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Original Article

Effect of Shenmai Injection on Long-Term Prognosis of Patients with Chronic Heart Failure: A Multicenter, Large Sample Capacity, Long-Term Follow-Up Retrospective Cohort Study*

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ABSTRACT **Objective:** To explore the effect of Shenmai Injection (SMI) on the long-term prognosis of patients with chronic heart failure (CHF). **Methods:** The Hospital Information System was used to extract data of CHF patients, and the retrospective cohort study was conducted for analysis. In non-exposed group, standardized Western medicine treatment and Chinese patent medicine or decoction were applied without combination of SMI while in the exposed group, SMI were applied for more than 7 days. Evaluation indicators are followed with New York Heart Association functional classification (NYHA classification), left ventricular ejection fraction (LVEF), N-terminal brain natriuretic peptide precursor (NT-ProBNP), cardiogenic death and heart failure (HF) readmission. Statistical analysis includes Kaplan-Meier analysis and Cox regression which are used to explore the relationship between SMI and outcome events. **Results:** A total of 1,211 eligible CHF patients were involved and finally 1,047 patients were followed up successfully. After treatment, the cases of NYHA classification decline in the exposed and non-exposed groups accounted for 64.30% and 43.45%, respectively; the improvement values of LVEF were 8.89% and 7.91%, respectively; the improvement values of NT-ProBNP were 909 pg/mL and 735 pg/mL, respectively. After exposure on SMI, the rates of cardiogenic death and HF readmission reduced from 15.43% to 10.18% and 38.93% to 32.37%. According to Kaplan-Meier analysis, the log-rank *P* value of SMI and cardiogenic death was 0.014, while the counterpart of SMI and HF readmission was 0.025. Cox regression analysis indicated that for cardiogenic death, age, cardiomyopathy, diabetes, and NYHA classification were risk factors while β-blockers, aldosterone receptor antagonists, Chinese patent medicine/decoction and SMI were protective factors. Likewise, for HF readmission, age, cardiomyopathy, and NYHA classification were risk factors while SMI was a protective factor. **Conclusion:** Combination with SMI on the standardized Western medicine treatment can effectively reduce cardiogenic mortality and readmission rate in CHF patients, and thereby improve the long-term prognosis.

KEYWORDS Shenmai Injection, chronic heart failure, cohort study, outcome events, long-term prognosis

Heart failure (HF) is an end/late stage of various heart diseases with high readmission rate and mortality rate, which brings a heavy financial burden to families and society. Although the prognosis for chronic heart failure (CHF) has improved significantly with the development of modern medicine, the readmission rate is still as high as 25%–30% after discharged 30–90 days. Worse, the mortality rate of severe patients reaches more than 50% within 5 years yet.[1-3]

As previous studies confirmed, combination with Chinese medicine (CM) intervention with standardized Western medicine treatment can relieve symptoms, reduce readmission and mortality rates of CHF patients.[4] Therefore, CM is more and more popularly used in CHF patients for its abilities in stabilizing the disease, improving heart function, and bettering the

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quality of life. Our survey covering 2,961 CHF patients from 7 CM hospitals indicated that the most commonly used CM injection is Shenmai Injection (参脉注射液, SMI) during hospitalization.[5] Clinically, SMI is widely used in the treatment of acute and critical illness, such as tumor, stroke and other diseases.[6-8] Previous study has shown that adding SMI with routine treatment can better improve the heart function and prognosis of CHF patients effectively. However, these studies still suffered for limited sample size, short follow-up time, and the use of alternative outcome events, which could not reflect the true impact under the real world on the long-term prognosis of CHF patients.[9]

In this study, the Hospital Information System (HIS) was used to extract clinical data of CHF patients from reality. Then, a retrospective cohort study was further conducted to explore the long-term prognosis of CHF patients under the background of multiple factors. Finally, this study aims to provide a reliable evidence-based medical evidence for SMI in the treatment of CHF.

METHODS

Participants

The study has been approved by the Medical Ethics Committee of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine ((2017) Clinical Research Application No. (019)). Seven CM hospitals in Shandong Province with third-grade Class A were included, such as the Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Weifang Traditional Chinese Medicine Hospital, Rizhao Traditional Chinese Medicine Hospital, Jinan Chinese Medicine Hospital, Qingdao Haici Medical Group, Zibo Traditional Chinese Medicine Hospital, Weihai Traditional Chinese Medicine Hospital. According to the International Disease Classification ICD-10 code, HIS was used to retrieve information of CHF inpatients from January 1, 2012 to December 31, 2017.

