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接受紅麴處方藥治療之高脂血症患者其肝硬化的眞實世界風險和結果：一項回顧性世代研究

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一、摘要

研究目的：持續性高脂血症會引發脂肪肝及肝硬化。雖紅麴可有效改善血脂，但紅麴對新發生的肝硬化風險仍有待釐清。本研究目的在評估使用紅麴對新發生的肝硬化風險及預後之益處。

病人族群和研究方法：本回溯性世代研究從2010-2016年的健保資料篩選出156,587名新診斷的高脂血症成年病患，經使用傾向分數配對挑選了34,367名有使用紅麴的患者和 34,367 名使用lovastatin的患者。本研究追蹤了兩組世代在2010-2019年期間所發生的肝硬化病例，並使用多變項Cox比例風險模型來計算使用紅麴與肝硬化風險的校正後危害比(hazard ratios, HRs)及95%信賴區間(confidence intervals, CIs)。

結果：與使用lovastatin的患者相比，使用紅麴處方藥的高血脂患者發生肝硬化的風險較低（HR 0.60,95%CI 0.57-0.63），且這種關聯在各次族群中均有統計上的顯著差異。本研究也觀察到紅麴的使用頻率與降低肝硬化風險兩者間有生物漸增性趨勢(趨勢p值< 0.0001)。使用紅麴處方藥也與減少肝硬化後的黃疸(HR 0.56，95% CI 0.43-0.72)、腹水(HR 0.37，95% CI 0.28-0.50)、肝昏迷(HR 0.36，95% CI 0.26-0.50)和死亡風險(HR 0.48，95% CI 0.38-0.61)有關。

結論：雖本研究顯示紅麴的使用有益於肝硬化的風險及預後，但應將缺乏病患服藥順從資訊這點納入考量。本研究沒有推斷出RYR優於lovastatin的因果關係。

二、研究材料與方法

數據來源：本研究用了臺灣全民健康保險學術研究資料庫來收集研究患者的資訊，且根據臺灣衛生福利部的規定，由於患者身份資訊在數據中已被亂碼而無法辨識，因此不需要研究參與者的知情同意。本研究已獲得臺北醫學大學人體試驗委員會審核通過（TMU-JIRB-202303013; TMUJIRB-201905042;TMUJIRB-201902053）。

研究設計：在臺灣全民健康保險的近2340萬人口資料中，我們篩選出156,587 名成人在2010年至2016年間首次被診斷為高脂血症，其中使用紅麴處方藥者有66927人，使用lovastatin有89660人，本研究將使用lovastatin的患者作為對照組。因本研究旨在調查新診斷的高脂血症患者，因此我們用了2年的洗除期間來排除曾經有接受過高脂血症治療的患者。而在醫師診斷為高脂血症或使用降血脂藥物（紅麴或lovastatin）之前，兩個族群並無肝硬化的病史。本研究使用傾向分數配對來選取實驗組及對照組以獲得相似的族群特徵。經匹配後，在本研究中使用紅麴處方藥組有34,367名患者，使用lovastatin之對照組有34,367名患者。本研究追蹤兩組患者至 2019 年 12 月 31 日止，在追蹤期間發生之肝硬化事件被視為追蹤結果。

為了排除未亡時間偏倚，本研究在追蹤期間是由使用藥物（lovastatin 或紅麴處方藥）的起始時間開始計算，追蹤一直持續到 2019 年底前是否有新發生之肝硬化，並檢查且刪除因死亡、轉移或失聯的個案。

納入標準和定義：本研究是將高脂血症患者定義為至少有一次門診就診並經醫生診斷的患者，再通過資料庫中的醫療記錄來確認肝硬化和其他醫療狀況。表 S1(ICD-9-CM codes of hyper-lipidemia, liver cirrhosis, and medical conditions) 中列出了這些診斷代碼的詳細資訊。為了嚴格篩選出在臺灣全民健保範圍內使用紅麴處方藥的族群，本研究定義其為至中醫診所就診

並由中醫師開立紅麴處方藥者。肝硬化患者被定義為至少有兩次就診，且醫生的主要診斷為肝硬化。本研究之低收入狀況的患者是經地方和中央主管機關認定核可有資格獲得免除醫療自付額的患者。腎臟透析被視為一種臨床狀況(Table 1中的共變項)，其定義依據為管理代碼（D8, D9）。

三、統計分析方法

1.為了減少干擾因子造成之偏差，本研究使用傾向分數配對法來平衡使用紅麴處方藥和使用lovastatin兩組之間的背景特徵變項，再通過使用非精簡多變數logistic回歸模型和貪婪匹配演算法（無替換），本研究將紅麴處方藥組與lovastatin組進行配對，該多變項羅吉斯迴歸模型中包含了決定共變項的臨床狀況(表1)。這種方法可以消除於測量共變項中的大部分偏差。

2. 本研究用了卡方檢定來表示紅麴和 lovastatin 兩組之間的共變項是否達到均衡，然後再使用多變量Cox比例風險模型來計算追蹤期間紅麴和 lovastatin 兩組之間的肝硬化校正後危害比（HRs）及95%信賴區間（CIs）。

3.分層分析為依照年齡、性別、低收入、急診就診數、住院次數和查爾森合併症指標來進行，以檢視在這些次族群中使用紅麴處方藥與發生肝硬化風險的關聯。

4.在敏感性分析中，本研究排除了從追蹤期開始時（前1、2、3、4、5 和 6 個月）肝硬化的事件，計算紅麴處方藥與肝硬化的校正後 HRs 和 95%CIs。為了排除競爭死因的偏差，本研究在敏感性分析中另外排除了追蹤期間發生的死亡。

5.本研究依RYR的累積使用量來估計與RYR使用頻率與肝硬化校正後的危害比及95%信賴區間。

6.Kaplan-Meier存活曲線估計法用於檢驗 RYR 和 lovastatin 族群於追蹤期間無發生肝硬化的比率曲線。

四、研究結果

對 68734 例高脂血症患者進行傾向性評分配對，使紅麴處方藥(n = 34367)和 lovastatin (非RYR組)（n = 34367）兩組之間之病人臨床基本特徵無顯著差異。因非酒精性脂肪性肝(NASH)和肥胖並未納入配對，在病人臨床基本特徵中紅麴組的非酒精性脂肪肝(p = 0.0007)和肥胖（p<0.0001）的比例較高(表 1)。於追蹤期間共有8215例患者發生肝硬化(Table 2)，在校正了未亡時間偏倚後，與使用 lovastatin 的患者相比，使用紅麴處方藥的患者發生肝硬化的風險較低 (HR 0.61, 95% CI 0.58–0.64)。Kaplan-Meier 存活曲線估計法的結果(Figure 2)顯示於追蹤期間，使用RYR組之肝硬化發生率低於lovastatin組（p< 0.0001）。

在Table 2中(追蹤期間使用RYR和非RYR的調整HRs和95%CIs)，顯示使用紅麴處方藥的女性(HR 0.60, 95% CI 0.56–0.64)、男性(HR 0.60, 95% CI 0.56–0.64)、20–39歲 (HR 0.52, 95% CI 0.44–0.62)、40–49歲 (HR 0.58, 95% CI 0.52–0.64)、50–59歲(HR 0.65, 95% CI 0.60-0.69), 60–69 歲 (HR 0.58, 95% CI 0.52– 0.64)以及大於70歲 (HR 0.58, 95% CI 0.49–0.68)都比使用lovastatin的患者有較低的肝硬化風險。而在低收入戶或非低收入戶的群組中，使用紅麴處方藥都有較低的肝硬化風險。

以就醫次數來看，急診0次(HR 0.47, 95% CI 0.45-0.50)、急診1次(HR 0.72, 95% CI 0.65-0.81)、住院 0 次(HR 0.52, 95% CI 0.49-0.55)及住院 1 次(HR 0.87, 95% CI 0.77-0.99)的患者中，紅麴使用與肝硬化風險降低有顯著關係。本研究發現，與使用 lovastatin 相比，紅麴組在查爾森合併症指標為0分(HR 0.45, 95% CI 0.42 -0.49)、1分(HR 0.52, 95% CI 0.48-0.57)和2分(HR 0.71,95%CI 0.63-0.81)的患者族群中亦是有較低的肝硬化風險比。(Table 2)

