Received: 1 November 2021 | Revised: 6 February 2022 | Accepted: 8 February 2022

DOI: 10.1002/phar.2675

PHARMACOTHERAPY accp

ORIGINAL RESEARCH ARTICLE

Effects of statin therapy and treatment duration on cardiovascular disease risk in patients with nephrotic syndrome: A nested case–control study

Xinliang Zou[1] | Li Nie[2] | Yi Liao[3] | Zhihui Liu[4] | Wanxiang Zheng[1] | Xiaolong Qu[1] | Xiang Xu[1] | Haoran Qin[1] | Haidong Wang[3] | Jianping Liu[1] | Guoxiang He[1,5] | Tao Jing[1]

[1]Department of Cardiology, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, China

[2]Department of Internal Medicine, Central Hospital of Wandong, Wansheng, Chongqing, China

[3]Department of Thoracic Surgery, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, China

[4]Department of Burn Surgery, Southwest Hospital, Third Military Medical University (Army Medical University), Chongqing, China

[5]Department of Cardiology, Guiqian International General Hospital, Guiyang, China

Correspondence
Tao Jing, Department of Cardiology, Southwest Hospital, Third Military Medical University (Army Medical University), Gao Tanyan Street, Sha Pingba District Chongqing, China.
E-mail: xnkjt@sohu.com

Funding information
This work was funded by the Graduate Student Research Innovation Project, Chongqing, China, 2019 (CYS19371). Promotion for Appropriate Technology in Health, Project: Standardized Diagnosis and Treatment of Coronary Atherosclerotic Heart Disease, Chongqing, China, 2018 (No. 2018jstg036). Chongqing Medical Scientific Research Project (2022ZDXM005). The funders had no role in the study design, data collection and analysis, decision to publish, or manuscript preparation.

Abstract

Background: Although statins are the cornerstone of lipid management, hardly any of the existing studies on statin treatment of dyslipidemia in nephrotic syndrome (NS) addressed patient-centered outcomes of cardiovascular events.

Objective: To evaluate whether statin treatment impacts the outcomes of cardiovascular events in patients with NS.

Design: A single-center, retrospective, nested case–control study analyzed data from the First Affiliated Hospital of Army Medical University.

Patients: Patients diagnosed with NS from January 1, 1999, to November 30, 2014, were selected and followed up for 5 years.

Measurements and Main Results: A total of 2706 patients with NS were enrolled in this study cohort. Among these, 115 patients diagnosed with cardiovascular disease (CVD) at the end of the observational period and 235 CVD-free controls enrolled by 1:2 matching with gender, age, and index time were included in the study. Propensity score matching was used to match (1:1) the baseline characteristics of the cases and controls. The chi-square test was performed based on whether the patient used a statin as an exposure factor, and binary logistic regression analysis of the association between cardiovascular events and statin therapy duration was conducted. Subgroup analyses for relevant variables were also performed. The chi-square test showed that statin therapy was significantly associated with a reduction in CVD risk in patients with NS ($p = 0.002$). Furthermore, the risk of cardiovascular events in patients with

NS decreased as the length of statin treatment increased (OR = 0.82 [95% CI 0.73–0.89], $p < 0.001$).

Conclusions: For NS patients with dyslipidemia, statin therapy may be used to decrease CVD risk, and extended treatment was associated with more significant risk reduction.

KEYWORDS
cardiovascular disease, lipid disorders, nephrotic syndrome, statin treatment

1 | INTRODUCTION

Nephrotic syndrome (NS) is a common clinical syndrome characterized by massive proteinuria, hypoalbuminemia, and different degrees of edema. It is often complicated by hyperlipidemia and/or venous thrombosis.[1] Elevated serum low-density lipoprotein cholesterol (LDL-C) levels can cause arterial intima lipid infiltration, increasing the possibility of atherosclerosis (AS), which is a risk factor for NS complicated by cardiovascular events.[2]

Previous studies have suggested that proteinuria is the main driving force of NS, causing hypoproteinemia and lipid metabolism disorders.[3] However, the LDL-C levels in some patients with NS fail to return to normal, as symptoms are alleviated. The continuous elevation of LDL-C in these patients accelerates the process of renal disease and promotes the occurrence and progression of cardiovascular disease (CVD).[4]

