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ORIGINAL RESEARCH

Effects of Additional Chinese Herbal Medicines Treatment in Patients with Type 2 Diabetes Mellitus Combined with Stable Angina Pectoris: A Retrospective Cohort Study

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Background: Chinese herbal medicines (CHMs) are used for type 2 diabetes mellitus combined with stable angina pectoris (T2DM-SAP), but their long-term effects lack real-world evidence.

Objective: To evaluate the effects of additional CHMs on angina readmission rates compared to standard treatment alone in patients with T2DM-SAP.

Methods: This retrospective cohort study included 704 patients with T2DM-SAP. Participants were stratified into two groups based on cumulative CHMs use (≥ 3 months). The CHMs group included 115 patients, while the non-CHMs group included 589 patients. A 1:1 propensity score matching (PSM) was used to balance differences between groups. The primary outcome was angina readmission. The secondary outcomes were SAP readmission and unstable angina pectoris (UA) readmission. Kaplan-Meier survival curves were plotted before and after matching. Sensitivity analysis was performed using Cox proportional hazards model. Baseline prescriptions were collected and herbal frequency and efficacy were counted.

Results: After matching, there were 106 patients in each of the two groups. Before matching, compared with the non-CHMs group, the adjusted hazard ratio (aHR) of angina readmission in the CHMs group was 0.49 [95% confidence interval (CI): 0.34, 0.71, $P<0.001$]. After matching, the aHR was 0.37 [95% CI: 0.22, 0.60, $P<0.001$]. The reliability of the results was confirmed by sensitivity analyses adjusted for different covariates. The CHMs group demonstrated a significantly longer median time to angina readmission compared to the non-CHMs group (55.66 vs 13.90 months, $P<0.001$). Similar results were also shown after matching. 115 prescriptions involving 220 herbs were collected.

Conclusion: Additional CHMs treatment can significantly reduce the incidence of angina readmission and prolongs the interval to recurrent events in T2DM-SAP patients.

Keywords: type 2 diabetes mellitus, stable angina pectoris, angina readmission, Chinese herbal medicine, integrative therapy, retrospective cohort study

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by elevated blood glucose.[1] In 2024, over 3.4 million adults aged 20–79 years died due to diabetes or diabetes-related complications, and approximately 11.9% of

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global health expenditure was allocated to diabetes treatment.[2] Based on current trends, the diabetes-related burden will pose long-term challenges to global public health and economic development. Cardiovascular disease (CVD) is one of the serious complications of T2DM. In patients suffering from T2DM, there is a 2–3 times higher probability of developing CVD when compared with those without T2DM.[3] A systematic literature review involving 4.5 million patients with T2DM showed that CVD is the leading cause of death in patients with T2DM, and coronary heart disease (CHD) is the main type of cardiovascular disease.[4] Stable angina pectoris (SAP) is a common type of CHD, often caused by physical exertion and emotional stress. It can manifest as a feeling of chest tightness and discomfort in the precordial area, and it may lead to impairment of cardiac function.[5] T2DM is an independent risk factor for SAP. The disorder of glucose metabolism accelerates the progression of SAP and increases the risk of adverse cardiovascular events.[6]

The current clinical approach for patients with T2DM-SAP involves coordinated management encompassing diabetes-specific strategies (glycemic control and weight management), cardiovascular protective measures (blood pressure regulation, lipid-lowering therapy, and antiplatelet therapy for high-risk populations), along with comprehensive lifestyle interventions addressing both conditions.[7] Although the above treatments can reduce the incidence of adverse cardiovascular events, long-term use of drugs such as acetylsalicylic acid can bring adverse reactions, and the problem of restenosis after cardiovascular surgery also persists.[8,9] As a result, the risk of readmission remains high.[10] A prospective cohort study identified angina attacks as the most common cardiovascular outcome event in SAP,[11] underscoring the need for targeted management in this population. While SAP is classified as a relatively stable stage of CHD, poor disease control often leads to progression to unstable angina pectoris (UA).[12] This highlights SAP as a critical therapeutic window. Integrative therapy during this phase can reduce the frequency of angina attacks, improve cardiac function, and thereby lower the risk of readmission. Moreover, such interventions may delay or prevent progression to UA, which is of great significance for enhancing long-term prognosis. Chinese herbal medicines (CHMs) has a long history in treating T2DM-SAP.[13] Previous Meta-analyses have demonstrated that CHMs treatment can effectively reduce glycemic, lipid, and inflammatory markers in patients with T2DM-CHD, including those with SAP, as well as improve cardiac function.[14] CHMs are able to act on targets such as Interleukin-6 (IL-6) and Protein Kinase B (AKT) through the Phosphatidylinositol 3-Kinase/Protein Kinase B (PI3K/AKT) Signaling Pathway, thereby exerting anti-inflammatory effects, myocardial protection, and regulation of glucose and lipid metabolism.[15] Such multi-target synergy uniquely addresses the intertwined metabolic-cardiovascular pathology in T2DM-SAP, offering therapeutic advantages over single-pathway approaches.

However, few real-world cohort studies have investigated the long-term impact of CHMs on cardiovascular outcomes, particularly angina readmission in patients with T2DM-SAP. Therefore, the objective of this retrospective cohort study is to evaluate the effects of additional CHMs on angina readmission rates compared to standard treatment alone in patients with T2DM-SAP.

Methods

Study Design

The study retrospectively included inpatients with T2DM-SAP at the First Affiliated Hospital of Henan University of Chinese Medicine (FAH-HUCM) from 2012 to 2019. The protocol of the study conformed to the principles of the Declaration of Helsinki. The study was reviewed and approved by the Ethics Committee of FAH-HUCM. The study was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR1900022168). This article complies with the STROBE statement.[16]

Diagnostic Criteria

For the diagnosis of T2DM, patients must meet the following criteria.[17] Based on the presence of typical symptoms (polydipsia, polyphagia, polyuria, and unexplained weight loss), any one of the following conditions should be satisfied: (1) random glucose $\geq$ 11.1 mmol/L; (2) glucose $\geq$ 7.0 mmol/L after 8 hours of fasting; (3) 2-hour glucose $\geq$ 11.1 mmol/L on oral glucose tolerance test; (4) hemoglobin A1c $\geq$ 6.5%. In the absence of typical symptoms, venous glucose testing should be repeated at other times to help diagnose the disease.

