

ORIGINAL PAPER

Effects of red yeast rice prescription (LipoCol Forte) on adverse outcomes of surgery

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Summary

Background: The influence of red yeast rice (RYR) on perioperative outcome remains unknown.

Aim: We aimed to compare the complications and mortality after surgery between patients treated with and without RYR prescription.

Design: In this surgical cohort study of 3.6 million surgical patients who underwent major inpatient surgeries, 2581 patients who used RYR prescription pre-operatively were compared with 25 810 non-RYR patients selected by matching for age and sex.

Methods: Patients' demographics and medical conditions were collected from the claims data of the National Health Insurance in Taiwan. Complications and mortality after major surgeries in association with RYR prescription were investigated by calculating adjusted odds ratios (ORs) and 95% confidence intervals (CIs) by multiple logistic regression.

Results: Compared with patients without RYR prescription, patients prescribed RYR had lower risks of post-operative bleeding (OR 0.36, 95% CI 0.15–0.89), pneumonia (OR 0.54, 95% CI 0.36–0.83), stroke (OR 0.66, 95% CI 0.47–0.92) and 30-day in-hospital mortality (OR 0.37, 95% CI 0.15–0.92). Decreased risk of intensive care (OR 0.64, 95% CI 0.54–0.77), shorter length of hospital stay ($P < 0.001$) and lower medical expenditures ($P = 0.0008$) during the index surgical admission were also noted for patients with RYR prescription compared to those for patients without RYR prescription.

Conclusions: This study showed a potentially positive effect of RYR on outcomes after major surgeries. However, patient non-compliance for taking medication should be noted. Our findings require future prospective studies to validate RYR prescription for improving perioperative outcomes.

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Introduction

Traditional Chinese medicine (TCM) has been commonly used in Asian populations.¹ TCM has also been considered complementary and alternative medicine, with an increasing trend of utilization in Western countries.^{2,3} Although the therapeutic effects of TCM have been investigated among patients with various diseases, such as stroke, cancer, pain and allergic rhinitis, in several well-designed studies,⁴ limited information is available about whether TCM is helpful in improving outcomes in patients undergoing surgery.

Red yeast rice (RYR) also called *Monascus purpureus* Went rice, is an herbal medicine that has been frequently prescribed by physicians at TCM clinics. Despite its limitations, the effects of RYR have been proven to reduce total cholesterol, low-density lipoprotein cholesterol, triglycerides and lipid ratios in patients with hyperlipidemia.⁵⁻¹² Even among patients using antipsychotics, a daily dose of at least 200mg of RYR for 30 days was suggested to be effective for preventing and/or treating hyperlipidemia.¹³ The anti-inflammatory effect of RYR was also found to be helpful in reducing cardiovascular diseases.^{10,11} In addition, some studies suggested that people who used RYR had decreased risk of cancer compared with that in patients who did not use RYR.¹⁴ There is growing evidence suggesting that aside from improving lipid profiles, RYR could also be used to improve general health.

Among 66 countries reporting surgical data, it was estimated that 312.9 million operations took place in 2012, representing a 33.6% increase over 8 years.¹⁵ A high prevalence of dyslipidemia was also investigated in the Chinese population, and the use of RYR was common in the Chinese population.¹⁶ However, the effects of RYR on perioperative outcomes in surgical patients remain unknown. Using claims data from the insurance program in Taiwan, we conducted a population-based study to compare the risk of complications and mortality after major surgeries in patients with and without the use of RYR prescription.

Materials and methods

Source of data

Taiwan's Health Insurance Program was implemented in 1995 and now covers more than 99% of the 23 million residents with comprehensive health services. Details of the database for the insurance program and related available information have been described in our previous studies.^{4,17,18} To protect personal privacy, the electronic database was decoded and patient identifications were scrambled for further public access for research. According to the corresponding regulations, informed consent is not required because of the use of decoded and scrambled patient identification. Our study was also evaluated and approved by the joint institutional review boards of Taipei Medical University (TMU-JIRB-201808012; TMU-JIRB-201710033; TMU-JIRB-201701050; TMU-JIRB-201506001).

