T2DM in different dose subgroups.

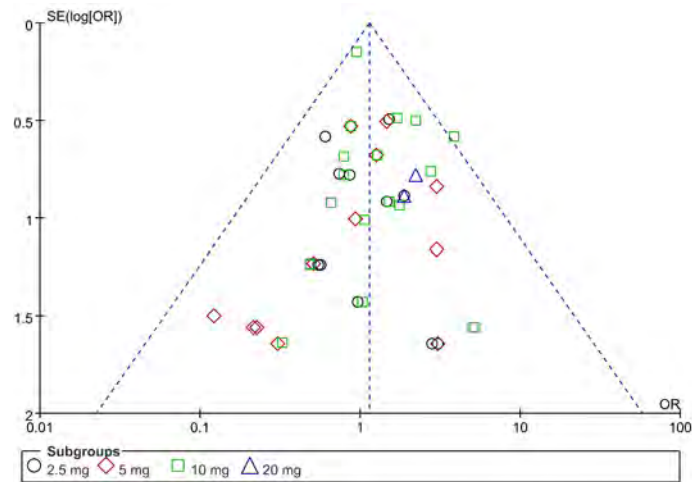


Figure 4. Funnel plot for publication bias evaluation of dapagliflozin versus placebo for hypoglycemia events in patients with T2DM in different dose subgroups.

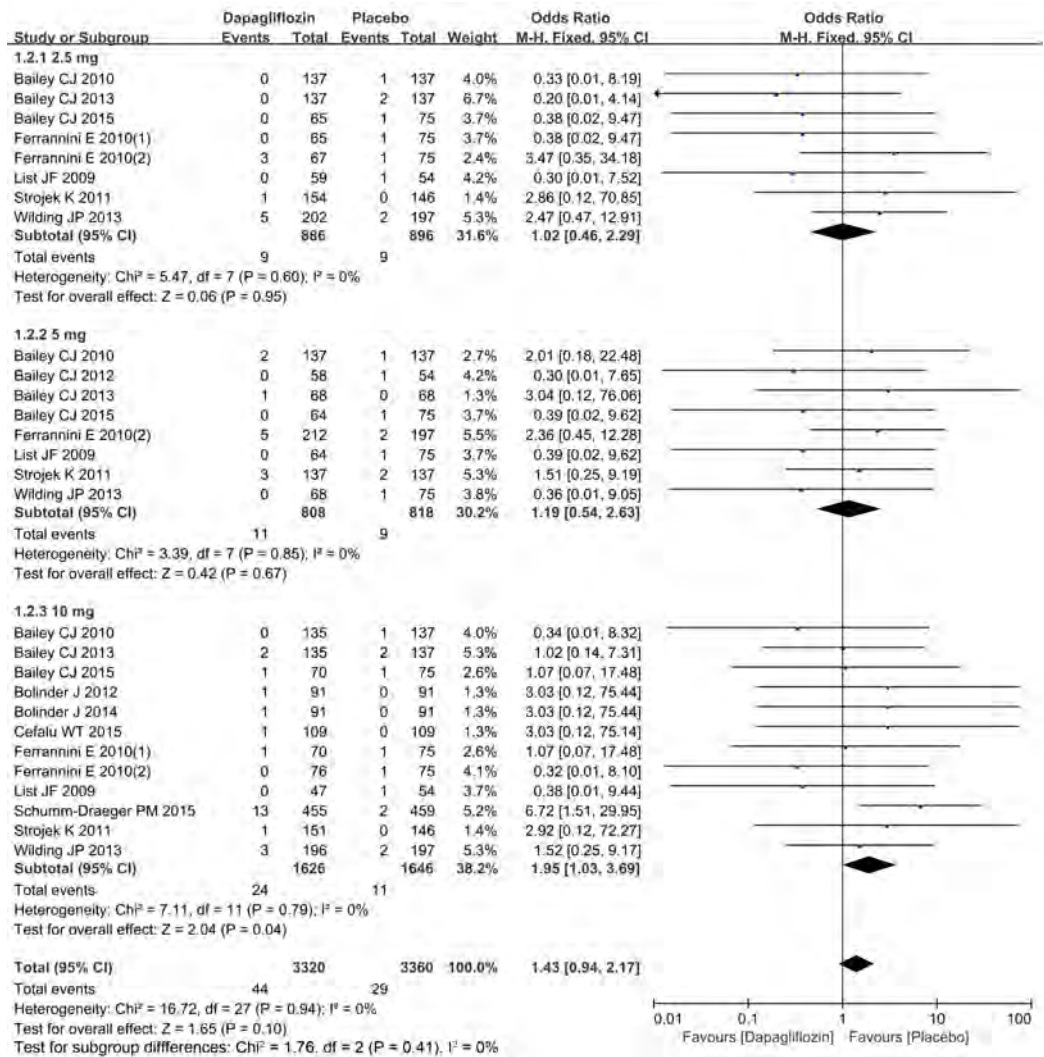


Figure 5. Comparison of dapagliflozin versus placebo for hypotension events in patients with T2DM in different dose subgroups.

effect model was used for meta-analysis. Funnel plot of publication bias evaluation is presented in **Figure 6**. There was no risk of publication bias among subgroups in the study. No significant differences were observed in the comparison results of dapagliflozin with placebo in the incidence of hypotension event [OR = 1.43, 95%CI (0.94, 2.17), $P = 0.10$], as shown in **Figure 5**.

4.3. Renal Adverse Event

A total of 13 studies were implemented [3] [9] [10] [12] [13] [15]-[20] [22] [23] to compare renal adverse events. Heterogeneity was detected in study subgroups (2.5 mg, 5 mg, 10 mg), indicating that there was no statistically significant heterogeneity ($I^2 = 0\%$, $P = 0.42$), ($I^2 = 0\%$, $P = 0.85$), ($I^2 = 0\%$, $P = 0.89$) between studies included in the analysis (**Figure 7**). Therefore, the M-H fixation effect model was used for meta-analysis. Funnel plot of publication bias evaluation is presented in **Figure 8**. There was no risk of publication bias among subgroups in the study. Compared with placebo, dapagliflozin (10 mg subgroup) significantly increased the incidences of renal adverse events [OR = 1.57, 95%CI (1.17, 2.09), $P = 0.002$], as shown in **Figure 7**.

4.4. Genital Tract Infections

A total of 19 studies were implemented [3] [6]-[23] to compare genital tract infections. Heterogeneity was detected in the study subgroups (2.5 mg, 5 mg, 10 mg, 20 mg), indicating that there was no statistically significant heterogeneity ($I^2 = 0\%$, $P = 0.81$), ($I^2 = 0\%$, $P = 0.98$), ($I^2 = 0\%$, $P = 0.64$), ($I^2 = 0\%$, $P = 0.82$) between studies included in the analysis (**Figure 9**). Therefore, the M-H fixation effect model was used for meta-analysis. Funnel plot of publication bias evaluation is presented in **Figure 10**. There was no risk of publication bias among

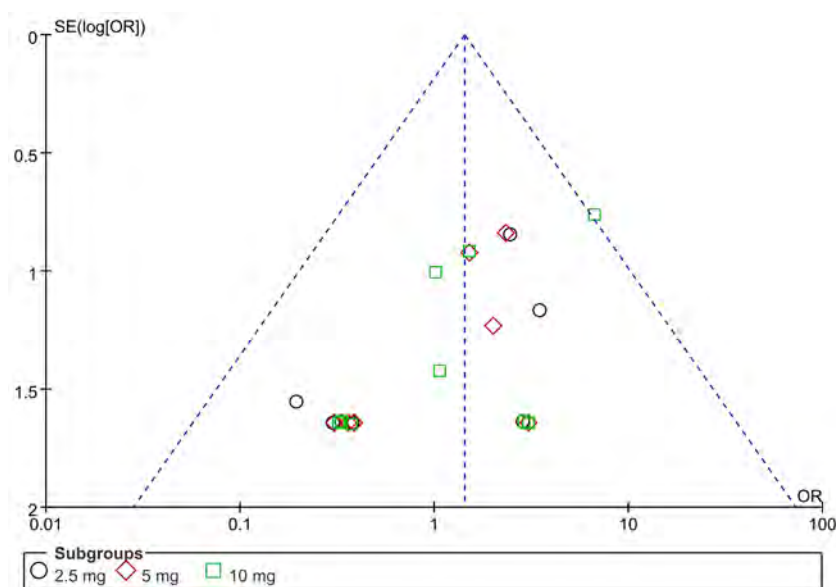


Figure 6. Funnel plot for publication bias evaluation of dapagliflozin versus placebo for hypotension events in patients with T2DM in different dose subgroups.

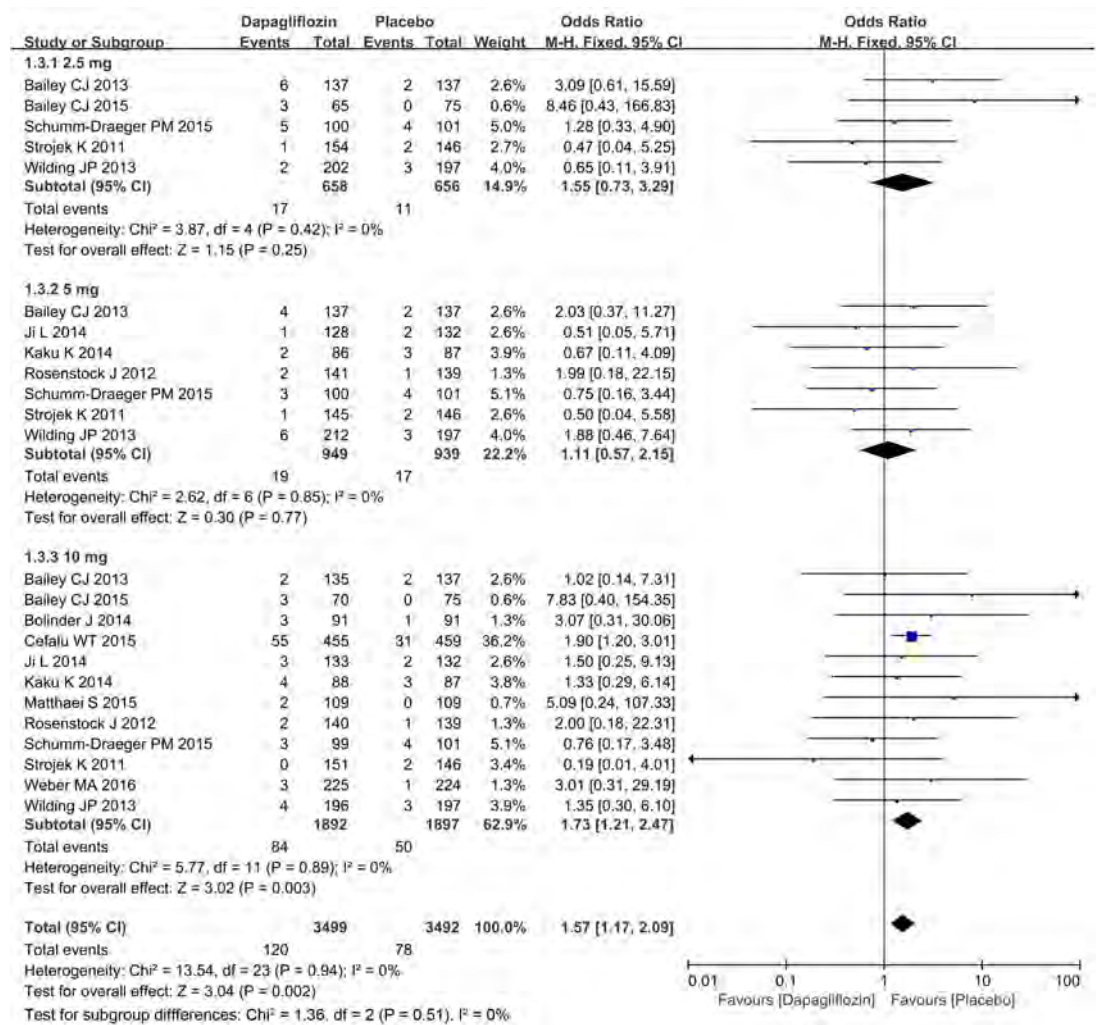


Figure 7. Comparison of dapagliflozin versus placebo for renal adverse events in patients with T2DM in different dose subgroups.

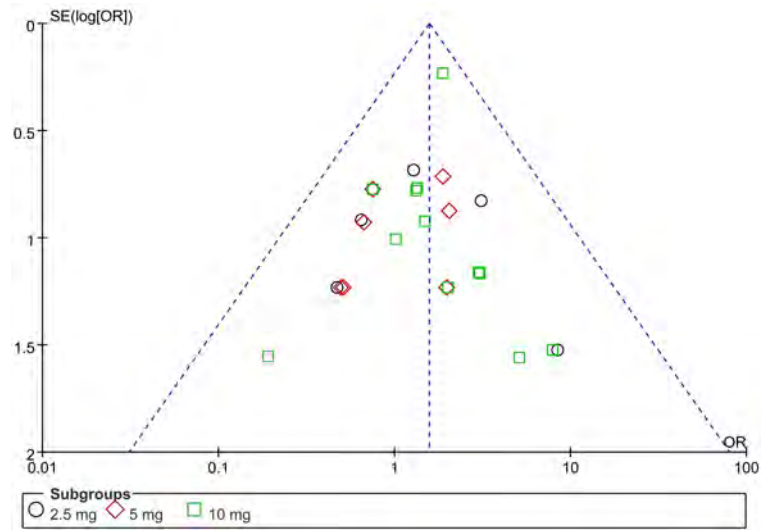


Figure 8. Funnel plot for publication bias evaluation of dapagliflozin versus placebo for renal adverse events in patients with T2DM in different dose subgroups.

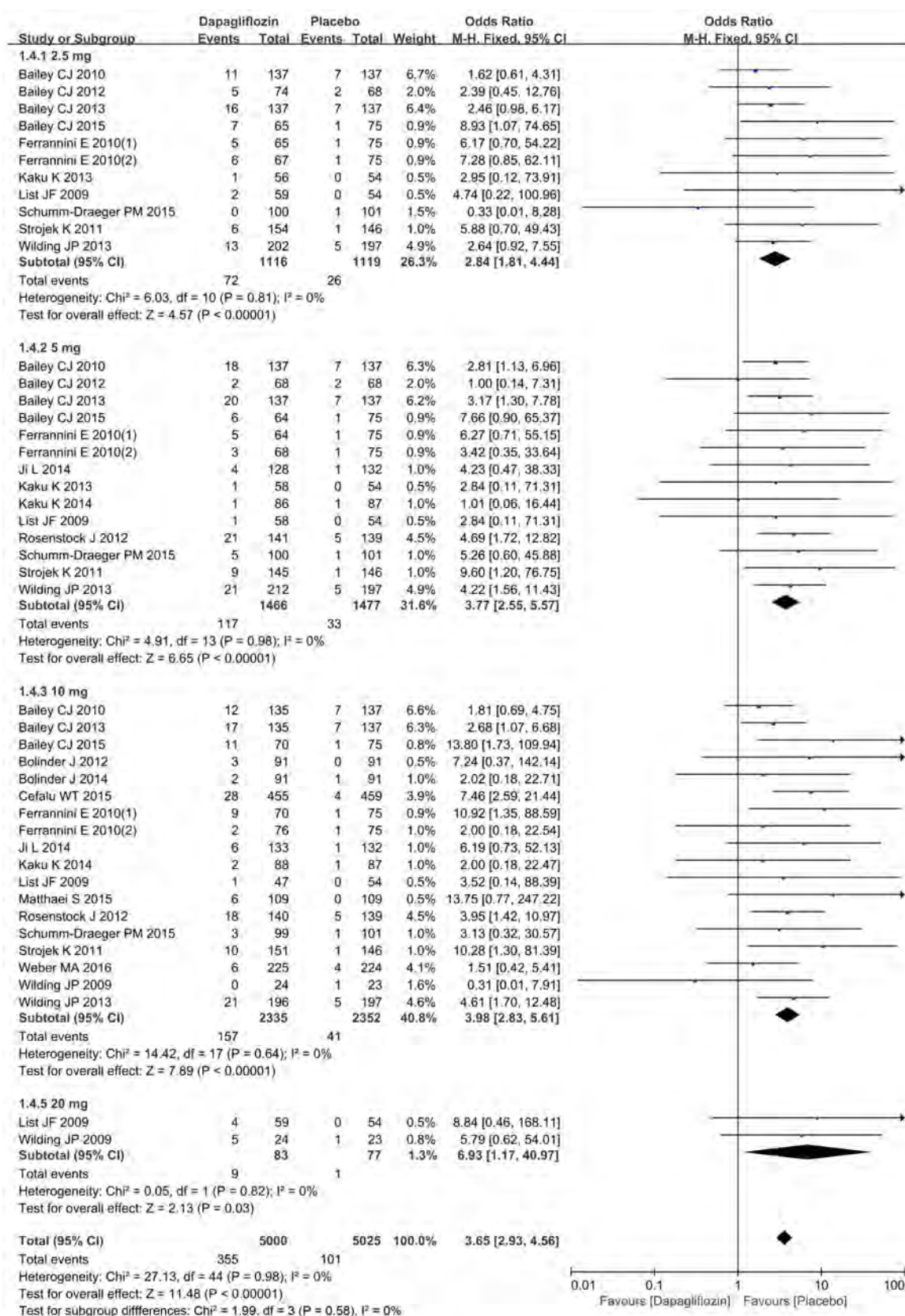


Figure 9. Comparison of dapagliflozin versus placebo for genital tract infections in patients with T2DM in different dose subgroups.

