




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}

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

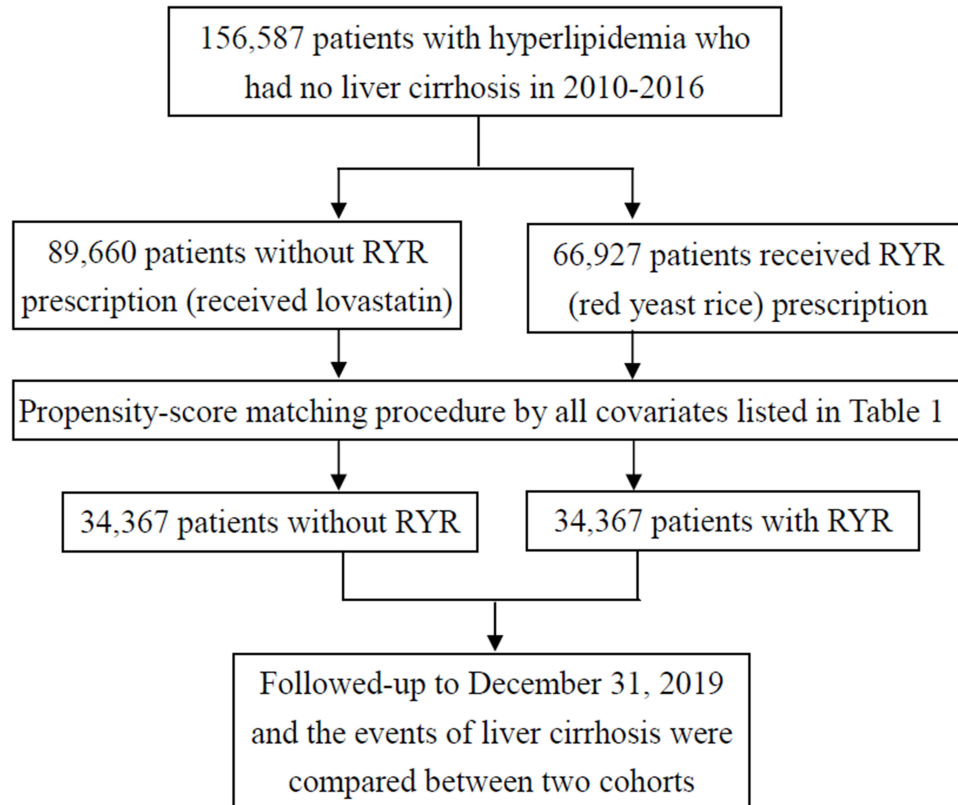


Figure 1 The selection process of adequate study subjects.

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.

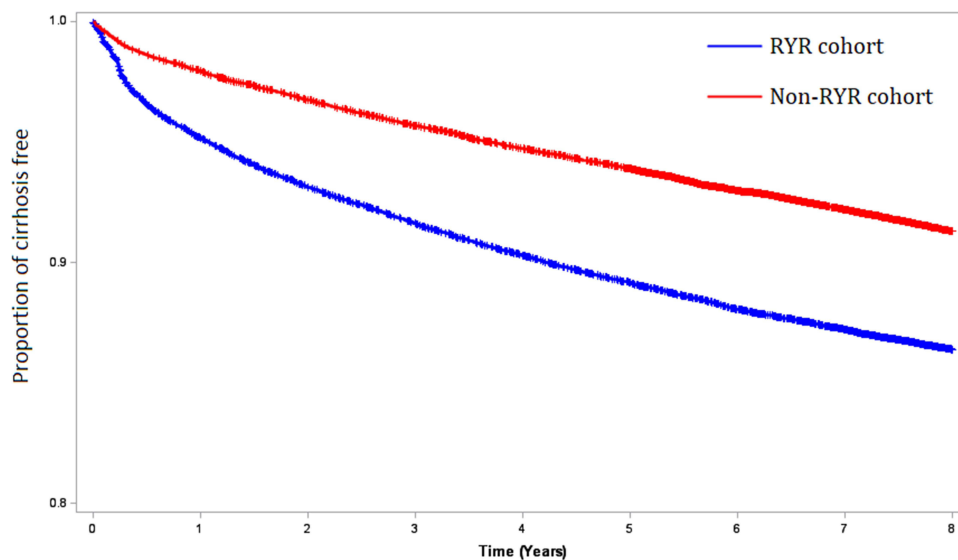


Figure 2 Kaplan-Meier model for measuring the cirrhosis-free probability in hyperlipidemia patients with and without RYR prescription (log rank test, $P < 0.0001$).

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 dose–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- κ B/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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