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在线全文

胆结石患病风险预测模型的构建和多中心验证研究*

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【摘要】 目的 基于我国的多中心体检人群数据构建和验证胆结石患病风险预测模型，以期能及早识别胆结石高风险患者，增强人们对该疾病的预防与控制意识。**方法** 最终纳入96426名研究对象，其中来自重庆医科大学附属第一医院的35976名研究对象被划分为训练集（80%，*n*=28 781）和内部验证集（20%，*n*=7 195）。来自济宁市第一人民医院、天津医科大学肿瘤医院和重庆市开州人民医院的研究对象将作为外部验证集对模型进行验证。采用logistic回归分析探究与胆结石病（gallstone disease，GSD）相关的风险因素，并利用列线图分别构建完整和简化的风险预测模型。校准曲线、受试者特征曲线下面积（AUC）和决策曲线分析用于验证这些模型的准确性和临床效用。此外，本研究基于研究结果建立了一个在线网站便于预测模型的使用（完全模型：https://wenqianyu.shinyapps.io/Completemodel/，简化模型：https://wenqianyu.shinyapps.io/Simplified/）。**结果** 女性、高龄、较高的体质量指数、空腹血糖、尿酸、总胆红素、γ-谷氨酰转肽酶和脂肪肝与GSD患病风险呈正相关。胆囊息肉、总胆固醇、高密度脂蛋白胆固醇、低密度脂蛋白胆固醇和天冬氨酸转氨酶与GSD患病风险呈负相关。完全模型内部验证AUC为74.1%（95%置信区间：72.9%～75.3%）和简化模型内部验证AUC为73.7%（95%置信区间：72.5%～75.0%），两种模型的决策曲线分析和校准曲线结果显示，GSD的完全和简化风险预测模型表现出优异的预测性能。此外，完全模型与简化模型的预测性能差异无统计学意义（*P*>0.05）。**结论** 本研究所建立的胆结石患病风险预测模型，以及在线GSD患病风险评估工具可以帮助患者和临床医生进行胆结石患病风险的预测。我们推荐在实践中使用简化模型以提高筛查高风险人群的效率。使用简化模型有助于增强普通人群的自我防控意识和GSD的早期干预。

【关键词】 胆结石 预测模型 列线图 回顾性研究

Establishment and Validation of a Predictive Model for Gallstone Disease in the General Population: A Multicenter Study

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【Abstract】 Objective Gallstone disease (GSD) is one of the common digestive tract diseases with a high worldwide prevalence. The effects of GSD on patients include but are not limited to the symptoms of nausea, vomiting, and biliary colic directly caused by GSD. In addition, there is mounting evidence from cohort studies connecting GSD to other conditions, such as cardiovascular diseases, biliary tract cancer, and colorectal cancer. Early identification of patients at a high risk of GSD may help improve the prevention and control of the disease. A series of studies have attempted to establish prediction models for GSD, but these models could not be fully applied in the general population due to incomplete prediction factors, small sample sizes, and limitations in external validation. It is crucial to design a universally applicable GSD risk prediction model for the general population and to take individualized intervention measures to prevent the occurrence of GSD. This study aims to conduct a multicenter investigation involving more than 90 000 people to construct and validate a complete and simplified GSD risk prediction model. **Methods** A total of 123 634 participants were included in the study between January 2015 and December 2020, of whom 43 929 were from the First Affiliated Hospital of Chongqing Medical University (Chongqing, China), 11 907 were from the First People's Hospital of Jining City (Shandong, China), 1 538 were from the Tianjin Medical University Cancer Institute and Hospital (Tianjin, China), and 66 260 were from the People's Hospital of Kaizhou District (Chongqing, China). After excluding patients with