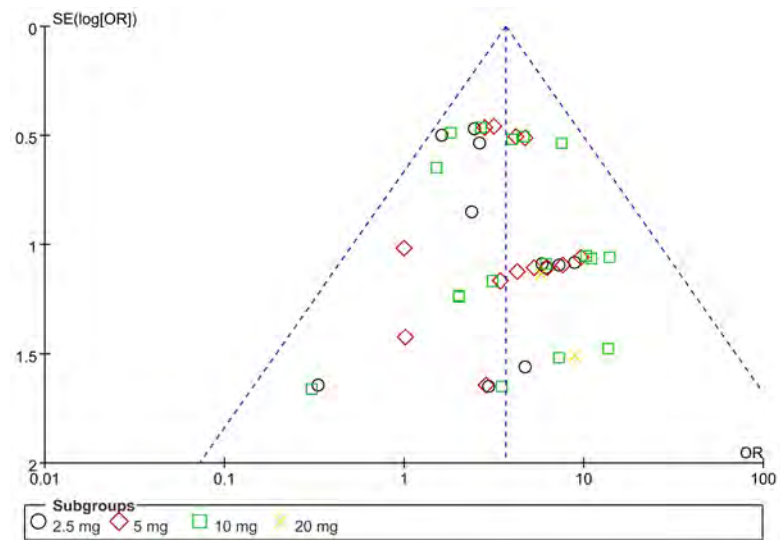


Figure 10. Funnel plot for publication bias evaluation of dapagliflozin versus placebo for genital tract infections in patients with T2DM in different dose subgroups.

subgroups in the study. Compared with placebo, dapagliflozin (2.5 mg, 5 mg, 10 mg, 20 mg subgroup) significantly increased the incidences of genital tract infections [OR = 3.65, 95%CI (2.93, 4.56), $P < 0.00001$], as shown in **Figure 9**.

4.5. Urinary Tract Infections

A total of 19 studies were included [3] [6]-[23] to compare urinary tract infections. Heterogeneity was detected in the study subgroups (1 mg, 2.5 mg, 5 mg, 10 mg, 20 mg), indicating that there was no statistically significant heterogeneity ($I^2 = 0\%$, $P = 0.53$), ($I^2 = 0\%$, $P = 0.86$), ($I^2 = 0\%$, $P = 0.77$), ($I^2 = 0\%$, $P = 0.97$), ($I^2 = 0\%$, $P = 0.88$) between studies included in the analysis (**Figure 11**). Therefore, the M-H fixation effect model was used for meta-analysis. Funnel plot of publication bias evaluation is presented in **Figure 12**. There was no risk of publication bias among subgroups in the study. Compared with placebo, dapagliflozin (5 mg, 10 mg subgroup) significantly increased the incidences of urinary tract infections [OR = 1.36, 95%CI (1.15, 1.61), $P = 0.0004$], as shown in **Figure 11**.

5. Discussion

The meta-analysis suggests that dapagliflozin had no difference in the risk of hypoglycemia and hypotension events compared with placebo, and was safer than sulfonylurea, insulin and other hypoglycemic agents with a higher risk of hypoglycemia. Studies have illustrated that Chinese adults with type 2 diabetes were more complicated due to hypertension and other cardiovascular risk factors [24]. Dapagliflozin can reduce blood glucose while reducing blood pressure and weight [25] [26], improve oxidative stress and endothelial function and reduce arteriosclerosis [27] [28], with potential cardiovascular benefits [29]. Multiple studies on the effects of renal function proved that the eGFR and urinary albumin-creatinine ratio were not significantly changed in the dapagliflozin

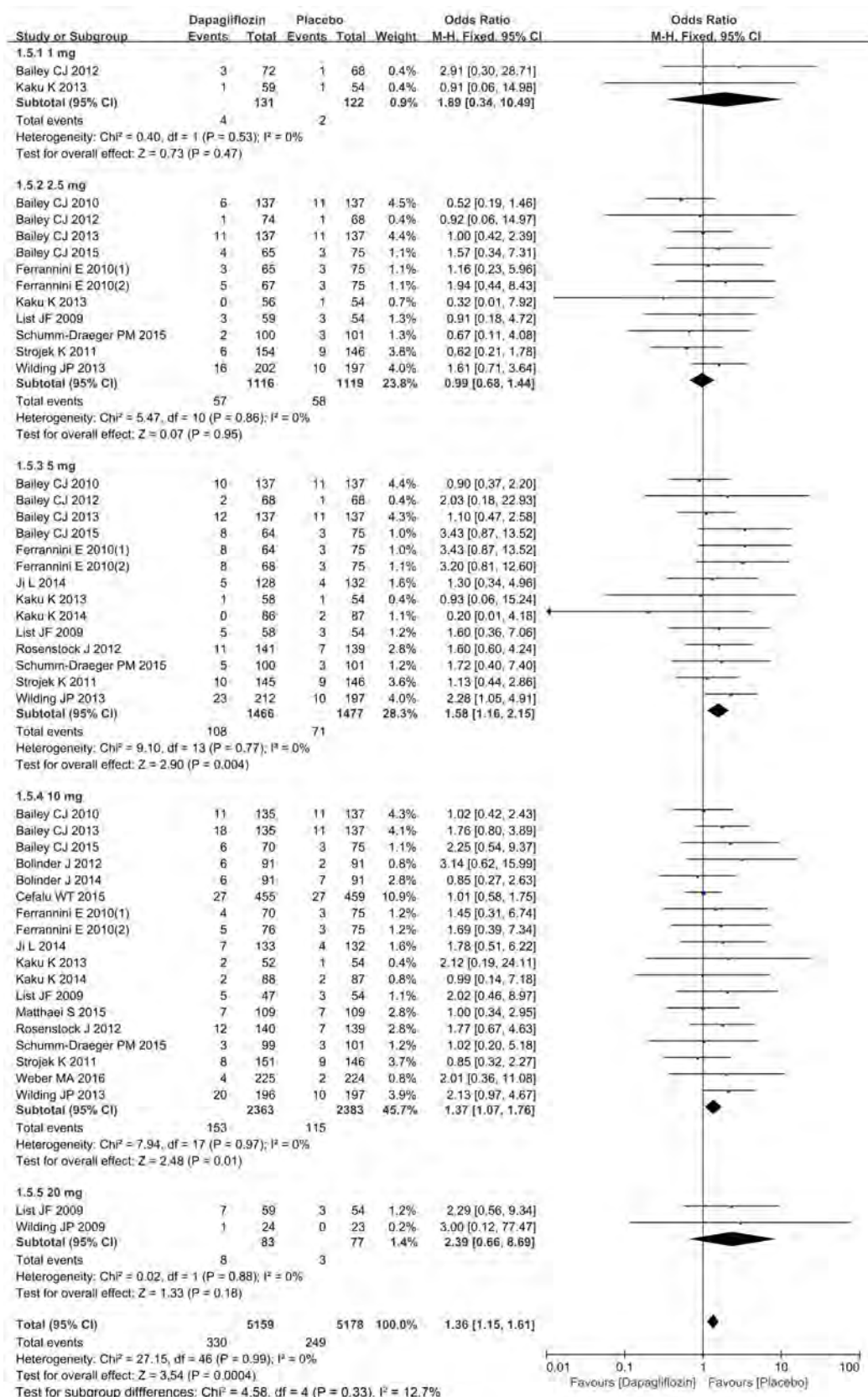


Figure 11. Comparison of dapagliflozin versus placebo for urinary tract infections in patients with T2DM in different dose subgroups.

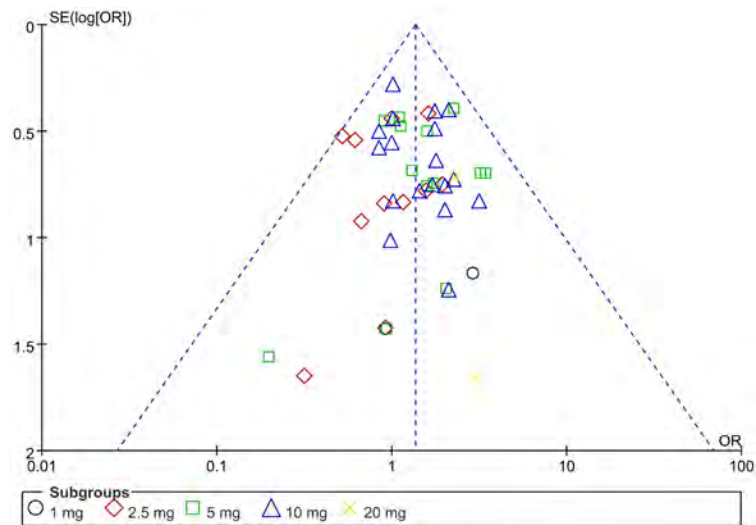


Figure 12. Funnel plot for publication bias evaluation of dapagliflozin versus placebo for urinary tract infections in patients with T2DM in different dose subgroups.

treatment group by contrast with the placebo group in patients with T2DM [30] [31] [32]. The higher risk of renal adverse events than placebo was associated primarily with the study by Cefalu WT *et al.*, which involved a population with a history of type 2 diabetes mellitus associated with pre-cardiovascular disease, hypertension. They defined renal adverse events as renal damage, acute renal failure, decreased creatinine clearance, increased serum creatinine, and decreased glomerular filtration rate, renal dysfunction and other serological indicators. For patients with stage 3 CKD or greater, dapagliflozin either requires dose adjustment or is contraindicated [33].

The 19 trials involved in this study are qualified English literature, all of which are single-center or multi-center studies with high methodological quality. There is no significant publication bias in all the literature, so the conclusions are reliable. However, a variety of factors such as the inclusion of subjects, patients with type 2 diabetes, disease severity, duration of illness, combination of other diseases with dapagliflozin dose and medication time may increase the clinical heterogeneity of the study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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A Nursing Case Report: The Laryngectomy Patient Secondary to *Pseudomonas aeruginosa* Pneumonia with Conscious Disturbance

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Abstract

The paper presents a description of the experience of the nursing for the *Pseudomonas aeruginosa* pneumonia patient with partial laryngectomy. The nursing of *Pseudomonas aeruginosa* pneumonia, conscious disturbance, electrolyte disorder, affection supports and mental nursing was provided in the process of the postoperative treatment. Our experience may provide useful insight for the nursing of laryngectomy patients secondary to pneumonia with conscious disturbance. A deeper knowledge about improving the quality of clinic special nursing for the partial or total laryngectomy patient is necessary, with the development of modern medical technologies and medicine.

Keywords

Laryngeal Carcinoma, *Pseudomonas aeruginosa*, Pneumonia, Conscious Disturbance, Nursing

1. Introduction

Laryngeal cancer (LC) is one of the most frequently diagnosed head and neck malignancies, causing 83 thousand deaths worldwide each year. In 2012, the highest age-standardized incidence rate of LC in Asia area was 6.3 per 100 thousand persons, respectively [1]. Currently, surgical operation is the most effective treatment. One tenth of perilaryngeal patients undergo partial or total laryngectomy [2]. A high incidence of postoperative complications occurred after partial or total laryngectomy [3]. Tracheostomal after laryngectomy causes the respiratory changing: respiratory mucosal warming, humidifying, filtering loss. And the risk of post-operative infection is usually related to the peri-operative

exposure of the wound to commensal bacteria colonizing mucous membranes and skin [4]. Above all increase the rate of pulmonary infection [5]. It was reported that the incidence of pulmonary infection after laryngectomy was 1.4%, *Pseudomonas aeruginosa*, *Escherichia coli*, *Streptococcus pneumonia* are the frequent pathogenic bacteria of pneumonia, of which *Pseudomonas aeruginosa* is the major pathogens [6] [7]. Therefore, all LC patients with postoperative tracheostomy would receive antibiotic prophylaxis with cephalosporin, aminoglycoside and metronidazole [8]. With the clinical abuse of the broad-spectrum antibiotics, the drug resistances are increased in *Pseudomonas aeruginosa*, and the incidence of *Pseudomonas aeruginosa* pneumonia is increasing these years. Elderly patients with pneumonia in early stage lack typical respiratory symptoms, 30% of who only have the symptom of acute disturbance of consciousness, shortness of breath and accelerated heart rate [9]. Above all, it will lead to the delay of treatment and care. Nurses play a critical role in patients' care throughout the pre- and postoperative period with special nursing for their safe transition back to society [10]. In this study, our purpose was to present our special nursing care of the laryngectomy patient secondary to *Pseudomonas aeruginosa* pneumonia with conscious disturbance for ENT nurses as a reference.

2. Clinical Data

A 71-year-old man had presented hoarseness during the past 1 year, visiting hospital in August, 2017. Pathological diagnosis was glottic cancer (T1N0M0). Cricohyoidoepiglottopexy (CHEP) was performed under general anesthesia with perfect preoperative preparation. Fervescence occurred at the third day postoperatively, the oral temperature increasing from 38°C to 39.5°C. Then conscious disturbance occurred at the 5th day; the Glasgow Coma Scale (GCS) scores were 12; be a purulent yellow-green expectoration; the skull CT scanning had no abnormality, but thorax CT diagnosed pulmonary inflammation and little pleural effusion; blood pictures were abnormal (blood calcium 1.6 mmol/L, blood kalium 3.0 mmol/L, blood sodium 122 mmol/L). Phlegm cultivation before use medicine was chosen firstly, then adjust antibiotic based on phlegm cultivation results (*Pseudomonas aeruginosa* and klebsiella species infection) and drug sensitivity test results (Amikacin). Therapeutic Methods were anti-inflammatory, temperature decreasing, eliminating phlegm, rehydration, monitoring of blood routine examination, hepatic and renal functions, electrolytes, blood glucose and others. The recovery of consciousness was at the 9th day postoperatively, with the GCS score 15. The patient tried to take food, oral temperature recovery to normal, but occurred irritating cough at the 10th day. Classifications of levels of bedside water-swallowing test (WST) are level 1 - 5. The result of 30 ml bedside water-swallowing test was level 4. Then, the swallow function returned to level 3 in 17th days, the vital signs were all stable, thorax CT and phlegm cultivation results returned normal. The patient discharged hospital with metal tracheal cannula. Postoperative special nursing care of the patient is in **Table 1**.

Table 1. Postoperative special nursing care of the patient.

Postoperative days	Abnormal symptom nursing observation	Nursing measures
5	Fervescence	Oral temperature (38°C - 39.5°C)
	Conscious disturbance	Blood sample was taken; GCS score 12
	Purulent yellow-green expectoration	Sputum Aspiration; Turning over and Patting the Body; Phlegm cultivation; drug sensitivity test results
9	Choking cough when taking food	The 30 ml bedside water-swallowing test (level 4); GCS score 15
17	Decrease of cough during food taking	The 30 ml bedside water-swallowing test (level 3)

3. Nursing Focus

3.1. The Nursing of *Pseudomonas aeruginosa* Pneumonia

The symptom of mucous membrane dryness, weakness of cough occurred in the early postoperative period. *Pseudomonas aeruginosa* pneumonia caused fever, delirium, purulent yellow-green expectoration, oxygen saturation down. Besides humid sputum suction, the pertinence measure to the symptom existed is: 1) Monitoring of vital signs was immediately carried out, blood pressure (108/55 mmHg), heart rate (>128 beats/min), the blood oxygen saturation (93%). Mask oxygen-inspiration (6 - 8 L/min) with tracheotomy tubes and intravenous fluids supplement had kept vital signs normal. 2) In early postoperative stage, the great dose of cefuroxime antibiotics was used to prevent the infection of Haemophilus influenzae and Meningococcus, invalid therapy for *Pseudomonas aeruginosa* and *Staphylococcus aureus* infection. Basis for phlegm cultivation results (*Pseudomonas aeruginosa* and klebsiella species infection) and drug sensitivity test results, the optimal dose of Amikacin and Imipenem-Cilastain was used. Meanwhile, the adverse drug reaction (ADR) was being monitored for 6 days continuously, like hepatic and renal function, hematuria and proteinuria, auditory function. 3) The color, characteristics, quantity of phlegm were closely observed and recorded every day. Once the infection of cervical incision, oral and nasal mucosa occurred, the specimens were taken to test pathogenic bacteria. 4) Moist skin were easy to be damaged with heavy perspiration caused by the fever (38°C - 39.5°C), especially the cervical pressure bandaging skin, the nasal entrance skin of nasogastric tube, electrode slices paste skin. Observation of skin humidity and skin temperature per hour can avoid complications. According to the grade of sputum density (level-1 mucoid, level-2 mucopurulent, level-3 purulent), the characteristics of sputum were changed from purulent (level 3) to mucoid (level 1) and no other complications occurred.

3.2. The Nursing of Conscious Disturbance

Hypoimmunity after surgical injury may be a main cause of bacterial infection in the elderly patients. And the bacterial toxins and imbalance of water-electrolyte

were the main factors of conscious disturbance. The change tendency of postoperative GCS scores was as follows (**Figure 1**). Sudden confusion (GCS score 12) appeared in the postoperative 5th day. GCS assessed 3 parts: best eye opening response (To speech-call the patient's name); best verbal response (Confused about time and place orientation); motor response (Localise to pain). Pupil sizes were normal, but the pupillary light reflex delayed. The skull CT scanning had no abnormality. Considering that conscious disturbance might be caused by *Pseudomonas aeruginosa* pneumonia. The level of consciousness could reflect the severity of pneumonia in some degree [11]. Therefore, the assessment of consciousness level played an important role for mastering the progress of disease. Communication with the family members was helpful for disease evaluation. During continued treatment, GCS was 13 scores, with best eye opening response (Spontaneous-observed before approaching the patient); best verbal response (confused about time and place orientation); motor response (Localise to pain) in the 7th day. Spontaneous motor activity like hand gestures increased and sleep time reduced. The pupillary light reflex recovered in the normal subject, GCS score 14 appearing to be confused about place orientation in the 8th day, encouraging the patient to communicate with written forms. The time of consciousness recovery was in the 9th day and GCS score 15 was assessed to be normal.

