ABSTRACT

Background Dyslipidaemia is different among patients with hypertension in different populations. The serum lipid profiles among Hakka patients with hypertension in southern China are still unclear.

Methods 35 448 patients with hypertension were enrolled in this study from January 2016 to October 2020, and their serum lipids were analysed.

Results Low high-density lipoprotein-cholesterol (HDL-C) (29.9%) accounted for the highest proportion in dyslipidaemia, followed by high triglyceride (TG) (20.7%), high total cholesterol (TC) (14.0%) and high low-density lipoprotein-cholesterol (LDL-C) (7.9%) in all subjects. The largest proportion of dyslipidaemia types was independent low HDL-C (12.7%). The proportion of low HDL-C was 15.5% in non-elderly men, 6.4% in non-elderly women, 16.7% in elderly men and 8.5% in elderly women, respectively. The largest proportion of dyslipidaemia types was independent high TG in non-elderly female patients (15.7%) and elderly patients (8.9%). The results showed that higher LDL-C, TC and TG levels in non-elderly patients than elderly patients. TG, TC and LDL-C levels decreasing with the increasing age, the differences were statistically significant. The levels of TG, TC, HDL-C and LDL-C in women were higher than in men among various age groups. Homocysteine level was increasing with increasing age.

Conclusions Serum lipid levels varied in different groups according to age and sex in patients with hypertension. Dyslipidaemia is more common in non-elderly patients than elderly. TG, TC and LDL-C levels were higher in female patients than male.

INTRODUCTION

Over the past decade, the incidence of hypertension has increased yearly, and hypertension has become a major global disease burden. In 1975, the number of people with hypertension worldwide was 590 million (prevalence was 14.5%). In 2015, this number increased to 1.13 billion (prevalence was 15.3%). It is predicted that hypertension people worldwide will continue to increase to 1.56 billion by 2025. There are approximately 245 million patients with hypertension in China.

Serum lipids mainly refer to cholesterol, triglycerides and lipids in serum. Dyslipidaemia is a manifestation of lipid metabolism disorder, and the damage it causes to human health is mainly manifested in cardiovascular diseases, especially coronary heart disease and other atherosclerotic diseases. Dyslipidaemia is a risk factor for atherosclerotic cardiovascular disease. The prevalence of dyslipidaemia varies in different ethnic groups and regions. The prevalence of dyslipidaemia in American and Japanese adults was 60.8% and 35.6%, respectively. A study has shown that the prevalence of dyslipidaemia in Nigerians is more than 70%. The prevalence of high total cholesterol (TC), high-low density lipoprotein cholesterol (LDL-C), high low-density lipoprotein cholesterol (HDL-C) and high triglycerides (TG) in Chinese adults was 6.9%, 8.1%, 20.4% and 13.8%, respectively. Results of a study on serum total lipoprotein and LDL-C levels in Chinese adults showed that the serum total lipoprotein and LDL-C levels of adults in China were high, and the recognition, treatment and control rates of high TC are extremely low worldwide, at only 11.0%, 5.1% and 2.8%, respectively.

Dyslipidaemia and hypertension are common chronic diseases and important
risk factors for cardiovascular and cerebrovascular diseases. One study showed that even in patients with well-controlled blood pressure, the risk of cardiovascular disease was significantly increased with the level of LDL-C stratification. According to the calculation of the model, 1–1.65 million cases of acute myocardial infarction, 1.4–2.5 million cases of stroke and 450 000–850 000 cases of cardiovascular death can be avoided if active treatment for high blood pressure and cholesterol can be carried out to reach the target values in the next 15 years in China. It has become an important part of the cardiovascular disease prevention and control system in China to carry out comprehensive intervention for multiple risk factors based on hypertension.

Although some studies have analysed serum lipid profiles in patients with hypertension, the results are different in different populations. In this study, serum lipid profiles were analysed in patients with hypertension in a southern Chinese Hakka population. The aim of this study was to determine characteristics of serum lipid levels in patients with hypertension among Hakka population.

MATERIALS AND METHODS

Study design, setting and patient involvement

This study is a hospital-based, retrospective, descriptive study of blood lipid profiles in a population with hypertension by collating data from blood lipid measurements in patients with hypertension who were admitted to hospital. No patients or members of the public were involved in the design of this study.