Lipid management is a significant part of the treatment strategy for patients with NS. Usually, it is similar to general hyperlipidemia treatment; however, there is no clear clinical evidence to guide the choice of lipid-lowering therapy for patients with NS. The 2019 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines suggest statin therapy as the first-line treatment strategy for primary prevention of arteriosclerotic cardiovascular disease (ASCVD) in patients aged between 40 and 75 years with diabetes mellitus (DM), chronic kidney disease (CKD), and chronic renal impairment, as well as for those determined to be at sufficient ASCVD risk after a clinician–patient risk discussion.[5] Nevertheless, for patients with NS without significant renal impairment (estimated glomerular filtration rate, eGFR ≥60 mL/min) and with proteinuria lasting less than 3 months, it is not clear whether statins can effectively reduce the occurrence of CVD and improve prognosis.[6] Furthermore, the nephrology and cardiology departments have not reached a consensus on whether these patients need to start statin therapy, and there are no relevant recommendations in the guidelines. In addition, very few articles have reported on the use of statins in patients with NS, and data on outcome indicators such as all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, and stroke are almost nonexistent.

In the present retrospective, nested case–control study, we reported on the use of statins in NS patients with cardiovascular events in comparison with patients without cardiovascular events. In addition, the degree of association between cardiovascular risk and statin therapy in patients with NS was statistically analyzed, and subgroup analyses based on different risk factors were conducted to analyze whether statin treatment has an impact on the outcomes of cardiovascular events. Our data provide strong evidence for the primary prevention of CVD and the treatment of lipid metabolism disorders in patients with NS.

2 | METHODS

2.1 | Study design and population

This retrospective nested case–control study analyzed data from the First Affiliated Hospital of Army Medical University to estimate the effectiveness of statin therapy in reducing the risk of CVD in patients with NS. This study was approved by the Ethics Committee of the First Affiliated Hospital of the Army Military Medical University (approval number: KY2019153). Written informed consent was obtained from all patients. This study protocol was registered at the China Clinical Trial Registration Center (ChiCTR2000029241).

A total of 2706 patients aged 18–85 years diagnosed with NS from January 1, 1999, to November 30, 2014, were selected and followed up for 5 years. According to previous literature, it has been estimated that the odds ratio of statin on CVD outcome is 0.6.[7] PASS (Version 21.0) was used to calculate the required sample size $N = 355$ ($\alpha = 0.15$, power = 0.80). Of these patients, 115 (4.2%) were diagnosed with CVD at the end of the observational period, and 235 CVD-free patients enrolled by 1:2 matching with gender, age, and index time were included in this study.

Inclusion criteria were (1) diagnosis of primary NS (minimal change disease (MCD)), mesangial proliferative glomerulonephritis (MPGN), focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, and membranous nephropathy (MN) or secondary NS (Henoch–Schonlein purpura nephritis and lupus nephritis); (2) all patients with NS had a confirmed diagnosis based on biopsy. There was no limit on sex or medical treatment.

Exclusion criteria were (1) hypertensive nephropathy or diabetic nephropathy; (2) diagnosis of acute kidney injury, CKD treated with dialysis, or detected eGFR <45 ml/min once; (3) CVD was diagnosed at the first visit; and (4) non-cardiovascular death, loss of follow-up, or missing medical records.

2.2 | Study measures

All patients diagnosed with CVD were enrolled as cases, which were then matched to controls who were established to be CVD-free at the end of the observational period based on propensity scores. The primary outcomes of interest were the following CVDs: stable coronary artery disease, non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death. The diagnosis of coronary heart disease was excluded when all patients were enrolled, based on clinical manifestations, electrocardiogram, etc. During the follow-up period after the first diagnosis of NS, the first coronary angiography result indicates the diagnosis of coronary heart disease; a non-fatal stroke occurs at any time during the period. All patients were statin-naive before inclusion in the cohort, and during the observational period, all patients diagnosed with stable coronary heart disease and myocardial infarction had imaging evidence of coronary angiography.

We collected data from the electronic medical records of all patients and telephone follow-up information, including demographics, personal history, previous biological specimen test results, statin therapy, and cumulative duration of statin therapy. The serology test results included the levels of high-density lipoprotein cholesterol (HDL-C), LDL-C, eGFR, albumin (ALB), and fibrinogen (Fbg). Comorbid health conditions, serology test results, or other factors were measured at cohort entry. In cases and each of their matched controls, statin therapy exposure measurement was examined over equivalent periods before the cases' events.

2.3 | Statistical analysis

Continuous data were presented as mean ± standard deviation, and categorical data were presented as numbers and percentages (%). The *t*-test (or chi-square test or Fisher's exact test, as appropriate) was used to compare baseline characteristics. All presented p-values were two-sided, and statistical significance was set at $p < 0.05$. Data analysis was performed using SPSS (Version 26.0) and R software (Version 4.1.1).