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incomplete clinical medical data, 35 976 patients from the First Affiliated Hospital of Chongqing Medical University were divided into a training data set (n=28 781, 80%) and a validation data set (n=7 195, 20%). Logistic regression analyses were performed to investigate the relevant risk factors of GSD, and a complete risk prediction model was constructed. Factors with high scores, mainly according to the nomograms of the complete model, were retained to simplify the model. In the validation data set, the diagnostic accuracy and clinical performance of these models were validated using the calibration curve, area under the curve (AUC) of the receiver operating characteristic curve, and decision curve analysis (DCA). Moreover, the diagnostic accuracy of these two models was validated in three other hospitals. Finally, we established an online website for using the prediction model (The complete model is accessible at https://wenqianyu.shinyapps.io/Completemodel/, while the simplified model is accessible at https://wenqianyu.shinyapps.io/Simplified/). **Results** After excluding patients with incomplete clinical medical data, a total of 96 426 participants were finally included in this study (35 876 from the First Affiliated Hospital of the Chongqing Medical University, 9 289 from the First People's Hospital of Jining City, 1 522 from the Tianjin Medical University Cancer Institute, and 49 639 from the People's Hospital of Kaizhou District). Female sex, advanced age, higher body mass index, fasting plasma glucose, uric acid, total bilirubin, gamma-glutamyl transpeptidase, and fatty liver disease were positively associated with risks for GSD. Furthermore, gallbladder polyps, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and aspartate aminotransferase were negatively correlated to risks for GSD. According to the nomograms of the complete model, a simplified model including sex, age, body mass index, gallbladder polyps, and fatty liver disease was constructed. All the calibration curves exhibited good consistency between the predicted and observed probabilities. In addition, DCA indicated that both the complete model and the simplified model showed better net benefits than treat-all and treat-none. Based on the calibration plots, DCA, and AUCs of the complete model (AUC in the internal validation data set=74.1% [95% CI: 72.9%-75.3%], AUC in Shandong=71.7% [95% CI: 70.6%-72.8%], AUC in Tianjin=75.3% [95% CI: 72.7%-77.9%], and AUC in Kaizhou=72.9% [95% CI: 72.5%-73.3%]) and the simplified model (AUC in the internal validation data set=73.7% [95% CI: 72.5%-75.0%], AUC in Shandong=71.5% [95% CI: 70.4%-72.5%], AUC in Tianjin=75.4% [95% CI: 72.9%-78.0%], and AUC in Kaizhou=72.4% [95% CI: 72.0%-72.8%]), we concluded that the complete and simplified risk prediction models for GSD exhibited excellent performance. Moreover, we detected no significant differences between the performance of the two models (P>0.05). We also established two online websites based on the results of this study for GSD risk prediction. **Conclusions** This study innovatively used the data from 96 426 patients from four hospitals to establish a GSD risk prediction model and to perform risk prediction analyses of internal and external validation data sets in four cohorts. A simplified model of GSD risk prediction, which included the variables of sex, age, body mass index, gallbladder polyps, and fatty liver disease, also exhibited good discrimination and clinical performance. Nonetheless, further studies are needed to explore the role of low-density lipoprotein cholesterol and aspartate aminotransferase in gallstone formation. Although the validation results of the complete model were better than those of the simplified model to a certain extent, the difference was not significant even in large samples. Compared with the complete model, the simplified model uses fewer variables and yields similar prediction and clinical impact. Hence, we recommend the application of the simplified model to improve the efficiency of screening high-risk groups in practice. The use of the simplified model is conducive to enhancing the self-awareness of prevention and control in the general population and early intervention for GSD.

【Key words】 Gallstone disease Prediction model Nomogram Retrospective study

胆结石病(gallstone disease, GSD)是一种常见的消化道疾病,其全球患病率为10%~20%[1]。胆囊切除术是治疗GSD的主要方式,但会给患者带来巨大的经济负担[2]。据报道,美国每年进行约70万例胆囊切除手术,相关费用高达60亿美元[3-4]。此外,GSD对患者的影响不仅仅局限在其本身带来的恶心、呕吐以及胆绞痛等症状,许多队列研究还将其与心血管疾病、胆道癌和结直肠癌等疾病相联系[5-7]。因此,早期识别GSD的患病风险非常重要。既往有许多研究尝试建立GSD相关的预测模型,但由于纳入模型的预测因素不全面、样本量小和外部验证人群的限制,这些模型在一般人群中无法得到很好的应用[8-10]。对于一般人群来说,建立一个普适性的GSD风险预测模型并采取个体化干预措施以预防GSD是至关重要的。因此,本研究旨在通过包含约9万人的多中心研究,构建和验证完全和简化的GSD患病风险预测模型,并基于研究结果开发GSD患病风险在线预测软件,以便临床应用。