3.3. The Nursing of Electrolyte Disorder

The common cause of delirium is electrolyte disturbance, like hyponatremia, hypokalemia, hyeochloremia in the elderly patients [12]. The level of blood calcium (1.6 mmol/L), blood kalium (3.0 mmol/L) and blood sodium (122 mmol/L) was lower than normal value, and the possible causes were the body electrolytes loss from hyperthermia and the severity of energy expenditure. The close observation of patients was kept as charge nurses. The main symptoms of hyponatremia are hypodynamia, poor appetite, sleepiness; the main symptoms of hypokalemia are myasthenia, cardiac arrhythmia; the main symptoms of hypocalcemia are muscular spasm and clonus. Dynamical electrocardiographic

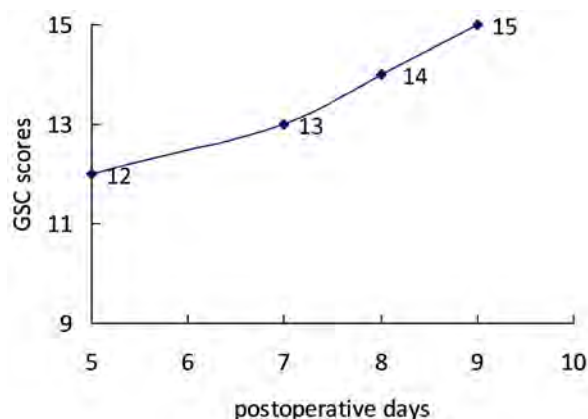


Figure 1. The variation curve of postoperative GCS scores.

monitoring was carried out, cardiac function including the heart rate, cardiac rhythm, waves cycles followed. Meanwhile, the patient's chief complaints can reflect the disease change, muscular tension was evaluated with modified Ashworth scale, muscle strength assessed with Lovett grading method. The patient complained occasional peripheral numbness of mouth, considered of hypocalcemia. Electrolyte in blood was measured immediately. With the correction of electrolyte disturbance, consciousness recovery occurred.

3.4. Affection Supports and Mental Nursing

Cheryl Bressler suggested that patients' active participant in the pre-operative period was important for the successful recovery [10]. Thus, the patient was arranged to have a pre-operative visit by a return-visit patient who has achieved a successful means of communication after the CHEP. They discussed their concerns and also identified post-operative communication methods. One study [3] indicated that psychological intervention is beneficial in improving life quality in patients with laryngeal cancer after surgery. Pre-operative psychological nursing measures included encouraging patients, and family support. It is difficult to accept the fact of losing the ability to speak after operation. Therefore, it is important for nurses to provide delicate care and encourage the patient to express himself. Instructing the patient to express himself with magic slates, writing materials, pictorial guides or hand signals had resulted in less anxiety and depression. Expressing the feeling, thoughts and aspiration with languages would last a long term in the period of pronunciation practice. The patient had been taught how to clean and sterilize the inner cannula, which would help to increase self-care capability before discharge. To develop the active states of mind to face the disease, building up self-confidence for high-quality life. Simultaneously, the patient's families provided much participation and support in the performance of comfort care mentally, like more concerns, medical expenditure support, Unhealthy Emotion Self-control. The final purpose of the nurse and family was to make the patient feel more psychological comfort.

4. Conclusions

The laryngectomy patients are faced with tremendous physical and emotional injuries. Especially, the complication with *Pseudomonas aeruginosa* pneumonia occurred delays the recovery in the post-operative period. Nurses play a vital role in providing the patients with education, and special nursing care, so they will have a safe transition back into society.

4.1. Intensive Nursing Care

It is suggested that head and neck surgery patients are admitted to Critical Care Unit (CCU) for 24-hour intensive nursing care in order to allow for airway oedema to stabilize and facilitate safe extubation [13]. The elderly patients' pulmonary ventilation function was damaged caused by pneumonia, then it would

result in hypoxemia. And in acute infection period, toxic encephalopathy and electrolyte disturbance will lead to delirium. Even as Marcantonio found [12] that postoperative delirium occurred in 117 (9%) of the 1341 patients studied; age 70 years or older, poor cognitive status and poor functional status were independent correlates. Therefore, once the symptoms of fever (above 38.5°C), mucus hypersecretion, the sputum nature changing and delirium occur for the early postoperative period, the nurses communicate with doctors immediately for the treatment. The characteristic symptoms of delirium are conscious disturbance, emotional disturbance, dysarthria and disorientation [14]. Close observation of patient's consciousness state with the Glasgow score scale is especially important every day. It is closely related to the accuracy of clinical nurses' subjective assessment. Above all, the safety of nursing head and neck cancer patients on a specialized ward with adequately trained nursing staff has already been evidenced [15].

4.2. To Prevent the Occurrence of Complications

Now the emergence of resistance is a major public health problem, and the excessive antibiotics use must be eliminated [4]. The possibility of *Pseudomonas aeruginosa* being the causative agent should be considered in patients presenting with lung empyema, especially in immunocompromised patients [16]. Nosocomial infections caused by *Pseudomonas aeruginosa* are difficult to treat because of the low permeability of its outer membrane and its remarkable ability to acquire further resistance to antibiotics [17]. Fever (above 38.5°C) and energy intake deficiency caused water-electrolyte imbalance of varied degrees which increased the risk of infection, and poor functional status were independent correlates of postoperative delirium [12]. Nurses should give priority to prevention of accompanies and emphasize on basic nursing measures, like early out of bed activity, turning over, patting the back, sputum aspiration timely, ample gastric feeding, consciousness state assessment. Due to language function loss, the observation of disease condition is even more important for the therapy. Postoperative laryngeal cancer patients secondary to *Pseudomonas aeruginosa* pneumonia with conscious disturbance occur in a relatively small amount. We collected the clinical data and nursing measures in the report, hoping to provide reference for nursing colleagues.

Limitation

The case nursing of laryngectomy Patient Secondary to *Pseudomonas aeruginosa* pneumonia with Conscious Disturbance is rare in clinic but severe complication, being increasingly recognized recently. Thus, our study just discusses the experiences and measures of special nursing care that others could learn from it. Unfortunately, limitation is that the information offered in this document does not offer any additional information, any medically trained person looking at Lab values would do.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Effect of Modified Breakfast-Education for Type 2 Diabetes Mellitus: A Single-Center Randomized Clinical Trial

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Abstract

Objective: The effect of postprandial blood glucose (BG) by eating modified noodles and health education in type 2 diabetic mellitus (T2DM) patients was observed. **Methods:** To select T2DM patients who need therapies in hospital from June to September 2017 and divide the patients into study ($n = 41$, Dried Noodles) and control ($n = 39$, Noodles with Soup) groups. After 3 months, the clinical/biochemical parameters and compliance of two groups were observed. **Results:** The study group has lower clinical/biochemical parameters and higher compliance than control group for 3 months of intervention. The difference between the two groups is statistically significant ($P < 0.05$). **Conclusion:** The improvement of breakfast and health education mode effectively controls T2DM, promotes the development of good living habits of patients, and improves self-management ability and compliance of patients.

Keywords

Breakfast, Education, Type 2 Diabetic Mellitus

1. Introduction

Diabetes mellitus (DM), one of the major diseases, is affecting human health, which has become a growing concern in the world. The number of DM patients has increased from 108 million in 1980 to 422 million in 2014, with a prevalence rate of 4.7%, rising to 8.5%. As being estimated by International Diabetes Federation (IDF), there will be 592 million people that suffer from DM by 2035 [1] [2] [3], and about 90% of these affected patients are Type 2 Diabetes Mellitus (T2DM) [2]. DM is a chronic disease with long-term and difficult therapeutic process,

which often causes various acute and chronic complications such as diabetic nephropathy and diabetic foot [2] [3]. Therefore, it is important for patients to promote the self-management of DM [4]. Diet therapy and health education are the basis for the treatment of diabetes in the “Five carriages” [4]. Breakfast provides 20% - 35% of the amount of daily energy requirements in diet therapy [3]. Therefore, the right way to eat breakfast could prevent patients from high BG after meals [1] [5]. However, the educational modes by words or pictures could not meet the needs of patients anymore [4]. The purpose of this clinical trial is to explore the effect of modified breakfast-education for T2DM patients.

2. Patients and Methods

2.1. Patient Selection

This study is approved by the Hospital Ethics Committee. All participants have signed informed consent before the study. The DM patients hospitalized in the Department of Endocrinology are chosen during the testing period from June 2017 to September 2017. The selection criteria are: 1) 18 - 80 years old; 2) According to the diagnostic criteria by American Diabetes Association (ADA) for T2DM in 2018 [6]; 3) The patients' conditions are suitable for using hypoglycemic drugs; 4) Participating in this study voluntarily. Exclusion criteria are: 1) Having diabetes during pregnancy; 2) With malignant tumors; 3) With severe liver and kidney or other organ diseases. Based on the results of the pre-test, the standard deviation was used to estimate the sample size. As a result, eighty-two patients are selected by convenience sampling method. According to the order of admission time, the subjects are divided into study and control group (41 cases in each group). In the control group, one of patients has hypoglycemic reactions and another one need the treatment of insulin pump due to high blood glucose (BG). Therefore, these two patients are excluded from this study. In the end, 39 cases are enrolled in the control group. There is no significant difference in baseline levels between the two groups (Table 1, $P > 0.05$).

2.2. Breakfast-Education Improvement

According to the Hattis-Benedict formula to calculate the Basal Energy Expenditure (BEE) for T2DM patients, the formula is as follows: BEE (male) = $66.47 + 13.75 \times \text{weight (Kg)} + 5.0 \times \text{height (cm)} - 6.76 \times \text{age (yrs)}$, BEE (female) = $655.10 + 9.56 \times \text{weight (Kg)} + 1.85 \times \text{height (cm)} - 4.68 \times \text{age (yrs)}$ [7]. The unit

Table 1. Table comparison of general information.

Group	<i>n</i>	Sex [<i>n</i> (%)]		Age ($\bar{x} \pm s$, yrs)	Disease course ($\bar{x} \pm s$, yrs)
		Male	Female		
Control	39	23 (61.5)	15 (38.5)	56.05 $\pm$ 8.39	7.76 $\pm$ 5.66
Study	41	18 (46.3)	22 (53.7)	56.34 $\pm$ 12.46	8.40 $\pm$ 6.99
χ^2/t		1.813		-0.121	-0.441
<i>P</i>		0.182		0.904	0.661

of BEE is Kilocalorie (Kcal). According to Chinese dietary guidelines, it is known that 188 g of cooked noodles have heat of 436 Kilo Joules (KJ) [8], as 2.32 KJ/g. The amount of noodle (g) = $(\text{BEE} \times 4.18 \text{ KJ}) / 2.32 \text{ KJ} \times 20\%$. The patients in control group are given noodles having soup. On the contrary, the noodles in the study group do not contain soup. The noodles of standard meal made from wheat flour.

2.3. Diabetes Education Model Improvement

The control group had used the conventional model, such as diet guidelines, BG recording cards and so on [4]. The study group is based on from diverse culture backgrounds of their patients with their own features. The study group is based on the education of the control group, and used peer education additionally. The method of educational intervention is as follows: In this study, doctors, nurses and peer leader participate in the study group supervising and guiding other patients. Specific programs: 1) Responsible physicians invited patients who could use smartphones to join WeChat APP on DM's Blood Glucose Management (BGM), and select peer leader from older patients who have a high level of knowledge, good self-management skills, strong abilities and enthusiasm; 2) Two nurses supervise and co-lead the peer leader to complete the APP online training course. At the same time, the APP members are organized to conduct offline education activities; 3) Peer leader have completed online and offline training courses. After that, should help patients improve APP personal information, supervising monitor blood sugar, and organizing educational activities; 4) Patients need to record their 03:00, fasting blood-glucose (FBG) and two-hour postprandial blood glucose (2hPBG) in the APP. Meanwhile, patients have gotten diabetes knowledge, food calories and medication management through DM's BGM. The mode of modified breakfast- education has lasted 3 months in clinical, with breakfast intervention daily and peer education of three times a day.

2.4. Assessment of Management Outcomes

The examination of clinical and biochemical parameters, includes Body Mass Index (BMI), waist circumference, 03:00 BG, FBG, 2hPBG and HbA1c. Dinner time is controlled between 18:00 and 19:00 in both groups. BG is monitored at 03:00 on the next day (patients do not have meal for about 8 hours). FBG is monitored from 06:00 to 08:00. The compliance of patients in these two groups is compared after education intervention, including three aspects: monitoring BG, living rules and obeying doctor's orders. Those parameters and compliance were detected before and after intervention, and it took almost 5 days.

2.5. Statistical Analysis

SPSS 22.0 is used for the statistical analysis. 1) Baseline balance, such as sex, age and disease course is tested, if having no difference, and then the next study; 2) The comparison of numerical data is performed by t test. Quantitative variables are showed by chi-square test. $P < 0.05$ is considered statistically significant.

3. Results

3.1. The Comparison of BG Levels before and after Intervention in Both Groups

After the intervention, the parameters of the study group are better than the control group, the difference was statistically significant (**Table 2**, $P < 0.05$).

3.2. The Comparison of Compliance for Two Groups

Patients in the study group have higher compliance than those in the control group (**Table 3**, $P < 0.05$).

4. Discussion

The results in this study shows that modified breakfast -education modalities have done in the study group, whose clinical and biochemical parameters were lower than the control group, the difference is statistically significant ($P < 0.05$). At the same time, the patients' compliance is higher than the control group ($P < 0.05$).

Parillo *et al.* [9] pointed out that BG is significantly lower than bread and potato flour after eating pasta. Ridner *et al.* [10] also certified that pasta made from durum wheat shows a lower Glycaemic Index (GI) than rice and pasta. The reason is that different forms of food have affected patients' digestibility [9] [11].

Table 2. Comparison of clinical and biochemical outcomes of two groups before and after intervention.

Clinical/Biochemical parameters	Control ($n = 39$)		t	P	Study ($n = 41$)		t	P	t_1	P_1	t_2	P_2
	Before intervention	After intervention			Before intervention	After intervention						
BMI (kg/m^2)	25.83 $\pm$ 2.06	24.58 $\pm$ 2.73	2.279	0.025	25.84 $\pm$ 1.30	22.88 $\pm$ 1.35	10.108	0.000	-0.027	0.978	3.548	0.001
Waist circumference (cm)	84.15 $\pm$ 4.97	81.48 $\pm$ 4.72	2.426	0.018	83.05 $\pm$ 5.97	78.02 $\pm$ 5.73	3.884	0.000	0.896	0.373	3.469	0.001
03:00BG (mmol/L)	8.45 $\pm$ 2.29	7.31 $\pm$ 1.47	2.604	0.011	7.93 $\pm$ 1.90	5.92 $\pm$ 1.52	5.284	0.000	1.095	0.277	4.165	0.000
FBG (mmol/L)	8.41 $\pm$ 2.55	7.77 $\pm$ 1.85	1.265	0.210	8.46 $\pm$ 1.71	6.00 $\pm$ 1.38	7.155	0.000	-0.100	0.920	4.846	0.000
2hPBG (mmol/L)	12.53 $\pm$ 3.11	12.20 $\pm$ 3.37	0.450	0.654	12.58 $\pm$ 2.70	10.46 $\pm$ 2.48	3.698	0.000	-0.08	0.936	2.636	0.010
HbA1c (%)	8.38 $\pm$ 0.81	7.69 $\pm$ 0.89	3.578	0.001	8.18 $\pm$ 0.54	6.07 $\pm$ 0.96	11.152	0.000	1.278	0.205	5.449	0.000

The t/P value of the control and study group refer to the comparison between pre-intervention and after the intervention in 3 months; The t_1/P_1 value refer to the comparison of two groups before the intervention; The t_2/P_2 value refer to the comparison of two groups after the intervention.

Table 3. Comparisons of compliance of two groups before and after intervention.

Compliances	Control ($n = 39$)		χ^2	P	Study ($n = 41$)		χ^2	P	χ_1^2	P_1	χ_2^2	P_2
	Before intervention	After intervention			Before intervention	After intervention						
Monitoring BG	22 (56.4)	24 (61.5)	0.212	0.645	24 (58.5)	37 (90.2)	10.818	0.001	0.037	0.848	9.095	0.003
Living rules	23 (59.0)	25 (64.1)	0.217	0.642	26 (63.4)	35 (85.4)	5.185	0.023	0.166	0.684	4.820	0.028
Obedying doctor's orders	21 (53.8)	22 (25.4)	0.052	0.820	23 (56.1)	36 (87.8)	10.212	0.001	0.041	0.840	9.881	0.002

The χ^2/P value of the control and study group refer to the comparison between pre-intervention and after the intervention in 3 months; The χ_1^2/P_1 value refer to the comparison of two groups before the intervention; The χ_2^2/P_2 value refer to the comparison of two groups after the intervention.

When noodles are contact with water, their starch particles absorb moisture to expand the molecular chain, resulting in volume expansion. As the water temperature increasing, the starch granules continue to swell and dissolve into the water, forming viscous liquid. Cooked noodles continue immersion in warm soup could be gelatinized, being useful for digestion and absorption [12]. When the patients in control group have eaten loose noodles with soup, glucose is released into the blood quickly, leading to postprandial BG increase significantly. In the study group, cooked noodles being removed from hot soup is gradually cooling, and then degeneration of amylose in starch made the gelatinized starch from amorphous into crystalline state, not easily digested by amylase, and reducing the rate of digestion [12] [13]. Patients in the study group have eaten dry noodles, which would be harder to chew through the teeth. Therefore, this kind of noodles should be mechanical grinded by stomach, which extends the time of digesting and absorbing; Meanwhile, the speed of the release of glucose into the bloodstream slows down, and increasing postprandial BG is slow as well. At the same time, dry noodles impede the penetration of digestive enzymes into the starch, reducing the rate of starch degradation and the production of glucose [12] [13]. Therefore, the patient's postprandial BG level from test group is lower than the control group.

GI is an index that describes the human body's digestion and absorption rate, but BG responses to food. The testing food can be considered as low GI food when GI of this food is less than 55; it is medium GI food when GI index between 55 and 70; it is high GI food when GI more than 70 [11] [14]. According to the Food Glucose Production Index compiled by the Sichuan Provincial Nutrition Society, patients in the control group are given wet noodles as high GI foods (GI was 81.6). When these wet noodles enter the patient's gastrointestinal tract, it is digested easily by digestive enzymes and absorbed by intestinal mucosa, and then postprandial BG rise significantly. The study group is fed dry noodles made from wheat flour which GI is 46.0. Therefore, it is considered as low GI food. After entering the patient's gastrointestinal tract, dry noodles are not easily digested by digestive enzymes and absorbed by the intestinal mucosa, so the BG level is low [11] [14] [15].

Starch is an important part of carbohydrate-based noodles, accounting for about 65% to 75% [14]. Studies have shown that patient eat higher carbohydrates, the higher BG level will be [16]. In this study, the patients in the control group not only take in thin, loose and noodle soup, but also soup containing starch. Their intake is two times of the patients in the study group. Therefore, the postprandial BG level is significantly higher than the study group.