Propensity score matching was used to match (1:1) the baseline characteristics of cases and controls (package "MatchIt," "Matching," and "tableone," method = nearest, caliper = 0.2). Standardized mean difference (SMD) was used to covariate balance between propensity score-matched groups. SMD with absolute values less than 0.1 was considered to indicate balance. Imbalance variables at baseline served as confounding factors that required adjustment for propensity score matching. A contingency table was then constructed to assess the association between cardiovascular events and statin therapy in patients with NS using the chi-square test. We further evaluated the effect of statin therapy on cardiovascular events in patients with NS in relation to gender, age, smoking status, drinking status, body mass index (BMI), eGFR, HDL-C, LDL-C, ALB, Fbg, and whether they suffered from diabetes, hypertension, or atrial fibrillation. Moreover, binary logistic regression analysis of the association between cardiovascular events and statin therapy duration was implemented.

3 | RESULTS

3.1 | Patient characteristics

A total of 2706 patients with NS were enrolled in this study cohort. Among them, the two pathological types with the highest proportion were MPGN (29.01%) and MN (28.34%). The corresponding patients' average ages were 37.08 years (SD = 14.65) and 54.54 years (SD = 14.34), respectively. One hundred and fifteen cases (4.2%) had cardiovascular outcomes within 5 years of follow-up, with an average time of 2.57 years. Finally, 115 cases and 235 controls were recruited and interviewed. Seventy-nine (68.7%) cases received statin treatment, and 36 (31.3%) did not. In the control group, 203 (86.4%) patients received statins, and 32 (13.6%) did not.

3.2 | Propensity score matching

After 1:1 propensity matching of patients with CVD, a population of 148 patients was acquired. The proportion of statin usage in the control group increased after matching, and the types of statins between the groups were similar (Figure 1). We compared the baseline characteristics of cases and controls before and after propensity score matching (PSM), finding no significant imbalance in baseline information between the two groups after matching (Table 1). The time to reach end points in cases before and after matching was 2.57 ± 1.52 years and 2.72 ± 1.51 years, respectively. In this study, many confounding factors were well adjusted through PSM (Figure 2). There was a significant difference in cumulative extension of treatment duration between two groups (cases vs. controls = 2.04 ± 3.41 months vs. 7.62 ± 9.55 months, $p < 0.001$).

3.3 | Chi-square test

The 2 × 2 crosstabs chi-square test results revealed that statin therapy was associated with a lower risk of cardiovascular events in patients with NS ($\chi^2 = 9.18$, odds ratio (OR) = 0.27 [95% confidence interval (CI) 0.11–0.65], $p = 0.002$).

3.4 | Subgroup analysis

There was no significant difference in the effects of statins on cardiovascular outcomes in females, those younger than 60 years, no active smoking, no alcohol consumption, BMI ≥ 25 kg/m^2,