For the diagnosis of SAP, patients must meet the following criteria.[18] Firstly, typical symptoms need to be present, including typical triggering factors of the attack (physical exertion or emotional fluctuations), the location of the attack (behind the sternal body), the nature of the pain (a feeling of pressure, tightness, or stuffiness), the duration (relatively short, ranging from several minutes to dozens of minutes), and the methods of relief (rest or sublingual administration of nitroglycerin). Secondly, at least one of the following requirements should be met: (1) ST-T segment changes on electrocardiogram (ECG) during the attack indicative of myocardial ischemia; (2) a positive exercise stress test; (3) history of PCI or coronary artery bypass grafting (CABG); (4) coronary artery stenosis ≥ 50% demonstrated on coronary angiography or coronary computed tomography angiography (CTA); (5) history of myocardial infarction (MI); (6) CHD confirmed by radionuclide imaging.

Inclusion and Exclusion Criteria

Patients must meet the following inclusion criteria: (1) diagnosis of T2DM; (2) diagnosis of SAP; (3) age ≥ 18 years; (4) complete inpatient medical records and follow-up data. Patients must be excluded based on the following criteria: (1) type 1 diabetes, gestational diabetes, or other specific diabetes types; (2) other types of cardiovascular disease, such as UA and MI; (3) severe respiratory diseases, malignancies, autoimmune disorders, or hematologic diseases; (4) incomplete medical records affecting data analysis; (5) loss to follow-up with missing outcomes.

Data Collection

This study retrospectively extracted basic demographic information (sex, age), behavioral history (smoking history, drinking history), disease-related information (course of disease, laboratory indicators), comorbidities (hypertension, hyperlipidemia, etc), and treatment-related information (non-CHMs treatment, CHMs treatment). The collection of these data was based on the electronic medical records (EMRs) of the Hospital Information System (HIS). All data collection was performed independently by two persons. An expert reviewed the extracted data based on the EMRs. When there was any disagreement in the data extraction, an expert would be consulted to make a determination.

Follow-up

Follow-up data were collected through two primary forms: (1) outpatient and inpatient EMRs; (2) telephone contact. Follow-up visits were conducted between September and November in 2023. In order to improve the quality of the follow-up visits, training was provided to the visiting staff before the visits according to the research protocol. Through follow-up visits, patients' treatment, outcomes, and other information were collected in detail. The information was entered and saved into the database and submitted to the data manager for review.

Exposure

All patients received guideline-directed conventional treatment. The intervention of CHMs involved prescribing individualized herbal decoctions for T2DM-SAP based on syndrome differentiation. Through methods such as literature review and expert consultation, the exposure threshold was defined as a cumulative duration of CHMs treatment ≥ 3 months. Therefore, the continuous use of CHMs intervention for three months or longer was defined as the exposure factor in this study. The duration of CHMs use was obtained from outpatient and inpatient EMRs, as well as follow-up data. Patients who had taken CHMs ≥ 3 months were assigned to the CHMs group, while other patients were assigned to the non-CHMs group.

Outcomes

The primary outcome was angina readmission. The secondary outcomes were SAP readmission and UA readmission, which were differentiated based on the nature of the patient's first angina readmission. In this study, these two categories of secondary outcomes were mutually exclusive, with each patient's first angina readmission assigned to only one of them. Whether the patient was re-admitted due to SAP or UA, it was considered as the occurrence of the primary outcome. The time of the outcome event was recorded. The outcome event was considered not to have occurred if the patient was not readmitted to the hospital or if the reason for hospitalization was not due to angina.

Statistical Analysis

Variables with a missing percentage of ≥ 20% were removed. Multiple imputation was conducted for variables with < 20% missing values, and the seed number was set to 123 (Supplementary Table 1). According to the defined exposure factors, the cohort was categorized into the CHMs group and the non-CHMs group. Because there were differences between groups, propensity score matching (PSM) was used to balance the differences. A seed number of 1234, a caliper value of 0.02, and a matching ratio of 1 to 1 were established. Confounders were set based on baseline analysis, clinical experience and relevant guidelines, including sex, age, course of T2DM, course of SAP, diabetic peripheral vasculopathy (DPV), cerebrovascular disease, triglyceride (TG), low density lipoprotein (LDL), serum creatinine (SCR), fasting blood glucose (FBG), diastolic blood pressure (DBP), systolic blood pressure (SBP), antihyperglycemic medications, antihypertensive medications, antilipidemic medications, antithrombotic medications, and antianginal medications. Quantitative data were described by mean ± standard deviation or median (upper and lower quartiles). Comparisons between groups were made using the *t* test or Wilcoxon rank sum test. Qualitative data were described using frequency and percentages. Comparisons between groups were made using the Chi-square test or Fisher's exact probability method. The baseline characteristics before and after matching were described. The Kaplan-Meier method was used to calculate the rate of angina readmission. The Log rank test was adopted to examine the difference in readmission rates between the two groups. Cox proportional hazards model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the angina readmission and survival time in both groups. Sensitivity analyses were performed to confirm the reliability of the results by adjusting for different covariates in the pre and post matched cohorts. 115 baseline prescriptions were collected. The names of Chinese herbs were standardized, and the frequency of herbs and the efficacy frequency of herbs were counted. This analysis integrated both quantitative and qualitative approaches. The study was considered statistically significant at $P<0.05$. The tool used was R software (version 4.3.3).

Results

Patients' Characteristics

The study collected 965 patients. Patients were further identified based on inclusion and exclusion criteria. Finally, 704 patients entered the cohort. Among them, 589 patients were in the non-CHMs group and 115 in the CHMs group. To ensure balanced comparability between the two groups, a 1:1 PSM was applied. This robust statistical method effectively minimizes selection bias by balancing observed baseline covariates between groups, enhances the validity of comparative analyses, and approximates the conditions of a randomized controlled trial. After matching, each group contained 106 well-matched patients (Figure 1).