在 Table 3 中的敏感度分析顯示，在追蹤期間排除最初1個月內肝硬化事件後，紅麴組的校正後危害比為0.62，而排除前二個月後危害比為0.62、排除前三個月後危害比為0.64、排除前四個月後危害比為0.66、排除前五個月後危害比為0.68以及排除前六個月後危害比0.69。在排除追蹤期間發生的死亡事件後，使用紅麴的患者比使用 lovastatin 的患者發生肝硬化的風險更低(HR 0.62, 95% CI 0.59-0.65)。 在Table 3中的敏感度分析顯示，在追蹤期間除最初 1 個月內肝硬化事件後，紅麴組的校正後危害比為0.62，而排除前二個月後危害比為0.62、排除前三個月後危害比為0.64、排除前四個月後危害比為0.66、排除前五個月後危害比為0.68以及排除前六個月後危害比0.69。在排除追蹤期間發生的死亡事件後，使用紅麴的患者比使用lovastatin的患者發生肝硬化的風險更低(HR 0.62, 95% CI 0.59-0.65)。

在Table 4中顯示，相較於 lovastatin 組，使用紅麴的頻率增加與發生肝硬化的風險降低有顯著的生物漸增趨勢(劑量效應關係 $p < 0.0001$)，使用超過5次的紅麴處方藥的人所呈現的危害比為0.59(95% CI 0.55-0.63)。

在Table 5中顯示，使用紅麴的患者在追蹤過程中死亡率較低(HR 0.48,95% CI 0.38-0.61)，肝硬化相關併發症如黃疸(HR 0.56, 95% CI 0.43-0.72)、腹水 (HR 0.37, 95% CI 0.28-0.50)以及肝昏迷(HR 0.36, 95% CI 0.26-0.50)等風險也低。

表 S2 列出了按疾病狀況或使用藥物來劃分的肝硬化風險與RYR使用之間關聯的分層分析結果。

在表S3中，使用RYR組的酒精性肝硬化、非酒精性肝硬化和未指定肝硬化的調整HR分別為0.37（95%CI 0.18-0.73）、0.64（95%CI 0.51-0.81）和0.61（95%CI 0.58-0.64）。

表S4 顯示了在傾向性評分配對之前 RYR 和lovastatin組之間的病人基本特徵。

表S5則是顯示在傾向性評分配對之前，使用 RYR 與追蹤期間發生肝硬化的風險降低有關(HR 0.61, 95% CI 0.58–0.64)。

表 S6顯示，與RYR組相比，接受pravastatin (HR 1.73,95%CI 1.63-1.83) 和 simvastatin（HR 1.76,95%CI 1.68-1.84）的患者發生肝硬化的風險增加。然而，接受rosuvastatin治療的患者（HR 0.72,95%CI 0.69-0.75）比接受RYR治療的患者發生肝硬化的風險更低。

五、研究侷限：

首先，本研究的限制是缺乏臨床檢查數據，例如總膽固醇、肝功能指數(GOT/GPT)、脂肪肝超音波檢查以及肝硬化的嚴重程度，因此無法用高膽固醇血症的嚴重程度來評估紅麴的使用與發生肝硬化的風險之間的關係。第二，無法確定對紅麴或 lovastatin 的服藥順從性是否良好，因本研究不是臨床試驗，因此觀察性研究無法提供實際服藥順從狀況(包括紅麴和lovastatin)。在合理的假設內，本研究認為使用紅麴和 lovastatin 的患者的順從性可能為平衡分佈。第三，本研究缺乏病人的知識、心態、生活方式(如吸菸和飲酒)和家庭支持，因此無法在多變項迴歸中控制這些因素，也無法進行次群組或敏感性分析。再者，本研究亦無法得知或證明紅麴與肝硬化風險之間的機制，需要後續的實驗室研究及臨床試驗來證實。最後，本研究雖考慮了社會人口學資訊、病人醫療狀況、接受治療狀況、查爾森合併症指標和使用藥物等等狀況，但這些因素無法涵蓋所有潛在的干擾因素，因此本研究無法排除殘餘的干擾偏差之可能性。

六、結論

總結來說，這項研究顯示使用紅麴對高脂血症患者之肝硬化風險和預後皆有益處。但由於回顧性世代研究的因果推斷和患者的藥物順從性的限制，因此需要謹慎看待此研究結果。本研究無法推斷紅麴與肝硬化的因果關係，也並非聲稱紅麴優於 lovastatin 。本研究結果建議後續應進行臨床隨機對照試驗，以確認紅麴與 statin 類藥物對降低三酸甘油脂、低密度膽固醇以及預防代謝相關的脂肪肝、非酒精性脂肪性肝或酒精引起的肝硬化的影響。

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ORIGINAL RESEARCH

Real-World Risk and Outcome of Liver Cirrhosis in Patients with Hyperlipidemia Treated with Red Yeast Rice: A Retrospective Cohort Study

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Objective: Sustained hyperlipidemia contributes to fatty liver and liver cirrhosis. Red yeast rice (RYR) effectively improved the lipid profile; however, the effects of RYR on the risk of incident liver cirrhosis remain to be elucidated. We aimed to evaluate the beneficial effects of RYR use on the risk and outcome of liver cirrhosis.

Patients and methods: We identified 156,587 adults who had newly diagnosed hyperlipidemia in 2010–2016 from health insurance data in this retrospective cohort study. Using propensity score matching, we selected 34,367 patients who used RYR and 34,367 patients who used lovastatin. Events of incident liver cirrhosis that occurred in the two cohorts during the follow-up period of 2010–2019 were identified. We calculated adjusted hazard ratios (HRs) and 95% confidence intervals (Cis) for liver cirrhosis risk associated with RYR use in the multiple Cox proportional hazard model.

Results: Compared with patients who used lovastatin, patients who used RYR had a decreased risk of liver cirrhosis (HR 0.60, 95% CI 0.57–0.63), and this association was significant in various subgroups. A biological gradient relationship between the frequency of RYR use and decreased liver cirrhosis was observed (p for trend < 0.0001). Reduced postcirrhosis jaundice (HR 0.56, 95% CI 0.43–0.72), ascites (HR 0.37, 95% CI 0.28–0.50), hepatic coma (HR 0.36, 95% CI 0.26–0.50), and mortality (HR 0.48, 95% CI 0.38–0.61) were also associated with RYR use.

Conclusion: We demonstrated the beneficial effects of RYR use on the risk and outcome of liver cirrhosis; however, the lack of compliance data should be considered. However, our study did not infer causality or claim the superiority of RYR over lovastatin.

Keywords: hyperlipidemia, liver cirrhosis, lovastatin, outcome, red yeast rice, risk

Introduction

Liver cirrhosis is prevalent and results in various complications and mortality in low-income, middle-income, and high-income countries.[1] Globally, liver cirrhosis remains one of the leading causes of death, as there were more than 1.32 million deaths in 2017 compared with less than 899,000 deaths in 1990.[2] It is already known that liver cirrhosis is the end stage of progressive liver fibrosis, and the most common causes are alcohol-related liver disease, chronic viral hepatitis B and C, and nonalcoholic fatty liver disease.[1,2]

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Non-high-density lipoprotein cholesterol independently predicts new onset of nonalcoholic fatty liver disease.[3] Remnant cholesterol was independently associated with the risk of metabolic dysfunction-associated fatty liver disease and predicted all-cause, cardiovascular, and cancer-related mortalities in patients with metabolic dysfunction-associated fatty liver disease.[4] Individuals with nonalcoholic fatty liver disease showed significantly higher risks for cirrhosis and hepatocellular carcinoma.[5] Serum cholesterol is also a significant and independent predictor of poor outcome and mortality in patients with liver cirrhosis.[6,7] However, more than half of patients with dyslipidemia have no awareness of dyslipidemia, and most of them do not use medication to control their condition.[8]