1 资料与方法

1.1 研究对象

本研究初始纳入了2015年1月–2020年12月间的123 634名研究对象,其中43 929名来自重庆医科大学附属第一医院,11 907名来自济宁市第一人民医院,1 538名来自天津医科大学肿瘤医院,66 260名来自重庆市开州人民医院。

每位参与者均签署了知情同意书, 且本研究已获得四川大学华西公共卫生学院(四川大学华西第四医院)伦理委员会的批准, 批准号Gwll2021055。

GSD由当地医院具有至少3年工作经验的专业人员通过腹部超声影像诊断。诊断标准: ①胆囊腔内有高回声区域, 并伴有阴影, 该区域随着体位变化而移动; ②常规胆管有强烈的光亮区域, 伴有声影, 在肝脏附近有胆管扩张。此外, 我们也纳入了因胆结石而接受胆囊切除术的患者。健康个体定义为未满足上述诊断标准的参与者, 此外, 我们排除了临床数据不完整的参与者, 最终纳入96 426名研究对象。其中来自重庆医科大学附属第一医院的研究对象按照80%：20%的比例被随机分为训练数据集(n=28 781, 80%)和内部验证集(n=7 195, 20%)。来自济宁市第一人民医院、天津医科大学肿瘤医院和重庆市开州人民医院的研究对象将作为外部验证集对模型进行验证。具体流程图见图1。

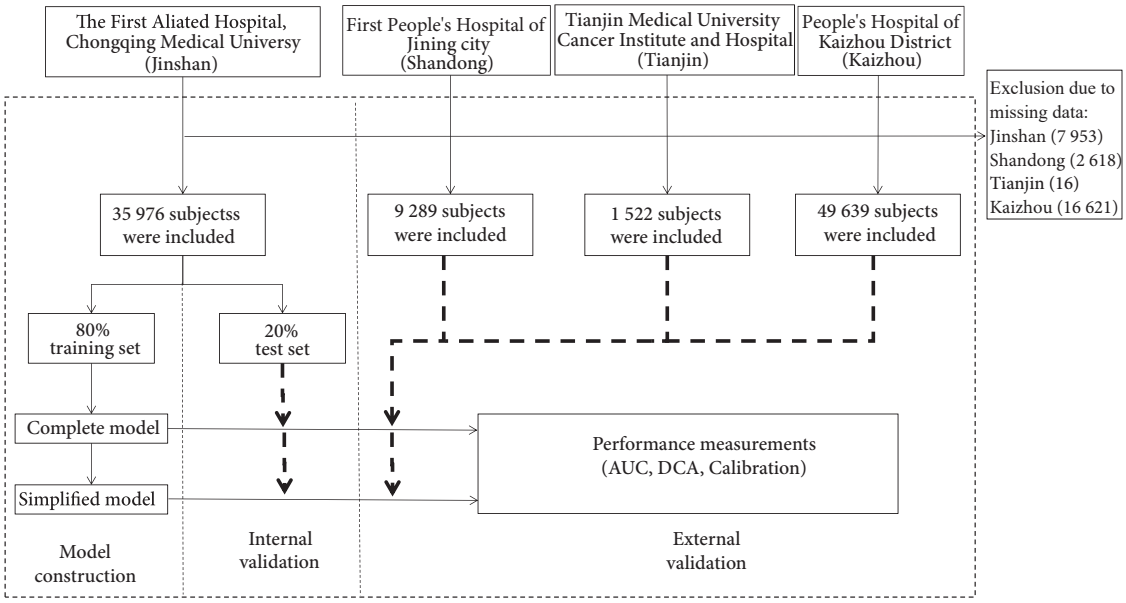

图 1 模型建立与验证的流程图

Fig 1 Machine learning workflow of model construction and validation

1.2 研究变量

基于以往的研究和临床实践经验[11-16], 我们收集了13个潜在的诱导或恶化GSD的风险因素作为变量, 包括性别、年龄、体质量指数(body mass index, BMI)、胆囊息肉(gallbladder polyp, GP)、脂肪肝(fatty liver disease, FLD)、空腹血糖(fasting plasma glucose, FPG)、总胆固醇(total cholesterol, TC)、高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)、总胆红素(total bilirubin, TB)、尿酸(uric acid, UA)、天冬氨酸转氨酶(aspartate aminotransferase, AST)和γ-谷氨酰转肽酶(gamma-glutamyl transpeptidase, GGT)。