Before matching, a total of 704 patients were included in the analysis, including 589 patients in the non-CHMs group and 115 patients in the CHMs group. There were significant differences in age, course of SAP and cerebrovascular disease between the two groups ($P<0.05$). The patients in the CHMs group were younger, with a median age of 62 years old; 53.91% ($n=62$) were male and 46.09% ($n=53$) were female; the median duration of T2DM was 10 years, and the median duration of SAP was 2 years. After 1:1 PSM, 212 patients were included in the analysis, with 106 patients in each group. After matching, the baseline characteristics of the two groups were balanced and comparable, as evidenced by the standardized mean differences (SMDs) of covariates, which were reduced to generally acceptable levels (Supplementary Table 2). After matching, the average age of the CHMs group was 62.92±10.39 years, of which 53.77% were male ($n=57$). The median duration of T2DM was 10 years, and the median duration of SAP was 2 years. Before and after matching, there was no difference between the two groups in terms of treatment. After matching, in the CHMs group, 93.40% ($n=99$) of the patients used antihyperglycemic medications, and 73.58% ($n=78$) of the patients used antihypertensive medications. 74.53% of patients ($n=79$) used antilipidemic medications, 65.09% of patients ($n=69$) used antithrombotic medications, and 68.87% of patients ($n=73$) used antianginal medications (Tables 1 and 2).

Effects of CHMs on T2DM-SAP

Before matching, the CHMs group exhibited a significantly lower risk of angina readmission compared with the non-CHMs group (29.57% vs 50.42%, Log rank test, $P<0.001$; Figure 2A). This trend remained consistent after matching, with the CHMs group still showing a significantly reduced risk of angina readmission (29.25% vs 47.17%, Log rank test,

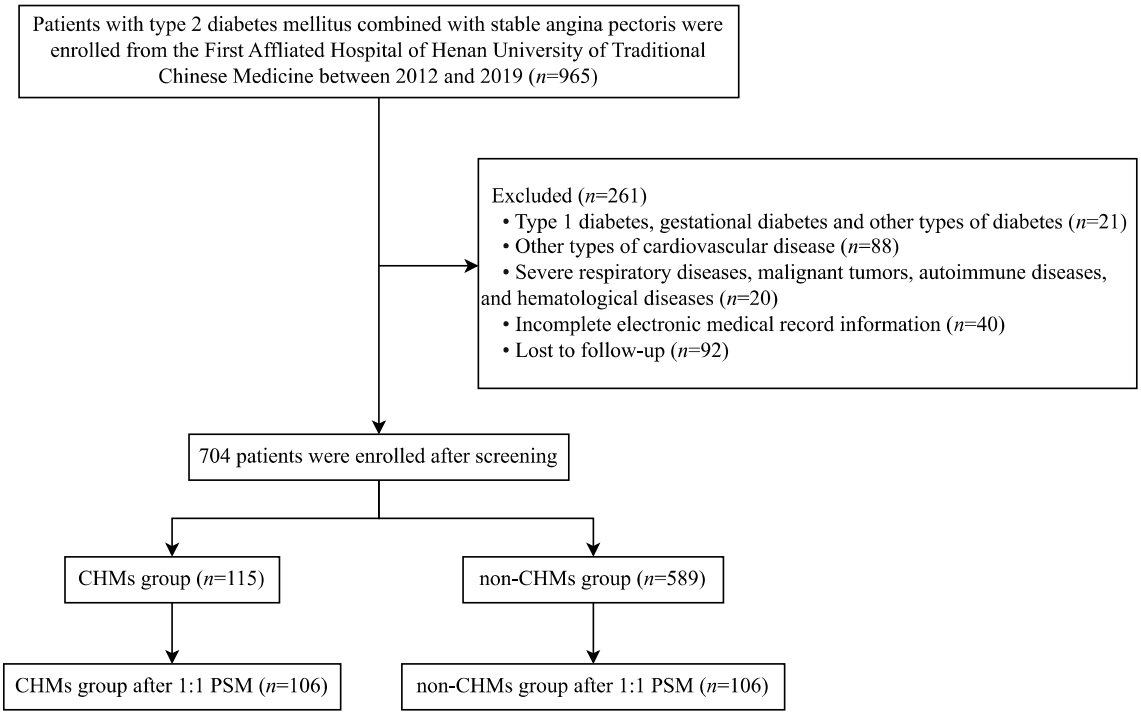

Figure 1 Study Flow Diagram of T2DM-SAP Patients.

P=0.0012; Figure 2B). In terms of SAP readmission, before matching, the CHMs group had a significantly lower risk than the non-CHMs group (20.87% vs 35.31%, Log rank test, *P*=0.0014; Figure 2C). After matching, the CHMs group continued to demonstrate a significantly lower risk of SAP readmission (19.81% vs 30.19%, Log rank test, *P*=0.039;

Table 1 Baseline Characteristics of the Two Groups Before PSM

Characteristic	Overall (*n*=704)	Non-CHMs Group (*n*=589)	CHMs Group (*n*=115)	*P*
Demographics				
Age	66.00 (58.00–74.00)	67.00 (59.00–75.00)	62.00 (55.00–69.50)	<0.001
Sex				0.777
Female	336 (47.73%)	283 (48.05%)	53 (46.09%)	
Male	368 (52.27%)	306 (51.95%)	62 (53.91%)	
Behavioral history-*n* (%)				
Smoking	156 (22.16%)	130 (22.07%)	26 (22.61%)	0.997
Drinking	138 (19.60%)	110 (18.68%)	28 (24.35%)	0.203
Course of disease (yr)-mean ± sd				
T2DM	9.00 (3.00–15.00)	8.00 (3.00–15.00)	10.00 (3.50–15.00)	0.283
SAP	3.00 (0.00–8.25)	3.00 (0.00–10.00)	2.00 (0.00–6.50)	0.038
Laboratory investigations-mean ± sd				
FBG	7.21 (5.79–9.01)	7.20 (5.78–9.01)	7.34 (5.83–8.89)	0.677
SBP	138.00 (128.75–150.00)	139.00 (129.00–150.00)	136.00 (128.00–147.00)	0.314
DBP	80.00 (75.00–89.00)	80.00 (75.00–90.00)	80.00 (75.00–85.00)	0.194
HR	76.00 (70.00–80.00)	76.00 (70.00–80.00)	78.00 (70.00–80.00)	0.820
TC	4.24 (3.52–5.01)	4.24 (3.51–4.98)	4.19 (3.61–5.06)	0.610
TG	1.48 (1.06–2.07)	1.48 (1.05–2.08)	1.47 (1.13–1.85)	0.671
LDL	2.79 (2.16–3.42)	2.78 (2.17–3.41)	2.83 (2.09–3.45)	0.862
SCR	66.25 (54.75–80.82)	66.30 (55.00–82.00)	65.40 (52.20–75.90)	0.182

(*Continued*)

Table 1 (Continued).