Statins are commonly used to control non-high-density lipoprotein cholesterol in the clinical setting of Western medicine.[9] In the clinical setting of traditional Chinese medicine, physicians have used scientifically processed red yeast rice (RYR, also known as *Monascus purpureus* Went rice, contains monacolin K [lovastatin]) to control the status of hyperlipidemia, such as Xuezhikang®, HypoCol®, and LipoCol Forte®.[10–14] The clinical trial in Taiwan indicated that the 8-week treatment with RYR (patients received a twice-daily dose of 600 mg for 8 weeks) showed significantly greater reduction than the placebo treatment in low-density lipoprotein cholesterol levels, total cholesterol/high-density lipoprotein cholesterol, low-density lipoprotein cholesterol/high-density lipoprotein cholesterol and apolipoprotein B/apolipoprotein A-I ratios.[15]

The effects of statin use on the reduced risk of developing liver cirrhosis were investigated in previous studies.[14–19] Some studies also suggested that reduced complications and mortality were found in patients with liver cirrhosis who underwent statin treatment.[20–22] Because reliable references suggested that RYR is beneficial in lowering lipid profiles and reducing the risks of stroke, diabetes, and postoperative adverse events,[10–15] we considered that use of RYR is probably also associated with reduced liver cirrhosis. However, little was known regarding the association between the use of RYR and the risk of liver cirrhosis.

A triple-blind randomized clinical trial considered that RYR is safe to add to statins medications significantly decreases total cholesterol.[23] There were only few case reports that remind the potential side effects of RYR, such as hepatotoxicity and symptomatic myopathy, and these effects being partially similar to the effects of statins.[24,25] Many studies also suggested that the intake of RYR improves lipid profiles may be a treatment option for dyslipidemic patients who cannot tolerate statin therapy.[26,27]

Based on the above evidences and suggestions, we used real-world data to evaluate the risk of liver cirrhosis in patients with hyperlipidemia who underwent RYR treatment in this study. However, our purpose is not to infer causality or claim the superiority of RYR over lovastatin.

Methods

Source of Data

We collected patient information from the academic research database of the public medical insurance, which was maintained by the government in Taiwan. Details of this research database were described and evaluated previously.[10–12,28] According to the regulation of the Ministry of Health and Welfare in Taiwan, informed consent from the study participants is not required because patient identification was decoded and scrambled in data. Our study was evaluated by the Institutional Review Board of Taipei Medical University (TMU-JIRB-202303013; TMU-JIRB-201905042; TMUJIRB-201902053).

Study Design

Among nearly 23.4 million people covered in government health insurance in Taiwan, we identified 156,587 patients aged years and older who were first diagnosed with hyperlipidemia with the use of RYR (n = 66927) and lovastatin (n = 89660) or in 2010–2016 in this study. We considered patients who used lovastatin as the control group (without the use of RYR). Patients who sought treatment for hyperlipidemia within the washout period of 2 years were excluded, as this study aimed to investigate patients with newly diagnosed hyperlipidemia. Both cohorts had medical records of liver cirrhosis before physician's diagnosis of hyperlipidemia or used lipid-lowering medications (RYR or lovastatin). Between cohorts with and without the use of RYR, we conducted propensity score matching to obtain similar baseline

characteristics. After the matching procedure, there were 34,367 patients in the RYR cohort and 34,367 patients in the non-RYR cohort in this study. Both cohorts were followed up to December 31, 2019. The events of newly diagnosed liver cirrhosis that occurred during the follow-up period were considered as outcomes between the RYR and non-RYR cohorts in this study. There was no immortal time bias in this study because the follow-up started from the time of the use of medication (lovastatin or RYR) or the index date and lasted until the occurrence of liver cirrhosis, censoring due to death, migration, or loss of follow-up by the end of 2019. We evaluated the risk of incident liver cirrhosis between the RYR cohort and the non-RYR cohort (use of lovastatin) during the follow-up period (Figure 1).

Criteria and Definitions

We defined patients with hyperlipidemia as those who had at least one visit for outpatient care with a physician's diagnosis. Cirrhosis and other medical conditions were also identified by the records of medical visits in the database. Details of these diagnosis codes are listed in Table S1. To strictly identify the RYR cohort under the coverage of Taiwan's Health Insurance Program, we defined people who visited TCM clinics and received a prescription for RYR from a physician. The criteria and definition were verified and the corresponding details of RYR prescription could be found in our previous studies.[10–12]

Patients with liver cirrhosis were defined as having at least two visits for medical care with a physician's primary diagnosis of liver cirrhosis. The criteria were used and verified in our previous study.[28] We identified patients with low-income status as those who qualified for waived medical copayment, and this status was verified by the local and central government. Renal dialysis was considered one of the medical conditions that were defined by administration code (D8, D9).

Statistical Analysis

To reduce confounding bias, we used a propensity score-matched pair procedure to balance the covariates between the RYR and non-RYR cohorts. By using a nonparsimonious multivariable logistic regression model with a greedy matching

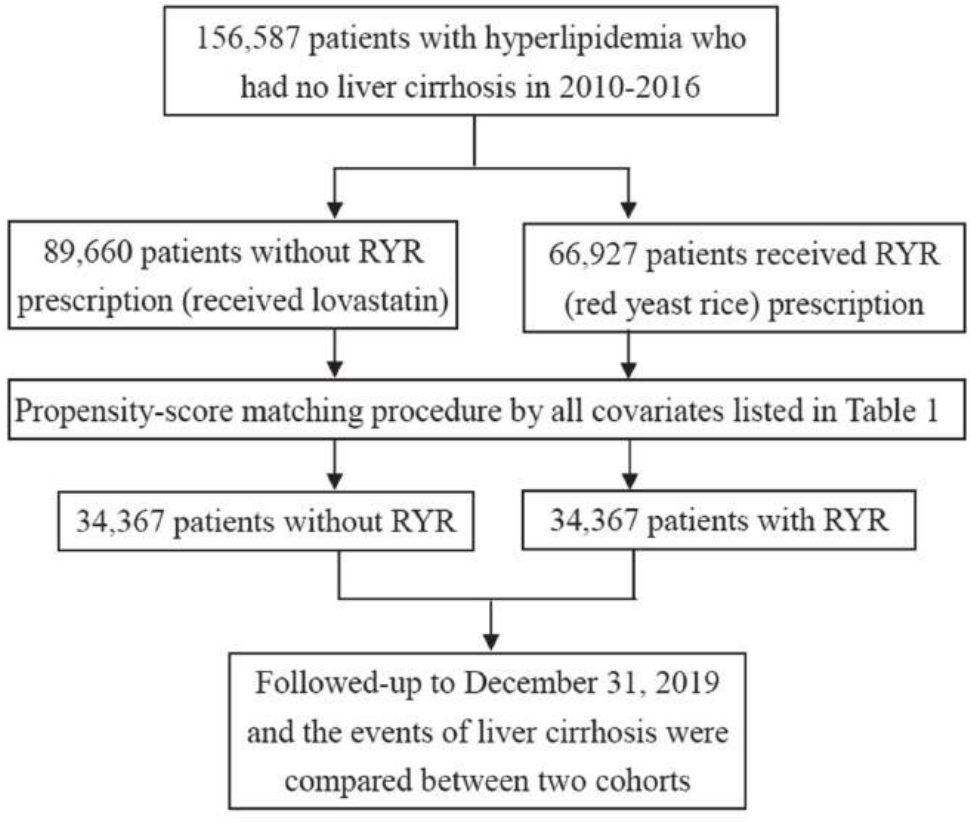

Figure 1 The selection process of adequate study subjects.

algorithm (without replacement). We matched RYR patients to non-RYR patients and the clinical significance guided the initial choices of covariates (listed in Table 1) were included in this multivariable logistic regression model. This method could remove a majority of bias from measured covariates.