The diet of T2DM patients need to limit the amount of carbohydrates in the staple food. When eating carbohydrate foods with the same calorie content, patients try to select low GI food which is digested slowly in the gastrointestinal tract. It is useful to control the BG and reduce the fluctuation of insulin [13] [16].

In addition, effective health education could not only improve the patient's

ability to recognize their own diseases, but also change their bad living habits, promote their compliance with doctor's orders, effectively reducing BG. The study shows that the patients in the study group are better than the control group in monitoring BG, living patterns, and complying with doctor's orders. The difference is statistically significant ($P < 0.05$). The reason is that peer education as an objectively existing behavior, which is impacted by successful experience, speech persuasion, patients' physiological and psychological conditions. It could support the self-management of DM patients [17]. Peer leaders' treatment experience and suggestions are more likely to be accepted by the patients if they have been suffering from the same disease as these patients, which will lead to the improvement of self-efficacy, compliance of management, and control of postprandial BG [17]. Thom *et al.* illustrate that the pre- and postprandial BG levels in the study group are lower than those in the control group after peer education, for low-income patients [17].

Therefore, medical staff should conduct peer education on patients according to their actual conditions, which can effectively improve postprandial BG in patients with T2DM and improve self-management.

5. Conclusion

In summary, the breakfast and diabetes education modalities are improved for patients with T2DM, which have reduced 2hPBG effectively after breakfast, promoting the development of good living habits, and improving patient self-management and compliance. However, this study has shortcomings such as shorter intervention time and less sample size, which needs further verification. The sample size and effects of interventions at different time periods are looked forward to increasing in the future.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Meta-Analysis on Efficacy and Safety of Modified Guizhi Shaoyao Zhimu Tang with the Western Medicines in Treating Rheumatoid Arthritis

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Abstract

Objective: To assess the efficacy and safety of modified Guizhi Shaoyao Zhimu Tang (GSZT) with the Western medicines in treating rheumatoid arthritis. **Methods:** All the relevant studies were collected by searching the Pubmed, Web of science, Embase, Cochrane Library, SpringerLink, China National Knowledge Infrastructure (CNKI), VIP Journals database, and Wanfang database from their inception to October 2017. After the assessment, the eligible ones were subject to Jadad score. The meta-analysis was conducted by RevMan 5.3 software. **Results:** Totally 10 randomized controlled trials (RCTs) involving 962 patients were enrolled. The clinical efficacy of analysis showed that modified GSZT with the Western medicines can significantly improve the clinical total effective rate [OR = 4.64, 95%CI (3.03, 7.12), $P < 0.00001$], the duration of morning stiff [MD = -14.58, 95%CI (-16.49, -12.68), $P < 0.00001$], erythrocyte sedimentation rate (ESR) [MD = -12.62 95%CI (-18.69, -6.54), $P < 0.001$], rheumatoid factor (RF) [MD = -49.88, 95%CI (-77.6, -22.09), $P < 0.001$], C-reactive protein (CRP) [MD = -5.34, 95%CI (-5.86, -4.82), $P < 0.001$]. The adverse events had been seen in both of the two groups, however, the clinical symptoms of the group on modified GSZT with the Western medicines were obviously reduced than the other one [OR = 0.25, 95%CI (0.10, 0.61), $Z = 3.06$, $P < 0.01$]. This system review shows that the modified GSZT with the Western medicines improved the clinical efficacy, symptoms and the blood biochemical indicators were improved significantly than that of Western medicines alone on rheumatoid arthritis. At the same time, it can reduce adverse effects and enhance safety.

Keywords

Rheumatoid Arthritis, Guizhi Shaoyao Zhimu Tang, RA, Meta

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that is characterized by joint erosion, stiffness, deformity, loss of function, and with high morbidity [1] [2]. However, the cause of RA is unknown. RA belongs to the category of “bi syndrome” in Traditional Chinese Medicine (TCM). It is caused by invading cold and dampness inside body and blood qi stasis in the theory of TCM. At present, the effective treatments of routine western drugs include glucocorticoid, non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs) and biologic agents. While the long term use of these drugs can produce the multiple side effects, and cause much socio-economic costs and safety, and even some patients cannot tolerate the situation [3]. But the TCM has special effects in the treatment of RA [4]. Recently, the TCM is attracting the attention of the public, because of the potential and positive effects in treatment of autoimmune disease. The TCM mainly contains Chinese herbs. In the ancient period of China, there was a formula that was most commonly used in the management of RA. Guizhi Shaoyao Zhimu Tang (GSZT) is the classical Chinese medicine which is extensively used in clinical application. In this article, the potentially therapeutic effect and safety of the GSZT combined with the Western medicine for the treatment of RA were systematically evaluated.

2. Materials and Methods

2.1. Literature Retrieval Strategy

The search strategy was developed by Cochrane collaboration and the relevant studies were collected by searching the Pubmed, Web of science, Embase, Cochrane Library, SpringerLink, CNKI, VIP Journals database, and Wanfang database from their inception to October 2017. A multiple number of medical terms such as “rheumatoid arthritis”, “RA” and “Guizhi Shaoyao Zhimu Tang” were utilized for medical subject heading (MeSH) to find out the articles, which have been published on the base of combine conventional western medicines for the treatment of RA. The retrieval is conducted in the form of free combination with a keyword, manual retrieval had been used to trace the references in the literature. No language or time restrictions were applied in the search.

2.2. Document Inclusion and Exclusion Criteria

Trials were considered to be eligible for research propose if they fully meet the following criteria: 1) all patients fulfilled the 1987 revised American College of

Rheumatology criteria for the disease [5], 2) the experimental group was treated with the combined conventional Western medicine and the GSZT, and the control group was just treated with conventional Western medicine, 3) the research type satisfied the RCT data, 4) the outcomes included at least one of the following therapeutic effects: duration of morning stiffness (DMS), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), C-reactive protein (CRP), there were no restrictions regarding gender, age, severity or duration of RA. The safety evaluation index is the adverse reactions.

2.3. Data Extraction

The two researchers independently screened and extracted the retrieved documents, and the differences were determined and resolved by the third person, including study design, randomization and diagnostic criteria.

2.4. Quality Evaluation

According to the quality criteria of Cochrane Review's Handbook, the literature quality is evaluated and Jadad scale method was independently used for the evaluation of methodological quality of articles [6]. The specific contents include: 1) random grouping sequence method, 2) blind method, include double-blind method and single blind method, 3) allocation concealment, 4) reports about the withdrawal.

2.5. Statistical Analysis

Data analysis was performed by using the RevMan 5.3 software provided by the Cochrane collaboration. The statistical data were analyzed by odds ratio (OR) and 95% confidence intervals (CI) and the metering data was expressed by mean difference (MD) and 95%CI. A fixed-effect model was employed if there was no statistical heterogeneity among studies, otherwise, the random effect model was used [7]. Heterogeneity is assessed by Chi-square test, and the degree of inconsistency Higgins I^2 is measured between studies whether the percentage of total variation across studies is due to heterogeneity rather than chance [8]. If the source of heterogeneity is unable to be determined, the descriptive analysis will be adopted. The distribution of the research data, in the study, was analyzed by funnel plot. The reliability analysis of publication bias was carried out.

3. Results

3.1. Study Selection and Characteristics

According to the above mentioned research strategy we got information from 1313 articles which are potentially relevant. 1078 studies were screened after removal of duplicates. There were ten relevant studies that finally met the inclusion criteria for the meta-analysis. The general situation of the study selection was shown in **Figure 1**.

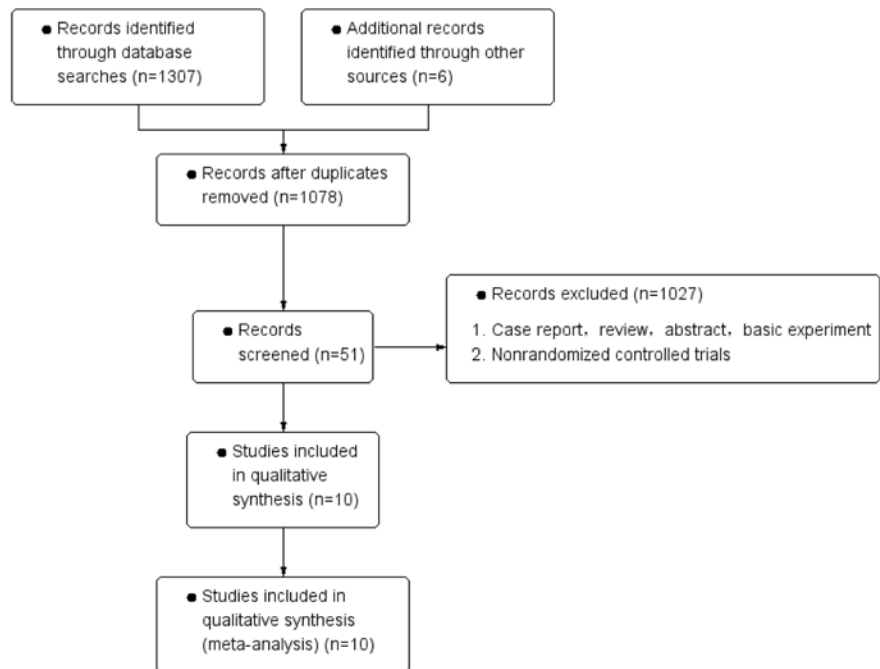


Figure 1. Flow diagram of study selection process.

3.2. General Situation and Quality Evaluation of the Included Literature

A total of 10 RCTs were included [9]-[18], and the conventional Western medicine involves three major categories in these studies. They are non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs) and glucocorticoids (GCs). NSAIDs included Meloxicam (MLX), voltaren, nimesulide (Nime), celecoxib (CXB), loxoprofen. DMARDs included methotrexate (MTX), sulfasalazine (SSZ) and Leflunomide (LEF). The experimental group was based on the control group with GSZT. The general description about literature and the results of methodological quality evaluation are shown in **Table 1**.

3.3. Meta Analysis Results

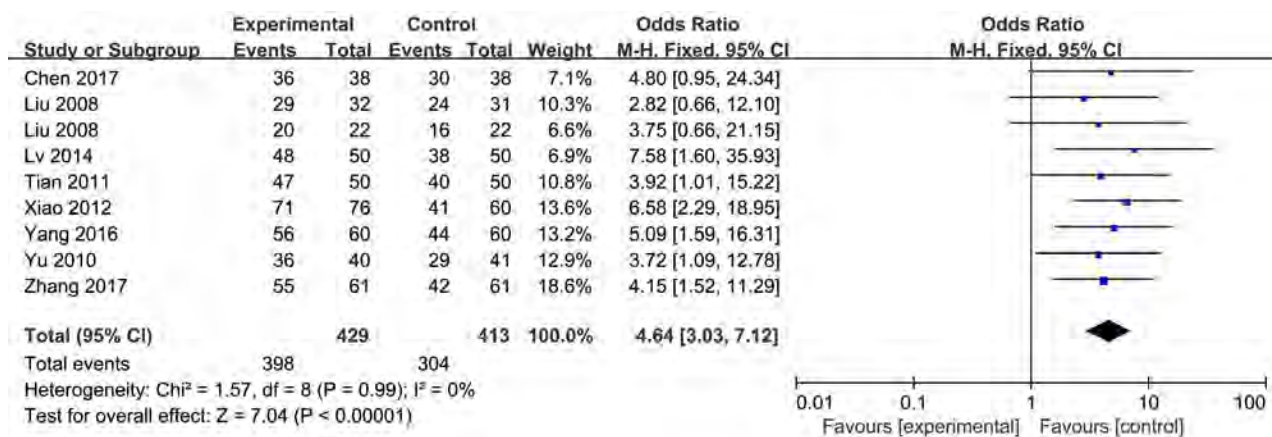
3.3.1. Comparison of Disease Efficacy for RA

In the articles that met the criteria, 9 trials were compared for the efficacy of RA patients and the specific values were given [9]-[17]. According to the data which we had screened in combination, we can see that 9 trials included in the study were homogeneity (no heterogeneity) and showed insignificant difference ($X^2 = 1.57$, $P = 0.99$, $I^2 = 0\%$). The fixed effect model was used and showed [OR = 4.64, 95%CI (3.03, 7.12), $Z = 7.04$, $P < 0.00001$]. Therefore, it is considered that there is a statistically significant difference in the efficacy of the combination therapy between the combination therapy trial group and the Western medicine treatment control group alone. In addition, the lower and lower limit of 95%CI of OR is more than 1. It can be seen that the clinical efficacy of the experimental group is better than the Western medicine alone control group in RA. See **Figure 2**.

Table 1. Characteristics of the ten trials included in the meta-analysis.

Author	random allocation	allocation concealment	blind method	withdraw	Jadad score	Interventions		Duration	Outcomes
						experimental	control		
Yu 2010 [9]	yes	unclear	unclear	unclear	3	GSZT	MTX 7.5 mg qw, SSZ 1 g bid	12 weeks	TE, DMS, ESR, CRP, AE
Liu 2008 [10]	unclear	unclear	unclear	unclear	2	GSZT	MTX 7.5 mg qw, MLX 7.5 mg bid	4 weeks	TE
Liu 2008 [11]	unclear	unclear	unclear	unclear	2	GSZT	LEF 20 mg qd	4 weeks	TE
Lv 2014 [12]	yes	unclear	unclear	unclear	3	GSZT	MTX 7.5 mg qw, voltaren 75 mg qd	12 weeks	TE, ESR, RF, AE
Zhang 2017 [13]	yes	unclear	unclear	yes	4	GSZT	LEF 20 mg qd, Nime 0.1 g bid	12 weeks	TE, DMS, ESR, RF, CRP
Yang 2016 [14]	unclear	unclear	unclear	unclear	2	GSZT	CXB 0.2 g qd	12 weeks	TE
Tian 2011 [15]	unclear	unclear	unclear	unclear	2	GSZT	NSAIDs, GCs	8 weeks	TE, DMS, ESR
Xiao 2012 [16]	unclear	unclear	unclear	unclear	2	GSZT	MTX 5 10 mg qw, voltaren 75 mg qd	12 weeks	TE, ESR
Chen 2017 [17]	yes	unclear	unclear	unclear	3	GSZT	MTX 10 mg qw, voltaren 75 mg qd	12 weeks	TE, DMS, ESR, RF, CRP, AE
Liu 2017 [18]	yes	unclear	unclear	unclear	3	GSZT	LEF 20 mg qd, loxoprofen 60 mg tid	8 weeks	ESR, RF, CRP

Note: GSZT Guizhi Shaoyao Zhimu Tang, MTX methotrexate, SSZ sulfasalazine, MLX Meloxicam, LEF Leflunomide, Nime nimesulide, CXB celecoxib, GCs glucocorticoids, TE therapeutic effect, DMS duration of morning stiffness, ESR erythrocyte sedimentation rate, RF rheumatoid factor, CRP C-reactive protein, AE adverse event.

**Figure 2.** Meta-analysis forest map of the effect comparison.

3.3.2. Effect on Duration of Morning Stiffness

Four trials reported the effects on the DMS between the experimental group and control group was carried out. The meta-analysis showed that 4 trials included in the study were homogeneity (no heterogeneity), and showed a insignificant difference ($X^2 = 1.05$, $P = 0.79$, $I^2 = 0\%$). The fixed effect model was used and showed [MD = -14.58, 95%CI (-16.49, -12.68), $Z = 14.99$, $P < 0.00001$] [9] [13] [15] [17]. According to this analysis, it can be considered that there is a statistically significant difference in the effect of the DMS between the combined trial

group and the Western medicine alone group. The lower and lower limit of 95%CI of the OR was less than 0, indicating that the experimental group could improve the efficacy of the DMS better than the control group. See **Figure 3**.

3.3.3. Effect on Blood Biochemical Indexes

Seven trials reported the effects on the serum level of the ESR [9] [12] [13] [15] [16] [17] [18], four trials reported the effects on the serum level of the RF [12] [13] [17] [18], and four trials reported the effects on the serum level of the CRP [9] [13] [17] [18]. The meta-analysis showed that there was a large heterogeneity between the ESR and RF tests ($P < 0.001$), However, CRP test has homogeneity ($P = 0.91$), we analyzed the outcome in fixed effect model. All three blood biochemical indexes in experimental group were better than those in the control group, and the differences were statistically significant ($P < 0.001$). As shown in **Table 2**.

3.3.4. Safety Evaluation

Only 3 trials were referred to adverse events during the treatment, the cases were clearly mentioned and observed [9] [12] [17]. No heterogeneity was identified among the trials ($X^2 = 1.93$, $P = 0.38$, $I^2 = 0\%$) based on the fixed-effect model. See **Figure 4**, the meta-analysis demonstrated a meaningfully higher rate of AEs induced by the Western medicines alone than by the modified GSZT combined with the Western medicines [OR = 0.25, 95%CI (0.10, 0.61), $Z = 3.06$, $P = 0.002 < 0.01$]. The control group had 6 cases of nausea and vomiting, 7 cases of epigastric discomfort, 3 cases of abnormal liver function, 2cases of leukopenia, 6 cases of oral ulcer and dry mouth. In the experimental group, there are 1 case of nausea and vomiting, 7 cases of epigastric discomfort, 1 case of skin rash, 1 case of

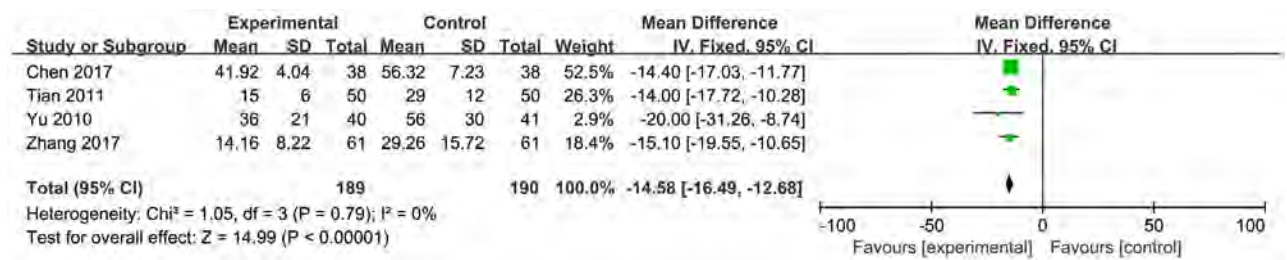


Figure 3. Meta-analysis forest map of the effect on the DMS.