Subjects

Data of 35 448 patients with hypertension (21 158 men and 14 290 women) admitted to Meizhou People’s Hospital from January 2016 to October 2020 were collected. Hypertension was defined as systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg. The inclusion criteria were as follows: (1) Clinically diagnosed as hypertension; (2) Serum lipid data were complete; (3) Adults. The exclusion criteria were as follows: (1) Incomplete data of serum lipid; (2) Minors. Patients’ information was collected, such as gender, age and family history.

Serum lipid measurements

Approximately 3 mL of blood was taken from each subject, and serum was immediately separated. The serum lipid levels of the samples were evaluated by an Olympus AU5400 system (Olympus Corporation, Tokyo, Japan). TC, TG, LDL-C, HDL-C, apolipoprotein A1 (Apo-A1) and apolipoprotein B (Apo-B) analyses were carried out using the cholesterol esterase/peroxidase enzymatic method, glycerophosphate oxidase/peroxidase enzymatic method, direct surfactant removal method, direct immunoinhibition method and immunoturbidimetry method, respectively, according to the manufacturers’ instructions. Patients with a clear past history of hyperlipidaemia and/or a current serum lipid test that met criteria according to the 2016 Chinese Guidelines were diagnosed with dyslipidaemia.

Statistical analysis

Statistical analysis was performed using SPSS statistical software V.21.0 (IBM, New York, USA). Student’s t-test, Mann-Whitney U test or one-way analysis of variance was used for continuous data analysis. When data followed normal distribution, parametric tests otherwise non-parametric methods are used to compare the groups. Mann-Whitney U test was used for comparative analysis of quantitative variables of non-normal distribution. Genotype composition ratios and allele frequencies between groups were analysed by the $\chi^2$ test. The significance level for all tests was set to $p<0.05$.

RESULTS

General serum lipid levels of patients with hypertension

A total of 35 448 patients with hypertension were enrolled, including 9242 non-elderly (<65 years old) men, 5863 non-elderly women, 11 916 elderly (≥65 years old) men and 8427 elderly women. The difference between the average ages of non-elderly men (55.09±7.52 years) and non-elderly women (55.64±6.87 years) was similar to that between the average ages of elderly men (74.26±6.57 years) and elderly women (75.33±7.17 years). TC, HDL-C, LDL-C, Apo-A1 and Apo-B levels were higher and TG/HDL-C, TC/HDL-C, LDL-C/HDL-C ratios were lower in non-elderly women than in non-elderly men. TG, TC, HDL-C, LDL-C, TG/HDL-C, Apo-A1 and Apo-B levels were higher and LDL-C/HDL-C ratio and homocysteine (Hcy) level were lower in elderly women than in elderly men. The level of HDL-C was higher in elderly men than in non-elderly men, reverse result was found in women. TG, TC, LDL-C, TG/HDL-C, TC/HDL-C, LDL-C/ HDL-C, Apo-A1, Apo-B levels were lower in elderly men than non-elderly men. Similar results were found in women (table 1).

The distribution of dyslipidaemia in patients with hypertension

Low HDL-C (29.9%) accounted for the highest proportion of dyslipidaemia, followed by high TG (20.7%), high TC (14.0%) and high LDL-C (7.9%) across all subjects. Different parameters were combined according to the normal status of various indexes of serum lipids to analyse the differences between non-elderly patients and elderly patients, between men and women. The largest proportion of dyslipidaemia types was independent low HDL-C (12.7%). The proportion of low HDL-C was 15.5% in non-elderly men, 6.4% in non-elderly women, 16.7% in elderly men and 8.5% in elderly women, respectively. The non-elderly women had lower the proportions of low HDL-C, high LDL-C +low HDL-C +high TG, high LDL-C +low HDL-C +normal TG, normal LDL-C +low HDL-C +high...
TG and normal LDL-C +low HDL-C +normal TG than non-elderly men, although they had higher proportions of high TC, high LDL-C, high LDL-C +normal HDL-C +high TG, high LDL-C +normal HDL-C +normal TG, normal LDL-C +normal HDL-C +high TG than non-elderly men. Among the elderly, a similar result was found. In addition, elderly men had a lower proportion of different combinations of dyslipidaemias than non-elderly men except for normal LDL-C +low HDL-C +normal TGs, while the proportions of different combinations of dyslipidaemias were lower in elderly women than in non-elderly women except for low HDL-C, high LDL-C +low HDL-C +normal TGs and normal LDL-C +low HDL-C +normal TGs (table 2).