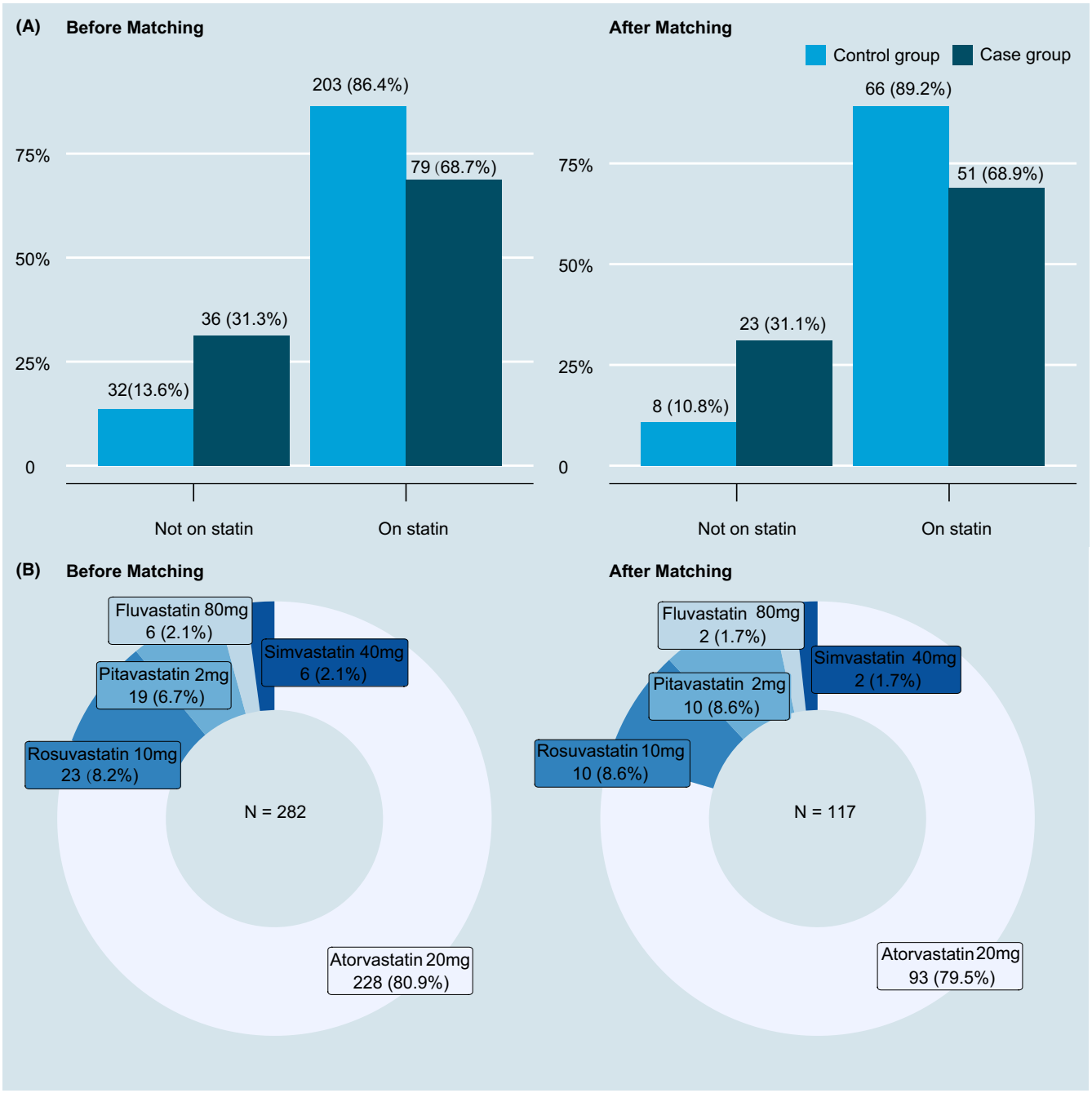

FIGURE 1 Distribution, type, and dosage of statins used in the population. The proportion of statin therapy in cases and controls before and after matching (A). Types, dosages, and proportion of statins before and after matching (B). Count data were presented as numbers and percentages (%)

diabetes, eGFR ≥ 90 ml/(min·1.73 m^2), HDL-C < 1.04 mmol/L, LDL-C < 2.6 mmol/L, ALB ≥ 30 g/L, and Fbg < 3.8 g/L (Figure 3).

3.5 | Binary logistic regression analysis

Our data suggested that the risk of cardiovascular events in patients with NS decreased as the length of statin treatment increased (OR = 0.82 [95% CI 0.73–0.89], $p < 0.001$).

4 | DISCUSSION

Statins have been used to prevent primary and secondary CVD for over 30 years. In vivo and in vitro experiments have confirmed that statins can regulate the expression of endothelial nitric oxide synthase, inhibit the production of pro-inflammatory cytokines and reactive oxygen species, stabilize atherosclerotic plaques, and reduce platelet reactivity, delaying the processes of cardiac hypertrophy and myocardial fibrosis.[8] Many experimental studies

TABLE 1 Baseline characteristics of patients with NS before and after PSM

	Before PSM			After PSM		
	Controls ($n = 235$)	Cases ($n = 115$)	SMD	Controls ($n = 74$)	Cases ($n = 74$)	SMD
Male gender	143 (60.9)	70 (60.9)	<0.001	42 (56.8)	38 (51.4)	0.109
Age (years)	42.14 ± 18.41	66.21 ± 11.87	1.554	61.7 ± 12.4	62.2 ± 12.3	0.046
Active smoking	66 (28.1)	40 (34.8)	0.145	25 (33.8)	24 (32.4)	0.029
Drinking	61 (26.0)	41 (35.7)	0.211	25 (33.8)	24 (32.4)	0.029
Diabetes mellitus	29 (12.3)	16 (13.9)	0.046	15 (20.3)	13 (17.6)	0.069
Hypertension	81 (34.5)	64 (55.7)	0.436	43 (58.1)	40 (54.1)	0.082
Atrial fibrillation	14 (6.0)	9 (7.8)	0.074	5 (6.8)	4 (5.4)	0.057
BMI (kg/m^2)	25.20 ± 3.60	24.21 ± 3.00	0.296	24.7 ± 3.73	24.4 ± 3.37	0.089
Serology test results						
eGFR ($ml/min/1.73\ m^2$)	93.13 ± 20.92	69.87 ± 13.53	1.320	75.0 ± 12.5	73.6 ± 15.4	0.099
HDL-C (mmol/L)	1.42 ± 0.48	1.36 ± 0.44	0.141	1.41 ± 0.47	1.36 ± 0.46	0.097
LDL-C (mmol/L)	4.21 ± 1.08	4.16 ± 1.84	0.037	4.16 ± 1.18	4.11 ± 1.73	0.035
ALB (g/L)	28.87 ± 5.00	28.56 ± 6.08	0.054	28.5 ± 5.15	28.9 ± 6.01	0.063
Fbg (g/L)	4.18 ± 1.14	4.26 ± 1.18	0.071	4.10 ± 1.09	4.19 ± 1.20	0.079

Note: Values were presented as n (%) or mean ± SD.