Chi-square tests were used to present the balance of covariates between patients with and without RYR. We then used multivariate Cox proportional hazard models to calculate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of liver cirrhosis between the RYR and non-RYR cohorts during the follow-up period. Stratified analyses by age, sex, low income, emergency room visits, hospitalizations, and the Charlson Comorbidity Index were performed to examine the association between RYR use and the risk of developing liver cirrhosis in these subgroups. In the sensitivity analysis, we excluded the initial events of liver cirrhosis during the start of the follow-up period (the first 1, 2, 3, 4, 5, and 6 months) to evaluate the adjusted HRs and 95% CIs of liver cirrhosis associated with RYR. To correct for the competing risk of mortality, we performed a sensitivity analysis and excluded the deaths that occurred during the follow-up period. The cumulative use of RYR was estimated for the calculated adjusted HRs and 95% CIs of liver cirrhosis associated with the frequency of RYR use. Kaplan–Meier survival analysis was used to test the cirrhosis-free curve during the follow-up period between RYR and non-RYR cohorts.

Results

After propensity score matching among 68734 patients with hyperlipidemia (Table 1), there was no significant difference in baseline characteristics between the RYR (n = 34367) and non-RYR (n = 34367) cohorts. Because non-alcoholic steatohepatitis and obesity were not included in the matching, patients with RYR had higher proportions of non-alcoholic

Table 1 Baseline Characteristics Between Cohorts with and without Use of Red Yeast Rice Prescription

	No RYR N=34367		RYR prescription N=34367		p-value
	n	(%)	n	(%)	
Sex					1.0000
Female	19741	(57.4)	19,741	(57.4)	
Male	14626	(42.6)	14,626	(42.6)	
Age, years					1.0000
20–29	407	(1.2)	407	(1.2)	
30–39	1920	(5.6)	1920	(5.6)	
40–49	6582	(19.2)	6582	(19.2)	
50–59	13,417	(39.0)	13,417	(39.0)	
60–69	8548	(24.9)	8548	(24.9)	
70–79	3016	(8.8)	3016	(8.8)	
≥80	477	(1.4)	477	(1.4)	
Low income					1.0000
No	33854	(98.5)	33,854	(98.5)	
Yes	513	(1.5)	513	(1.5)	
Number of hospitalizations					1.0000
0	18,338	(53.4)	18,338	(53.4)	
1	7062	(20.6)	7062	(20.6)	
2	3130	(9.1)	3130	(9.1)	
≥3	5837	(17.0)	5837	(17.0)	
Number of emergency visits					1.0000
0	12,111	(35.2)	12,111	(35.2)	
1	7216	(21.0)	7216	(21.0)	
2	4259	(12.4)	4259	(12.4)	
≥3	10,781	(31.4)	10,781	(31.4)	

(*Continued*)

Table 1 (Continued).

	No RYR N=34367		RYR prescription N=34367		p-value
	n	(%)	n	(%)	
Medical conditions					
Hypertension	17814	(51.8)	17,814	(51.8)	1.0000
Diabetes	11844	(34.5)	11,844	(34.5)	1.0000
Mental disorders	13805	(40.2)	13,805	(40.2)	1.0000
COPD	2025	(5.9)	2025	(5.9)	1.0000
Ischemic heart disease	5904	(17.2)	5904	(17.2)	1.0000
Heart failure	618	(1.8)	618	(1.8)	1.0000
Renal dialysis	217	(0.6)	217	(0.6)	1.0000
CCI, score					1.0000
0	7055	(20.5)	7055	(20.5)	
1	7260	(21.1)	7260	(21.1)	
2	4942	(14.4)	4942	(14.4)	
≥3	15,110	(44.0)	15,110	(44.0)	
Anti-hypertension drug use					1.0000
No	22290	(64.9)	22,290	(64.9)	
Yes	12077	(35.1)	12,077	(35.1)	
Anticoagulant drug use					1.0000
No	33925	(98.7)	33,925	(98.7)	
Yes	442	(1.3)	442	(1.3)	
NASH					0.0007
No	29507	(85.9)	29,195	(85.0)	
Yes	4860	(14.1)	5172	(15.0)	
Obesity					<0.0001
No	33502	(97.5)	33,254	(96.8)	
Yes	865	(2.5)	1113	(3.2)	

Abbreviations: CCI, Charlson comorbidity index; NASH, non-alcoholic steatohepatitis; RYR, red yeast rice.

steatohepatitis (p = 0.0007) and obesity (<0.0001) compared with cohort without RYR. A total of 8215 patients developed liver cirrhosis during the follow-up period (Table 2). After correcting for immortal time bias, patients who used RYR had a reduced risk of developing liver cirrhosis compared with patients who used lovastatin (HR 0.61, 95% CI 0.58–0.64). In Figure 2, the Kaplan–Meier analysis showed that the RYR cohort had a lower incidence of liver cirrhosis than the lovastatin cohort during the follow-up period (p < 0.0001).

In Table 2, the use of RYR was associated with a reduced risk of developing liver cirrhosis in women (HR 0.60, 95% CI 0.56–0.64), men (HR 0.60, 95% CI 0.56–0.64), and people aged 20–39 years (HR 0.52, 95% CI 0.44–0.62), 40–49 years (HR 0.58, 95% CI 0.52–0.64), 50–59 years (HR 0.65, 95% CI 0.60–0.69), 60–69 years (HR 0.58, 95% CI 0.52–0.64), and ≥70 years (HR 0.58, 95% CI 0.49–0.68). Among people with (HR 0.56, 95% CI 0.41–0.77) and without low income (HR 0.60, 95% CI 0.57–0.63), reduced liver cirrhosis was found in people who used RYR. The association between RYR use and a reduced risk of developing liver cirrhosis was significant in people with no emergency room visits (HR 0.47, 95% CI 0.45–0.50), one emergency room visit (HR 0.72, 95% CI 0.65–0.81), no hospitalizations (HR 0.52, 95% CI 0.49–0.55), and one hospitalization (HR 0.87, 95% CI 0.77–0.99). We also found that the RYR cohort had reduced liver cirrhosis compared with the lovastatin cohort in people with Charlson Comorbidity Index scores of 0 (HR 0.45, 95% CI 0.42–0.49), 1 (HR 0.52, 95% CI 0.48–0.57), and 2 (HR 0.71, 95% CI 0.63–0.81).

In Table 3, the sensitivity analysis showed that the adjusted HRs of liver cirrhosis associated with RYR use for excluding cirrhosis events in the initial 1 month, 2 months, 3 months, 4 months, 5 months and 6 months of the following period were 0.62 (95% CI 0.59–0.65), 0.62 (95% CI 0.60–0.65), 0.64 (95% CI 0.61–0.67), 0.66 (95% CI 0.63–0.70), 0.68 (95% CI 0.64–0.71), and 0.69 (95% CI 0.65–0.72), respectively. After excluding the deaths that occurred in the follow-up period, surviving patients who used RYR had a lower risk of liver cirrhosis than surviving patients who did not use RYR (HR 0.62, 95% CI 0.59–0.65).