Characteristic	Overall (*n*=704)	Non-CHMs Group (*n*=589)	CHMs Group (*n*=115)	*P*
Comorbidities-*n* (%)				
Hypertension	529 (75.14%)	450 (76.40%)	79 (68.70%)	0.103
Hyperlipidemia	170 (24.15%)	138 (23.43%)	32 (27.83%)	0.374
DPV	55 (7.81%)	41 (6.96%)	14 (12.17%)	0.086
Cerebrovascular disease	285 (40.48%)	252 (42.78%)	33 (28.70%)	0.007
FLD	76 (10.80%)	62 (10.53%)	14 (12.17%)	0.721
Concurrent treatment-*n* (%)				
Antihyperglycemic medications	637 (90.48%)	530 (89.98%)	107 (93.04%)	0.396
Antihypertensive medications	547 (77.70%)	465 (78.95%)	82 (71.30%)	0.093
Antilipidemic medications	522 (74.15%)	437 (74.19%)	85 (73.91%)	1
Antithrombotic medications	465 (66.05%)	391 (66.38%)	74 (64.35%)	0.753
Antianginal medications	507 (72.02%)	431 (73.17%)	76 (66.09%)	0.151

Abbreviations: CHMs, Chinese herbal medicines; T2DM, Type 2 diabetes mellitus; SAP, Stable angina pectoris; FBG, Fasting blood glucose; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HR, Heart rate; TC, Total cholesterol; TG, Triglyceride; LDL, Low density lipoprotein; SCR, Serum creatinine; DPV, Diabetic peripheral vasculopathy; FLD, Fatty liver disease.

Table 2 Baseline Characteristics of the Two Groups After PSM

Characteristic	Overall (*n*=212)	Non-CHMs GROUP (*n*=106)	CHMs GROUP (*n*=106)	*P*
Demographics				
Age	63.43±10.70	63.94±11.04	62.92±10.39	0.490
Sex				0.782
Female	95 (44.81%)	46 (43.40%)	49 (46.23%)	
Male	117 (55.19%)	60 (56.60%)	57 (53.77%)	
Behavioral history-*n* (%)				
Smoking	49 (23.11%)	24 (22.64%)	25 (23.58%)	1
Drinking	47 (22.17%)	21 (19.81%)	26 (24.53%)	0.508
Course of disease (yr)-mean ± sd				
T2DM	10.00 (4.00–15.00)	10.00 (4.00–15.75)	10.00 (4.00–15.00)	0.735
SAP	2.00 (0.00–6.00)	3.00 (0.50–5.00)	2.00 (0.00–7.00)	0.527
Laboratory investigations-mean ± sd				
FBG	7.29 (5.81–8.99)	7.16 (5.79–9.04)	7.38 (5.83–8.68)	0.980
SBP	135.00 (125.00–148.00)	134.50 (123.25–149.50)	135.50 (126.50–146.75)	0.932
DBP	80.00 (71.75–86.00)	80.00 (70.00–88.00)	80.00 (74.25–85.00)	0.951
HR	76.00 (70.00–80.00)	76.00 (70.00–80.00)	76.00 (70.00–80.00)	0.511
TC	4.17 (3.54–4.92)	4.07 (3.44–4.84)	4.23 (3.62–5.14)	0.177
TG	1.49 (1.13–2.05)	1.51 (1.05–2.19)	1.49 (1.15–1.89)	0.641
LDL	2.79 (2.15–3.44)	2.75 (2.20–3.34)	2.86 (2.09–3.58)	0.708
SCR	65.30 (52.30–77.67)	62.95 (51.83–78.53)	67.85 (52.62–76.62)	0.608
Comorbidities-*n* (%)				
Hypertension	144 (67.92%)	71 (66.98%)	73 (68.87%)	0.883
Hyperlipidemia	52 (24.53%)	24 (22.64%)	28 (26.42%)	0.632
DPV	26 (12.26%)	15 (14.15%)	11 (10.38%)	0.530
Cerebrovascular disease	67 (31.60%)	35 (33.02%)	32 (30.19%)	0.768
FLD	20 (9.43%)	9 (8.49%)	11 (10.38%)	0.814

(*Continued*)

Table 2 (Continued).

Characteristic	Overall (*n*=212)	Non-CHMs GROUP (*n*=106)	CHMs GROUP (*n*=106)	*P*
Concurrent treatment-*n* (%)				
Antihyperglycemic medications	198 (93.40%)	99 (93.40%)	99 (93.40%)	1
Antihypertensive medications	150 (70.75%)	72 (67.92%)	78 (73.58%)	0.450
Antilipidemic medications	160 (75.47%)	81 (76.42%)	79 (74.53%)	0.873
Antithrombotic medications	139 (65.57%)	70 (66.04%)	69 (65.09%)	1
Antianginal medications	143 (67.45%)	70 (66.04%)	73 (68.87%)	0.769

Abbreviations: CHMs, Chinese herbal medicines; T2DM, Type 2 diabetes mellitus; SAP, Stable angina pectoris; FBG, Fasting blood glucose; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HR, Heart rate; TC, Total cholesterol; TG, Triglyceride; LDL, Low density lipoprotein; SCR, Serum creatinine; DPV, Diabetic peripheral vasculopathy; FLD, Fatty liver disease.

Figure 2D). Regarding UA readmission, before matching, the risk was significantly lower in the CHMs group compared with the non-CHMs group (7.83% vs 15.11%, Log rank test, P=0.038; Figure 2E). After matching, a similar pattern was observed, with the CHMs group having a significantly lower risk of UA readmission (8.49% vs 16.98%, Log rank test, P=0.041; Figure 2F). The difference was statistically significant (P<0.05).