Table 2. Comparison of the improvement of RA on ESR, RF, CRP in the two groups.

Evaluation index	Trials	Interventions		Heterogeneity test			Effect model	Total effect		
		Experimental	Control	X²	I²	P		MD [95%CI]	Z	P
ESR	7	317	318	241.67	98%	<0.001	random	-12.62 [-18.69, -6.54]	4.07	<0.001
RF	4	209	209	219.45	99%	<0.001	random	-49.88 [-77.6, -22.09]	3.52	<0.001
CRP	4	199	200	0.55	0%	0.91	fixed	-5.34 [-5.86, -4.82]	20.04	<0.001



Figure 4. Meta-analysis forest map of the effect on the adverse events.

dizziness, 1 cases of diarrhea and 1 cases of oral ulcer. As shown in **Table 3**, these side effects, however, which could be alleviated or disappeared after symptomatic treatment in experimental group.

3.3.5. Publication Bias

A funnel plot analysis was carried out on the efficacy of the 9 studies in RA, the distribution of each study is symmetrical, and the funnel plot is basically symmetric. It can be concluded that there is no publication bias, and the meta-analysis was credible. See **Figure 5**.

4. Discussions

Guizhi Shaoyao Zhimu Tang, a Chinese medicinal formula, is accepted as the most prevalent and effective treatment for RA in many Asian countries [19]. The essential herbs in this formula, GSZT, are well-known for the book as follow: “Synopsis of Prescriptions of the Golden Chamber”. It is the main prescription for the treatment of “arthralgia syndrome”. The theory of TCM holds that is “Medicinal and Edible”. Modern pharmacological research shows that the formula can significantly reduce the PGE2 content in the inflammatory tissue of adjuvant induced arthritis, inhibit the migration of white blood cells, and reduce the permeability of capillaries [20]. Another study pointed out that the GSZT has similar efficacy to methotrexate in treatment of RA, which could inhibit the secretion of IL-2 and CRP in varying degrees [21]. It also shows the effects in treating RA by adjusting to IL-2, IL-6, IL-17, IL-27, IL-32, TNF- α , HRAS, CD14, CD40, and TLR-MAPKs signaling pathway, TLR-NF- κ B signaling pathway, NLR signaling pathways and TNF signaling pathway [13] [22]. The animal experiments have also been found that the GSZT can have a protective effect on collagen II-induced arthritis (CIA), and can significantly inhibit the histopathological changes of rheumatoid arthritis and restrain the expression of RANKL/OPG [23] [24]. It is indicated that the GSZT has the function of anti-rheumatism, inhibiting the immune response, and also provides the molecular basis for the treatment of RA. Therefore, the treatment of RA is quite effective in clinic.

This system systematically evaluated the inclusion criteria of clinical studies. The results showed that the GSZT combined with the Western medicine was better than the Western medicine alone in the treatment of RA. According to the funnel plot analysis, this meta-analysis is credible. The experimental group was

Table 3. Effect of adverse events in the two groups.

Interventions	Adverse events								Total
	nausea vomiting	epigastric discomfort	skin rash	dizziness	abnormal liver function	leukopenia	diarrhea	oral ulcer dry mouth	
Experimental	1	1	1	1	1	0	1	1	7 [9] [17]
Control	6	7	0	0	3	2	0	6	24 [9] [12] [17]

Note: 1) The conditions of [9] [12] [17] applied the Western medicine shows in **Table 1**. 2) The AEs of [9], 1 case of nausea vomiting, 1 case of epigastric discomfort, 1 case of skin rash, 1 case of dizziness, 1 case of abnormal liver function in the experimental group; 4 case of nausea vomiting and epigastric discomfort, 3 case of oral ulcer, 3 case of abnormal liver function, 1 case of leukopenia in the control group. 3) The AEs of [12], no AEs in the experimental group and 5 case of epigastric discomfort in the control group; 4) The AEs of [17], 1 case of diarrhea in the experimental group; 2 case of nausea vomiting, 2 case of epigastric discomfort, 3 case of dry mouth in the control group.

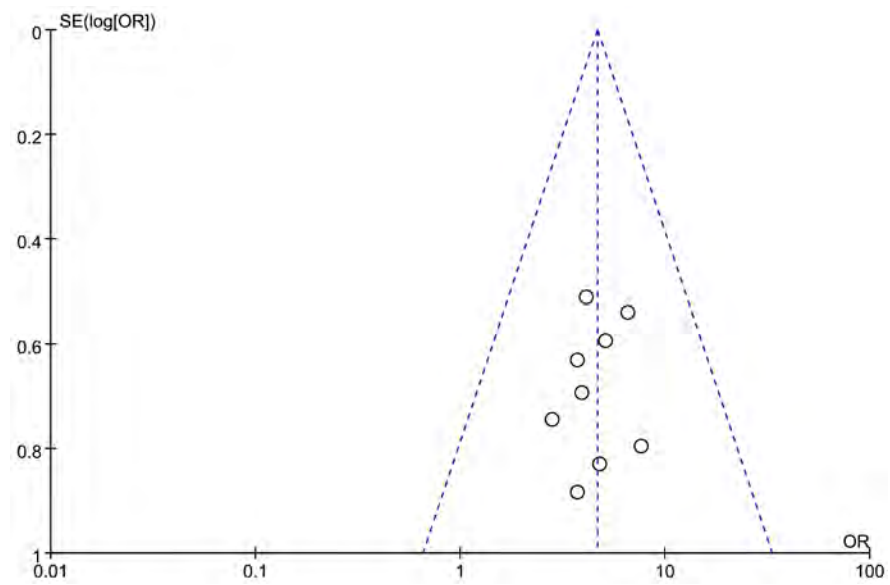


Figure 5. Funnel plot for publication bias in the included trials.

also better than the western medicine treatment group in terms of clinical symptoms, laboratory indicators and adverse reactions. From the large amount of retrieved study, it can be seen that although there are many adverse reactions in the treatment of RA with conventional Western medicine alone, the treatment of western medicine in China is still widely applied due to its exact clinical efficacy and clinical pharmacology. This study confirmed the efficacy and safety that the modified GSZT combined with Western medicine is more effective, regardless of clinical efficacy, or clinical symptoms, laboratory indicators and safety are better, and can better reflect the complementary advantages of Chinese and Western medicine. It would have good clinical promotion and application value.

This study confirmed the efficacy and safety of the GSZT combined with western medicine in the treatment of RA from the perspective of evidence-based medicine. However, through detailed analysis of the articles, the quality of articles was low, and the sample size was also low. Randomization, withdrawal, and loss of follow-up were mostly unknown. They didn't mention the blinded method and allocation concealment, and the specific interventions into the RCT

dose have different size and duration. The factors certainly influenced the reliability of the result of the meta-analysis. In order to guide clinical practice more scientifically, it is necessary to design a randomized double-blind controlled trial with high quality and provide more reliable evidence-based medical evidence for clinical guidance.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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On Practice of the Effect of Systematic Family Nursing Guidance on the Quality of Life of Elderly Patients with Implanted Cardiac Pacemaker

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Abstract

Objective: To inquire into the effect of systematic family nursing guidance on improving the Quality of Life for elderly patients with implanted cardiac pacemaker. **Methods:** 41 elderly patients in accordance with the corresponding requirements were studied after offering systematic family nursing guidance and surveyed through the questionnaires about the QOL (quality of life) respectively 1 month, 3 months and 6 months after leaving hospital. **Results:** Compared with that of 1 month and 3 months after the operation, the questionnaire scores for 6 months after the operation were found to have significant improvement, and the differences were statistically significant. **Conclusion:** Systematic family nursing guidance can effectively improve the QOL for elderly patients with implanted cardiac pacemaker, which makes them spend their old age in comfort and happiness.

Keywords

Cardiac Pacemaker, Elderly Patients, Family Nursing Guidance, Quality of Life, SF-36 Health Survey

1. Introduction

With the growing incidence of heart pace-making and conductance dysfunction in recent years, there is an increase for the cases of cardiac permanent pacemaker implanting [1], and the elderly patients have become the major groups of cardiac pacing therapy in China at present. According to the surveys, implanting cardiac permanent pace-makers have some negative effects on the patients' qual-

ity of life [2] [3]. Especially among the elderly patients, due to their falling of physiological function and of behavioral competence, such problems were found after implanting cardiac pacemakers as carrying a heavy physiological burden, being severely lack of self-care and substantially reducing social activities of connections, even though a small number of patients place a heavy burden on their family life. To inquire into it, 41 elderly patients with implanted cardiac pacemakers were offered systematic family nursing guidance and their quality of life was followed up. The details were as below.

2. Materials and Methods

2.1. Materials

According to the new standard age division of WHO (World Health Organization), those people who are between 60 and 74 years old are defined as quasi elderly people, and those over 75 years old are elderly ones. So that 41 patients with implanted cardiac permanent pacemakers (male, 25; female, 16), whose age ranging from 60 to 82 years old, were chosen as the study objects, and their average age was 71 ± 0.926 years old. All of them are informed consent patients willing to receive the nursing guidance, excluding those who are not supported by their families or those who have lost their ability to learn. The types of the pacemakers used as: 1) dual chamber pacemaking, dual chamber apperceive and dual mode of triggering or inhibiting (DDD) for 6 patients; 2) ventricular Pacing, ventricular perception and then demonstrate an inhibitory reaction (VVI) for 21 patients; 3) atrial pacing, atrial perception and lead to an inhibitory reaction (AAI) for 7 patients; 4) dual chamber pacemaking, dual chamber perception, dual responses of triggering or inhibiting and the heart rate of the patient can be accommodated (DDDR) for 2 patients; 5) ventricular pacemaking, ventricular perception, mode of inhibition, and can adapt to the patient's heart rate changes (VVIR) for 5 patients. All of the patients are the elderly people living in the same community with the same regional cultural backgrounds, including the same dialect, the same living environment, the same customs and communication condition, and the same folk beliefs and economical environment, which can make sure the comprehension, the implementation and the compliance of the patients are more similar with regard to the systematic family nursing guidance.

2.2. Methods

All the following methods of nursing guidance do not violate ethics or morality, without any harm to the patients.

2.2.1. Family Nursing Guidance Method

When leaving the hospital, all the elderly patients were offered a full evaluation of their psychology, physiology and family support, then make systematic family nursing guidance, create health records and designate special persons to take charge of guidance and management. After being discharged from hospital, the regular follow-ups were made by telephone and through home visit according to

the family nursing guidance: in general, within 1 month will have twice home visit and telephone follow-up once during one or two days; within 3 months will have home visit once a month, telephone follow-up once during one or two weeks; within 6 months will have home visit twice, telephone follow-up once a month, if necessary, the home visit and telephone follow-up can be added more times. Furthermore, during the process, the new things that may occur or have existed had to be concerned and evaluated so that targeted guidance could be provided. The following is details:

1) Psychological guidance

The majority of the patients leaving hospital were evaluated to show such mental stress as worry, concern, intension and even anxiety, which lead the patient to feel restless, have difficulty in falling asleep, do not dare to raise arms, fear doing exercise and be too cautious to handle things, which finally will have strongly negative impact on the quality of life [4]. Therefore, the active psychological counseling was adopted to solve these problems: firstly, listen attentively to the patients' catharsis of negative emotions and let the patients describe the details of their emotion, then accurately find the cause of the psychological stress, finally guide the patients to reduce and eliminate those factors. For instance, to help the patients objectively analyze the odds of accidents after implanting the pacemakers without exaggeration, cope patiently with each of their doubts, explain the reasons why palpitation, dizziness and malaise occur when the pacemakers work, introduce such knowledge as the service life, the time for battery depletion and change of pacemakers to patients to alter their negative perceptions of pacemakers. After that, the patients are encouraged to do some things that can adjust emotions and attitudes with the accompanying of family members and nurses. For example: being involved in social activities; cultivating such hobbies as reading books or newspapers, painting, playing chess, weaving, listening to music, singing, dancing, riding a bicycle or playing Taiji, visiting friends or relatives to enjoy affection. Thus, through eliminating the patients' doubts, their attention can be distracted, then they can actively pursue their happiness so much to fade away the negative effects of pacemakers, patients can also be more confident and in a positive frame of mind to face life, which shortens their psychological adaptation process.

2) Behavior guidance

Behavior guidance including the following 7 aspects: 1) Guide the patients to make a medical card with the name, the diagnosis, the type of the pacemakers, the date of implantation, the address, the telephone number, contacting hospital name and the primary nurse. They are required to carry the card with themselves so that they can receive help timely when some unexpected condition occurs. 2) Guide the patients to design self-monitoring record including date, time, pulse, hematopiesis, adverse effects, the time for taking medicine, then generated all information into a table. 3) Guide the patients to learn to feel pulse, measure hematopiesis and make a correct monitoring record. 4) Instruct the patients to exercise the intraoperative limb, gradually increase the intensity and the

range of intraoperative limb activities, avoid taking repeatedly violently actions such as swinging arms and expanding chest and striking the operated-side limb. 5) Instruct the patients to use pacemakers correctly, steering away from high-voltage electric field and magnetic field, also moving away from the environment of strong magnetic field; not to apply electrotherapy, magnetic therapy and magnetic resonance, to make their mobile phones away from the pacemakers, but have access to household appliances and take an elevator, an aircraft and an electric vehicle. Avoid heavier physical labor and excessive weight on the shoulder; keep the skin dry and clean where a pacemaker is implanted, wear soft underwear, and prevent patients from scratching to avoid infection when facing itchy skins. 6) Instruct the patients to make possible arrangement for their daily life to combine rest, entertainment with housework, record the monitoring sheet regularly, take medicine regularly, take food on time and choose the highly digestible foods rich in vitamins and fiber. 7) Guide the patients to master self-protective methods and simple emergency measures like: heart palpitation, chest distress and lack of strength etc., the patients should stop all activities to have a bed rest, and then contact the hospital by telephone after the symptom is alleviated, finally go to the hospital if necessary.

3) Family Members' Guidance

Family members were introduced the knowledge related to precautions and rehabilitation training after implanting the pacemakers in the patients so that they can offer comprehensive monitoring to the patients in life. Instruct the family members accompany the patients come to hospital to follow up within the time prescribed; usually communicate with the family members of the patients and encourage them to look after the patients, visit or accompany the elderly so that they can feel family warmth and affection, experience the joy of life and ignite their confidence in life.

2.2.2. Evaluation Method

The SF-36 scale (Chinese version) was adopted [5] [6] to follow up inquiry into the patients' quality of life, it yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures: Physiological Function (PF), Role-physical (RP), Bodily Pain (BP), Vitality (VT), Social Function (SF), Role Emotional (RE) and Mental Health (MH). There are total 36 items. And the eight scaled scores are the weighed sums of the questions in this section. Each scale is then directly transformed into a 0 - 100 scale on the assumption that each question carries equal weight. So the higher some patient's scores is, the higher his quality of life is.

2.2.3. Statistical Methods

All the data collected were dealt through the software-SPSS11.5. Dimensional scores are expressed by means of ($\bar{x}$) plus or minus standard deviation ($\pm S$). The results of measurements in different time but the same dimension are compared between groups by nonparametric tests.

3. Results

The patients' quality of life has increasingly improved after the system family nursing guidance, 3 months after surgery, the scores of quality of life were higher than that of 1 month after surgery, 6 months after surgery, the scores of quality of life were higher than that of 3 months after surgery (**Table 1**). The nonparametric comparison were carried out on the three group score, and the results have significant differences: between 1 month and 3 months postoperative ($P = 0.001$ and $P = 0.000$), between 3 month and 6 months after operation ($P = 0.000$), and between 1 month and 6 months after surgery ($P = 0.000$), which were also statistically significant (**Table 2**), showing that system family nursing guidance were effective in improving the patients' quality of life with implanted pacemakers.

4. Results Analysis

Systematic nursing is an advanced nursing method proposed with the change of medical model. It emphasizes that nursing is to help patients solve health

Table 1. Evaluation of scores on quality of life for patients guided by systematic family care ($\bar{x} \pm S$, $n = 41$).

team	1 month	3 months	6 months
Physical Function (PF)	70 $\pm$ 3.604	75 $\pm$ 4.100	84 $\pm$ 2.824
Role Physical (RP)	54 $\pm$ 0.958	66 $\pm$ 1.769	86 $\pm$ 3.515
Bodily pain (BP)	77 $\pm$ 2.461	84 $\pm$ 2.957	92 $\pm$ 2.292
General Health (GH)	72 $\pm$ 1.933	75 $\pm$ 2.186	84 $\pm$ 1.651
Vitality (VT)	60 $\pm$ 2.586	71 $\pm$ 3.767	83 $\pm$ 2.488
Social Function (SF)	51 $\pm$ 0.821	69 $\pm$ 1.967	80 $\pm$ 1.745
Role Emotional (RE)	60 $\pm$ 1.440	71 $\pm$ 1.376	85 $\pm$ 1.730
Mental Health (MH)	49 $\pm$ 0.790	67 $\pm$ 1.491	85 $\pm$ 2.409

Table 2. Comparison of patients' quality of life scores between the three groups.

team	1 and 3 months		3 and 6 months		1 and 6 months	
	Z	P	Z	P	Z	P
Physical Function (PF)	-3.742	0.001	-5.749	0.000	-9.491	0.000
Role Physical (RP)	-5.207	0.000	-5.207	0.000	-10.414	0.000
Bodily pain (BP)	-5.207	0.000	-5.207	0.000	-10.414	0.000
General Health (GH)	-3.897	0.000	-5.862	0.000	-9.759	0.000
Vitality (VT)	-5.114	0.000	-5.254	0.000	-10.368	0.000
Social Function (SF)	-5.208	0.000	-5.208	0.000	-10.416	0.000
Role Emotional (RE)	-5.207	0.000	-5.207	0.000	-10.414	0.000
Mental Health (MH)	-5.207	0.000	-5.207	0.000	-10.415	0.000

Comments: Z (Standardized Test Statistic); P (adj. sig).

problems from the aspects of physical, psychological and social support, which are more scientific, systematic and complete than the traditional nursing method. For this reason, by uses the characteristics of systemic care, this study applied the perspectives and methods of systemic care to family nursing, to implement a planned, purposeful, and step-by-step approach to patients with pacemakers returning home, thus to improve the effectiveness of family nursing guidance.