Table 2 The Adjusted Risk of Incident Liver Cirrhosis Between People with and without Use of Red Yeast Rice Prescription During the Follow-Up Period

		Incident liver cirrhosis					
		n	PYs	Events	Incidence†	HR	(95% CI)‡
All	No RYR	34367	321,051	5172	16.1	1.00	(reference)
	RYR	34367	270,278	3043	11.3	0.60	(0.57–0.63)
Women	No RYR	19741	186,572	2830	15.2	1.00	(reference)
	RYR	19741	155,816	1629	10.5	0.60	(0.56–0.64)
Men	No RYR	14626	134,479	2342	17.4	1.00	(reference)
	RYR	14626	114,461	1414	12.4	0.60	(0.56–0.64)
Age, 20–39 years	No RYR	2327	21,510	400	18.6	1.00	(reference)
	RYR	2327	19,126	209	10.9	0.52	(0.44–0.62)
Age, 40–49 years	No RYR	6582	61,380	1130	18.4	1.00	(reference)
	RYR	6582	53,443	631	11.8	0.58	(0.52–0.64)
Age, 50–59 years	No RYR	13417	126,621	2035	16.1	1.00	(reference)
	RYR	13417	106,317	1268	11.9	0.65	(0.60–0.69)
Age, 60–69 years	No RYR	8548	79,775	1207	15.1	1.00	(reference)
	RYR	8548	65,362	690	10.6	0.58	(0.52–0.64)
Age, ≥70 years	No RYR	3493	31,765	400	12.6	1.00	(reference)
	RYR	3493	26,030	245	9.41	0.58	(0.49–0.68)
No low income	No RYR	33854	316,644	5070	16.0	1.00	(reference)
	RYR	33854	266,383	2973	11.2	0.60	(0.57–0.63)
Low income	No RYR	513	4407	102	23.1	1.00	(reference)
	RYR	513	3895	70	18.0	0.56	(0.41–0.77)
Emergency visits, 0	No RYR	12111	97,548	3405	34.9	1.00	(reference)
	RYR	12111	86,551	1777	20.5	0.47	(0.45–0.50)
Emergency visits, 1	No RYR	7216	69,830	854	12.2	1.00	(reference)
	RYR	7216	57,053	534	9.36	0.72	(0.65–0.81)
Emergency visits, 2	No RYR	4259	42,773	350	8.18	1.00	(reference)
	RYR	4259	34,776	250	7.19	0.89	(0.75–1.05)
Emergency visits, ≥3	No RYR	10781	110,901	563	5.08	1.00	(reference)
	RYR	10781	91,898	482	5.24	1.11	(0.98–1.26)
Hospitalizations, 0	No RYR	18338	159,652	4127	25.8	1.00	(reference)
	RYR	18338	136,959	2251	16.4	0.52	(0.49–0.55)
Hospitalizations, 1	No RYR	7062	70,464	648	9.20	1.00	(reference)
	RYR	7062	57,475	460	8.00	0.87	(0.77–0.99)
Hospitalizations, 2	No RYR	3130	32,110	182	5.67	1.00	(reference)
	RYR	3130	26,332	151	5.73	1.03	(0.82–1.29)
Hospitalizations, ≥3	No RYR	5837	58,824	215	3.65	1.00	(reference)
	RYR	5837	49,512	181	3.66	1.06	(0.87–1.30)
CCI score, 0	No RYR	7055	56,365	1925	34.2	1.00	(reference)
	RYR	7055	50,176	985	19.6	0.45	(0.42–0.49)
CCI score, 1	No RYR	7260	63,619	1558	24.5	1.00	(reference)
	RYR	7260	54,968	845	15.4	0.52	(0.48–0.57)
CCI score, 2	No RYR	4942	47,756	630	13.2	1.00	(reference)
	RYR	4942	39,311	392	9.97	0.71	(0.63–0.81)
CCI score, ≥3	No RYR	15110	153,310	1059	6.91	1.00	(reference)
	RYR	15110	125,823	821	6.53	0.98	(0.89–1.08)

Notes: †Per 1000 person-years. ‡Adjusted for all covariates listed in Table 1.

Abbreviations: CI, confidence interval; CCI, Charlson comorbidity index; HR, hazard ratio; PYs, person-years; RYR, red yeast rice.

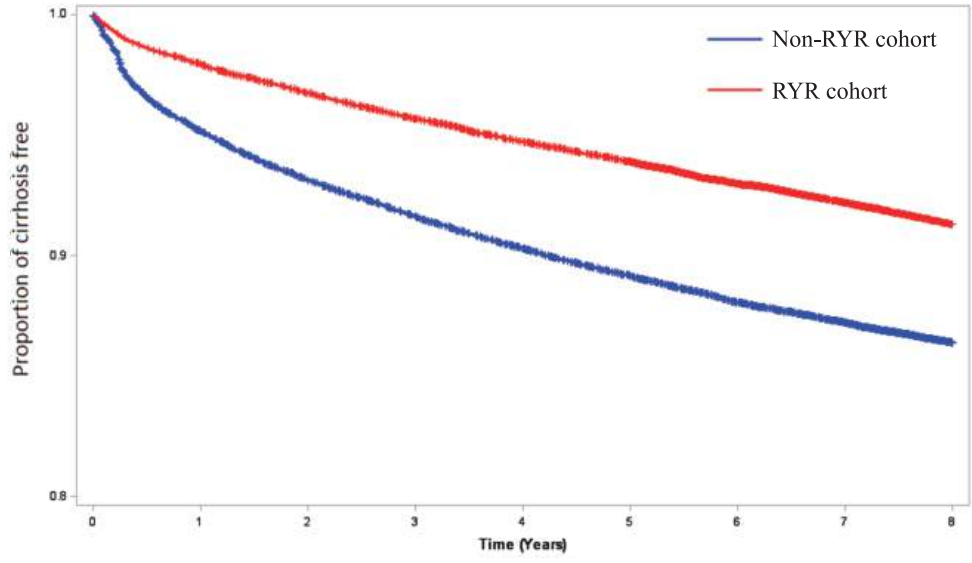

Figure 2 Kaplan-Meier model for measuring the cirrhosis-free probability in hyperlipidemia patients with and without RYR prescription (log rank test, P < 0.0001).

Compared with non-RYR use (Table 4), the frequency of RYR use was associated with a reduced risk of developing liver cirrhosis (≥5 prescriptions: HR 0.59, 95% CI 0.55–0.63), and there was a biological gradient relationship (p < 0.0001). Reduced risks of cirrhosis-related complications and mortality were found in people who used RYR (Table 5), such as jaundice (HR 0.56, 95% CI 0.43–0.72), ascites (HR 0.37, 95% CI 0.28–0.50), hepatic coma (HR 0.36, 95% CI 0.26–0.50), and mortality (HR 0.48, 95% CI 0.38–0.61).

The stratified analysis by medical conditions and medication for the association between the risk of liver cirrhosis and RYR is presented in Table S2. In Table S3, the adjusted HRs for alcoholic cirrhosis, nonalcoholic cirrhosis, and unspecified cirrhosis among people who used RYR were 0.37 (95% CI 0.18–0.73), 0.64 (95% CI 0.51–0.81), and 0.61 (95% CI 0.58–0.64), respectively.

Table 3 Sensitivity Analysis for the Risk of Liver Cirrhosis Associated with Red Yeast Rice Prescription After Excluding the Initial Incident Events

After excluding the incident liver cirrhosis cases during initial		Incident liver cirrhosis					
		N	PYs	Events	Incidence*	HR	(95% CI)†
One month	No RYR	34126	321,039	4931	15.4	1.00	(reference)
	RYR	34251	270,273	2927	10.8	0.62	(0.59–0.65)
Two months	No RYR	33936	321,015	4741	14.8	1.00	(reference)
	RYR	34158	270,261	2834	10.5	0.62	(0.60–0.65)
Three months	No RYR	33681	320,960	4486	14.0	1.00	(reference)
	RYR	34068	270,242	2744	10.2	0.64	(0.61–0.67)
Four month	No RYR	33451	320,896	4256	13.3	1.00	(reference)
	RYR	33994	270,221	2670	9.88	0.66	(0.63–0.70)
Five months	No RYR	33322	320,848	4127	12.9	1.00	(reference)
	RYR	33948	270,204	2624	9.71	0.68	(0.64–0.71)
Six months	No RYR	33198	320,791	4003	12.5	1.00	(reference)
	RYR	33897	270,181	2573	9.52	0.69	(0.65–0.72)
Excluded deaths	No RYR	32704	311,720	4909	15.7	1.00	(reference)
	RYR	33332	264,844	2945	11.1	0.62	(0.59–0.65)

Notes: *Per 1000 person-years. †Adjusted for all covariates listed in Table 1.
Abbreviations: CI, confidence interval; HR, hazard ratio; PYs, person-years; RYR, red yeast rice.