Sensitivity Analysis

Model 1 was a univariate analysis. According to model 1, in the unmatched cohort, patients in the CHMs group had a lower risk of angina readmission than those in the non-CHMs group (HR=0.47, 95% CI: 0.33, 0.67, P<0.001). In the matched cohort, it also showed that the CHMs group had a better therapeutic effect than the non-CHMs group (HR=0.48, 95% CI: 0.31, 0.76, P=0.002). The results of the unmatched and matched groups consistently showed that the risk of angina readmission was significantly reduced in patients who received CHMs treatment. To demonstrate the reliability of the results, the sensitivity analysis was performed. Covariates were adjusted separately for the unmatched cohort and the matched cohort. Model 2 adjusted for demographic information. Model 3 adjusted for disease course, behavioral history and comorbidities based on model 2. Model 4 was adjusted for all covariates. Finally, after adjusting for all factors, in the unmatched cohort, patients in the CHMs group also had a lower risk of angina readmission than those in the non-CHMs group (adjusted hazard ratio (aHR)=0.49, 95% CI: 0.34, 0.71, P<0.001). In the matched cohort, aHR=0.37, 95% CI: 0.22, 0.60, P<0.001). The results all showed that patients in the CHMs group had a lower risk angina readmission than those in the non-CHMs group. These data support the prognostic benefit of additional CHMs treatment for patients with T2DM-SAP after controlling for other potentially influential factors, and the results of this study are reliable (Table 3).

CHMs Delay Angina Readmission Intervals

Before matching, the median follow-up time of patients was 90.35 months. A total of 331 patients occurred angina readmission. According to the exposure factors, these 331 patients were divided into two groups. The CHMs group had 34 patients, and the non-CHMs group had 297 patients. The median interval time for angina readmission in the CHMs group was significantly longer than that in the non-CHMs group (55.66 months vs 13.90 months, P<0.001, Figure 3A). After matching, the median follow-up time of patients was 88.97 months. A total of 81 patients occurred angina readmission. According to the exposure factors, the CHMs group had 31 patients and the non-CHMs group had 50 patients. The median interval time for angina readmission in the CHMs group was significantly longer than that in the non-CHMs group (55.95 months vs 13.75 months, P<0.001, Figure 3B).

Statistics of Herbs in the Baseline Prescriptions

A total of 115 baseline prescriptions were collected from the patients in the CHMs group. There was no standardized core formula, as all CHM prescriptions were individualized based on syndrome differentiation. The Chinese names of herbs were standardized according to the *Zhonghua Bencao* and the *Pharmacopoeia of the people's Republic of China*.[19,20] These herbal prescriptions altogether contained 220 herbs. And herbs were classified according to their efficacy. The top

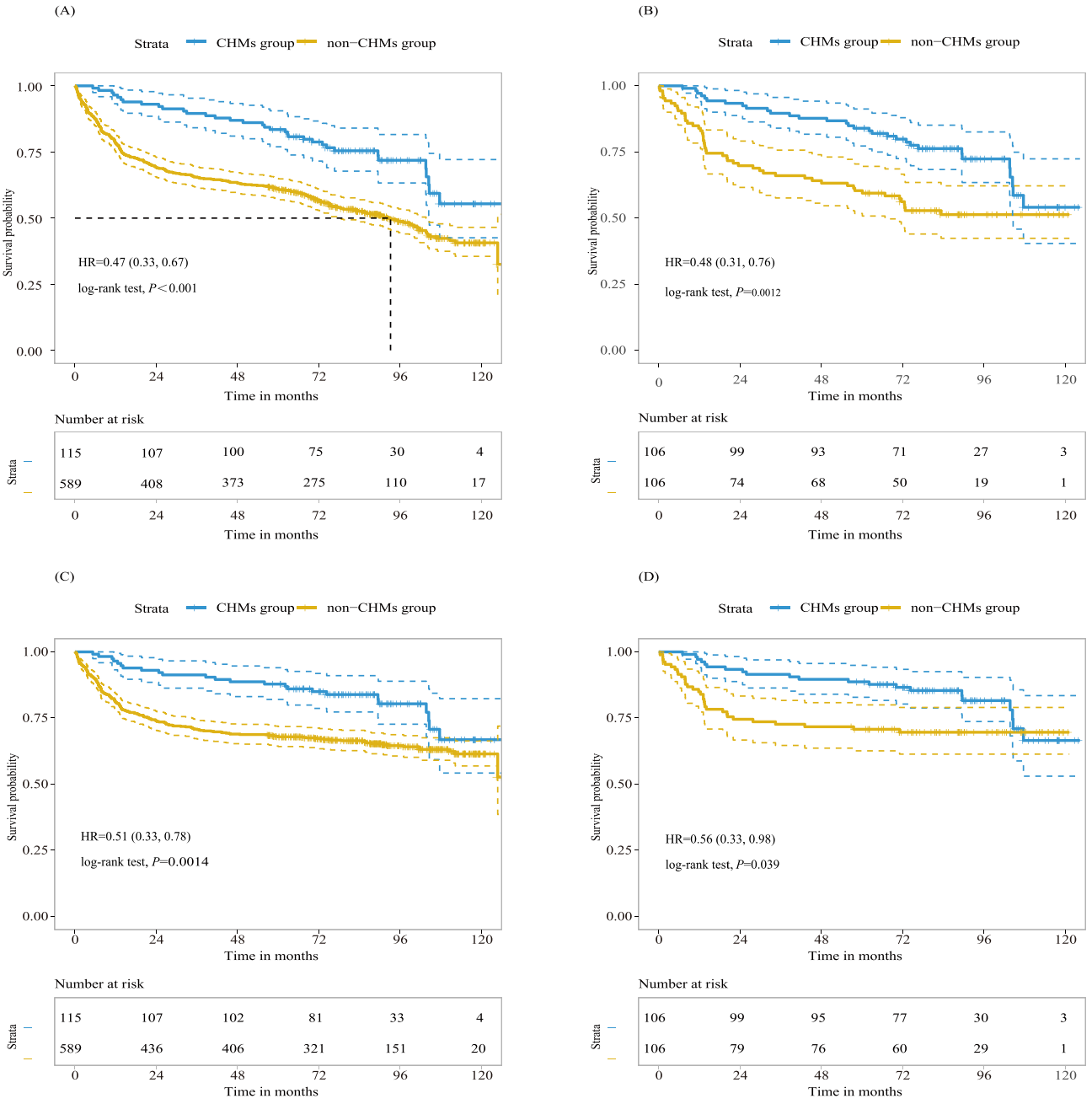

Figure 2 Continued.