Differences in TG levels in patients with hypertension according to different age groups and sex

The differences in TG levels among various age groups of patients with hypertension have statistically significant (figure 1A). TG levels in the 60–69, 70–79 and 80–89 year-old age women were higher than that of men. The differences were statistically significant (figure 1B). Among the male patients, TG level in the <50-year-old age patients was higher than those in 50–59, 60–69, 70–79, 80–89 and ≥90 year-old age patients, and the TG level of the 50–59 year-old age patients was higher than those of the 70–79, 80–89 and ≥90 year-old age patients, while the TG level of 60–69 year-old age group was higher than that in the 80–89, and ≥90 year-old age patients (figure 1C). Among female patients, TG levels in the 70–79, 80–89 and ≥90 year-old age groups were lower than those in the <50-year-old age group, and the TG levels of the 70–79, 80–89 and ≥90 year-old age patients were lower than those in the 50–59 year-old age patient; the TG levels of the 80–89, and ≥90 year-old age groups were lower than those in the 60–69 year-old age group (figure 1D).

Differences in TC levels in patients with hypertension according to different age groups and sex

There were statistically significant differences in TC levels among various age groups of patients with hypertension (figure 2A). There were statistically significant differences in TC levels among various age groups of patients with hypertension when women were compared with men, TC levels in all various age women were higher than that of men (figure 2B). Among male patients, the TC level in the <50-year-old age patients was higher than those in the 50–59, 60–69, 70–79, 80–89 and ≥90 year-old age patients, the TC level of 50–59 year-old age group was higher than in the 70–79, 80–89 and ≥90 year-old age groups, and the TC level of the 60–69 year-old age group was higher than that in the 80–89, and ≥90 year-old age groups (figure 2C). Among female patients, the TC levels in 70–79, 80–89 and ≥90 year-old age groups were lower than those in the <50, and 50–59 year-old age groups (figure 2D).
| Condition | Non-elderly (<65 years old, n=15 105) | Elderly (≥65 years old, n=20 343) |
|-----------|--------------------------------------|----------------------------------|
|           | Number | Male | Female | Number | Male | Female |
|           |        |      |        |        |      |        |
| Total     | 35 448 | 9242 | 5863   | 11 916 | 8427 |
| Elevated TC | 4965 (14.0%) | 1301 (14.1%) | 1243 (21.2%)† | 995 (8.3%)§ | 1426 (16.9%)†§ |
| Elevated TG | 7334 (20.7%) | 2487 (26.9%) | 1582 (27.0%) | 1595 (13.4%)§ | 1670 (19.8%)†§ |
| Low HDL-C | 10 591 (29.9%) | 3422 (37.0%) | 1088 (18.6%)† | 4227 (35.5%)‡ | 1854 (22.0%)†§ |
| Elevated LDL-C | 2797 (7.9%) | 762 (8.2%) | 619 (10.6%)† | 669 (5.6%)§ | 747 (8.9%)†§ |
| Elevated LDL-C + low HDL-C + elevated TG | 140 (0.4%) | 60 (0.6%) | 21 (0.4%)* | 31 (0.3%)§ | 28 (0.3%) |
| Elevated LDL-C + low HDL-C + normal TG | 257 (0.7%) | 91 (1.0%) | 20 (0.3%)† | 101 (0.8%) | 45 (0.5%)† |
| Elevated LDL-C + normal HDL-C + elevated TG | 694 (2.0%) | 216 (2.3%) | 182 (3.1%)† | 110 (0.9%)§ | 186 (2.2%)†§ |
| Elevated LDL-C + normal HDL-C + normal TG | 1610 (4.5%) | 376 (4.1%) | 364 (6.2%)† | 417 (3.5%)‡ | 453 (5.4%)†‡ |
| Normal LDL-C + low HDL-C + elevated TG | 2259 (6.4%) | 896 (9.7%) | 329 (5.6%)† | 631 (5.3%)§ | 403 (4.8%)‡ |
| Normal LDL-C + low HDL-C + normal TG | 4505 (12.7%) | 1429 (15.5%) | 377 (6.4%)† | 1985 (16.7%)‡ | 714 (8.5%)†§ |
| Normal LDL-C + normal HDL-C + normal TG | 14 099 (39.8%) | 3184 (34.5%) | 2579 (44.0%)† | 4557 (38.2%)§ | 3779 (44.8%)† |
| Normal LDL-C + normal HDL-C + elevated TG | 3043 (8.6%) | 947 (10.2%) | 805 (13.7%)† | 542 (4.5%)§ | 749 (8.9%)†§ |