It was showed as the result that the major problems the patients suffered from within 1 month after operation were mental disorder, weakened physiological and declining social function, and all the scores were lower in those three scales, which may be closely related to the physiological and psychological characteristics as well as pacemakers' working: firstly, the elderly patients' cognitive hypofunction, with the implantation and working of pacemakers, they became more dependent upon the pacemakers, cared about and even worried about them all the time; secondly, the increase of sensitivity for the elderly patients lead them to mistake the palpitation resulting from competitive cardiac rhythm and the discomfort arising from discharge for dysfunction of pacemakers themselves; thirdly, the implanted pacemakers among the elderly patients were usually single-chamber cardiac ones, often with such syndrome as dizziness, fullness in head breath hard and lacking in strength, which increased the patients' concerns [7]; lastly, due to their slowing metabolism and the blood supply shortage [8] of their skin, the time for wound healing was relatively long, and they feared wound dehiscence with a sense of discomfort and pruritus, finally adding some burden, so they were afraid of falling asleep, didn't dare to attend social activities, feared doing housework and were timid and overcautious in daily life.

After 3 months, the patients' mental disorders have greatly been improved. The majority of them got used to pacemakers' working, and the scores increased significantly. In the meantime, their abilities to deal with daily life have been restored gradually, they also participated in community activities more frequently, and their scores have grown to a large degree. 6 months after the operation, their mental disorders were almost gone, their daily life was not affected by the working pacemakers, most of them were willing to participate in social activities and communicate with others, and they were optimistic, showing a positive attitude towards life.

5. Conclusion

In conclusion, systematic family nursing guidance can prevent and solve all kinds of problems for patients with implanted pacemakers coming across. It is also proved to be an effective nursing method, and can significantly improve the patients' quality of life with implanted pacemakers. It is remarkable that during nursing guidance, it is necessary to establish the trustfulness to the voices of patients, making explanations to them patiently, observing carefully the patients' behavior and performance and instructing them attentively, which can make the

elderly patients smoothly get rid of such trouble and return to families and the society. This study is limited to improve the quality of life for the patients, and the research on the improvement of the quality of life for the patients' families still needs to be further carried out.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Etiological Analysis of 419 Cases of Digestive Tract Hemorrhage

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Abstract

Aim: To study common cause of digestive tract hemorrhage and the relationship between etiology and age. **Methods:** Retrospective analysis about the data of 419 cases of digestive tract hemorrhage in digestive internal medicine from January 2016 to January 2018 in Jingzhou Central Hospital. **Results:** 419 cases of digestive tract hemorrhage include 305 cases of hemorrhage in upper digestive tract and 114 cases of hemorrhage in lower digestive tract. The first 5 causes of upper digestive tract hemorrhage in middle-aged and young group were: duodenal bulb ulcer, gastric ulcer, esophageal and stomach bottom varices bleeding in cirrhosis of schistosomiasis, compound ulcer, esophageal and stomach bottom varices bleeding in hepatitis B cirrhosis. The first 5 causes of upper digestive tract hemorrhage in elderly group were: gastric ulcer, duodenal bulb ulcer, esophageal and stomach bottom varices bleeding in hepatitis B cirrhosis, esophageal and stomach bottom varices bleeding in cirrhosis of schistosomiasis, gastric cancer. The first 5 causes of lower digestive tract hemorrhage in middle-aged and young group were: ulcerative colitis, colorectal polyps, hemorrhoids, crohn's disease, ischemic bowel disease. The first 5 causes of lower digestive tract hemorrhage in elderly group were: colorectal polyps, colon cancer, ulcerative colitis, ischemic bowel disease, hemorrhoids. **Conclusion:** In the cases of upper digestive tract hemorrhage, peptic ulcer should be paid attention to in middle-aged and young people, and elderly should be noted in gastric cancer. Ulcerative colitis should be paid attention to in middle-aged and young people with lower digestive tract hemorrhage, and elderly should be noted in colorectal polyps and colon cancer.

Keywords

Digestive Tract Hemorrhage, Upper Digestive Tract Hemorrhage, Lower Digestive Tract Hemorrhage, Etiology Analysis

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1. Introduction

Digestive tract hemorrhage is a common clinical disease, both upper digestive tract hemorrhage and lower tract hemorrhage, which is characterized by acute onset and dangerous condition. So to judge the etiology of digestive tract hemorrhage quickly and give corresponding treatment is very important [1]. Previous academics have studied the causes of digestive tract hemorrhage, but the main research group focused on the elderly people. And the etiology analysis of lower tract hemorrhage was more reports [2] [3]. In this paper, there will be retrospective analysis about the data of 419 cases of digestive tract hemorrhage in digestive internal medicine from January 2016 to January 2018 in Jingzhou Central Hospital. The causes of upper digestive tract hemorrhage and lower digestive tract hemorrhage were analyzed in two parts, in order to provide reference for the diagnosis and treatment of digestive tract hemorrhage in clinic.

2. Materials and Methods

2.1. Case Data

A retrospective analysis of 419 cases of digestive tract hemorrhage that have complete clinical data and confirmed in Jingzhou Central Hospital digestive internal medicine from January 2016 to January 2018. In this study, age is the variable, and the subjects were divided into the middle-aged and young group as well as elderly group. The minimum age for the case was 15 years old, and the maximum age is 85 years old. Younger than 60 years old are young and middle-aged groups, and the remaining cases are the elderly group. Among them, 305 cases of upper digestive tract hemorrhage, 227 cases of male, 78 cases of female, 178 cases of middle-aged and young group (15 - 59 years old), 127 cases of elderly group (60 - 85 years old). 114 cases of lower digestive tract hemorrhage, 64 cases of male, 50 cases of female, 80 cases of middle-aged and young group (15 - 59 years old), 34 cases of elderly group (60 - 85 years old).

2.2. Inclusion Criteria

All retrospective study patients were diagnosed with electronic gastroscopy or electronic colonoscopy and other clinical criteria (the clinical symptoms of hematemesis, black feces, or the fecal occult blood test are positive, bleeding spots or active bleeding under electronic gastroscope or electronic colonoscopy). An electronic gastroscope or electronic colonoscopy operator has more than 5 years of experience in digestive endoscopy.

2.3. Statistical Analysis

SPSS23.0 statistical software was used for statistical analysis. Comparison between young group and elderly group using χ^2 test or Fisher exact probability method of the four-grid table data, $P < 0.05$ was considered statistically significant.

3. Results

Of all the selected clinical cases, there were 291 males and 128 females. Among men, 153 cases were hematemesis or black stool, 138 cases were positive for fecal occult blood test. Among women, 75 cases were hematemesis or black stool, 53 cases were positive for fecal occult blood test. The specific results are shown in **Table 1**.

3.1. Etiology Composition of Upper Digestive Tract Hemorrhage

305 cases of upper digestive tract hemorrhage include 178 cases of middle-aged and young group, 127 cases of elderly group. The distribution of main etiology in the young and middle-aged group was as follows: 130 cases of ulcerative disease (73.03%), which include 74 cases of duodenal bulb ulcer (41.57%), 35 cases of gastric ulcer (19.66%), 13 cases of compound ulcer (7.30%), 4 cases of residual gastric ulcer (2.25%), 3 cases of anastomotic ulcer (1.69%), 1 case of esophageal ulcer (0.56%). 36 cases of cirrhosis of the esophagus and gastric fundus varicose hemorrhage (20.22%), which include 24 cases of esophageal and stomach bottom varices bleeding in cirrhosis of schistosomiasis (13.48%), 10 cases of esophageal and stomach bottom varices bleeding in hepatitis B cirrhosis (5.62%), 2 cases of esophageal and stomach bottom varices bleeding in alcoholic cirrhosis (1.12%). The distribution of main etiology in the elderly group was as follows: 78 cases of ulcerative disease (61.42%), which include 35 cases of gastric ulcer (27.56%), 24 cases of duodenal bulb ulcer (18.90%), 7 cases of compound ulcer (5.51%), 6 cases of residual gastric ulcer (4.72%), 4 cases of esophageal ulcer (3.15%), 2 cases of anastomotic ulcer (1.57%). 28 cases of cirrhosis of the esophagus and gastric fundus varicose hemorrhage (22.05%), which include 13 cases of esophageal and stomach bottom varices bleeding in hepatitis B cirrhosis (10.24%), 12 cases of esophageal and stomach bottom varices bleeding in cirrhosis of schistosomiasis (9.45%), 3 cases of esophageal and stomach bottom varices bleeding in alcoholic cirrhosis (2.36%). 13 cases of malignant tumor (10.24%), which include 11 cases of gastric cancer (8.66%), 2 cases of esophageal cancer (1.57%). The statistical results show that duodenal bulb ulcer is predilection in the young and middle-aged group, and gastric cancer is predilection in the elderly group. The differences have statistically significant. Although the incidence of other diseases was different, the difference was not statistically significant. Statistical analysis of the etiology between the two groups is shown in **Table 2**.

3.2. Etiology Composition of Lower Digestive Tract Hemorrhage

114 cases of lower digestive tract hemorrhage, 80 cases of middle-aged and

Table 1. Clinical characteristics of the patients.

Clinical manifestation	Male cases (case)	Female cases (case)
Hematemesis or black stool	153	75
Fecal occult blood test positive	138	53

Table 2. The distribution of upper digestive tract hemorrhage in all age groups case (%).

Etiology	Young and middle-aged group	Elderly group	P value
duodenal bulb ulcer	74 (41.57)	24 (18.90)	<0.01
gastric ulcer	35 (19.66)	35 (27.56)	>0.05
compound ulcer	13 (7.30)	7 (5.51)	>0.05
residual gastric ulcer	4 (2.25)	6 (4.72)	>0.05
anastomotic ulcer	3 (1.69)	2 (1.57)	>0.05
esophageal ulcer	1 (0.56)	4 (3.15)	>0.05
esophageal and stomach bottom varices bleeding in cirrhosis of schistosomiasis	24 (13.48)	12 (9.45)	>0.05
esophageal and stomach bottom varices bleeding in hepatitis B cirrhosis	10 (5.62)	13 (10.24)	>0.05
esophageal and stomach bottom varices bleeding in alcoholic cirrhosis	2 (1.12)	3 (2.36)	>0.05
esophageal cancer	0 (0.00)	2 (1.57)	>0.05
liver cancer	2 (1.12)	0 (0.00)	>0.05
gastric cancer	2 (1.12)	11 (8.66)	<0.01
esophagus and cardia mucosa tear syndrome	4 (2.25)	2 (1.57)	>0.05
gastric polyps	2 (1.12)	1 (0.79)	>0.05
acute erosive gastritis	1 (0.56)	4 (3.15)	>0.05
esophageal papilloma	1 (0.56)	0 (0.00)	>0.05
chronic atrophic gastritis with erosion	0 (0.00)	1 (0.79)	>0.05

young group, 34 cases of elderly group. The distribution of etiology in the young and middle-aged group was as follows: 49 cases of inflammatory bowel disease (61.25%), which include 43 cases of ulcerative colitis (53.75%), 6 cases of crohn's disease (7.50%). 13 cases of colorectal polyps (16.25%). 7 cases of hemorrhoids (8.75%). 6 cases of ischemic bowel disease (7.50%). 4 cases of colon ulcers (5.00%). 1 case of type B paratyphoid (1.25%). The distribution of etiology in the elderly group was as follows: 12 cases of colorectal polyps (35.29%). 6 cases of colon cancer (17.65%). 6 cases of inflammatory bowel disease (17.65%), which include 5 cases of ulcerative colitis (14.71%), 1 case of crohn's disease (2.94%). 4 cases of ischemic bowel disease (11.76%). 3 cases of hemorrhoids (8.82%). 2 cases of ileocecal vascular malformation (5.88%). 1 case of colon ulcers (2.94%). The statistical results show that ulcerative colitis is predilection in the young and middle-aged group, colorectal polyps and colon cancer is predilection in the elderly group. The differences have statistically significant. There was no statistically significant in the incidence of other diseases. Statistical analysis of the etiology between the two groups is shown in **Table 3**.

Table 3. The distribution of lower digestive tract hemorrhage in all age groups case (%).

Etiology	Young and middle-aged group	Elderly group	P-value
ulcerative colitis	43 (53.75)	5 (14.71)	<0.01
crohn's disease	6 (7.50)	1 (2.94)	>0.05
colorectal polyps	13 (16.25)	12 (35.29)	<0.05
hemorrhoids	7 (8.75)	3 (8.82)	>0.05
ischemic bowel disease	6 (7.50)	4 (11.76)	>0.05
colon ulcers	4 (5.00)	1 (2.94)	>0.05
colon cancer	0 (0.00)	6 (17.65)	<0.01
type B paratyphoid	1 (1.25)	0 (0.00)	>0.05
ileocecal vascular malformation	0 (0.00)	2 (5.88)	>0.05

4. Discussion

Digestive tract hemorrhage has the characteristic of acute onset and rapid progression of the course, often due to excessive blood loss leading to shock. It is a common clinical critical illness. In recent years, with the continuous development of digestive endoscope technology, especially the development of capsule endoscopy and small enteroscopy, the new concept of digestive tract segmentation has gained more and more recognition. The new definition uses the duodenal papilla and the ileocecal valve as an anatomical sign, the digestive tract is divided into the upper digestive tract, the middle digestive tract and the lower digestive tract. Thus, the small intestinal bleeding is independent, called middle digestive tract hemorrhage. The upper and lower digestive tract hemorrhage discussed in this paper is referred to in the new classification method.

In this study, it includes 305 cases of upper digestive tract hemorrhage and 114 cases of lower digestive tract hemorrhage; the ratio is 2.68:1; there are more cases of upper digestive tract hemorrhage than lower digestive tract hemorrhage. It is consistent with previous research results [4]. In the cases of upper digestive tract hemorrhage, it includes 227 cases of male, 78 cases of female; the proportion of males and females is 2.91:1. The number of male cases is higher than female cases. It suggests that the incidence of upper digestive tract hemorrhage is related to sex, this result is consistent with previous research in China [5]. Among them, the first 5 causes in middle-aged and young group were: duodenal bulb ulcer, gastric ulcer, esophageal and stomach bottom varices bleeding in cirrhosis of schistosomiasis, compound ulcer, esophageal and stomach bottom varices bleeding in hepatitis B cirrhosis. Of these, there are 3 types of peptic ulcer and 2 types of cirrhosis of the esophagus and gastric fundus varicose hemorrhage. In the case of duodenal bulb ulcer, the difference between young group and old group is statistically significant. This is consistent with the relevant reports [5]. This may be related to the stressful life of young people in today's society and unhealthy habits such as drinking, smoking, staying up late. In all of the causes, esophageal and stomach bottom varices bleeding in cirrhosis of

schistosomiasis in the middle-aged and young group accounted for up to 13.48%. This may be related to the location of Jingzhou in the schistosomiasis endemic area. Many people have been in contact with the epidemic water. However, there was no related examination of schistosomiasis infection until clinical symptoms appear such as esophagus and gastric fundus varicose hemorrhage. Hepatitis B cirrhosis is in the 5th place, it shows that the current status of hepatitis B infection in China is still severe [6]. Strengthening the prevention and treatment of hepatitis B is still long way to go.

In cases of upper digestive tract hemorrhage in the elderly group, the first 5 causes were: gastric ulcer, duodenal bulb ulcer, esophageal and stomach bottom varices bleeding in hepatitis B cirrhosis, esophageal and stomach bottom varices bleeding in cirrhosis of schistosomiasis, gastric cancer. Elderly patients with arteriosclerosis, gastrointestinal mucosal blood supply is not sufficient, so leading to mucosal atrophy, gastric acid and pepsin invasion could easily cause ulcers [4]. And elderly patients often have a history of taking aspirin or NSAIDs drugs. It can also cause gastric mucosal injury and gastric ulcer. The proportion of gastric cancer is 8.66%, compared with the middle-aged and young groups; the difference is statistically significant. Malignant tumors are often found in elderly patients, and there are no specific manifestations in the early days. When there are obvious clinical symptoms such as hematemesis, black stool, and so on, it is in the middle and late stages. The therapeutic effect is poor. Therefore, it is of great significance to make a census of malignant tumor in elderly patients.

In the cases of lower digestive tract hemorrhage, the first 5 causes in middle-aged and young group were: ulcerative colitis, colorectal polyps, hemorrhoids, crohn's disease, ischemic bowel disease. The first 5 causes in elderly group were: colorectal polyps, colon cancer, ulcerative colitis, ischemic bowel disease, hemorrhoids. Ulcerative colitis occupation ratio in middle-aged and young group is significantly higher than in elderly group, colon cancer and colorectal polyps occupation ratio in elderly group is significantly higher than in middle-aged and young group, the difference is statistically significant, consistent with Guoxiuli and other reports [7]. Ulcerative colitis often occurs in middle and young people, clinical symptoms often occur at age 20 - 40, diarrhea and mucous blood stool are found in most patients, the prevalence of ulcerative colitis in China has increased markedly in recent years [1], this result is consistent with this study. Patients with colon cancer are still mainly occurred in elderly, it also confirms the traditional idea that malignancy is often occurs in elderly people. Colorectal polyps are the new organisms which overgrowth in the colorectal mucosa. According to the pathological results, it can be divided into inflammatory polyps, hyperplastic polyps and adenomatoid polyps, and the incidence of adenomatoid polyps is the highest. Adenomatoid polyps are divided into tubular adenoma, villous adenoma and mixed-type adenoma. At present, colon adenoma-colon cancer sequential theory has been accepted by the vast number of medical workers, the diagnosis of colonic polyps is of great significance for the prevention of colon cancer [8]. Foreign related research reports [9], the common

cause of lower digestive tract hemorrhage are intestinal diverticulum, ischemic bowel disease, perianal disease, in this study, the common causes of lower digestive tract hemorrhage are ulcerative colitis, colorectal polyps, ischemic bowel disease, perianal disease (hemorrhoids), this difference may be related to different living habits, environmental factors and ethnic differences between China and foreign countries.