5 most frequently used herbs were *Glycyrrhiza uralensis* (Gan Cao), *Poria cocos* (Fu Ling), *Atractylodes macrocephala* (Bai Zhu), *Pinellia ternata* (Ban Xia) and *Citrus reticulata* (Chen Pi). The top 20 most frequently used Chinese medicines were shown in the Table 4. According to the summary of herbal efficacy, the top 5 types of herbs were tonifying and replenishing medicinal, blood-activating and qi-moving medicinal, heat-clearing medicinal, qi-regulating medicinal and dampness-draining diuretic medicinal (Table 5).

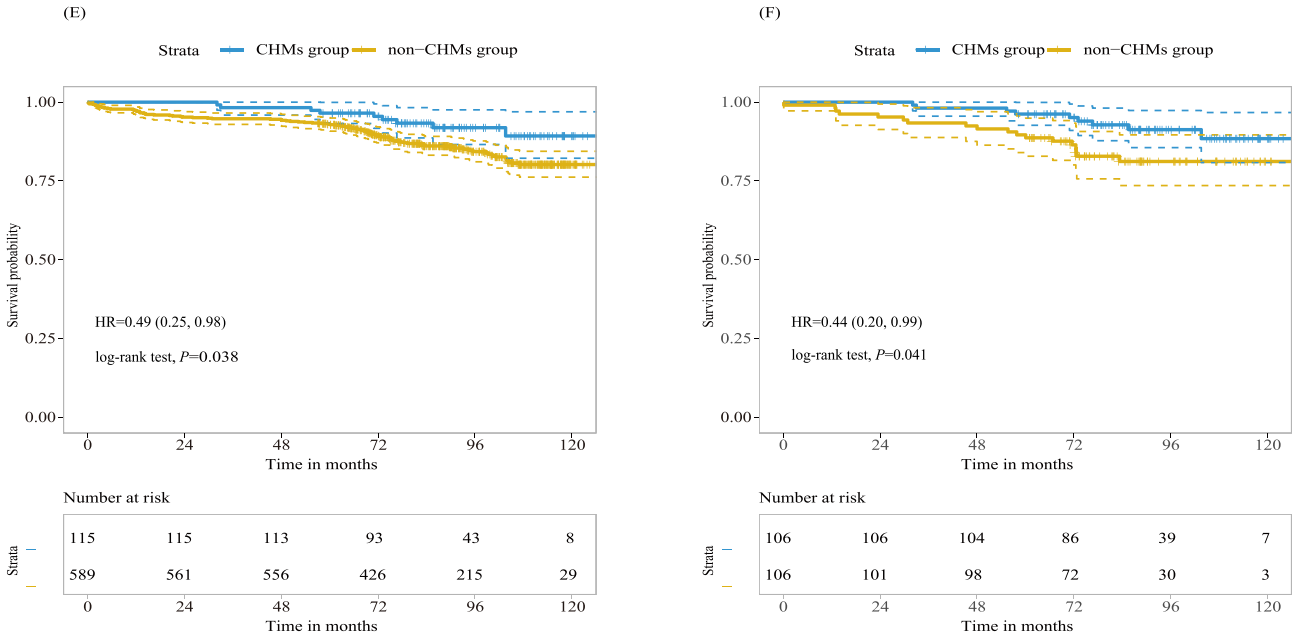

Figure 2 Kaplan-Meier Survival Curves for Outcomes of the Two Groups Before and After PSM.
Notes: (**A**) Kaplan-Meier survival curves for angina readmission in the two groups before PSM. (**B**) Kaplan-Meier survival curves for angina readmission in the two groups after PSM. (**C**) Kaplan-Meier survival curves for SAP readmission in the two groups before PSM. (**D**) Kaplan-Meier survival curves for SAP readmission in the two groups after PSM. (**E**) Kaplan-Meier survival curves for UA readmission in the two groups before PSM. (**F**) Kaplan-Meier survival curves for UA readmission in the two groups after PSM.

Discussion

DM and CHD are two of the four major chronic diseases in the world, which have become major diseases affecting global human health. SAP patients with CHD are more serious than those with CHD alone, and the risk of rehospitalization and cardiovascular death will be increased.[21] Patients with SAP combined with T2DM often present more severe coronary artery lesions and worse prognosis.[22] Although significant progress has been made in previous basic research and drug research, the clinical efficacy and prognosis level of T2DM-SAP are still unsatisfactory. CHMs based on traditional syndrome differentiation and personalized prescription comprehensive treatment have shown good efficacy in the treatment of this disease. Therefore, this study aimed to evaluate the effect of additional CHMs treatment in patients with T2DM-SAP.

A total of 704 cases participated in this study, including 115 cases in the CHMs group and 589 cases in the non-CHMs group. To eliminate the effect of confounding factors between the two groups on the results, PSM was used. After matching, there were 106 cases in each group. The readmission rate of angina pectoris in the CHMs group was lower

Table 3 Cox Proportional Hazards Models of the Two Groups Before and After PSM

Model	Unmatched Cohort		Matched Cohort	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Model 1	0.47 (0.33, 0.67)	<0.001	0.48 (0.31, 0.76)	0.002
Model 2	0.48 (0.33, 0.68)	<0.001	0.49 (0.31, 0.77)	0.002
Model 3	0.48 (0.33, 0.68)	<0.001	0.47 (0.30, 0.73)	0.001
Model 4	0.49 (0.34, 0.71)	<0.001	0.37 (0.22, 0.60)	<0.001

Abbreviations: HR, hazard ratio; CI, confidence interval. Model 1 did not adjust for any covariates. Model 2 adjusted for demographic information (sex and age). Model 3 adjusted for demographic information (sex and age), behavioral history (smoking, drinking), disease course (course of T2DM and course of SAP) and comorbidities (hypertension, hyperlipemia, diabetic peripheral vasculopathy, cerebrovascular disease, fatty liver disease). Model 4 adjusted for all covariates.