Compared with men.
Compared with the non-elderly.
*P<0.05.
†P<0.01 for both the non-elderly and the elderly.
‡P<0.05.
§P<0.01 for both men and women.
TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B; Hcy, homocysteine.
Differences in HDL-C levels in patients with hypertension according to different age groups and sex

HDL-C levels in the 50–59, 60–69, 80–89 and ≥90 year-old age patients were higher than that in <50-year-old age patients (figure 3A). There were statistically significant differences in HDL-C levels among various age groups of patients with hypertension when women were compared with men, HDL-C levels in all various age groups in women were higher than that in men (figure 3B). Among the male patients, HDL-C levels in the 70–79 and 80–89 year-old age groups were higher than those in the <50-year-old age group, and the HDL-C level of the 70–79 year-old age group was higher than that in 50–59 year-old age group (figure 3C). Among female patients, HDL-C levels in the 70–79, and 80–89 year-old age groups were lower than in the <50, and 50–59 year-old age groups, respectively, while the HDL-C level of the 80–89 year-old age group was lower than that in 60–69 year-old age group (figure 3D).

Differences in LDL-C levels in patients with hypertension according to different age groups and sex

There were statistically significant differences in LDL-C levels among the various age groups of patients with hypertension, except the 50–59 year-old age group compared with the <50-year-old age group (figure 4A). There were statistically significant differences in LDL-C levels among the various age groups of patients with hypertension when women were compared with men, except in the <50-year-old age group (figure 4B). Among male patients, the LDL-C level in the <50-year-old age group was higher than that in 60–69, 70–79, 80–89 and ≥90 year-old age groups, and the LDL-C level of the 50–59 year-old age
The levels of high-density lipoprotein cholesterol (HDL-C) in various age groups. (A) Comparison between the <50-year-old age group and various age groups older than 50 years, *p<0.05, **p<0.01. Comparison between the 50–59 year-old age group and various age groups older than 70 years, p<0.05, #p<0.01. Comparison between 60–69 year-old age group and various age groups older than 80 years, p<0.05, &&p<0.01. (B) Comparison between men and women in the same age group, *p<0.05, **p<0.01. (C) Among men, a comparison between the <50-year-old age group and various age groups older than 50 years, *p<0.05, **p<0.01. Comparison between the 50–59 year-old age group and various age groups older than 70 years, p<0.05, #p<0.01. Comparison between 60–69 year-old age group and various age groups older than 80 years, &&p<0.01. (D) Among women, a comparison between the <50-year-old age group and various age groups older than 50 years, *p<0.05, **p<0.01. Comparison between the 50–59 year-old age group and various age groups older than 70 years, &p<0.05, &&p<0.01. Comparison between the 60–69 year-old age group and various age groups older than 80 years, &&p<0.01.

Differences in Hcy levels in patients with hypertension according to different age groups and sex

The Hcy levels in the 70–79, 80–89 and ≥90 year-old age groups were higher than those in the <50 and 50–59 year-old age groups (figure 4C). Among female patients, the LDL-C levels in the 70–79, 80–89 and ≥90 year-old age groups were lower than those in the <50, and 50–59 year-old age groups, while the LDL-C levels of the 80–89 and ≥90 year-old age groups were lower than those in the 60–69 year-old age group. In addition, the LDL-C level in the 60–69 year-old age group was higher than those in the <50-year-old age group (figure 4D).