Table 4 Risk of Liver Cirrhosis in People with Use Frequency of Red Yeast Rice Prescriptions

	Incident liver cirrhosis					
	n	PYs	Events	Incidence*	HR	(95% CI)†
No-RYR cohort (used lovastatin)	34367	321,051	5172	16.1	1.00	(reference)
RYR cohort, frequency of RYR use						
1	9998	76,790	873	11.4	0.63	(0.59–0.68)
2	4789	36,763	433	11.8	0.63	(0.57–0.70)
3	3249	25,002	291	11.6	0.61	(0.54–0.69)
4	2468	19,011	218	11.5	0.59	(0.51–0.67)
≥5	13,863	112,713	1228	10.9	0.59	(0.55–0.63)

Notes: *Per 1000 person-years. †Adjusted for all covariates listed in Table 1.
Abbreviations: CI, confidence interval; HR, hazard ratio; PYs, person-years; RYR, red yeast rice.

Table 5 Complications and Mortality After Liver Cirrhosis in People with and without Use of Red Yeast Rice Prescription

	No RYR (N=34,367)				RYR (N=34,367)			
	Events	Incidence*	HR	(95% CI)†	Events	Incidence*	HR	(95% CI)†
Jaundice	164	0.54	1.00	(reference)	101	0.39	0.56	(0.43–0.72)
Ascites	154	0.51	1.00	(reference)	69	0.27	0.37	(0.28–0.50)
Hepatic coma	130	0.43	1.00	(reference)	55	0.21	0.36	(0.26–0.50)
Mortality	263	0.86	1.00	(reference)	98	0.38	0.48	(0.38–0.61)

Notes: *Per 1000 person-years. †Adjusted for all covariates listed in Table 1.
Abbreviations: CI, confidence interval; HR, hazard ratio; RYR, red yeast rice.

Table S4 shows the baseline characteristics between the RYR and non-RYR cohorts (before propensity score matching). In Table S5, the analysis before propensity score matching showed that RYR use was associated with a reduced risk of developing liver cirrhosis during the follow-up period (HR 0.61, 95% CI 0.58–0.64). Compared with RYR cohort, patients received pravastatin (HR 1.73, 95% CI 1.63–1.83) and simvastatin (HR 1.76, 95% CI 1.68–1.84) had increased risk of liver cirrhosis. However, patients received rosuvastatin (HR 0.72, 95% CI 0.69–0.75) had reduced risk of liver cirrhosis than those received RYR (Table S6).

Discussion

To our knowledge, this study was the first to document the beneficial effects of the use of RYR on the risk of liver cirrhosis among patients with hyperlipidemia. In this retrospective cohort study based on real-world insurance data, we also found a dose–response relationship between the use of RYR and the risk of cirrhosis development after controlling for potential confounding factors. These findings were also observed among various subgroups of age, sex, or medical conditions, and the sensitivity analysis strengthened the association between the use of RYR and a decreased risk of liver cirrhosis.

Based on the Taiwan insurance database, the effects of statin use on the reduced risk of developing liver cirrhosis have been investigated in several studies.[16–19,21] A previous study suggested that statin use was associated with a reduced risk of developing cirrhosis in a dose-dependent manner among patients with HCV infection.[16] Another study showed that a cumulative does–response association occurred between statin use and a reduced risk of developing decompensated liver cirrhosis among patients with alcohol use disorder.[17] The effectiveness of statins in reducing the risk of developing decompensated liver cirrhosis in patients with diabetes is dose-dependent.[18] Patients with chronic hepatitis B who underwent statin therapy experienced a dose-dependent reduction in the risk of cirrhosis and its decompensation.[19] Statin use decreases the decompensation rate in both hepatitis B virus- and hepatitis C virus-related cirrhosis.[21] Although a study investigated the beneficial effects of RYR on liver cancer, no information has revealed the effects of RYR on

reducing the risk of liver cirrhosis. In this study, we raised the possibility that patients with hyperlipidemia who received treatment with RYR had a relatively low risk and fewer adverse outcomes of liver cirrhosis.

Some explanations may explain the relationship between RYR and liver cirrhosis in the present study. First, total cholesterol and low-density lipoprotein cholesterol were reported to independently predict new onset of nonalcoholic fatty liver disease.[3,4] Individuals with nonalcoholic fatty liver disease and increased liver enzyme levels showed significantly higher risks for cirrhosis.[5] Several studies have suggested that lovastatin or other types of statins effectively reduce the level of total cholesterol or low-density lipoprotein cholesterol (LDL-C) and provide reliable evidence of benefits on liver cirrhosis risk.[16–19,21] Phytomedicine RYR contains monacolin K (lovastatin), which can reduce the levels of total cholesterol, LDL-C, and triglycerides.[13,15,26] Therefore, we speculated that the use of RYR is beneficial in reducing fatty liver and subsequent liver cirrhosis.

Second, sustained hyperlipidemia is considered a type of inflammation that is also a risk factor for liver cirrhosis.[29–31] RYR has potential anti-inflammatory effects.[32–34] This molecular study provides theoretical support for the wide application of RYR as an antioxidant dietary supplement that reduces oxidative stress-related inflammation and improves intestinal microbiota.[33] An animal study suggested that RYR was effective in combatting inflammation, insulin resistance, and nonalcoholic fatty liver diseases in mice, irrespective of monacolin K levels.[32] RYR was also suggested to protect against nonalcoholic fatty liver disease by inhibiting lipid synthesis and mediating hepatic inflammation in mice.[34]

Third, diabetes is considered a significant risk factor for the development of liver cirrhosis among Chinese people.[35] In a population-based study in China, individuals with diabetes had a higher risk of cirrhosis than those without diabetes.[36] Our previous reports suggested that a decreased risk of incident diabetes was found in people who used RYR.[11] Because of the above potential evidence and findings of this study, we hypothesized that the reduction in the risk of diabetes is beneficial for the prevention of liver cirrhosis.

Fourth, licensed physicians provided medical services for traditional Chinese medicine, which was considered the second medical opinion (western medicine, also called biochemical medicine, was the first choice) and is commonly used in Taiwan and other Asian countries.[37,38] Previous studies have suggested that people who use traditional Chinese medicine have better health-related lifestyles.[37,38] In this study, we hypothesized that patients with hyperlipidemia who were treated with RYR (as prescribed by physicians with specialties in traditional Chinese medicine) may have better knowledge, attitudes, and practices regarding disease prevention and health promotion. It is also possible that better knowledge, attitudes, and practices may also contribute to the decreased incidence of liver cirrhosis in patients who used RYR.

Jaundice, ascites, and hepatic coma are common cirrhosis-related complications,[1] while cirrhosis-related mortality increases the global burden of health.[2] Serum cholesterol predicts poor outcomes and mortality in patients with liver cirrhosis,[6,7] and some studies have suggested that statin treatment reduces complications and mortality in patients with liver cirrhosis.[20–22] Therefore, in this study, we considered it reasonable that RYR is beneficial in reducing complications and mortality after liver cirrhosis.

Before prescribing RYR for patients, physicians need to consider the safety of RYR use.[39] Although some case reports have indicated side effects from the consumption of RYR, including myopathy, hepatotoxicity, and erectile dysfunction,[40–42] several clinical trials have suggested that RYR has a good safety profile and could be considered for patients who cannot tolerate statin drugs.[26,39,43,44] As Xuezhikang® and HypoCol® are scientific Chinese medicines,[13,14] we evaluated RYR (LipoCol Forte®), which was prescribed by physicians in this study, and it had good manufacturing practices and was relatively stable and safe. Nevertheless, continuous monitoring by clinicians for muscular and hepatic safety is important, and we suggest comprehensive review by policy-makers to harmonize the regulatory status of these treatments. The side effects of RYR need to be cautioned and more assessments of the potential side effects of RYR are needed.