Of course, there are many shortcomings in this study. First, this study is a single center retrospective study. The number of cases is less and the etiology of digestive tract hemorrhage cannot be well represented. Secondly, the subjects included in this study were diagnosed by gastroscopy or enteroscopy. None of the patients who had symptoms of digestive tract hemorrhage without gastroscopy or enteroscopy examination were included in the study. For example, digestive tract hemorrhage is serious and surgical cases are not included in the study area. This may also affect the statistics of the digestive tract hemorrhage etiology. It is hoped that the follow-up researchers should take it as a warning, and make a better study on etiology of digestive tract hemorrhage.

5. Conclusion

In a word, in the etiology of upper digestive tract hemorrhage, the incidence of the duodenal ulcer in the middle-aged and young group was higher than that in the elderly group, and the incidence of the gastric cancer in the elderly group was higher than that in the middle-aged and young group. In the etiology of lower digestive tract hemorrhage, the incidence of the ulcerative colitis in the middle-aged and young group was higher than that in the elderly group, and the incidence of the colorectal polyps and colon cancer in the elderly group was higher than that in the middle-aged and young group. The difference is statistically significant. This is a reference for the digestive endoscopy physician in gastrointestinal endoscopy for patients with digestive tract hemorrhage.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Analysis of the Pathological Examination Results of 100 Colon Polyps Cases after EMR or ESD Operation

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Abstract

Aim: To study the characteristics of EMR (endoscopic mucosal resection) or ESD (endoscopic submucosal dissection) postoperative pathological examination of colonic polyps in different age groups, and the difference of pathological examination after EMR or ESD operation. **Methods:** A retrospective analysis was made of the EMR or ESD postoperative pathological data of 100 cases of colonic polyps patients in the Jingzhou Central Hospital digestive internal medicine. The time is from March 2016 to March 2018. **Results:** In 100 cases of EMR or ESD operation, there are 65 cases of young and middle-aged group. Pathological examination results include: 34 cases of adenomatous polyp, 18 cases of inflammatory polyp, 11 cases of benign tumors, 1 case of malignant tumor, 1 case of hyperplastic polyp. There are 35 cases of elderly group. Pathological examination results include: 27 cases of adenomatous polyp, 2 cases of inflammatory polyp, 2 cases of benign tumors, 4 cases of malignant tumor. 71 cases of complete EMR operation include: 51 cases of adenomatous polyp, 17 cases of inflammatory polyp, 3 cases of benign tumors; 29 cases of complete ESD operation include: 10 cases of adenomatous polyp, 3 cases of inflammatory polyp, 10 cases of benign tumors, 5 cases of malignant tumor, 1 case of hyperplastic polyp. **Conclusion:** For the pathological examination results after EMR or ESD operation, the proportion of inflammatory polyps in the young and middle-aged group was greater than that in the elderly group. The proportion of adenomatous polyps in the elderly group was larger than that in the young and middle-aged group. The proportion of adenomatous polyps in EMR was greater than that of ESD. The proportion of benign tumors and malignant tumors in ESD was greater than that of EMR. The difference has statistical significance.

*Contributed equally.

Keywords

Colon Polyps, Endoscopic Mucosal Resection, Endoscopic Submucosal Dissection, Pathological Examination Results

1. Introduction

With the development of gastrointestinal endoscopy, EMR and ESD are widely used methods in treatment of gastrointestinal polyps disease [1]. EMR refers to the injection of drugs in the submucosa of the lesion to form a liquid pad, and then cut off a chunk of mucous tissue. EMR avoids the defects of the traditional methods that the removal of mucosal biopsy tissue samples is too small and many cases have failed to make a correct diagnosis. It is an effective and reliable method for the treatment of precancerous lesions and early cancer. It has become one of the first choices for diagnosis and treatment of early cancer and critical lesions. The advantage is that it can increase the area and depth of resection, and achieve a radical cure. It is mainly suitable for the resection of partial sessile polyps, flat or shallow sunken type polyps, leiomyoma, early cancer (including esophagus, stomach, colon early cancer). EMR operation is safe and reliable, with fewer complications. ESD is a new therapeutic method in recent years and is also a promising technique for clinical applications. To allow more early gastrointestinal cancer to be completely resected under endoscopy, the pain of the laparotomy and the removal of the organ can be avoided. This study retrospectively analyzed the pathological examination results of 100 cases of colonic polyps after EMR or ESD operation in the evaluation of EMR and ESD postoperative pathological examination characteristics.

2. Object and Methods

First we need to claim that this investigation was approved by the Jingzhou central hospital ethics committee. We collect 100 patients in March 2016 to March 2018 in the Jingzhou center hospital digestive internal medicine, which using colonoscopy colon polyps was observed. The types of polyps that conform to the standard include: lateral developmental polyps, sessile or rebagliati polyps, polyp canceration without infringing submucosa (In combination with endoscopic ultrasonography to observe). EMR operation was used which diameters larger than 0.5 cm and less than 2.0 cm. ESD operation was used for colonic polyps with a diameter greater than 2.0 cm. Patients with severe cardiopulmonary disease, hemopathy, coagulation dysfunction and diseased elevation negative are excluded. All patients were given preoperative consent before colonoscopy and treatment. Both surgical treatments use endoscopic with EMR or ESD in our hospital endoscopy center. After the operation, lesion resection complete and check in the pathological department. All of the research objects are: the male 55 cases, female 45 cases, EMR operation 71 cases, ESD operation 29 cases. Young and middle-aged group (Less than 60 years of age) is 65 cases; elderly group

(Greater than or equal to 60 years of age) is 35 cases. Referring all of the pathological examination results after the operation, EMR and ESD postoperative pathological examination characteristics are analyzed with a retrospective method.

3. Statistical Analysis

Using SPSS23.0 statistical software for statistical analysis, the data analysis using the χ^2 test or Fisher's exact probability method of four table data, $P < 0.05$ for the difference is statistically significant.

4. Results and Conclusion

65 cases of young and middle-aged group completed EMR or ESD operation, pathological examination results include: 34 cases of adenomatous polyp (52.31%), 18 cases of inflammatory polyp (27.69%), 11 cases of benign tumors (16.92%), 1 case of malignant tumor (1.54%), 1 case of hyperplastic polyp (1.54%); 35 cases of elderly group completed EMR or ESD operation, pathological examination results include: 27 cases of adenomatous polyp (77.14%), 2 cases of inflammatory polyp (5.71%), 2 cases of benign tumors (5.71%), 4 case of malignant tumor (11.43%), 0 case of hyperplastic polyp (0.00%). Among them, adenomatous polyp elderly group share is greater than the young and middle-aged group, the difference is statistically significant ($P < 0.05$). Inflammatory polyp young and middle-aged group share is greater than the elderly group. The difference is statistically significant ($P < 0.05$). Specific results are shown in **Table 1**.

Among 71 cases completed EMR operation, pathological examination results include: 51 cases of adenomatous polyp (71.83%), 17 cases of inflammatory polyp (23.94%), 3 cases of benign tumors (4.23%), 0 case of malignant tumors (0.00%), 0 case of hyperplastic polyp (0.00%); among 29 cases completed ESD operation, pathological examination results include: 10 cases of adenomatous polyp (34.48%), 3 cases of inflammatory polyp (10.34%), 10 cases of benign tumors (34.48%), 5 cases of malignant tumor (17.24%), 1 case of hyperplastic polyp (3.45%). Among them, adenomatous polyp in EMR operation group share is greater than the ESD operation group, the difference is statistically significant ($P < 0.01$). Benign tumors and malignant tumor in ESD operation group share is greater than the EMR operation group. The difference is statistically significant ($P < 0.01$). Specific results are shown in **Table 2**.

Table 1. EMR, ESD operation pathological examination results among all age groups case (%).

Pathological examination results	Young and middle-aged group	Elderly group	P-value
adenomatous polyp	34 (52.31)	27 (77.14)	<0.05
inflammatory polyp	18 (27.69)	2 (5.71)	<0.05
benign tumors	11 (16.92)	2 (5.71)	>0.05
malignant tumors	1 (1.54)	4 (11.43)	>0.05
hyperplastic polyp	1 (1.54)	0 (0.00)	>0.05

Table 2. EMR, ESD operation pathological examination results case (%).

Pathological examination results	EMR	ESD	P-value
adenomatous polyp	51 (71.83)	10 (34.48)	<0.01
inflammatory polyp	17 (23.94)	3 (10.34)	>0.05
benign tumors	3 (4.23)	10 (34.48)	<0.01
malignant tumors	0 (0.00)	5 (17.24)	<0.01
hyperplastic polyp	0 (0.00)	1 (3.45)	>0.05

5. Discussions

At present, colonic adenoma-colon cancer sequential theory has been got approval of the broad masses of medical workers. So the judgment of the properties of colonic polyps is of great significance for the secondary prevention of colon cancer [2]. In this study, there are 100 cases of colon polyps, 61 cases of adenomatous polyp (61.00%), in the highest proportion of all pathological findings. Elderly group share is greater than the young and middle-aged group, and the difference is statistically significant ($P < 0.05$). Colon adenomas are prone to progression to colon cancer. The elderly patients have high incidence of malignant tumor. The results of this study are consistent with this. In the young and middle-aged group, adenomatous polyp proportion is the highest, so for the young and middle-aged colonoscopy examination, revealed polypoid lesions should also be cautious; conventional endoscopic biopsy to understand the polyp property is very important. Inflammatory polyp in young and middle-aged group is greater than the elderly group, and the difference is statistically significant ($P < 0.05$). This may be related to the diameter of colonic polyps in young and middle-aged group that was smaller than that of elderly group, and the larger diameter polyps are more likely to be malignant. In the elderly group, the proportion of malignant tumor was greater than that of young and middle-aged group, but there is no statistically significant difference. This may be associated with the selection of polyps in EMR and ESD operations, because endoscopic polyp morphology changes obviously and large diameter cannot be done by EMR or ESD operation patients to surgical treatment. These cases data are not included in the research. In a word, for endoscopic colonic polyps that can be treated by EMR and ESD operation, higher proportion of inflammatory polyp in young and middle-aged group and higher proportion of adenomatous polyp in elderly group, need to be mindful for cancerous possibility.

Among 100 cases of colon polyps of this study, the implementation of EMR operation is 71 cases, and there are 29 cases with ESD operation. Adenomatous polyp implemented EMR ratio is greater than the ESD operation, and the difference is statistically significant ($P < 0.01$). Adenomatous polyp includes tubular adenoma, villous adenoma and tubular-villous adenoma. Among them, villous adenoma is the most likely to be malignant tumor, followed by tubular-villous adenoma. Tubular adenoma has the lowest probability of malignancy. In this

study, tubular adenoma is the highest proportion, and the polyps' diameter which uses EMR operation was smaller than the polyps which use ESD operation, with small malignant probability. Hence, the proportion of adenomatous polyp in EMR operation is greater than the ESD operation. Similar to this principle, in the tumor diseases, whether it is benign or malignant tumor, implementation of ESD operation proportion is greater than the implementation of EMR operation, and the difference is statistically significant ($P < 0.01$). At present, with the rapid development of digestive endoscopy technology, EMR and ESD operation in the treatment of digestive tract polyps play an increasingly important role. Studies from Huang Jin have shown that EMR and CIEMR (conventional endoscopic mucosal resection with circumferential incision) have a good effect in the treatment of rectal benign tumor [3]. Some scholars through retrospective study pointed out that: in the complex colon polyps, 75% of the patients have EMR operation treatment alternative to surgical treatment [4]. In the case of 21 months infants, who have huge gastric hyperplastic polyp, there is successful application of ESD removing polyps, and another study shows that ESD is used in esophageal verrucous malignant tumor resection [5] [6]. Related studies show that EMR and ESD pathological examinations after operation have differences with preoperative endoscopic biopsy results, and the difference is statistically significant. The pathological examination malignant degree after EMR and ESD operation is higher than the preoperative endoscopic biopsy [7]. This suggests that preoperative endoscopic biopsy results can only be used as a reference. Complete specimens submission to pathologic examination is the gold standard in pathological diagnosis after EMR and ESD operation.

This article has many shortcomings as a retrospective study. First of all, this study is a single center retrospective study. The number of cases collected is relatively small. The number of cases in each subgroup is less and has some impact on the statistical analysis. Secondly, because the EMR and ESD operation time in Jingzhou center hospital digestive endoscopy center is short, and the accumulation of experience is limited. For some polyps with complex structure or larger diameter, surgical treatment is often recommended. This part of the case is not covered by the study. It will also have implications for this study. At the end of this article, we hope to have more scholars on the research of EMR and ESD, so as to provide more and better clinical reference for digestive endoscopy physicians.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Relationship between IL-23R rs11209026 Gene Polymorphism and Susceptibility to Acute Coronary Syndrome

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Abstract

Background: Several studies illustrated that IL-23/Th17 axis could be an important pro-inflammatory pathway in atherosclerosis. As a key element in this inflammatory mechanism, interleukin-23 receptor (IL-23R) may play a critical role in the pathological process of atherosclerosis. Single nucleotide polymorphisms (SNPs) in IL-23R have recently been consistently found to be associated with atherosclerosis diseases. However, its association with acute coronary syndrome (ACS) is still indistinct. Here, we discussed whether genetic polymorphisms in IL-23R (rs11209026 G/A) were associated with susceptibility to ACS. **Methods:** Among 160 patients with ACS, it includes 80 patients with unstable angina pectoris (UAP), 80 patients with myocardial infarction (MI), and 80 control subjects were selected randomly. The polymorphisms of IL-23R (rs11209026 G/A) were analyzed by the Sanger method. **Results:** Data showed that percentages of rs11209026 AG genotypes were significantly lower in ACS group (including: UAP and MI) than in controls (odds ratio [OR] = 0.324, 95% confidence interval [CI]: 0.148 - 0.712, $p = 0.005$; OR = 0.351, 95% CI: 0.135 - 0.910, $p = 0.031$; OR = 0.303, 95% CI: 0.112 - 0.817, $p = 0.018$, respectively). Furthermore, there was no correlation between rs11209026 G/A SNP and dyslipidemia-associated ACS. **Conclusions:** The variant of the rs11209026 polymorphism in IL-23R gene might decrease the risk of ACS, and these data suggest that AG genotype of the rs11209026 G/A polymorphism may act as a protective factor for acute coronary syndrome and subtype of ACS.

*Contributed equally.

Keywords

IL-23R, Gene Polymorphism, Acute Coronary Syndrome

1. Introduction

As a major public health issue, coronary heart disease (a clinical form of coronary atherosclerosis) has been the leading cause of mortality and morbidity worldwide [1]. More and more evidence has confirmed that atherosclerosis is a chronic inflammatory disease of the arterial vessel wall. Many inflammatory cells and inflammatory mediators play an important role in the occurrence, development and thrombosis among atherosclerotic lesions [2]. Acute coronary syndrome (ACS) is a clinical syndrome of coronary heart disease (CHD); it is a progressive inflammatory disease of the coronary arterial vascular wall and remains among high risk of mortality, which includes unstable angina pectoris (UAP), non-ST elevation myocardial infarction (NSTEMI), and ST elevation myocardial infarction (STEMI) [1] [2].

The key mechanism of ACS is atherosclerotic plaque rupture or erosion and platelet thrombus could occlude the lumen of the atherosclerotic coronary. Atherosclerotic plaque rupture is the key mechanism of ACS. Inflammation plays an important role in the rupture of the vulnerable plaques by regulating the stability of atherosclerotic plaque, as well as the plaque's thrombogenic potential [3]. To understand the mechanisms of inflammation in AS and ACS, several systemic inflammatory markers have been indicated as risk factors in cardiovascular events, especially in ACS [4]. Recently, a new potential marker IL-23 has drawn great attention. Interleukin (IL)-23 is a heterodimeric proinflammatory cytokine composed of a p19 subunit and a p40 subunit, which is also part of IL-12 [5]. IL-23 is mainly produced by activated DCs, monocytes, and macrophages. The biological effect of IL-23 is achieved by binding to the specific with high affinity IL-23 receptor (IL-23R) on the surface of the target cell [6]. The IL-23R heterodimeric complex is composed of the IL-12R β 1 subunit and another specific IL-23R subunit, which is considered to be essential for the Th17 cell mediated immune response. Type 17 helper cells (Th17) are a recently discovered lineage of proinflammatory CD4⁺ T cells and IL-17 is a main effect cytokine produced by Th17 [7].

Moreover, abundant attention has focused on the novel inflammation pathway: IL-23/Th17 axis, which has been shown to play a central role in chronic inflammatory and autoimmune diseases. Notably, previous researches tended to consider IL-23R, and IL-23 plays a crucial role in initiating, maintaining and accelerating the IL-23/Th17 inflammatory signal transduction pathway. Several studies indicate that IL-23 can be involved in the development of atherosclerosis. Researchers have shown that mRNA levels of IL-23 and IL-23R were markedly

increased in carotid plaques and IL-23 increased IL-17 release in monocytes and particularly in peripheral blood mononuclear cells that could aggravate carotid atherosclerosis, which indicated the possible role for the IL-23/Th17 Axis [8]. Another report has presented that IL-23R rs6682925T/C polymorphism may act as a risk factor of CHD and subjects carrying rs6682925TC and CC genotypes had significantly increased mRNA level of IL-23R in PBMCs than those with TT genotype [9]. Meanwhile, Kave *et al.* suggested that IL-23R rs11209026 G > A polymorphism is negatively correlated with the risk of AS. The polymorphism of this gene polymorphism may inhibit the progression of AS [10]. Furthermore, IL-23R was suggested to play an important part of the IL-23/Th17 pathway and it may also play critical roles in atherosclerosis and atherosclerosis-related diseases.

While various clinically relevant single-nucleotide polymorphisms (SNPs) sites have been reported in the IL-23R gene in order to explore the probability of genetic susceptibility to atherosclerosis. However, the subjects of case group in the previous studies were coronary heart disease and participants involved in the control group were healthy people (no coronary angiography). Furthermore, all subjects in present study were underwent coronary angiography, and the patients in case group were all patients with clinically diagnosed acute coronary syndrome. In addition, there are few studies explore the correlation between IL-23R gene polymorphisms and genetic susceptibility to acute coronary syndromes. In the current study, the subjects of control group were all with normal coronary artery, and patients in this case group were all acute coronary syndromes. Additionally, no study has explored the association of genetic susceptibility between rs11209026 G/A and ACS. Therefore, our study aims to discuss the possible association between IL-23R rs11209026 G/A variants and incidence of ACS.