The Hcy levels in the 70–79, 80–89 and ≥90 year-old age groups were higher than those in the <50, 50–59 year-old age groups, while the Hcy levels of the 80–89 and ≥90 year-old age groups were higher than those in the 60–69 year-old age group. In addition, the Hcy level in the 50–59 year-old age group was lower than that in the <50-year-old age group (figure 5A). In the various age groups, women had lower levels of Hcy than men, and there were statistically significant differences in the <50, 50–59, 60–69, 70–79 and 80–89 year-old age groups (figure 5B). Among male patients, the Hcy level in the <50-year-old age group was lower than that in the 70–79, 80–89 and ≥90 year-old age groups, the Hcy level
of the 50–59 year-old age group was lower than that in the 70–79, 80–89 and ≥90 year-old age groups, and the Hcy level of the 60–69 year-old age group was lower than that in the 80–89, and ≥90 year-old age groups (figure 5C). Among female patients, the Hcy levels in the 70–79, 80–89 and ≥90 year-old age groups were higher than those in the 50–59 year-old age groups, while the Hcy levels of the 80–89 and ≥90 year-old age groups were higher than those in the 60–69 year-old age group (figure 5D).

**DISCUSSION**

Patients with hypertension often have dyslipidaemia. Some studies suggested that abnormal serum lipid levels may contribute to hypertension and that correcting serum lipid abnormalities may help control blood pressure. Dyslipidaemia is often still neglected in patients with hypertension, especially in those at higher risk of cardiovascular and cerebrovascular diseases. Therefore, it is of great importance to study the serum lipid profiles of patients with hypertension in the prevention and treatment of cardiovascular and cerebrovascular diseases. A study of more than 190 000 French patients with hypertension under the age of 55 showed that more than 50% of them had dyslipidaemia. A result of a hypertension investigation in the USA showed that 79% of white male and 65% of white female patients with hypertension have dyslipidaemia and that these proportions were higher than those among black male and female patients with hypertension (57% and 50%, respectively). The prevalence of dyslipidaemia among patients with hypertension was 64% in Nigerians. The mean prevalence of lipid disorders in patients with hypertension in an Algeria population was 16.1%. The prevalence of dyslipidaemia among the hypertensive population in the present study was similar to that in other studies among hypertensive populations from rural Northeast China and a rural Chinese population in Liaoning Province in China.

There are an increasing number of studies on the relationship between hypertension and dyslipidaemia and the related mechanism. Hypertension and dyslipidaemia not only have common metabolic abnormalities and internal associated factors but also influence each other through various mechanisms. First, dyslipidaemia damages the vascular endothelium and affects blood pressure. Vascular endothelial function is probably the link between hypertension and hyperlipidaemia. Arterial contractility is largely regulated by vascular endothelial function. Abnormal lipids may indirectly affect arterial elasticity by affecting vascular endothelial regulation, thereby leading to hypertension. The effect of hyperlipidaemia on vascular endothelial injury is closely related to oxidised low-density lipoprotein (ox-LDL). Ox-LDL promotes the development of atherosclerosis mainly by causing injury to and dysfunction of endothelial cells. The increase in oxidised cholesterol in hyperlipidaemia may impair the function of vascular endothelial cells. Studies have shown that oxidised cholesterol has cytotoxic effects on endothelial cells, smooth muscle cells and other cells and can also induce apoptosis of lymphocytes.

Second, dyslipidaemia affects blood pressure by affecting cell membrane structure and receptor function. Studies have shown that there are many kinds of abnormal ion transport in the cell membrane in patients with hypertension, so it is thought that hypertension is actually a cell membrane disease. When dyslipidaemia occurs, serum TG and cholesterol levels increase, and the cholesterol content in the cell membrane also increases. At the same time, the proportion of unsaturated fatty acids in the cell membrane decreased, while that of saturated fatty acids increased. The composition and content of fatty acids in the cell membrane are closely related to

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membrane fluidity. Dyslipidaemia causes abnormalities in cell membrane fluidity, permeability, material transport, enzyme activity and signal transduction and participates in the pathogenesis of hypertension through these mechanisms. 32 33

Third, dyslipidaemia affects blood pressure by affecting angiotensin II (Ang II). LDL-C and ox-LDL can aggravate local oxidative stress caused by vascular endothelial dysfunction, cause the vascular endothelium to secrete inflammatory mediators, induce local infiltration of monocytes macrophages and the formation of foam cells, and activate ACE to increase Ang II concentration. Ox-LDL can weaken endothelium-dependent vasodilation and affect endothelial function. 34 Ang II can induce the contraction of arterioles and smooth muscle, increase peripheral vascular resistance, and stimulate aldosterone secretion, and retain sodium, which is an important mechanism involved in the pathogenesis and persistence of hypertension. The effect of Ang II on blood pressure is largely affected by serum cholesterol levels, especially LDL-C levels. 35