Study design

Among 3.6 million surgical patients who underwent major inpatient surgeries in Taiwan in 2008–13, we examined medical claims and identified 2581 people aged ≥ 20 years who had received a physician's prescription for RYR within 24 months prior to the index surgery. Each patient who underwent surgery and received RYR prescription was randomly matched to a surgical patient who did not use RYR, using a frequency matched-

pair procedure (case-control ratio, 1:10) to adjust for age and sex.

Definition and criteria

For appropriately identifying RYR users in this study, we defined people who visited TCM clinics and received physician's prescription for RYR under the coverage of Taiwan's Health Insurance Program. In this study, an RYR prescription is concentrated Chinese herbal medicine, LipoCol Forte[®]. Different from biochemical medications, LipoCol Forte is a natural herbal medicine and each capsule of LipoCol Forte contains 600 mg *M. purpureus* Went rice including the index component lovastatin 5.7 mg. Under a physician's standard directions, patients with hyperlipidemia (total cholesterol ≥ 200 mg/dl and/or low-density lipoprotein cholesterol ≥ 130 mg/dl and/or triglyceride ≥ 200 mg/dl) take 2 capsules per day for at least 1 month. In this study, we defined major inpatient surgeries as procedures requiring general, epidural or spinal anesthesia and the index surgery with hospitalization for >1 day. Low-income status was defined as having a low income within 2 years before surgery, and this definition (waiving co-payment when receiving medical care) was verified by the Ministry of Health and Welfare.

The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) administration codes and physicians' diagnoses were used to identify the history of disease (within pre-operative 24 months) and post-operative complications (that occurred during the index admission) for surgical patients.^{4,17,18} These medical conditions and post-operative complications were determined from medical claims for the 24-month pre-operative period and included hypertension, mental disorders, diabetes, ischemic heart disease, chronic obstructive pulmonary diseases, liver cirrhosis, heart failure, renal dialysis, post-operative bleeding, pneumonia, septicemia, urinary tract infection, deep wound infection, stroke, acute myocardial infarction, acute renal failure and pulmonary embolism. A requirement for intensive care, the length of hospital stay and medical expenditures during the index surgical admission were also compared between patients with and those without pre-operative RYR prescription.

Statistical analysis

We used a frequency-matched analysis to balance the distribution of age and sex between surgical patients with and without RYR prescription. Categorical variables are summarized using frequencies (percentages) and were compared between people who used RYR prescription and those who did not by using chi-square tests. Continuous variables are summarized using means \pm standard deviations and were compared using t-tests. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of post-operative complications and mortality associated with RYR prescription were calculated by multiple logistic regression. Additional analyses stratified by age, sex, number of medical conditions, emergency care and inpatient care were also performed for examining surgical outcomes among RYR prescription recipients within these strata.

Results

Under the frequency matching procedure, Table 1 shows the balance in age and sex between surgical patients with and without RYR prescription. Higher proportions of neurosurgery, general anesthesia, hypertension, mental disorders, diabetes,

ischemic heart disease, chronic obstructive pulmonary diseases, liver cirrhosis and renal dialysis were found in patients with RYR prescription than those found in controls (all at significant differences of $P < 0.05$).

After adjustment in multiple logistic regressions (Table 2), patients with RYR prescription had lower risks of post-operative bleeding (OR 0.36, 95% CI 0.15–0.89), pneumonia (OR 0.54, 95% CI 0.36–0.83), stroke (OR 0.66, 95% CI 0.47–0.92) and 30-day mortality (OR 0.37, 95% CI 0.15–0.92) than did the control group. Using RYR prescription was associated with decreased risk of

intensive care after surgery (OR 0.64, 95% CI 0.54–0.77). Shorter length of hospital stay (6.1 ± 7.1 vs. 7.6 ± 9.7 days, $P < 0.0001$) and lower medical expenditures (2480 ± 3271 vs. 2709 ± 3795 US dollars, $P = 0.0008$) were also noted for patients with RYR prescription than for those without RYR prescription.