Inclusion Criteria

The inclusion criteria were as follows: (1) Consistent with the "Chinese Heart Failure Diagnosis and Treatment Guidelines" (2014 CHF diagnosis) issued by Chinese Medical Association Cardiovascular Branch;[10] (2) ages ranging from 45 to 75 years old; and (3) NYHA classification Ⅱ, Ⅲ, Ⅳ.

Exclusion Criteria

The exclusion criteria were as follows: (1) Acute heart failure; (2) having received coronary artery bypass surgery or cardiac resynchronization therapy; and (3) accompanied by non-cardiovascular events such as malignant tumors, mental illnesses, and severe liver and kidney dysfunction.

Division of Group

Non-exposed group: treatment such as standardized Western medicine treatment, Chinese patent medicine or Chinese medicine decoction but without SMI.

Exposed group: treatment combined with SMI for more than 7 days on the basis of non-exposed group.

Sample Size

According to the literature, the all-cause mortality in the exposed group during one-year follow-up was 7.9%, while this rate increased to 10.3% in the non-exposed group.[11] Previous studies have shown that cardiogenic death in CHF patients accounts for about 80% among all-cause death.[12] Based on these, PASS software (PASS for Windows 15.0; NCSS Corporation: Kaysville, Utah, USA) was used to calculate a reasonable sample size by supposing bilateral α=0.05 and β=0.1. A minimum number of 520 was required for both the exposed and non-exposed groups. Considering the 15% loss rate, a total of 1,200 participants were suggested. Since the shortest follow-up time of this study was two years, it was reasonable that the incidence of cardiogenic death was higher than that of one-year follow-up. Therefore, sufficient sample size has been established.

Follow-Up

Telephone was the main follow-up approach, supplementing with follow-up in the clinic. The follow-up ended until patient's death or the day December 31, 2019. The missed follow-up refers to the cases who were lost contact due to various reasons, such as changing the mobile phone number, phone shut down, not answering 3 or more times, and noncooperation from the patient. According to the methodological requirements, the missed follow-up rate was set to less than 15% to improve credibility of the research results.

Evaluation Indicators

During the period of hospitalization: the improvement values of New York Heart Association

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functional classification (NYHA classification), left ventricular ejection fraction (LVEF), N-terminal brain natriuretic peptide precursor (NT-ProBNP) before and after treatment were recorded as evaluation indicators.

During the period of follow-up: cardiogenic death was the primary outcome, and HF readmission was the secondary outcome. Cardiogenic death is collectively defined as death caused by various cardiac causes, such as death from HF, myocardial infarction, sudden cardiac death, arrhythmia, ischemic heart disease, pulmonary heart disease, and cardiac arrest, etc. HF readmission describes the patient readmitted into hospital due to HF again after discharge from hospital.

Data Extraction

HIS was used to obtain information of CHF patients that meet the inclusion criteria and did not meet the exclusion criteria from 7 hospitals. Then the collected data was cleaned up, integrated, and entered into the Epidate software (Epidate for Windows 3.1; EpiMan Group for EpiData Promotion, China). Baseline characteristics of patients during hospitalization were recorded, such as hospitalization identity, age, gender, primary disease, comorbidity, course of CHF, contact information, home address, usage of SMI (whether use or not, time of use, dosage), standardized Western medicine, Chinese patent medicine or Chinese medicine decoction, and the values of NYHA classification, LVEF, NT-ProBNP at the time of admission and discharge. Telephone follow-up and outpatient follow-up were used to track the occurrence of outcome events (including the time of cardiogenic death and HF readmission). All follow-up results were entered into the Epidate software.

Statistical Analysis

IBM SPSS Statistics (IBM SPSS Statistics for Windows 25.0; IBM Corporation: Armonk, NY, USA) was applied. Continuous variables normally distributed were described as mean ± standard deviation ($\bar{x} \pm s$). Continuous variables not normally distributed were described as inter quartile range (IQR). Categorical variables were expressed as frequencies by chi-square test. Kaplan-Meier survival analysis was used for univariate analysis of SMI and outcome events, and Cox regression was used for multivariate analysis. The statistical significance levels were both sides with P value <0.05, which is considered statistically significant.