Abbreviations: ALB, albumin; BMI, body mass index; eGFR, estimated glomerular filtration rate; Fbg, fibrinogen; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NS, nephrotic syndrome; PSM, propensity score matching; SMD, standardized mean difference.

and meta-analyses have provided high-quality clinical evidence for the safety and efficacy of statin therapy, which solidified cholesterol theory and laid the foundation for lipid-lowering therapy.[9-11] However, these benefits could only be observed and assessed in patients with high cardiovascular risk in clinical practice. The 2016 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemia do not recommend statin therapy for patients with a low cardiovascular risk (SCORE-risk < 5%).[12] Moreover, there is no clear recommendation for lipid-lowering treatment in patients with NS.

Hyperlipidemia is one of the most common complications of NS. Long-term uncorrected dyslipidemia may increase the risk of CVD.[13] This is especially true for patients with frequently relapsing NS (FRNS) or steroid-resistant NS (SRNS). In these patients, the vascular endothelial function might be impaired, and the risk of cardiovascular events may increase due to long-term exposure to hyperlipidemia, high oxidative stress, frequent infections, persistent proteinuria, hypoalbuminemia, thromboembolism, as well as the side effects of steroids, nonsteroidal drugs, and calcineurin inhibitors. Still, there is limited evidence for statins in the treatment of hyperlipidemia in patients with NS, as few studies have addressed cardiovascular events in this population. Therefore, we investigated the cardiovascular benefits of statin therapy in patients with NS with no significant decrease in renal function.

In this study, the time to cardiovascular outcomes in cases before and after matching was 2.57 and 2.72 years, respectively. Generally, we believe that it takes longer for NS to affect the cardiovascular system. However, a longer observation period may lead to more uncontrollable confounders, which presents a major challenge for researchers. Currently, reliable clinical evidence to observe the benefits of lipid-lowering therapy for NS patients with cardiovascular events is lacking. Although we used retrospective analysis in the present study, propensity score matching was adjusted for clinically common confounding factors and reduced their impact. In conclusion, the outcome difference in cardiovascular events between cases and controls was significantly associated with statin therapy ($p = 0.002$). Our results suggest that for NS patients with dyslipidemia, initiating statin therapy could reduce their risks of future cardiovascular events.

Even though the confounding factors were adjusted through PSM, there might still be heterogeneity between the groups. Therefore, we further analyzed the correlation of statin therapy with cardiovascular risk of patients with NS in prespecified subgroups. During the progression of disease in patients with NS, there may be a decrease in renal function, losing albumin, and hypercoagulable state.[1] Our data provided evidence to suggest that statin therapy is associated with lower cardiovascular risk in patients with NS who have eGFR levels below 90 ml/(min·1.73 m^2), Fbg above 3.8 g/L, and ALB below 30 g/L. We can speculate that eGFR, Fbg, and ALB are indicators of the progression of NS and can be used as indicators to guide the initiation of statin therapy. The prevailing view is that CKD is closely related to the increased risk of CVD and that dyslipidemia may develop with renal function deterioration.[14] Numerous studies have shown that statins are safe and effective in reducing lipid levels and CVD risk in patients with early-stage CKD.[15-17] Studies have shown that statin treatment can reduce cardiovascular risk and arterial inflammation in non-CKD subjects.[18] However, this cardiovascular benefit diminishes in patients with decreased renal