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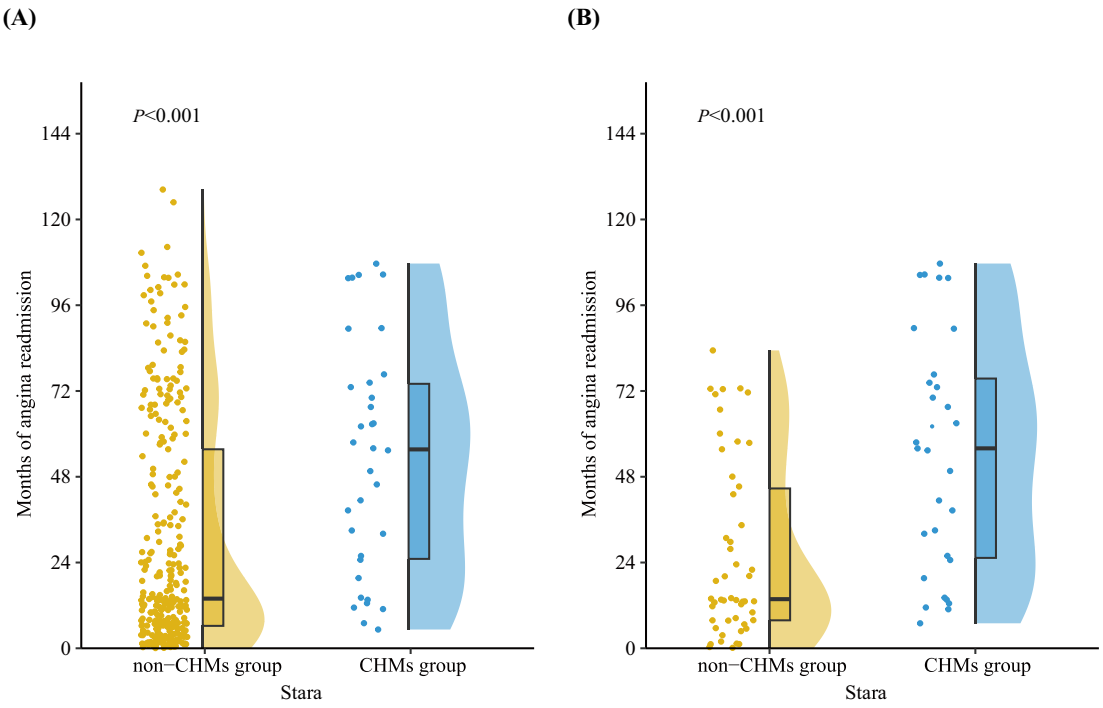

Figure 3 Angina Readmission Intervals of the Two Groups Before and After PSM.
Notes: (**A**) Angina readmission intervals of the two groups before PSM. (**B**) Angina readmission intervals of the two groups after PSM.

than that in the non-CHMs group before and after matching, and the difference was statistically significant. This study provides the main evidence that additional CHMs treatment is superior to conventional treatment in reducing the risk of angina readmission and delaying the time of angina readmission in patients with T2DM-SAP.

Table 4 Frequency Statistics of Herbs Used in the Treatment of T2DM-SAP

Herb	Chinese Name	Frequency	Percentage
Glycyrrhiza uralensis	Gan Cao	66	4.03%
Poria cocos	Fu Ling	66	4.03%
Atractylodes macrocephala	Bai Zhu	54	3.30%
Pinellia ternata	Ban Xia	52	3.17%
Citrus reticulata	Chen Pi	50	3.05%
Salvia miltiorrhiza	Dan Shen	46	2.81%
Ligusticum chuanxiong	Chuan Xiong	45	2.75%
Angelica sinensis	Dang Gui	38	2.32%
Cyathula officinalis	Chuan Niu Xi	36	2.20%
Paeonia lactiflora	Chi Shao	32	1.95%
Astragalus membranaceus	Huang Qi	32	1.95%
Carthamus tinctorius	Hong Hua	28	1.71%
Ophiopogon japonicus	Mai Dong	28	1.71%
Pueraria lobata	Ge Gen	26	1.59%
Prunus persica	Tao Ren	25	1.53%
Codonopsis pilosula	Dang Shen	25	1.53%
Citrus aurantium	Zhi Shi	24	1.47%
Coptis chinensis	Huang Lian	23	1.40%
Cinnamomum cassia	Gui Zhi	22	1.34%

Table 5 Frequency Statistics of Herb Efficacy in the Treatment of T2DM-SAP

Classification of Herbs	Frequency	Percentage
Tonifying and replenishing medicinal	375	22.89%
Blood-activating and qi-moving medicinal	282	17.22%
Heat-clearing medicinal	183	11.17%
Qi-regulating medicinal	141	8.61%
Dampness-draining diuretic medicinal	129	7.88%
Panting-relieving medicinal	117	7.14%
Exterior-releasing medicinal	88	5.37%
Liver-pacifying and wind-extinguishing medicinal	73	4.46%
Dampness-resolving medicinal	67	4.09%
Astringent medicinal	46	2.81%
Tranquilizing medicinal	43	2.63%
Digestant medicinal	25	1.53%
Hemostatic medicinal	21	1.28%
Wind-dampness-dispelling medicinal	18	1.10%
Orifice-opening medicinal	12	0.73%
Interior-warming medicinal	8	0.49%
Purgative medicinal	7	0.43%
Worm-expelling medicinal	3	0.18%