RESULTS

Baseline Characteristics in the Exposed and Non-exposed Groups

The enrollment process of participants is illustrated in Appendix 1. A total of 2,961 CHF patients are summarized who meet the inclusion criteria and do not meet the exclusion criteria from 7 CM hospitals. Among them, 1,472 patients use other or no CM injections, and 278 patients have incomplete information. There are 36 cases having outcome events during hospitalization (including cardiogenic death, worsening of HF, cardiogenic shock, and other reason death, etc.). Hence, a total of 1,175 CHF patients are included in the cohort with 509 cases in the exposed group and 666 cases in the non-exposed group. Additional 58 patients in the exposed group and 70 patients in the non-exposed group are lost during the period of follow-up, leading to a missed follow-up rate of 11.39% and 10.51%, respectively. Finally, the total missed follow-up rate is 10.89%. In conclusion, 1,047 patients are successfully followed up with 536 males (51.20%) and 511 females (48.80%) respectively, making up 451 cases in the exposed group and 596 cases in the non-exposed group. The median age is 71 years old (IQR 62 to 75 years), and the median follow-up time is 40.17 months (IQR 28.57 to 60.28). Baseline characteristics of the exposed and non-exposed groups are balanced. All results are shown in Table 1.

Levels of NYHA Classification, LVEF, and NT-ProBNP

The levels of NYHA classification, LVEF, and NT-ProBNP in the exposed group and the non-exposed group are similar before treatment but varied after treatment. For specific, the improvement level of indicators in the exposed group is higher than that of non-exposed group (Table 2).

Outcome Events

The highest two outcome events during follow-up are cardiogenic death and HF readmission. Strikingly, as displayed in Table 3, the incidence of cardiogenic death, HF readmission and total outcome events in the exposed group are significantly lower than in the non-exposed group. Under the conditions of baseline balance between exposed and non-exposed groups, the P-value of cardiogenic death, HF readmission, and

Table 1. Baseline Characteristics of Exposed and Non-Exposed Groups [Case (%)]

Characteristics	Exposed group (*n*=451)	Non-exposed group (*n*=596)	*P* value
Course (months, $\bar{x} \pm s$)	79.83 ± 53.03	64.76 ± 47.98	
Demographics			
Age (Year, $\bar{x} \pm s$)	67.15 ± 7.02	67.64 ± 6.66	0.559
Male	204 (45.23)	332 (55.70)	0.766
Protopathy			
Cardiomyopathy	46 (10.20)	38 (6.38)	0.700
CHD	315 (69.84)	393 (66.44)	0.159
Hypertension	37 (8.20)	61 (10.23)	0.602
Others	53 (11.75)	104 (17.45)	
Merger disease			
Atrial fibril-lation	75 (16.63)	180 (29.05)	0.934
Diabetes	132 (29.27)	155 (26.73)	0.863
Medicine			
ACEI/ARB	138 (30.60)	92 (15.44)	0.948
Beta-blockers	209 (46.34)	136 (22.82)	0.145
ARA	159 (35.25)	157 (26.34)	0.494
Diuretics	125 (27.72)	130 (21.81)	0.805
CPM/CMD	140 (31.04)	174 (29.20)	0.326
NYHA classification			0.248
Ⅰ	0	0	
Ⅱ	71 (15.74)	154 (25.84)	
Ⅲ	299 (66.30)	339 (56.88)	
Ⅳ	81 (17.96)	103 (17.28)	

Notes: CHD: coronary heart disease, ACEI/ARB: ace inhibitors/angiotensin Ⅱ receptor antagonist, ARA: aldosterone receptor antagonist, CPM/CMD: Chinese patent medicine/ Chinese medicine decoction

total outcome events in exposed and non-exposed groups are 0.042, 0.029 and 0.000, with significant difference between groups.