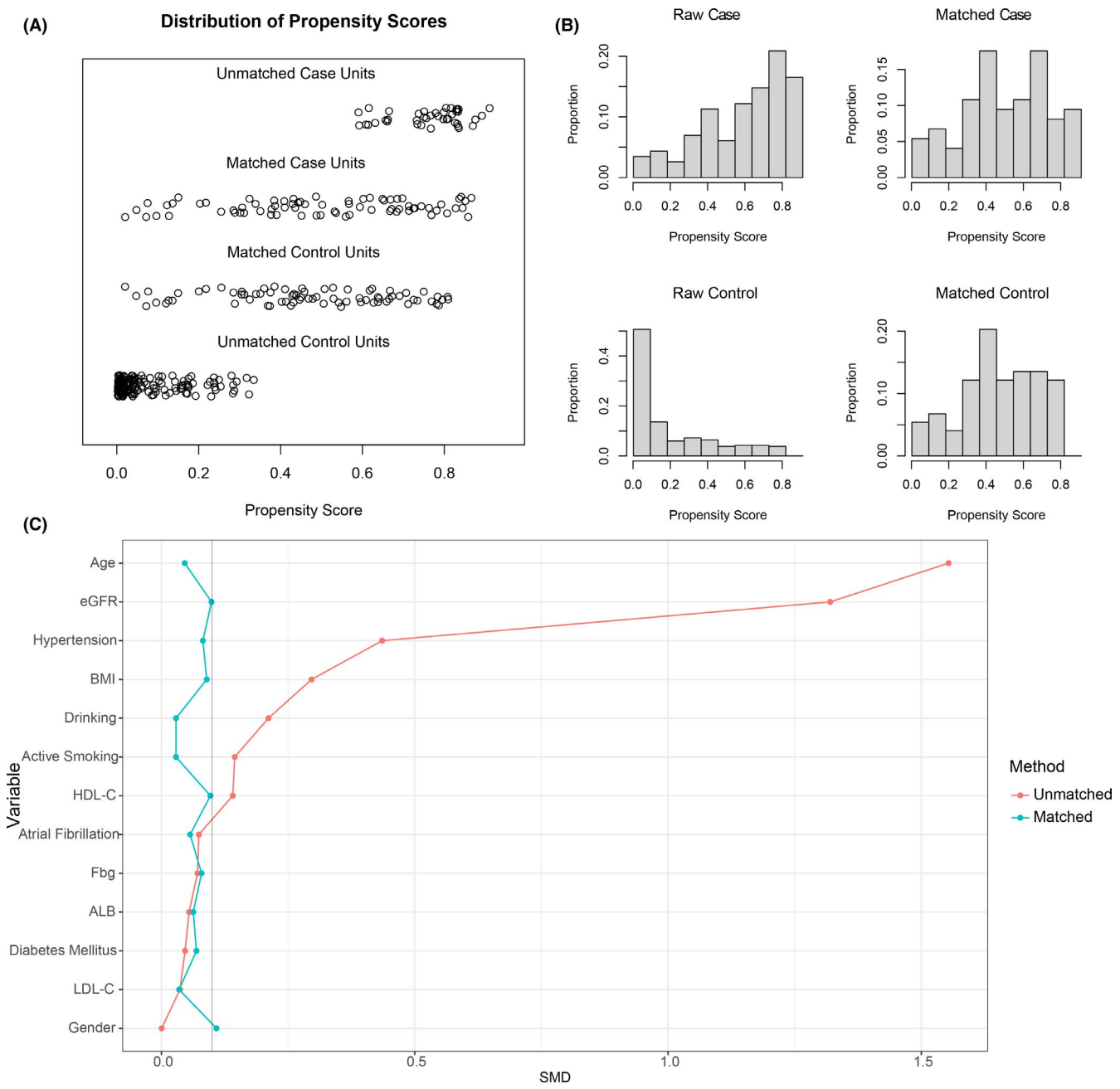

FIGURE 2 Comparison of propensity scores and SMD before and after matching. Through propensity score matching, data with significant differences in scores are eliminated, and the distribution of propensity scores of cases and controls is more similar (A); the density histogram (B) intuitively shows that the propensity scores between the two groups have been well adjusted after matching. The SMD line chart (C) indicates that the covariates of two groups are basically balanced after matching. Abbreviations: ALB, albumin; BMI, body mass index; eGFR, estimated glomerular filtration rate; Fbg, fibrinogen; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SMD, standardized mean difference

function due to persistent inflammation.[18] An animal experiment demonstrated that inflammation may reduce the efficacy of statins by enhancing cholesterol synthesis and intracellular lipid accumulation.[19] Pathophysiologic mechanisms of the pro-inflammatory state of CKD include dysregulation of calcium and phosphate, activation of the renin-angiotensin-aldosterone system, NF-κB pathway and inflammasome activation associated with uremic toxin accumulation, which may in part contribute the persistence of systemic inflammation after statin therapy in CKD.[20] Generally, due to the role of angiopoietin-like proteins 4 (ANGPTL4) in the pathophysiology of the body, hypertriglyceridemia can be effectively alleviated after proteinuria is relieved.[21] Consequently, this has led some clinicians to ignore the treatment of other components of dyslipidemia. In summary, we strongly believe that statin therapy should be actively initiated for patients with NS who do not respond to standard treatment, whose renal function begins to decline, and who