A previous cohort study showed that the HR of angina readmission events after PCI was 0.31 [95% CI: 0.134, 0.720, P=0.006]. Both investigations shared angina readmission as the primary endpoint.[23] Notably, the current analysis specifically enrolled patients with T2DM, and the follow-up period was longer, enhancing clinical generalizability to diabetic cardiovascular populations. A relevant randomized controlled trial has shown that in patients with T2DM-SAP, additional CHMs treatment to conventional treatment can reduce the frequency and duration of angina pectoris attacks.[24] However, this study only focused on short-term outcomes, whereas the present study focuses on long-term efficacy. Hyperlipidemia, hypertension and hyperglycemia are risk factors for adverse outcomes in patients with T2DM-SAP. Some studies have shown that additional CHMs therapy can reduce blood glucose, blood lipids, blood pressure, and inflammatory index in patients with T2DM-SAP.[25,26] However, these studies focused on the therapeutic effects of standardized prescriptions, such as Shengmai San and Tangluo Jiedu Recipe.[25,26] The comprehensive management of blood lipids, blood pressure and blood sugar can help delay the development of the disease, weaken clinical symptoms and improve the quality of life, thus further reducing the risk of angina readmission. Disease progresses continuously. When the control of SAP is poor, it is prone to progress to UA, significantly increasing the risk of death. Besides exploring the risk of readmission due to SAP, the study also paid attention to the risk of readmission due to progression to UA. Previous studies have not indicated what the probability is for T2DM-SAP to develop into T2DM-UA. In this cohort study, 14% of the patients progressed to T2DM-UA. There is no cohort study on the effect of CHMs for T2DM-SAP on the risk of angina readmission, and the study fills this gap and provides an evidence-based basis for additional CHMs treatment to reduce the risk of SAP readmission and UA readmission in patients with T2DM-SAP.

T2DM belongs to the category of "consumptive thirst", and SAP belongs to the category of "chest pain" in TCM. T2DM and SAP have similar etiology and pathological changes. Generally speaking, the core pathogenesis is root deficiency and branch excess. On the basis of qi deficiency, yang deficiency and yin deficiency, pathological products such as qi stagnation, blood stasis and phlegm dampness are produced.[27,28] Therefore, a combination of attacking and supplementing should be considered in treatment. In our analysis of herbal efficacy, the top 5 herbs were tonifying and replenishing medicinal, blood-activating and qi-moving medicinal, heat-clearing medicinal, qi-regulating medicinal and dampness-draining diuretic medicinal. This is consistent with the therapeutic idea of T2DM-SAP. The five most commonly used herbs were Gan Cao, Fu Ling, Bai Zhu, Ban Xia and Chen Pi. The high-frequency herbs used for treating T2DM-SAP obtained in this study are similar to those in a related research.[15] Hyperglycemia triggers metabolic disorders, causing abnormal lipid metabolism and promoting

atherosclerosis. At the same time, it induces oxidative stress, damages the vascular endothelium, activates the inflammatory response, and increases the risk of thrombosis. These factors interact with each other to promote the development of T2DM and induce angina attacks due to insufficient myocardial blood supply on top of coronary atherosclerosis.[29] Related studies have shown that herbs such as Gan Cao, Fu Ling and Bai Zhu and other herbs can play the role of anti-inflammation, anti-oxidative stress and regulation of glucose and lipid metabolism, which is beneficial to the treatment of T2DM-SAP.[30,31] Specifically, Gan Cao contains glycyrrhizin, which curbs nuclear factor-kappa B (NF-κB)-driven inflammation and oxidative stress, thereby easing insulin resistance and vascular damage.[30] Fu Ling, on the other hand, has polysaccharides that activate adenosine monophosphate-activated protein kinase (AMPK) to boost insulin sensitivity, while its triterpenoids reduce lipid peroxidation.[31] Together, these herbs target the linked metabolic and vascular pathologies underlying T2DM-SAP.

This study has the following advantages. Firstly, by adopting a retrospective cohort study design, it systematically included patients with T2DM-SAP and strictly controlled baseline clinical characteristics. In investigating the integrated application of CHMs and standard treatment, it quantitatively analyzed the impact of additional CHMs treatment on the risk of angina readmission in patients, confirming its positive role in reducing this risk. Such a comparative analysis based on real-world data offers solid methodological support for the clinical value of CHMs as an auxiliary intervention, and the relevant conclusions have important guiding significance for optimizing the comprehensive management strategy for patients with T2DM-SAP. Secondly, by extracting and analyzing baseline prescriptions, and identifying high-frequency herbs and key therapeutic classifications, it revealed the common treatment logic targeting the pathogenesis of T2DM-SAP, providing a reference that conforms to the essence of traditional Chinese medicine (TCM) for clinical practice. These advantages together highlight the unique contribution of this study in bridging TCM and modern research fields, and point out the direction for subsequent related explorations. Meanwhile, several limitations of this study need to note: firstly, as a retrospective cohort study, despite the use of PSM to balance baseline characteristics between groups, potential selection bias may still exist. Secondly, despite efforts to control confounding variables, unmeasured factors such as socioeconomic status, dietary habits, and lifestyle changes may independently influence the risk of angina readmission, introducing residual confounding. Thirdly, the personalized nature of CHM prescriptions leads to variations in herbal formulations. This not only affects the generalizability of the study conclusions but also raises concerns about safety and potential herb-drug interactions. Additionally, patients' medication adherence cannot be accurately assessed, making it impossible to determine whether irregular medication use might affect treatment outcomes. Finally, due to the lack of follow-up laboratory data such as metabolic indicators and inflammatory markers, we are unable to deeply explore the relevant pathological mechanisms underlying the potential action of CHMs. It is important to consider these limitations when interpreting study results, and future research could address these issues by improving methods of data collection and study design.

Conclusion

In conclusion, this study shows that for patients with T2DM-SAP, additional CHMs treatment can not only reduce the risk of re-hospitalization due to SAP or UA, but also delay the readmission interval. This provides evidence supporting the use of CHMs in treating patients with T2DM-SAP, and also has important guiding significance for optimizing the treatment plan and improving the prognosis of patients. Furthermore, these findings may guide future integrative therapy approaches for patients with T2DM-SAP. However, the specific effects of CHMs interventions still need to be studied in depth. We look forward to conducting large-scale, multi-center randomized controlled trials in the future to clarify the efficacy of CHMs in the treatment of T2DM-SAP.

Data Sharing Statement

The relevant data and materials of this study are available from the corresponding author upon request.

Ethical Statement

This study was approved by the Ethics Committee of FAH-HUCM (Approval No. 2019HL-013-01). According to applicable ethical regulations, the Ethics Committee waived written informed consent because of the retrospective nature of this EMR-based study. All patient information was de-identified and handled in strict compliance with confidentiality guidelines.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All the authors have declared no conflicts of interest in this study.

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