Correlation Analysis of SMI and Outcome Events

In correlation analysis, each related factor is set as independent variable X, and the outcome event (such as cardiogenic death and HF readmission) is set as dependent variables Y. The assignment of independent and dependent variables is summarized in Appendix 2. All data is imported into SPSS 25.0 software and analyzed by Kaplan-Meier survival model and Cox regression, in aims to explore the relationship between SMI and outcome events/survival time, and the relationship between various related factors and outcome events/survival time (P<0.05), respectively.

Single Factor Analysis of Cardiogenic Death

Kaplan-meier survival analysis curve (Appendix 3) of SMI and cardiogenic death suggests that cardiogenic death occurs in the exposed group is later than that in the non-exposed group when the cumulative survival is the same. Meanwhile, the survival rate in the exposed group is higher than that in the non-exposed group, with a significantly different log-rank P<0.05, as shown in Table 4.

Table 4. Kaplan-Meier Survival Analysis of Cardiogenic Death [Case (%)]

Group	Case	Occurence	Non-occurence	log-rank *P* value
Exposed	451	50 (10.18)	401 (89.82)	0.014
Non-exposed	596	92 (15.43)	506 (84.90)	

Multi-factor Analysis of Cardiogenic Death

As summarized in Table 5, the multivariate regression analysis of cardiogenic death manifests that age, cardiomyopathy, diabetes, and NYHA classification are risk factors for cardiogenic death. In contrast, betablockers, aldosterone receptor

Table 2. Changes of NYHA Classification, LVEF and NT-ProBNP before and after Treatment

Group	Case	YHA classification decline [*n* (%)]			LVEF ($\bar{x} \pm s$, %)			NT-ProBNP ($\bar{x} \pm s$, pg/mL)		
		0 level	1 level	2 level	BT	AT	IMP	BT	AT	IMP
Exposed	451	161 (35.70)	273 (60.53)	17 (3.77)	52.83 ± 11.74	61.72 ± 9.48	8.89 ± 10.72	2962 ± 4286	2053 ± 3215	909 ± 3633
Non-exposed	596	337 (56.54)	243 (40.77)	16 (2.68)	53.02 ± 13.34	60.93 ± 9.36	7.91 ± 11.38	2833 ± 4855	2098 ± 2140	735 ± 3989

Notes: 0 level: NYHA classification has not changed after the treatment, 1 level: the grade of NYHA classification dropped by one level after the treatment, 2 level: the grade of NYHA classification dropped by two level after the treatment; BT: before the treatment, AT: after the treatment, IMP: the improvement

Table 3. Outcome Events in Exposed and Non-exposed Groups [Case (%)]

Group	Case	Cardiogenic death	Heart failure readmission	Acute coronary syndrome	Death from other diseases	Others	Total outcome events
Exposed	451	50 (10.18)	146 (32.37)	6 (1.94)	2 (0.32)	2 (0.65)	206 (45.68)
Non-exposed	596	92 (15.43)	232 (38.93)	8 (1.34)	33 (5.54)	8 (1.34)	371 (62.25)
P value		0.042	0.029	0.954	0.000	0.246	0.000

Table 5. Cox Regression Analysis of Cardiogenic Death

Variable	B	DOF	*P*-value	Exp(B)	95.0% Exp(B) CI	
					Lower limit	Upper limit
Age	0.015	1	0.017	1.015	1.003	1.028
Sex	0.149	1	0.395	1.160	0.823	1.635
CHD	–0.055	1	0.779	0.947	0.646	1.388
Hypertension	–0.106	1	0.756	0.899	0.461	1.754
Cardiomyopathy	0.559	1	0.002	1.749	1.220	2.509
Diabetes	0.388	1	0.027	1.474	1.044	2.081
Atrial fibril-lation	0.156	1	0.367	1.169	0.833	1.640
ACEI/ARB	0.187	1	0.331	1.205	0.827	1.757
Beta-blockers	–1.044	1	0.000	0.352	0.215	0.576
Diuretics	0.071	1	0.764	1.074	0.673	1.713
ARA	–0.640	1	0.007	0.527	0.332	0.838
NYHA	0.606	1	0.000	1.834	1.366	2.462
CPM/CMD	–1.526	1	0.009	0.717	0.069	0.886
SMI	–0.196	1	0.048	0.822	0.573	0.980

Notes: B: partial regression coefficient, DOF: degrees of freedom, Exp(B): hazard Ratio (HR), CHD: coronary heart disease, ACEI/ARB: ace inhibitors/angiotensin Ⅱ receptor antagonist, ARA: aldosterone receptor antagonist, CPM/CMD: Chinese patent medicine/Chinese medicine decoction

antagonists, Chinese patent medicine/Chinese medicine decoction, and SMI are protective factors for cardiogenic death.