People with high total cholesterol/high-density lipoprotein ratio or triglycerides//high-density lipoprotein ratio, or both, have a greater risk for nonalcoholic fatty liver disease.[45–47] The levels of triglycerides is also highly associated with non-alcoholic fatty liver disease.[48,49] Many studies have suggested that RYR could significantly reduce the level of triglycerides.[50–53] Compared to patients receiving statins therapy, adding RYR to statin medications significantly decreases the serum level of total cholesterol in patients with dyslipidemia.[23] A previous study performed the animal experiment and found that RYR ameliorated non-alcoholic fatty liver disease through inhibiting lipid synthesis and NF-κB/NLRP3 inflammasome-mediated hepatic inflammation in mice. The above finding helps us to clarify the role of RYR

in reducing the risk of liver cirrhosis in this study.[34] In summary, of the above previous findings, we believed that RYR has additional effects to reduce lipid profile, risk of fatty liver, and the subsequent liver cirrhosis. We may expect future results of the clinical trial that was conducted to compare the beneficial effects on reducing lipid profile between RYR and statins.[54]

Study Limitations

The first limitation of our study is that we have no clinical examination data, such as levels of total cholesterol, GOT, and GPT; ultrasound of fatty liver; and the liver cirrhosis severity. We could not evaluate the severity of hypercholesterolemia for the relationship between RYR use and the risk of developing liver cirrhosis. Second, this retrospective study has limitations in that we could not determine whether compliance with RYR or lovastatin was optimal. However, we hypothesized that the compliance rate may be distributed equally in patients who used RYR and patients who used lovastatin. Because this is not a clinical trial, our observational study could not provide real compliance of use of medications (included RYR and lovastatin). Third, knowledge, attitudes, and practices regarding health care, lifestyle (such as smoking and alcohol drinking), and family support were also unavailable in this study. Thus, we could not control for these factors in multiple regression, and we could not perform subgroup or sensitivity analyses. In addition, we admit that the real mechanism of the association between RYR and the risk of liver cirrhosis remains unclear, and we could not prove it in this study. Finally, sociodemographic information, medical conditions, use of medical care, CCI, and medications were considered in our study, which could not cover all potential confounding factors. The possibility of residual confounding could not be excluded.

Conclusion

In conclusion, this study revealed beneficial effects of RYR use on the risk and outcome of liver cirrhosis among patients with hyperlipidemia. However, caution is needed because of the study limitations regarding the causal inference of retrospective cohort studies and patient compliance with medications. Our study did not infer causality or claim the superiority of RYR over lovastatin. We suggest that this study should be followed by a randomized controlled trial to examine the effects of both statins and RYR on reducing LDL-C and triglycerides and preventing cirrhosis caused by metabolic-associated steatotic liver disease, non-alcoholic steatohepatitis, or alcohol.

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. Chuen-Chau Chang and Ta-Liang Chen are co-first authors for this study.

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Disclosure

The authors report no conflicts of interest in this work.

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Table S1. ICD-9-CM codes of hyperlipidemia, liver cirrhosis, and medical conditions

Diseases	ICD-9-CM codes
Hyperlipidemia	272.0-272.4
Liver cirrhosis	571.2, 571.5, 571.6
Hypertension	401-405
Diabetes	250
Mental disorders	290-319
Chronic obstructive pulmonary disease	491, 492, 496
Ischemic heart disease	410-414
Heart failure	428
Non-alcoholic steatohepatitis	571.4, 571.8, 571.9
Obesity	278.0, 278.1

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification

Table S2. The stratified analysis by medical conditions and medication for the association between risk of liver cirrhosis and red yeast rice prescription

				Incident liver cirrhosis		
		n	PYs	Events	Incidence†	HR (95% CI)*
No hypertension	No RYR	16553	149741	2793	18.7	1.00 (reference)
	RYR	16553	127311	1592	12.5	0.57 (0.54-0.61)
Hypertension	No RYR	17814	171310	2379	13.9	1.00 (reference)
	RYR	17814	142966	1451	10.1	0.66 (0.62-0.71)
No diabetes	No RYR	22523	206110	3712	18.0	1.00 (reference)
	RYR	22523	174749	2001	11.5	0.55 (0.52-0.58)
Diabetes	No RYR	11844	114941	1460	12.7	1.00 (reference)
	RYR	11844	95529	1042	10.9	0.78 (0.72-0.85)
No mental disorders	No RYR	20562	182978	3902	21.3	1.00 (reference)
	RYR	20562	157010	2146	13.7	0.54 (0.51-0.57)
Mental disorders	No RYR	13805	138073	1270	9.20	1.00 (reference)
	RYR	13805	113268	897	7.92	0.85 (0.78-0.93)
No COPD	No RYR	32342	300770	5030	16.7	1.00 (reference)
	RYR	32342	253402	2924	11.5	0.60 (0.57-0.63)
COPD	No RYR	2025	20281	142	7.00	1.00 (reference)
	RYR	2025	16876	119	7.05	1.03 (0.80-1.31)
No ischemic heart disease	No RYR	28463	261229	4665	17.9	1.00 (reference)
	RYR	28463	220509	2708	12.3	0.59 (0.56-0.62)
Ischemic heart disease	No RYR	5904	59822	507	8.48	1.00 (reference)
	RYR	5904	49768	335	6.73	0.80 (0.69-0.92)
No heart failure	No RYR	33749	314806	5145	16.3	1.00 (reference)
	RYR	33749	265141	3029	11.4	0.61 (0.58-0.64)
Heart failure	No RYR	618	6245	27	4.32	1.00 (reference)
	RYR	618	5137	14	2.73	0.62 (0.32-1.20)
No renal dialysis	No RYR	34150	318845	5166	16.2	1.00 (reference)
	RYR	34150	268451	3036	11.3	0.61 (0.58-0.64)
Renal dialysis	No RYR	217	2206	6	2.72	1.00 (reference)
	RYR	217	1826	7	3.83	1.65 (0.54-5.02)
No anti-hypertension drug	No RYR	22290	199990	4003	20.0	1.00 (reference)
	RYR	22290	169851	2188	12.9	0.54 (0.52-0.57)
Anti-hypertension drug	No RYR	12077	121061	1169	9.66	1.00 (reference)
	RYR	12077	100427	855	8.51	0.86 (0.78-0.94)
No anticoagulant drug	No RYR	33925	316785	5157	16.3	1.00 (reference)
	RYR	33925	266448	3034	11.4	0.61 (0.58-0.64)
Anticoagulant drug	No RYR	442	4266	15	3.52	1.00 (reference)
	RYR	442	3829	9	2.35	0.67 (0.29-1.54)

CI, confidence interval; HR, hazard ratio; PYs, person-years; RYR, red yeast rice

*Adjusted for all covariates listed in Table 1

†Per 100 person-years

Table S3. Risk of liver cirrhosis during the follow-up period between cohorts with and without red yeast rice prescription

				Risk of liver cirrhosis		
		n	PYs	Events	Incidence*	HR (95% CI)†
Alcoholic cirrhosis	No RYR	34367	359042	32	0.09	1.00 (reference)
	RYR	34367	285436	11	0.04	0.37 (0.18-0.73)
Non-alcoholic cirrhosis	No RYR	34367	357859	203	0.57	1.00 (reference)
	RYR	34367	284967	112	0.39	0.64 (0.51-0.81)
Unspecified cirrhosis	No RYR	34367	321554	5109	15.9	1.00 (reference)
	RYR	34367	270557	2994	11.1	0.61 (0.58-0.64)

CI, confidence interval; HR, hazard ratio; PYs, person-years; RYR, red yeast rice

*Adjusted for all covariates listed in Table 1

†Per 100 person-years

Table S4. Baseline characteristics between cohorts with and without use of red yeast rice prescription (before propensity-score matching)