In the stratified analysis (Table 3), reduced risk of post-operative adverse events (including post-operative bleeding, pneumonia, stroke, intensive care and mortality) was associated with RYR prescription in sub-groups of females (OR 0.57, 95% CI 0.44–0.72), males (OR 0.69, 95% CI 0.55–0.86) and patients aged

Table 1. Characteristics of surgical patients with and without use of RYR prescription

Baseline characteristics	No RYR prescription (N = 25 810)		RYR prescription (N = 2581)		P-value
	n	(%)	n	(%)	
Sex					1.0000
Female	15 500	(60.1)	1550	(60.1)	
Male	10 310	(39.9)	1031	(39.9)	
Age, years					1.0000
20–29	750	(2.9)	75	(2.9)	
30–39	2870	(11.1)	287	(11.1)	
40–49	5570	(21.6)	557	(21.6)	
50–59	8130	(31.5)	813	(31.5)	
60–69	5630	(21.8)	563	(21.8)	
70–79	2450	(9.5)	245	(9.5)	
≥ 80	410	(1.6)	41	(1.6)	
Low income					0.7290
No	25 159	(97.5)	2513	(97.4)	
Yes	651	(2.5)	68	(2.6)	
Types of surgery					<0.0001
Skin	435	(1.7)	23	(0.9)	
Breast	626	(2.4)	76	(2.9)	
Musculoskeletal	7244	(28.1)	663	(25.7)	
Respiratory	1122	(4.4)	148	(5.7)	
Cardiovascular	721	(2.8)	60	(2.3)	
Digestive	5229	(20.3)	524	(20.3)	
Kidney, ureter, bladder	2110	(8.2)	253	(9.8)	
Delivery, CS, abortion	1272	(4.9)	87	(3.4)	
Neurosurgery	2672	(10.4)	312	(12.1)	
Eye	337	(1.3)	31	(1.2)	
Others	4042	(15.7)	404	(15.7)	
Types of anesthesia					0.0140
General	19 241	(74.6)	1981	(76.8)	
Epidural or Spinal	6569	(25.4)	600	(23.2)	
Number of hospitalizations					0.1026
0	18 859	(73.1)	1937	(75.1)	
1	4349	(16.9)	419	(16.2)	
2	1280	(5.0)	112	(4.3)	
≥ 3	1322	(5.1)	113	(4.4)	
Number of emergency visits					0.6529
0	16 336	(63.3)	1633	(63.3)	
1	5495	(21.3)	570	(22.1)	
2	2119	(8.2)	203	(7.9)	
≥ 3	1860	(7.2)	175	(6.8)	
Medical conditions					
Hypertension	6022	(23.3)	890	(34.5)	<0.0001
Mental disorders	4128	(16.0)	671	(26.0)	<0.0001
Diabetes	3456	(13.4)	415	(16.1)	0.0001
Ischemic heart disease	1785	(6.9)	283	(11.0)	<0.0001
COPD	925	(3.6)	108	(4.2)	0.1203
Liver cirrhosis	704	(2.7)	88	(3.4)	0.0449
Heart failure	417	(1.6)	49	(1.9)	0.2809
Renal dialysis	559	(2.2)	17	(0.7)	<0.0001

COPD, chronic obstructive pulmonary disease; RYR, red yeast rice.

Table 2. Risk of post-operative complications and mortality in surgical patients with and without use of RYR prescription