Single Factor Analysis of HF Readmission

Kaplan-Meier survival analysis curve (Appendix 4) of SMI and HF readmission indicates that the incidence of HF readmission within 1 year after discharge is higher but decreases with the extension of time. Compared with the non-exposed group, HF readmission in the exposed group occurs later under the same cumulative survival. Meanwhile, a significant log-rank *P* value is obtained as shown in Table 6.

Table 6. Kaplan-meier Survival Analysis of HF Readmission [Case (%)]

Group	Case	Occurence	Non-occurence	log-rank *P* value
Exposed	451	146 (32.37)	305 (67.63)	0.025
Non-exposed	596	232 (38.93)	365 (61.07)	

Multi-factor Analysis of HF Readmission

The multivariate regression analysis of HF readmission suggests that age, cardiomyopathy, and NYHA classification are risk factors for HF readmission. Correspondingly, SMI is a protective factor for HF readmission as seen in Table 7.

Table 7. Cox Regression Analysis of HF Readmission

Variable	B	DOF	*P*-value	Exp(B)	95.0% Exp(B) CI	
					Lower limit	Upper limit
Age	0.017	1	0.000	1.017	1.008	1.025
Sex	–0.096	1	0.366	0.908	0.737	1.119
CHD	0.070	1	0.556	1.073	0.849	1.355
Hypertension	–0.102	1	0.610	0.903	0.610	1.337
Cardiomyopathy	0.633	1	0.008	1.531	1.332	1.850
Diabetes	0.074	1	0.512	1.076	0.864	1.342
Atrial fibril-lation	0.103	1	0.330	1.108	0.901	1.363
ACEI/ARB	0.026	1	0.829	1.027	0.810	1.301
Beta-blockers	0.154	1	0.187	1.166	0.928	1.465
Diuretics	0.116	1	0.401	1.123	0.857	1.473
ARA	0.191	1	0.137	1.211	0.941	1.558
NYHA	0.343	1	0.000	1.410	1.190	1.671
CPM/CMD	0.155	1	0.317	1.167	0.862	1.581
SMI	–0.309	1	0.006	0.734	0.589	0.915

Notes: B: partial regression coefficient, DOF: degrees of freedom, Exp(B): hazard Ratio (HR), CHD: coronary heart disease, ACEI/ARB: ace inhibitors/angiotensin Ⅱ receptor antagonist, ARA: aldosterone receptor antagonist, CPM/CMD: Chinese patent medicine/Chinese medicine decoction

DISCUSSION

Through analysis, SMI combined with standardized Western medicine treatment has demonstrated advantages in improving NYHA classification, LVEF and NT-ProBNP levels during hospitalization. Compared with other comprehensive hospitals, the incidence of cardiogenic death and HF readmission is lower as shown in this study. One possibility is that patients in CM hospitals are less serious than in comprehensive hospitals.[13] In exposed group, the incidence of cardiogenic death, HF readmission is lower than non-exposed group with significant difference. According to Kaplan-Meier survival analysis curve of cardiogenic death/HF readmission, SMI hopefully decreases the probability of cardiogenic death and HF readmission compared with non-exposed group. We further explored the factors that influence the occurrence of outcome events in the context of multiple factors. The multivariate regression analysis reveals that SMI is a protective factor. Likewise, the multivariate regression analysis of HF readmission points that SMI is a protective factor.

The results proved that Chinese patent medicine/Chinese medicine decoction is a protective factor for cardiogenic death but not for HF readmission. It can

be explained as Chinese patent medicines or Chinese medicine decoction are mostly used during follow-up. Also, the efficacy of Chinese patent medicine or Chinese medicine decoction is gradual, and can be adjusted freely according to the overall condition of the patients. Thus it finally contributes to the long-term prognosis of the patients. Notably, the occurrence of cardiogenic death in the exposed group is 0.822 times that of the non-exposed group, namely a 17.8% decrement after applying with SMI. In similar, the HF readmission in the exposed group is 0.734 times that of the non-exposed group, referring to a 26.6% decrement.