2. Materials and Methods

2.1. Patients and Controls

This case-control study recruited 240 patients who presented with cardiovascular symptoms to Jingzhou Central Hospital. All patients who underwent coronary angiography and other types of heart diseases, severe liver, kidney, brain or lung dysfunction, malignant tumor, autoimmune diseases, connective tissue diseases, infectious diseases were excluded from the study. Coronary stenosis was considered significant in the presence of a luminal diameter narrowing of >50% of at least one pericardial coronary artery. According to the Foundation of the American College of Cardiology/American Heart Association (ACCF/AHA), the 240 patients were divided into case group (Acute coronary syndrome) and control group (normal coronary arteries). The cases group including 160 patients and was divided into two subgroups. Unstable angina group including 80 patients with unstable angina pectoris (UAP), Myocardial infarction (MI) group contain 44 patients with non-ST-elevation myocardial infarction (NSTEMI) and

36 patients with ST-elevation myocardial infarction (STEMI). The control group involved 80 patients who were normal coronary arteries. All the participants involved in this study completed a standard questionnaire about their personal history, which included data on age, sex, smoking status, history of hypertension, history of diabetes and some biochemical indicators obtained from patient cases. All individuals enrolled were from the Han population in China. This study was approved by the ethics committee of Jingzhou Center Hospital. All subjects were signed the informed consent.

2.2. DNA Extraction and Genotyping

Whole blood samples were collected in EDTA-K2 tubes from all subjects and then frozen. Genomic DNA was extracted from frozen whole blood using the Sangon Biotech DNA Extraction Kit and Purification Kits were used to purify genomic DNA of all subjects, and the DNA extracts were stored at -70°C until the time of analysis. The rs11209026 G/A polymorphisms were genotyped by the Sanger DNA sequencing method assay. The target sequencing fragment was amplified by the ABI 7500 PCR instrument (Applied Biosystems, Inc). Oligonucleotide primers were designed by Primer Premier5 for the PCR. The applied primer sequences included 5'-AAACAGTCACTCTGTGGCCTAAAG-3' (Forward-Primer) and 5'-GGAAAGACATTTGT AGAGAGTTTGG-3' (Reverse-Primer). The total volume of the PCR was 50 μl , including 25 μl 2 $\times$ Taq PCR MasterMix, 2 μl each primer (10 $\mu\text{mol/L}$), 15 μl Sterilized ddH₂O, 6 μl DNA template (<1 μg). The reaction conditions of PCR: initial denaturation for 3 minutes at 95°C , followed by 30 cycles of 30 seconds at 95°C (denaturation), 30 seconds at 54°C (annealing), 1 minute at 72°C (elongation), and 10 minutes at 72°C after 30 cycles (final elongation). 2% agarose electrophoresis was used to detect the specificity of the amplified products after the PCR reaction. The amplified products was a fragment of 443 base pairs The DNA sequencing of all amplified products was completed by Sangon Biotech (Wuhan) Co., Ltd. (Forward primer sequencing).

2.3. Statistical Analysis

Continuous data that was distributed normally was described using mean $\pm$ standard deviations (SD); Continuous data that was distributed non-normally was described using median and quartile range; Categorical data was described using the number of cases and the percentage (%). According to types of the data above, the Student t-test/one-way anova, the Mann-Whitney test and the chi-square (χ^2) test were used to analyse the difference of groups respectively. The χ^2 goodness-of-fit test was used to analyse Hardy-Weinberg equilibrium. The crude odds ratios (OR) with 95% confidence interval (CI) were used to assess the frequencies of genotypes and alleles. A two-tailed p-value of <0.05 has been considered statistically significant. Statistical Package for Social Science (SPSS) software version 23 was used for the general statistical analyses.

3. Results

3.1. Clinical Characteristics of Patients and Controls

The clinical characteristics of all the participants are shown in **Table 1**. There was no significant difference in gender ($p > 0.05$), age ($p > 0.05$), TC (Total Cholesterol) ($p > 0.05$), LDL-C (Low Density Lipoprotein Cholesterol) ($p > 0.05$), Apolipoprotein B ($p > 0.05$) between the ACS patients and the Control group subjects (normal coronary arteries). And the participants of ACS comparison with the controls, UAP and MI patients exhibited higher level of FBG, TG, HDL-C and BMI, increased frequency of smoking, hypertension, diabetes and dyslipidemia, all of which are the defined risk factors of ACS (**Table 1**).

3.2. Distributions of the IL-23R rs11209026 Polymorphisms in the ACS Cases and Controls

Detection of IL-23R rs11209026 polymorphisms genotypes by Sanger method and the genotype distributions of SNP of IL-23 receptor and allele frequencies are summarized in **Table 2**. Genotypes of the rs11209026 polymorphism among

Table 1. Clinical characteristics of participants in the study.

Characteristics	Subtype of ACS		Controls (n = 80)	P		
	UAP (n = 80)	MI (n = 80)		MI vs controls	UAP vs controls	MI vs UAP
Gender (M/F)	50/30	47/33	43/37	>0.05	>0.05	>0.05
Age (years, mean $\pm$ SD)	60.66 $\pm$ 9.05	59.23 $\pm$ 10.04	58.39 $\pm$ 9.43	>0.05	>0.05	>0.05
BMI (kg/m ²)	24.94 $\pm$ 2.27	25.9 $\pm$ 4.24	23.83 $\pm$ 3.31	>0.05	>0.05	>0.05
Smoking n (%)	39 (48.8)	44 (55)	25 (31.3)	<0.01	<0.05	>0.05
Hypertension n (%)	58 (72.5)	65 (81.3)	44 (55)	<0.01	<0.01	>0.05
Diabetes n (%)	22 (27.5)	31 (38.8)	7(8.7)	<0.01	<0.01	>0.05
Dyslipidemia (%)	43 (53.8)	53 (66.3)	18 (25.7)	<0.01	<0.01	>0.05
FBG (mmol/L)	6.28 $\pm$ 2.58	6.50 $\pm$ 2.94	5.12 $\pm$ 0.71	<0.01	<0.01	>0.05
TC (mmol/L)	4.33 $\pm$ 1.18	4.39 $\pm$ 1.14	4.47 $\pm$ 0.95	>0.05	>0.05	>0.05
TG (mmol/L)	2.23 $\pm$ 1.95	1.74 $\pm$ 0.99	1.33 $\pm$ 0.26	<0.01	<0.01	>0.05
LDL-C (mmol/L)	2.28 $\pm$ 0.89	2.55 $\pm$ 1.04	2.53 $\pm$ 0.61	>0.05	>0.05	>0.05
HDL-C (mmol/L)	1.13 $\pm$ 0.29	1.08 $\pm$ 0.31	1.33 $\pm$ 0.26	<0.01	<0.01	>0.05
Apob (g/L)	0.85 $\pm$ 0.29	0.93 $\pm$ 0.27	0.86 $\pm$ 0.20	>0.05	>0.05	>0.05
UA (μ mol/L)	383.29 $\pm$ 99.79	364.44 $\pm$ 91.57	320.96 $\pm$ 85.93	<0.01	<0.01	>0.05
BUN (mmol/L)	5.53 $\pm$ 1.93	5.45 $\pm$ 1.71	4.85 $\pm$ 1.38	<0.05	<0.05	>0.05
Cr (μ mol/L)	73.90 $\pm$ 23.49	81.68 $\pm$ 22.45	64.18 $\pm$ 21.05	<0.01	<0.01	<0.05

UAP: unstable angina pectoris; MI: myocardial infarction; BMI: body mass index; FBG: Fasting Blood Glucose; TC: Total Cholesterol; TG: Triglyceride; LDL-C: Low Density Lipoprotein Cholesterol; HDL-C: High Density Lipoprotein Cholesterol; Apob: Apolipoprotein B; UA: Uric acid; BUN: blood urea nitrogen; Cr: creatinine; $P < 0.05$ is significant.

Table 2. The genotypes and alleles frequencies of the rs11209026 polymorphism within IL-23R gene in all groups.

rs11209026	Controls (n = 80)	ACS (n = 160)				Subtype of ACS					
						UAP (n = 80)			MI (n = 80)		
		n (%)	n (%)	χ^2	P	n (%)	χ^2	P	n (%)	χ^2	P
Genotypes											
GG	63 (78.8)	147 (91.9)	8.400	0.004	73 (91.3)	4.902	0.027	74 (92.5)	6.144	0.013	
AG	17 (21.3)	13 (8.1)			7 (8.8)			6 (7.5)			
Alleles											
G	143 (89.4) ^a	307 (95.9) ^a	7.840	0.005	153 (95.5) ^a	4.505	0.034	154 (96.3) ^a	5.668	0.017	
A	17 (10.6) ^a	13 (4.1) ^a			7 (4.4) ^a			6 (3.8) ^a			

^aFrequency of a group of A alleles = total number of A alleles in the group/(total number of A alleles + total number of G alleles in the group).

the controls were in accordance with the Hardy-Weinberg equilibrium ($p > 0.05$). As for the ACS cases and controls, percentages of GG and AG genotypes were 91.9% and 8.1% in the ACS patients ($\chi^2 = 8.400$, $P = 0.0004$), and were 78.8% and 21.3% in the controls (normal coronary arteries). As for the subtype of ACS cases and the controls, frequency of GG and AG genotypes were 91.3%, 8.8% in the UAP patients ($\chi^2 = 4.902$, $P = 0.027$); were 92.5%, 7.5% in the MI patients ($\chi^2 = 6.144$, $P = 0.013$), and were 78.8% and 21.3% in the controls. In addition, the AA genotype was not identified in the present study. Also, A allele of the rs11209026G/A SNP showed clearly decreased percentage in ACS compared with controls (4.1% vs. 10.6%, $p < 0.005$). Additionally, significant difference in the IL-23R A allele frequencies was detected in either UAP or MI patients contrasted with controls (4.4% vs. 10.6%, $p < 0.034$; 3.8% vs. 10.6%, $p < 0.017$).

3.3. Associations of the Polymorphisms of IL-23R Gene (rs11209026) with ACS Risk

Multinomial logistic regression results in current research adjusted by: age and sex. The Association analysis between genotype of rs11209026 and risk of ACS in case group and control group are reported in **Table 3**. From the results obtained so far, it seem that the risk of ACS patients who carriers with rs11209026 AG genotype was 0.324 times than those with AA genotype carriers (OR: 0.324, 95% CI: 0.148 - 0.712, $p = 0.005$). Similar tendencies were observed in UAP and MI group, patients with AG genotype 0.351 (UAP) and 0.303 (MI) times more odds of developing atherosclerosis than those with AA genotype (OR: 0.351, 95% CI: 0.135 - 0.910, $p = 0.031$ and OR: 0.303, 95% CI: 0.112 - 0.817, $p = 0.018$, respectively). These results indicate that rs11209026 G/A SNP is associated with decreased susceptibility to ACS.

3.4. Association between rs11209026 G/A and Dyslipidemia in ACS

Dyslipidemia is a crucial risk factor of ACS. We, therefore, explored whether

rs11209026 G/A was associated with dyslipidemia in ACS. In the ACS group, 96 participants were diagnosed with dyslipidemia. Percentages of rs11209026 AG genotype and A allele were not significantly difference in patients with dyslipidemia than those without dyslipidemia (OR = 1.067, 95% CI: 0.330 - 3.451, $p = 0.913$ and OR = 1.064, 95% CI: 0.337 - 3.356, $p = 0.915$, respectively, **Table 4**). In order to survey whether rs11209026 G/A SNP is independently correlated with dyslipidemia, we investigated this polymorphism with dyslipidemia in the normal coronary arteries group (control). However, there was no difference in the

Table 3. Association analysis between genotype of rs11209026 and risk of ACS in case group and control group by the logistic regression.

rs11209026	ACS (n = 160)		Subtype of ACS			
			UAP (n = 80)		MI (n = 80)	
	OR (95%CI) ^a	P ^a	OR (95%CI) ^a	P ^a	OR (95%CI) ^a	P ^a
Genotypes						
GG	1		1		1	
AG	0.324 (0.148 - 0.712)	0.005	0.351 (0.135 - 0.910)	0.031	0.303 (0.112 - 0.817)	0.018
Alleles						
G	1		1		1	
A	0.353 (0.166 - 0.751)	0.007	0.381 (0.152 - 0.955)	0.040	0.327 (0.125 - 0.853)	0.022

^aData were adjusted for age and sex. ^bThe reference category is: normal coronary arteries (Controls); P-Value is statistically significant (<0.05).

Table 4. Rs11209026 G/A and dyslipidemia status in ACS patients and controls.

rs11209026	Dyslipidemia (+)	Dyslipidemia (-)	OR (95%CI) ^a	P ^a
ACS patients	96	64		
Genotypes				
GG	88 (91.7)	59 (92.2)	1	
AG	8 (8.3)	5 (7.8)	1.067 (0.330 - 3.451)	0.913
Alleles				
G	184 (95.8)	123 (96.1)	1	
A	8 (4.2)	5 (3.9)	1.064 (0.337 - 3.356)	0.915
Controls	44	36		
Genotypes				
GG	37 (84.1)	26 (72.2)	1	
AG	7 (15.9)	10 (27.8)	0.452 (0.148 - 1.378)	0.163
Alleles				
G	81 (92.0)	62 (86.1)	1	
A	7 (8.0)	10 (13.9)	0.501 (0.177 - 1.415)	0.501

^aData were adjusted for age and sex.

genotypes and alleles of the SNP between controls with dyslipidemia and those without dyslipidemia (**Table 4**). Based on the information contained in this data, rs11209026 G/A SNP is not involved in the development of dyslipidemia associated ACS.

4. Discussion

In the recent year, several researches have indicated that IL-23 can be involved in the development of atherosclerosis. For instance, patients with peripheral arterial disease have heightened serum levels of IL-23, and increased IL-23 expression is seen in human carotid lesions [11] [12]. In a mouse model of ischemic stroke, IL-23 levels were upregulated in both the circulation and in the brain [13]. While, effects of IL-23R on ACS have not been reported. The results of the present study revealed an association between rs11209026 G/A SNP of the IL-23 receptor gene and individual susceptibility to ACS. Our results were obtained by analyzing 160 ACS participants (included: 80 UAP patients and 80 MI patients) and 80 healthy controls, and showed that rs11209026 G/A SNP in the IL-23R was associated as a protective factor for ACS. To further characterize the effect of rs11209026 G/A polymorphism on dyslipidemia-associated ACS, we found no correlated between rs11209026 G/A SNP and dyslipidemia-associated ACS.

Furthermore, several studies have reported the association between IL-23R rs11209026 polymorphism and effect of atherosclerosis. Kave *et al.* have reported that the genetic variant of rs11209026 polymorphism may in fact cause protection against atherosclerosis progression in Iran population [10]. However, another study indicated that it was failed to reveal an association between MI and the rs11209026 G/A SNP in white British population [14]. While, our results showed that percentages of IL-23R rs11209026 GG and AG genotypes were significantly different between the ACS group and the control group ($p < 0.05$), and the A allele frequency of the acute coronary syndrome group was lower than the control group (4.1% vs. 10.6%, $p = 0.005$), suggesting that polymorphism changes at this site may be associated with the hereditary susceptibility of acute coronary syndrome (**Table 2**). Interestingly, after adjusted the gender and age of these data by unconditional logistic regression, our data revealed that the rs11209026 AG genotype was a protective factor for acute coronary syndrome and subtype of ACS (**Table 3**). In addition, after analysis the differences in results between current study and other studies indicates that the genetic susceptibility of rs11209026 G/A polymorphism to atherosclerosis is not only related to the disease phenotype of selected patient's, but also related to the selected control group and the source of the study population.

Although rs11209026 G/A SNP may have functional and phenotypic consequences on ACS, the molecular basis of the genetic variation is remains unclear. The SNP rs11209026 G/A, located in exon 9 of the IL-23R, has been associated with strong protection against Crohn's disease (allele A), which means that allele A is underrepresented in the disease population [15] [16]. We and others have recently observed protective nature of rs11209026 allele A. It is important to de-

termine whether this allele itself has a protective function or merely a protective association. Furthermore, the A allele causes an amino acid change close to the end of the coding sequence of exon 9, which induce the more common (allele G) arginine at residue 381 becomes a glutamine (R381Q) [17] [18]. Then, Di Meglio *et al.* inspected healthy participants and compared IL-23 responsiveness in allele A carriers compared with allele G carriers. Moreover, their results illustrated that reduced IL-17A and STAT3 phosphorylation in the presence of allele A and suggested that the protective effects of the IL-23R R381Q were mediated through selective attenuation of IL-23-induced Th17 effector function [19]. Choosing a similar population of healthy participants, Pidasheva *et al.* demonstrated that IL23R-Q381 (allele A) is a loss-of-function allele and furthermore revealed that carriers of A allele had decreased surface IL-23R expression while reserving similar levels of IL23RmRNA [20]. In addition, Raymond *et al.* explored this protective allele A was associated with mRNA splicing, and they illustrated that the presence of the A allele increases expression of the soluble form of IL23R mRNA (which then functions as a decoy receptor) and lowers the ability to develop a Th17 phenotype upon IL-23 stimulation [17]. Moreover, the present research revealed that the frequency of rs11209026 allele A was lower in the acute coronary syndrome group and its subgroup than in the control group, and maybe was a protective factor for acute coronary syndrome. Therefore, we speculate that rs11209026 allele A plays a protective role in acute coronary syndrome through the molecular mechanism discussed above.

5. Conclusion

The current study indicated that rs11209026 G/A polymorphism was associated with the decreased risk of ACS and it seems that the high prevalence rate of variable allele A in the normal coronary arteries group (compared to ACS patients) created protection against atherosclerosis progression. However, the current study did not explore the relationship between the molecular mechanism of IL-23R gene polymorphism and the susceptibility to ACS, and the amount of specimens was small. Therefore, its association with the susceptibility to acute coronary syndrome and its molecular mechanism in pathological process of atherosclerosis need further verification.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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