1.3 统计学方法

使用SPSS Statistics 25.0(IBM Corp., Armonk, New York, United States)和R语言4.2.1版本(R Core Team, 2022)进行统计分析, 双侧检验水准α为0.05。卡方检验和Wilcoxon秩和检验分别用于分析比较组间的分类变量和有序变量。我们通过多因素logistic回归分析筛选变量中的GSD预测因素, 并使用列线图和在线预测软件(R软件包DynNom, Jalali, A., 2019)简化结果[17]。受试者操作特征曲线(the receiver operating characteristic, ROC)的曲线下面积(the area under the curve, AUC)用于量化模型的辨别能力, 此外, 我们还使用Delong检验比较了完全模型和简化模型的AUC, 探索两个预测模型的准确性差异(R软件包pROC, Xavier Robin, 2011)[18]。通过校准曲线了解模型的预测概率与实际观察结果之间的关系, 评估模型的准确性和可靠性。校准曲线接近45°对角线, 表示模型的预测概率与实际结果一致。此外, 我们还使用决策曲线分析(the decision curve analysis, DCA)来计算在不同阈值概率下的净收益以评估GSD预测模型的临床效益和实用性。

2 结果

2.1 研究对象基本特征

表1描述了4个研究中心的研究对象的基线特征。GSD患者具有高龄, 较高的BMI, 脂肪肝, 较高水平的空

表 1 各研究中心的研究对象基线特征

Table 1 Baseline characteristics of the subjects from the four centers

Variable	Jinshan (*n*=35 976)			Shandong (*n*=9 289)			Tianjin (*n*=1 522)			Kaizhou (*n*=49 639)		
	Case	Control	*P*	Case	Control	*P*	Case	Control	*P*	Case	Control	*P*
Total	10 628	25 348		3 421	5 868		504	1 018		24 385	25 254	
Sex			<0.05			0.933			<0.05			<0.05
Male	5 672 (53.4)	14 945 (59.0)		2 087 (61.0)	3 585 (61.1)		242 (48.0)	424 (41.7)		10 900 (44.7)	13 908 (55.1)	
Female	4 956 (46.6)	10 403 (41.0)		1 334 (39.0)	2 283 (38.9)		262 (52.0)	594 (58.3)		13 485 (55.3)	11 346 (44.9)	
Age/yr.			<0.05			<0.05			<0.05			<0.05
≤30	537 (5.1)	6 050 (23.9)		105 (3.1)	1 178 (20.1)		12 (2.4)	176 (17.3)		868 (3.6)	4 247 (16.8)	
31-40	1 720 (16.2)	7 496 (29.6)		356 (10.4)	1 333 (22.7)		67 (13.3)	372 (36.5)		3 016 (12.4)	5 958 (23.6)	
41-50	2 613 (24.6)	5 497 (21.7)		881 (25.8)	1 722 (29.3)		94 (18.7)	207 (20.3)		7 277 (29.8)	7 568 (30.0)	
51-60	2 892 (27.2)	3 842 (15.2)		888 (26.0)	1 035 (17.6)		156 (31.0)	154 (15.1)		7 555 (31.0)	4 920 (19.5)	
61-70	1 961 (18.5)	1 876 (7.4)		504 (14.7)	347 (5.9)		91 (18.1)	65 (6.4)		3 932 (16.1)	2001 (7.9)	
>70	905 (8.5)	587 (2.3)		687 (20.1)	253 (4.3)		84 (16.7)	44 (4.3)		1 737 (7.1)	560 (2.2)	
BMI/(kg/m^2)			<0.05			<0.05			–			<0.05
<18.5	193 (1.8)	1 404 (5.5)		31 (0.9)	130 (2.2)		504 (100.0)	1 018 (100.0)		263 (1.1)	898 (3.6)	
18.5-23.99	4 582 (43.1)	13 936 (55.0)		840 (24.6)	2 106 (35.9)		0 (0.0)	0 (0.0)		8 580 (35.2)	12 292 (48.7)	
24.0-27.99	4 438 (41.8)	8 081 (31.9)		1 623 (47.4)	2 440 (41.6)		0 (0.0)	0 (0.0)		11 019 (45.2)	9 194 (36.4)	
≥28	1 415 (13.3)	1 927 (7.6)		927 (27.1)	1 192 (20.3)		0 (0.0)	0 (0.0)		4 523 (18.5)	2 870 (11.4)	
GP			<0.05			<0.05			0.65			<0.05
No	10 363 (97.5)	23 222 (91.6)		3 157 (92.3)	5 494 (93.6)		480 (95.2)	964 (94.7)		23 867 (97.9)	22 827 (90.4)	
Yes	265 (2.5)	2 126 (8.4)		264 (7.7)	374 (6.4)		24 (4.8)	54 (5.3)		518 (2.1)	2 427 (9.6)	