However, there are several disadvantages. First, for retrospective observation studies, some cases missed data inevitably. Selection bias generated when we exclude patients whose data were missing. Second, loss follow-up bias emerged for the different rates of lost follow-up between the exposed group and the non-exposed group as the relative long follow-up time of this study. Third, the different dose and application method may affect the treatment of SMI. Fourth, since the Cox regression cannot handle the collinearity between two variables, it may affect the accuracy of the results in reality. Finally, due to the limitations of the retrospective data, the study failed to study the safety of SMI.

Previous studies have shown that combination with SMI can better improve the patient's total effectiveness, Lee's score, BNP, 6-min walk test, LVEF, cardiac ultrasound and other cardiogenic function indicators.[14-16] Meanwhile, there hardly observe serious adverse reactions/events of SMI for CHF, indicating SMI was safe for clinical use.[17] However, these studies were limited by their small sample size within 35–120 cases. Additionally, the quality of the literature was poor. And the evaluation indicators used were not uniform. Hence it was difficult to use meta and other methods to provide a higher level of evidence-based Medical evidence.[9]

Although our research has some limitations, we adopt several methods to improve the accuracy of the research. First, we use the HIS to extract clinical data of CHF patients to confirm the completeness and reliability. Second, the study covers CHF patients from 7 CM hospitals in Shandong province. The sample size is relatively sufficient. Third, Cox regression pays more attention to the survival time of patients, and analyze data with censored survival time, and therefore to conduct an important model for prognosis research.[18] This study uses the Cox regression to explore the impact of SMI on the long-term prognosis of CHF patients under the multi-factor background by scientific method. Fourth, cardiogenic death is viewed as the primary outcome, and HF readmission is used as the secondary outcome, providing reliable indicators for research. Finally, the average follow-up time is 3.7 years while the longest is 5.54 years. This provides more reliable results for studying the long-term prognosis of CHF patients. Therefore, the multi-center, large-sample, long-term follow-up study we conducted can provide reliable evidence to a certain degree, for the study of the prognosis of SMI in the treatment of CHF.

SMI is composed of *Radix Ginseng Rubra* and *Radix Ophiopogonis*. The main chemical component of *Radix Ginseng Rubra* is ginsenoside,[19] which plays a role in anti-cardiomyocyte apoptosis, anti-myocardial hypertrophy. More, SMI is found to resist arrhythmia through multiple signaling pathways.[20] Specifically, it protects myocardium by scavenging oxygen free radicals and inhibiting lipid peroxidation.[21] The main medicinal components of *Radix Ophiopogonis* are ophiopogon japonicus polysaccharide and ophiopogon japonicus saponin. Experiments demonstrate that ophiopogon japonicus saponins protect ischemic myocardium by reducing lipid peroxidation injury and improving myocardial metabolism. Oral administration of the polysaccharide from *Radix Ophiopogonis* offered significant cardioprotective effect through enhancement of endogenous antioxidants.[22] SMI protects mitochondria from oxidative stress by increasing phosphate dehydrogenase levels, thereby improving the energy metabolism of cardiomyocytes.[23] *Radix Ginseng Rubra* and *Radix Ophiopogonis* synergistically promote the recovery of cardiogenic function, enhance myocardial contractility, reduce heart load, myocardial oxygen consumption and regulate autonomic disorders.[24]

According to this study, we proved that SMI as the adjuvant reagent can better improve the hemodynamic related indicators and indeed reduce the incidence of HF readmission and cardiogenic mortality in patients with CHF. This provides further evidence for the clinical application of SMI in CHF. We will continue to follow-up these patients, expand the sample size, and improve the methodological quality of the study in the hope of providing more reliable evidence for further clinical

application of SMI.

Conflict of Interest

The authors report no conflict of interest.

Author Contributions

This project was initiated and developed by Dai GH and Guan H. Dai GH, Guan H were involved in the design of the study. Guan H, Gao WL were involved in drafting and writing the manuscript. Sun C, Liu Z were involved in the extraction of data. Ren LL, Hou XM were involved in the follow-up of the patients. Guan H was involved in the statistical analysis of data. Zhang T was involved in data checking. All authors read and approved the final manuscripts.

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