	Lovastatin N=89660		RYR prescription N=66927		p-value
Sex	n	(%)	n	(%)	0.3605
Female	50787	(56.6)	38065	(56.9)	
Male	38873	(43.4)	28862	(43.1)	
Age, years					<0.0001
20-29	641	(0.7)	2995	(4.5)	
30-39	2890	(3.2)	9292	(13.9)	
40-49	10404	(11.6)	16326	(24.4)	
50-59	24994	(27.9)	21736	(32.5)	
60-69	24689	(27.5)	12021	(18.0)	
70-79	19052	(21.3)	3836	(5.7)	
≥80	6990	(7.8)	721	(1.1)	
Low income					<0.0001
No	85844	(95.7)	64706	(96.7)	
Yes	3816	(4.3)	2221	(3.3)	
Number of hospitalizations					<0.0001
0	29669	(33.1)	38362	(57.3)	
1	17182	(19.2)	13495	(20.2)	
2	11189	(12.5)	6196	(9.3)	
≥3	31620	(35.3)	8874	(13.3)	
Number of emergency visits					<0.0001
0	20921	(23.3)	25529	(38.1)	
1	15966	(17.8)	14946	(22.3)	
2	11926	(13.3)	8966	(13.4)	
≥3	40847	(45.6)	17486	(26.1)	
Medical conditions					
Hypertension	54762	(61.1)	25437	(38.0)	<0.0001
Diabetes	46159	(51.5)	14861	(22.2)	<0.0001
Mental disorders	39540	(44.1)	25570	(38.2)	<0.0001
COPD	13275	(14.8)	4124	(6.2)	<0.0001
Ischemic heart disease	24629	(27.5)	10748	(16.1)	<0.0001
Heart failure	7050	(7.9)	1533	(2.3)	<0.0001
Renal dialysis	3296	(3.7)	493	(0.7)	<0.0001
CCI, score					<0.0001
0	9675	(10.8)	19695	(29.4)	
1	16383	(18.3)	12934	(19.3)	

2	13225	(14.8)	11500	(17.2)	
≥3	50377	(56.2)	22798	(34.1)	
Anti-hypertension drug use					<0.0001
No	43895	(49.0)	48111	(71.9)	
Yes	45765	(51.0)	18816	(28.1)	
Anticoagulant drug use					<0.0001
No	83916	(93.6)	65672	(98.1)	
Yes	5744	(6.4)	1255	(1.9)	

Table S5. The adjusted risk of incident liver cirrhosis between people with and without use of red yeast rice prescription (before propensity-score matching)

				Incident liver cirrhosis		
		n	PYs	Events	Incidence†	HR (95% CI)*
All	No RYR	89660	856172	9156	10.7	1.00 (reference)
	RYR	66927	525274	6050	11.5	0.63 (0.60-0.65)
Women	No RYR	50787	492215	5032	10.2	1.00 (reference)
	RYR	38065	300619	3131	10.4	0.61 (0.58-0.64)
Men	No RYR	38873	363957	4124	11.3	1.00 (reference)
	RYR	28862	224656	2919	13.0	0.65 (0.62-0.69)
Age, 20-39 years	No RYR	3531	33580	527	15.7	1.00 (reference)
	RYR	12287	101192	935	9.24	0.52 (0.46-0.58)
Age, 40-49 years	No RYR	10404	99661	1504	15.1	1.00 (reference)
	RYR	16326	130204	1584	12.2	0.60 (0.55-0.64)
Age, 50-59 years	No RYR	24994	243354	2995	12.3	1.00 (reference)
	RYR	21736	169624	2173	12.8	0.69 (0.65-0.73)
Age, 60-69 years	No RYR	24689	239843	2431	10.1	1.00 (reference)
	RYR	12021	90340	1046	11.6	0.65 (0.60-0.70)
Age, ≥70 years	No RYR	26042	239843	1699	7.08	1.00 (reference)
	RYR	4557	33914	312	9.20	0.66 (0.59-0.75)
No low income	No RYR	85844	821588	8762	10.7	1.00 (reference)
	RYR	64706	508151	5802	11.4	0.62 (0.60-0.65)
Low income	No RYR	3816	34584	394	11.4	1.00 (reference)
	RYR	2221	17123	248	14.5	0.73 (0.61-0.88)

Emergency visits, 0	No RYR	20921	173176	5125	29.6	1.00 (reference)
	RYR	25529	183234	3663	20.0	0.49 (0.46-0.51)
Emergency visits, 1	No RYR	15966	153631	1566	10.2	1.00 (reference)
	RYR	14946	118771	1063	8.95	0.72 (0.66-0.79)
Emergency visits, 2	No RYR	11926	117746	823	6.99	1.00 (reference)
	RYR	8966	73661	529	7.18	0.95 (0.84-1.07)
Emergency visits, ≥3	No RYR	40847	411619	1642	3.99	1.00 (reference)
	RYR	17486	149609	795	5.31	1.07 (0.98-1.18)
Hospitalizations, 0	No RYR	29669	264103	6157	23.3	1.00 (reference)
	RYR	38362	287265	4644	16.2	0.54 (0.51-0.56)
Hospitalizations, 1	No RYR	17182	170561	1423	8.34	1.00 (reference)
	RYR	13495	110530	830	7.51	0.85 (0.78-0.94)
Hospitalizations, 2	No RYR	11189	112264	627	5.59	1.00 (reference)
	RYR	6196	52410	283	5.40	0.93 (0.80-1.09)
Hospitalizations, ≥3	No RYR	31620	309244	949	3.07	1.00 (reference)
	RYR	8874	75070	293	3.90	1.12 (0.97-1.29)
CCI score, 0	No RYR	9675	79369	2324	29.3	1.00 (reference)
	RYR	19695	142853	2574	18.0	0.48 (0.45-0.51)
CCI score, 1	No RYR	16383	145905	2840	19.5	1.00 (reference)
	RYR	12934	100198	1357	13.5	0.53 (0.50-0.57)
CCI score, 2	No RYR	13225	126937	1320	10.4	1.00 (reference)
	RYR	11500	92371	843	9.13	0.73 (0.67-0.81)
CCI score, ≥3	No RYR	50377	503961	2672	5.30	1.00 (reference)
	RYR	22798	189852	1276	6.72	0.99 (0.92-1.07)

CCI, Charlson comorbidity index; CI, confidence interval; HR, hazard ratio; PYs, person-years; RYR, red yeast rice

*Adjusted for all covariates listed in Table S1

†Per 100 person-years

Table S6. Risk of liver cirrhosis in people with use of statins (frequency of prescription) compared with the cohort with red yeast rice

			Incident liver cirrhosis		
Frequency of prescriptions	n	PYs	Events	Incidence*	HR (95% CI)†
RYR cohort	34367	270278	3043	11.3	1.00 (reference)
Pravastatin cohort†					
1	27010	232455	2761	11.9	1.41 (1.34-1.48)
2	16619	140589	1875	13.3	1.61 (1.52-1.71)
3	15355	130482	1831	14.0	1.73 (1.63-1.83)
4	9838	83492	1089	13.0	1.68 (1.57-1.81)
≥5	69307	626646	5874	9.37	1.32 (1.26-1.38)
Rosuvastatin cohort†					
1	64970	524484	4109	7.83	0.80 (0.76-0.83)
2	42299	341129	2682	7.86	0.82 (0.78-0.87)
3	39613	320928	2584	8.05	0.86 (0.81-0.90)
4	28355	230590	1802	7.81	0.84 (0.79-0.89)
≥5	349543	3267792	17394	5.32	0.72 (0.69-0.75)
Atrovastatin cohort†					
1	86122	734514	6130	8.35	0.93 (0.89-0.97)
2	54965	466426	3996	8.57	1.00 (0.95-1.05)
3	50820	433759	3771	8.69	1.03 (0.98-1.08)
4	35519	302760	2515	8.31	1.00 (0.95-1.06)
≥5	415187	3957392	21349	5.39	0.80 (0.77-0.83)
Fluvastatin cohort†					
1	20709	170427	1435	8.42	0.92 (0.86-0.98)
2	13385	107896	992	9.19	1.02 (0.95-1.10)
3	12382	99775	1012	10.1	1.14 (1.06-1.22)
4	8336	67240	624	9.28	1.03 (0.95-1.13)
≥5	84462	771615	5076	6.58	0.89 (0.84-0.93)
Simvastatin cohort†					
1	66375	594668	6439	10.8	1.37 (1.31-1.43)
2	40218	356175	4444	12.5	1.65 (1.57-1.73)
3	36795	325160	4314	13.3	1.76 (1.68-1.84)
4	23837	211841	2741	12.9	1.75 (1.67-1.85)
≥5	176313	1660017	15450	9.31	1.47 (1.42-1.53)

CI, confidence interval; HR, hazard ratio; PYs, person-years; RYR, red yeast rice.

*Per 1000 person-years