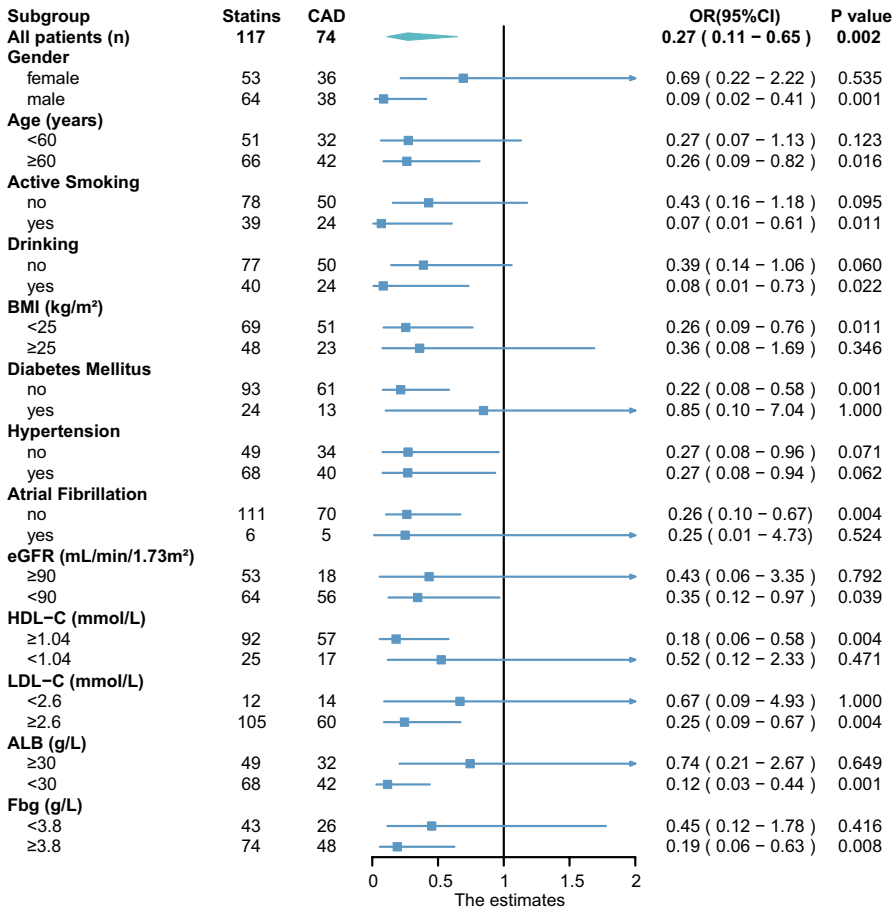

FIGURE 3 Primary Outcome in prespecified subgroups. The mean baseline eGFR of the patients included in this study was all higher than 60 ml/(min·1.73 m^2) and did not meet the diagnostic criteria for chronic kidney disease. Diabetic patients ruled out the pathological type of diabetic nephropathy. The subgroup analysis results should be regarded as exploratory rather than conclusive. Abbreviations: ALB, albumin; BMI, body mass index; eGFR, estimated glomerular filtration rate; Fbg, fibrinogen; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SMD, standardized mean difference

experience blood hypercoagulability and hypoproteinemia so as to prevent further deterioration of kidney function and reduce cardiovascular risk.

Based on the results of the age subgroup analysis, we can assume that statins may bring cardiovascular benefit in ≥60-year-old group (OR 0.26 [95% CI 0.09–0.82], $p = 0.016$), whereas the cardiovascular benefits of statins were not statistically significant in <60-year-old group (OR 0.27 [95% CI 0.07–1.13], $p = 0.123$). A previous study reported that statins could improve the blood lipid profile in all age groups, although the improvement was significantly better in patients aged ≥70 years than in those aged <70 years.[22] These results support our findings to a certain extent. Still, the lipid-lowering effect of statin therapy is only one aspect of concern. Ultimately, the cardiovascular risk associated with hyperlipidemia is attributed more to atherosclerosis.[23] Therefore, for relatively younger patients with NS, more clinical evidence of atherosclerosis or coronary artery calcification may be needed to support the initiation of statin therapy.