The adjustment of dyslipidaemia is beneficial for controlling of blood pressure. Patients with hypertension with hypercholesterolaemia are treated with statins or other lipid-lowering drugs. Follow-up showed that patients treated with statins had significantly lower blood pressure than those treated with other lipid-lowering drugs. The antihypertensive effect of statins was mostly independent of the decrease in cholesterol levels. 36 37 Another study showed that statins have no significant effect on blood pressure. 38 In addition, lowering blood pressure while lowering blood lipid has a synergistic effect on improving clinical prognosis. The results of the Anglo-Scandinavian Cardiac Outcomes Trial published in 2006 showed a significant synergistic effect of amlodipine and atorvastatin in the prevention of coronary heart disease events in patients with hypertension. The study showed that the use of statin therapy for the purpose of blood pressure reduction can further improve the clinical prognosis of patients with hypertension. This is the beginning of the theory of comprehensive management of risk factors and shows great progress in the treatment of hypertension. 39

Compared with the elderly, the non-elderly patients tended to have higher proportion of dyslipidaemia in both men and women. Therefore, greater intensity of lipid-controlling is required for the non-elderly and it is necessary for physicians to pay more attention to abnormal serum lipid for such patients. A study showed that the non-elderly patients who had acute myocardial infarction (AMI) tended to have higher LDL-C, and TC than that in elderly for both men and women. 40 Another study showed that LDL-C, TC and TG were higher in non-elderly AMI than in elderly for men. 41 There has been little research on these issues in patients with hypertension. The present study also showed that levels of TG, TC and LDL-C were higher in women than that in men. Previous studies have shown that oestrogen plays a role in regulating lipid metabolism, the concentrations of physiological sex hormones affect lipoprotein levels. 42 Follicle-stimulating hormone levels are associated with serum cholesterol levels. 43 The difference in lipid levels between men and women may be caused by differences in hormone levels, however, the role of progesterone and androgen only partially explains the differences in serum lipid levels, and the underlying physiological regulatory factors leading to the differences in lipid metabolism between men and women remain to be elucidated. 44 45 Other studies suggest that the difference in lipid level between men and women may be caused by the difference in rates of both lipolysis and lipogenesis between men and women. 46 47

Hypertension is closely related to hyperlipidaemia and is a risk factor that unifies a wide variety of cardiovascular events. A better understanding of the profile of serum lipids of patients with hypertension and the possible mechanism of dyslipidaemia leading to hypertension will be helpful for clinical treatment. One weakness of our study was that some records could not be tracked and verified, limiting the evaluation of these combined factors such as dietary structure, and lifestyle. Study showed that the major lifestyle interventions to modify serum HDL-C include physical exercise, caloric restriction and smoking cessation. 48 Appropriate dietary intake, including limiting salt and saturated fat consumption, can reduce the risk of developing hypertension and dyslipidaemias. 49 Another limitation of this study was that the relationship between hypertension and dyslipidaemia was not studied in depth, nor was the mechanism elucidated. The most investigated mechanisms are the renin-angiotensin-aldosterone system, oxidative stress, endothelial dysfunction and increased production of endothelin-1. 50 Our study did not examine and analyse the levels of important molecules involved in these possible mechanisms.

In summary, serum lipid levels varied in different groups according to ages and sex in patients with hypertension. Dyslipidaemia is more common in non-elderly patients than elderly. Levels of TG, TC and LDL-C were higher in female patients with hypertension than males. Therefore, in the clinic, serum lipid levels of patients with hypertension should receive more attention, especially those of non-elderly female patients.

Contributors HW designed the study. HW and ZY collected clinical data. HW, ZY and QH analysed the data. HW prepared the manuscript. All authors were responsible for critical revisions, and all authors read and approved the final version of this work. HW acts as guarantor.

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Competing interests None declared.

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Patient consent for publication Not applicable.

Ethics approval This study was approved by the Human Ethics Committees of Meizhou People’s Hospital.

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