Post-operative outcomes	No RYR prescription (N = 25 810)		RYR prescription (N = 2581)		Outcome risk OR (95% CI) ^a
	Events	%	Events	%	
30-day in-hospital mortality	135	0.5	5	0.2	0.37 (0.15–0.92)
Complications					
Pneumonia	452	1.8	24	0.9	0.54 (0.36–0.83)
Septicemia	876	3.4	73	2.8	0.89 (0.70–1.14)
Pulmonary embolism	17	0.1	5	0.2	3.30 (1.18–9.20)
Acute renal failure	142	0.6	14	0.5	0.96 (0.55–1.69)
Stroke	552	2.1	39	1.5	0.66 (0.47–0.92)
Urinary tract infection	1129	4.4	130	5.0	1.09 (0.90–1.33)
Deep wound infection	121	0.5	9	0.4	0.76 (0.38–1.51)
AMI	63	0.2	3	0.1	0.48 (0.15–1.59)
Post-operative bleeding	138	0.5	5	0.2	0.36 (0.15–0.89)
ICU stay	2468	9.6	171	6.6	0.64 (0.54–0.77)
Post-operative adverse events ^b	2983	11.6	206	8.0	0.63 (0.54–0.74)
Medical expenditure, USD ^c	2709 ± 3795		2480 ± 3271		P = 0.0008
Length of hospital stay, days ^c	7.6 ± 9.7		6.1 ± 7.1		P < 0.0001

AMI, acute myocardial infarction; CI, confidence interval; OR, odds ratio; RYR, red yeast rice.

^aAdjusted for all covariates listed in Table 1. ^bAdverse events included with 30-day in-hospital mortality, pneumonia, stroke, post-operative bleeding and admitted to intensive care unit; After excluding those used statin within pre-operative 24-months in RYR group (n = 2491), the adjusted OR of RYR associated with post-operative adverse events was 0.62 (95% CI = 0.53–0.73). ^cMean ± SD; RYR prescription was associated with length of hospital stays (beta = -1.4, P < 0.0001) and medical expenditure (beta = -247.9, P = 0.0007) after adjusted all covariates listed in Table 1 in the multiple linear regressions.

≥50 years. The association between RYR prescription and reduced risk of post-operative adverse events was significant in patients with no hospitalization (OR 0.63, 95% CI 0.52–0.78), ≥2 hospitalizations (OR 0.44, 95% CI 0.28–0.67), no emergency visit (OR 0.68, 95% CI 0.55–0.84), one emergency visit (OR 0.60, 95% CI 0.43–0.85), ≥2 emergency visits (OR 0.55, 95% CI 0.38–0.79), one medical condition (OR 0.56, 95% CI 0.43–0.74) and ≥2 medical conditions (OR 0.53, 95% CI 0.39–0.70).

The adjusted ORs of post-operative adverse events for patients with 1–90, 91–180, ≥181 cumulative consumption of RYR capsules were 0.70 (95% CI 0.57–0.85), 0.63 (95% CI 0.41–0.97) and 0.65 (95% CI 0.47–0.91), respectively, compared with people without RYR prescriptions (Table 4).

Discussion

In this population-based study with multiple regression adjustment, we found that patients who used RYR prescription had decreased post-operative complications, intensive care use, mortality, length of hospital stay and medical expenditures compared with patients with no use of RYR prescription. The significant association between reduced risk of post-operative adverse events and RYR prescription could be observed in several sub-groups.

For eliminating the confounding bias from age and sex, we used frequency matching by age and sex for investigating peri-operative outcomes between patients with and without use of RYR prescription. Information from previous reports suggested that economic status, history of diseases, coexisting medical conditions, types of surgery and types of anesthesia were factors associated with perioperative outcomes.^{17,18} People with hypertension, diabetes and heart diseases were common potential users of lipid-lowering agents.^{19–22} For calculating appropriate risk of post-operative complications and mortality in patients with RYR prescription, we applied multiple logistic regression to control the above potential confounding factors.

Regarding the beneficial effects of RYR prescription on peri-operative outcomes, we proposed some possible explanations.