FLD			<0.05			<0.05			<0.05			<0.05
No	6 216 (58.5)	18 783 (74.1)		1 764 (51.6)	3 692 (62.9)		231 (45.8)	733 (72.0)		14 340 (58.8)	18 607 (73.7)	
Yes	4 412 (41.5)	6 565 (25.9)		1 657 (48.4)	2 176 (37.1)		273 (54.2)	285 (28.0)		10 045 (41.2)	6 647 (26.3)	
FPG			<0.05			<0.05			<0.05			<0.05
Normal	8 104 (76.3)	22 694 (89.5)		2 571 (75.2)	5 021 (85.6)		326 (64.7)	898 (88.2)		18 312 (75.1)	22 016 (87.2)	
Moderate	1 068 (10.0)	1 413 (5.6)		410 (12.0)	447 (7.6)		83 (16.5)	68 (6.7)		3 160 (13.0)	1 929 (7.6)	
High	1 456 (13.7)	1 241 (4.9)		440 (12.9)	400 (6.8)		95 (18.8)	52 (5.1)		2 913 (11.9)	1 309 (5.2)	
TC			<0.05			<0.05			<0.05			<0.05
Low	56 (0.5)	85 (0.3)		33 (1.0)	34 (0.6)		2 (0.4)	0 (0.0)		260 (1.1)	225 (0.9)	
Normal	6 278 (59.1)	16 804 (66.3)		2 139 (62.5)	3 953 (67.4)		189 (37.5)	500 (49.1)		18 103 (74.2)	19 673 (77.9)	
High	4 294 (40.4)	8 459 (33.4)		1 249 (36.5)	1 881 (32.1)		313 (62.1)	518 (50.9)		6 022 (24.7)	5 356 (21.2)	
HDL-C			<0.05			<0.05			–			<0.05
Low	608 (5.7)	990 (3.9)		200 (5.8)	301 (5.1)		504 (100.0)	1 018 (100.0)		958 (3.9)	782 (3.1)	
Normal	9 595 (90.3)	22 987 (90.7)		3 114 (91.0)	5 322 (90.7)		0 (0.0)	0 (0.0)		22 560 (92.5)	23 299 (92.3)	
High	425 (4.0)	1 371 (5.4)		107 (3.1)	245 (4.2)		0 (0.0)	0 (0.0)		867 (3.6)	1 173 (4.6)	
LDL-C			<0.05			<0.05			–			<0.05
Normal	5 834 (54.9)	15 458 (61.0)		1 800 (52.6)	3 451 (58.8)		504 (100.0)	1 018 (100.0)		4 162 (17.1)	5 257 (20.8)	
High	4 794 (45.1)	9 890 (39.0)		1 621 (47.4)	2 417 (41.2)		0 (0.0)	0 (0.0)		20 223 (82.9)	19 997 (79.2)	
UA			0.502			<0.05			0.267			<0.05
Normal	6 017 (56.6)	14 448 (57.0)		2 594 (75.8)	4 640 (79.1)		434 (86.1)	897 (88.1)		20 414 (83.7)	20 941 (82.9)	
High	4 611 (43.4)	10 900 (43.0)		827 (24.2)	1 228 (20.9)		70 (13.9)	121 (11.9)		3 971 (16.3)	4 313 (17.1)	
TB			0.277			–			0.389			–
Normal	9 576 (90.1)	22 933 (90.5)		3 421 (100,0)	5 868 (100.0)		451 (89.5)	925 (90.9)		24 385 (100.0)	25 254 (100.0)	
High	1 052 (9.9)	2 415 (9.5)		0 (0.0)	0 (0.0)		53 (10.5)	93 (9.1)		0 (0.0)	0 (0.0)	
AST			<0.05			0.058			<0.05			<0.05
Normal	9 811 (92.3)	23 562 (93.0)		3 302 (96.5)	5 705 (97.2)		491 (97.4)	1 006 (98.8)		22 835 (93.6)	23 793 (94.2)	
High	817 (7.7)	1 786 (7.0)		119 (3.5)	163 (2.8)		13 (2.6)	12 (1.2)		1 550 (6.4)	1 461 (5.8)	
GGT			<0.05			–			–			<0.05
Normal	8 274 (77.9)	20 892 (82.4)		3 421 (100.0)	5 868 (100.0)		504 (100.0)	1 018 (100.0)		19 375 (79.5)	20 929 (82.9)	
High	2 354 (22.1)	4 456 (17.6)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		5 010 (20.5)	4 325 (17.1)	