In this study, baseline LDL-C level did not differ between cases and controls. According to the current clinical treatment strategies, statin therapy is usually started after the lipid metabolism disorder reaches a certain degree in persistent NS patients, and it is terminated once the lipid level approaches the normal range. In our subgroup analysis, for patients with NS who have an average LDL-C level higher than 2.6 mmol/L, statin therapy could still reduce their long-term cardiovascular risk. It seems that the critical value of blood lipid levels should be appropriately lowered when patients start statin treatment. In addition, lipid-lowering treatment should be dynamically adjusted according to the results of the biochemical examination. The effect of LDL particles on endothelial function mainly depends on their carbamylation or oxidation modification, especially carbamylated LDL (cLDL), which has important implications in predicting CVD risk in patients with CKD.[24] Compared with native LDL, oxidized LDL and cLDL may be better biomarkers for assessing the biological efficacy of statins and predicting CVD risk.

In our study, statin therapy significantly increased its impact as a protective factor from the outcomes of cardiovascular events in patients with NS with cumulative extension of treatment duration ($p < 0.001$). Our findings are consistent with the West of Scotland Coronary Prevention Study (WOSCOPS) results, which have followed up patients for 20 years, eventually reporting that a 5-year statin treatment cycle could bring long-term or even lifelong benefits.[25] A growing body of research shows that the benefits of statin therapy far exceed the currently known safety concerns.[9] In addition, the persistence of lipid-lowering therapy should depend on whether LDL-C is in the normal range, the percentage of LDL-C reduction, and the pleiotropic effects of statins. Using this information to guide the duration and dosage of medication may bring additional cardiovascular benefits to patients. Meanwhile, in clinical practice, the cost-effectiveness of statins should also be considered.

The present study has some limitations. Although our hypothesis was statistically supported, given the limited efficacy of evidence in nested case–control studies, the results of this study can only explain the correlation between statins and CVD in patients with NS, but not causality. Further prospective cohort studies or randomized controlled studies are needed to provide further support for the reported findings. The data were collected from one single clinical center, which means that the geographical distribution of patients was relatively limited (mainly in southwest China), and the sample size was relatively small. Since there are not enough samples to support the subgroup analysis differences, the subgroup analysis results should be regarded as exploratory rather than conclusive. It is necessary to expand the sample size to analyze the subgroups of interest further. Also, the time of diagnosis of NS in the cohort was when proteinuria was detected for the first time. Therefore, actual kidney disease might occur earlier, which might have a certain effect on determining the disease duration. Moreover, the patients with NS included in our study were not subjected to subgroup analysis according to their pathological characteristics. Patients with diabetic nephropathy and hypertensive nephropathy who were initially excluded and with different pathological types may have different reactivities when receiving statin therapy. Therefore, further analyses based on different pathological types may be needed. Furthermore, all patients in the study were adults, and a higher proportion had MPGN and MN. It is well known that children with NS have a higher proportion of the pathological type of MCD and a higher likelihood of future cardiovascular risk. Therefore, it is also necessary to study a cohort of children with NS.

The present study has several strengths. By collecting medical records through the hospital's artificial intelligence big data platform, the information related to the research cases was kept intact. Although we used a retrospective analysis, there was no significant difference between the baseline values of the cases and controls after matching. Finally, we believe that propensity score matching adjusted for clinically common confounding factors and effectively improved the reliability of the statistical results.

5 | CONCLUSION

In summary, statin therapy for NS patients with dyslipidemia may decrease 5-year CVD risk, which may be further reduced with the extension of the treatment. However, it is still necessary to conduct a study in children with NS, and prospective studies are also needed to evaluate the long-term benefits of statin therapy for patients with NS.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

The corresponding author is responsible for ensuring that the descriptions are accurate and agreed upon by all authors. Xinliang Zou contributed to conceptualization, methodology, data curation, visualization, investigation, software, writing—original draft, and writing—review and editing. Li Nie contributed to resources, data curation, methodology, and validation. Yi Liao contributed to conceptualization, methodology, resources, and writing—review and editing. Zhihui Liu, Wanxiang Zheng, Xiaolong Qu, Xiang Xu, Haoran Qin, Jianping Liu, and Guoxiang He contributed to formal analysis and writing—review and editing. Haidong Wang contributed to conceptualization and methodology. Tao Jing contributed to conceptualization, methodology, validation, writing—reviewing and editing, supervision, project administration, and funding acquisition. All authors read and approved the final manuscript.

ETHICAL APPROVAL

The study protocol conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Army Military Medical University, approval number (KY2019153).

CLINICAL TRIAL REGISTRATION

This study protocol was registered in the China Clinical Trial Registration Center (ChiCTR2000029241).

ORCID

Tao Jing https://orcid.org/0000-0001-5543-8702

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How to cite this article: Zou X, Nie L, Liao Y, et al. Effects of statin therapy and treatment duration on cardiovascular disease risk in patients with nephrotic syndrome: A nested case–control study. *Pharmacotherapy*. 2022;42:311–319. doi:10.1002/phar.2675