First, it was confirmed that RYR reduces total cholesterol, low-density lipoprotein cholesterol, triglyceride and lipid ratios for patients with hyperlipidemia.^{5–12} Because hyperlipidemia is an important risk factor for stroke, the preventive effect of RYR for stroke is also reasonable and this evidence explains why we observed a reduced risk of post-operative stroke in patients who used RYR prescription. Second, RYR contains a component (monocolin K) of lovastatin that inhibits β -hydroxy- β -methylglutaryl-CoA reductase.²³ Experimental and clinical studies suggest that statins exhibit anti-inflammatory activity that reduces the risk of pneumonia and related outcomes.^{24–26} This activity may help us to explain why patients with RYR prescription had a significant reduction in post-operative pneumonia risk in this study. Third, RYR extract inhibits high-glucose-induced β -galactosidase activation and reduces high-glucose-induced oxidative stress in proangiogenic cells in a dose-dependent manner.²⁷ RYR-olive extract supplement also significantly reduces lipoprotein-associated phospholipase A2 in correlation with the marked reduction in plasma oxidized low-density lipoprotein cholesterol, which may lead to a reduced risk for cardiovascular disease.²⁸ The antioxidative effect of RYR also helps us to explain the reduced complications and mortality after surgery in patients who used RYR prescription in this study.

In the clinical setting, TCM physicians always admonish their patients not to use statin drugs during the treatment course of RYR prescription. Adherence to statin therapy is challenging in clinical practice due to statin-associated muscle symptoms.^{20–22} However, we found that very few (3.5%) patients used statins during the course of RYR treatment in this study. The reduced risk of post-operative adverse events associated with RYR prescription remains significant after excluding patients with the use of statins. Because the association between RYR prescription and reduced risk of post-operative adverse events was not significant in some sub-groups, we suggest future clinical trials to solve this problem.

The complex of secondary metabolites of RYR increases the difficulty for researchers to understand its mechanism action.²⁹

Table 3. The stratified analysis for the association between RYR prescription and post-operative adverse events

		n	Adverse events ^a			
			Events	Rate, %	OR	(95% CI) ^b
Female	No RYR	15 500	1363	8.8	1.00	(reference)
	RYR	1550	87	5.6	0.57	(0.44–0.72)
Male	No RYR	10 310	1620	15.7	1.00	(reference)
	RYR	1031	119	11.5	0.69	(0.55–0.86)
Age 20–39 years	No RYR	3620	149	4.1	1.00	(reference)
	RYR	362	12	3.3	0.73	(0.38–1.41)
Age 40–49 years	No RYR	5570	445	8.0	1.00	(reference)
	RYR	557	41	7.4	0.80	(0.55–1.15)
Age 50–59 years	No RYR	8130	872	10.7	1.00	(reference)
	RYR	813	55	6.8	0.63	(0.47–0.85)
Age 60–69 years	No RYR	5630	852	15.1	1.00	(reference)
	RYR	563	57	10.1	0.57	(0.41–0.78)
Age ≥70 years	No RYR	2860	665	23.3	1.00	(reference)
	RYR	286	41	14.3	0.59	(0.41–0.85)
0 hospitalization	No RYR	18 859	1560	8.3	1.00	(reference)
	RYR	1937	119	6.1	0.63	(0.52–0.78)
1 hospitalization	No RYR	4349	724	16.7	1.00	(reference)
	RYR	419	57	13.6	0.76	(0.55–1.06)
≥2 hospitalizations	No RYR	2602	699	26.9	1.00	(reference)
	RYR	225	30	13.3	0.44	(0.28–0.67)
0 emergency visit	No RYR	16 336	1462	9.0	1.00	(reference)
	RYR	1633	118	7.2	0.68	(0.55–0.84)
1 emergency visit	No RYR	5495	699	12.7	1.00	(reference)
	RYR	570	45	7.9	0.60	(0.43–0.85)
≥2 emergency visits	No RYR	3979	822	20.7	1.00	(reference)
	RYR	378	43	11.4	0.55	(0.38–0.79)
0 medical condition	No RYR	13 535	1042	7.7	1.00	(reference)
	RYR	951	63	6.6	0.80	(0.60–1.06)
1 medical condition	No RYR	8048	1061	13.2	1.00	(reference)
	RYR	970	73	7.5	0.56	(0.43–0.74)
≥2 medical conditions	No RYR	4227	880	20.8	1.00	(reference)
	RYR	660	70	10.6	0.53	(0.39–0.70)

CI, confidence interval; OR, odds ratio; RYR, red yeast rice.

^aAdverse events included with 30-day in-hospital mortality, pneumonia, stroke, post-operative bleeding and admitted to intensive care unit.

^bAdjusted for all covariates listed in Table 1.

Table 4. Risk of post-operative adverse events associated with cumulative consumption of RYR capsules^a

Cumulative consumption of RYR, capsules	Adverse events after surgery				
	n	Events	Incidence, %	OR	(95% CI) ^b
0–90	1618	136	8.4	0.70	(0.57–0.85)
91–180	385	26	6.8	0.63	(0.41–0.97)
≥181	578	44	7.6	0.65	(0.47–0.91)

CI, confidence interval; OR, odds ratio; RYR, Red Yeast Rice.

^aDaily recommended dose is two capsules and per capsule included RYR 600 mg; adverse events included with 30-day in-hospital mortality, pneumonia, stroke, post-operative bleeding and admitted to intensive care unit.

^bAdjusted for all covariates listed in Table 1.

Because RYR preparations have considerable variability in monacolin K content, predicting or understanding dose-related efficacy and side-effect risks of RYR is not easy.³⁰ A previous study also found striking variability in monacolin content in 12 proprietary RYR products.³¹ A review article clearly recommended against RYR sales or consumption until the Food and Drug Administration was ready to inspect the content and purity of all RYR preparations marketed and to provide strict current good manufacturing practice quality controls, regulations and standards of extractions and ingredients.³⁰ Although RYR may

have potential as an alternative lipid-lowering agent, the need for improving quality control, standardization and exact labeling of RYR products has been highly suggested.³¹ Until this occurs, physicians should be cautious in recommending RYR to their patients for the treatment of hyperlipidemia and primary and secondary prevention of cardiovascular disease.³¹ Under the cumulative evidence in the available literature, the unpredictable strength and composition of RYR supplements sold at mainstream retail stores suggests that more regulations are necessary.³²

Intake of RYR decreases levels of total cholesterol, low-density lipoprotein cholesterol and triglycerides and may be a treatment option for dyslipidemic patients who cannot tolerate statin therapy.^{12,20–22} However, the side effects and adverse events after using RYR should be cautioned critically. A study found the presence of citrinin in one-third of the formulations tested in 12 proprietary RYR products.³¹ A recent study suggested the importance of exploring multiple databases in the safety assessment of RYR products, which should be monitored by clinicians for muscular and hepatic safety and called for urgent review by policymakers to standardize their regulatory status.³³ Only when the mild profile of adverse reactions can be confirmed in studies with adequate methodology for safety assessment might RYR be a safe and effective treatment option for dyslipidemia and cardiovascular risk reduction in statin intolerant patients.^{11,20–22}

Some study limitations must be noted when interpreting our findings. First, the insurance database lacked detailed information on sociodemographic and lifestyle factors, such as education, occupation, smoking, alcohol consumption and physical activity. Therefore, we could not evaluate their impacts on perioperative outcomes in this study. Second, some physicians may prescribe RYR with additional out-of-pocket money that was not covered in the public insurance payment. Therefore, some patients in the control group may have used non-insurance-covered RYR prescriptions, and this misclassification may lead to underestimation of the therapeutic effects of RYR prescription in the treatment group. That is, this discrepancy would likely have biased the study results toward the null hypothesis if such misclassifications occurred. Third, residual confounding in this study remains possible, although we used frequency matching and confounding adjustment in the multiple logistic regression. In addition, we have to emphasize that a physician's prescription is not equal to a patient's intake because patient non-compliance commonly occurs in non-clinical settings. Finally, our study was an observational study that could not provide causal inference for the association between RYR prescription and reduced risk of post-operative adverse events.

Conclusion

In conclusion, we found that patients who underwent surgery and received RYR prescription were protected from post-operative bleeding, pneumonia, stroke and in-hospital mortality after major surgery compared with patients who did not receive RYR prescription before surgery. However, the actual biochemical mechanism underlying RYR prescription requires future prospective studies to provide solid evidence.

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