BMI: body mass index; GP: gallbladder polyps; FLD: fatty liver disease; FPG: fasting plasma glucose; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TB: total bilirubin; UA: uric acid; AST: aspartate aminotransferase; GGT: gamma glutamyl transpeptidase. The values are presented as the number of cases (%).

腹血糖、低密度脂蛋白胆固醇、γ-谷氨酰转肽酶和总胆固醇, 以及较低水平的高密度脂蛋白胆固醇的特征。此外, 由于样本量的差异, 性别、胆囊息肉、尿酸和天冬氨酸转氨酶的结果在不同医院之间也存在差异。

2.2　建立预测模型

我们将向前逐步回归分析中显著的因素纳入多因素logistic回归模型(表2)。基于多因素logistic回归分析结果, 我们构建了完整的GSD风险预测列线图(图2A)。此外, 我们保留了在完全模型列线图中得分较高的因素(表3), 同样地基于多因素logistic回归结果绘制了简化模型的列线图(图2B)。

2.3　模型的内部与外部验证

完全模型的ROC曲线验证结果见图3。内部验证中, AUC为74.1%(95%置信区间: 72.9% ~ 75.3%)。外部验证

表 2　训练集完全模型的多因素logistic 回归分析

Table 2　Multivariate logistic regression analyses of factors for GSD in the training set (the complete model)

Variable	β	SE	P	OR	95% CI	
					Lower	Upper
Constant	−3.176	0.251	<0.05			
Sex (Male)						
Female	0.540	0.035	<0.05	1.715	1.602	1.837
Age (≤30 yr.)						
31-40 yr.	0.859	0.059	<0.05	2.361	2.102	2.652
41-50 yr.	1.568	0.058	<0.05	4.797	4.278	5.379
51-60 yr.	2.006	0.060	<0.05	7.433	6.609	8.360
61-70 yr.	2.265	0.065	<0.05	9.630	8.480	10.936
>70 yr.	2.655	0.081	<0.05	14.224	12.125	16.687
BMI (<18.5 kg/m^2)						
18.5-23.99 kg/m^2	0.440	0.093	<0.05	1.552	1.293	1.864
24.0-27.99 kg/m^2	0.687	0.096	<0.05	1.988	1.646	2.402
≥28 kg/m^2	0.948	0.105	<0.05	2.579	2.099	3.170
GP (No)						
Yes	−1.338	0.077	<0.05	0.262	0.225	0.305
FLD (No)						
Yes	0.361	0.035	<0.05	1.434	1.338	1.537
FPG (Normal)						
Moderate	0.177	0.052	<0.05	1.193	1.078	1.321
High	0.439	0.051	<0.05	1.552	1.405	1.715
TC (Low)						
Normal	−0.433	0.221	<0.05	0.649	0.420	1.001
High	−0.458	0.225	<0.05	0.633	0.407	0.983
HDL-C (Low)						
Normal	−0.195	0.066	<0.05	0.823	0.723	0.936
High	−0.483	0.096	<0.05	0.617	0.511	0.744
LDL-C (Normal)						
High	−0.097	0.042	<0.05	0.908	0.835	0.986
UA (Normal)						
High	0.133	0.035	<0.05	1.143	1.067	1.223
TB (Normal)						
High	0.204	0.048	<0.05	1.227	1.116	1.347
AST (Normal)						
High	−0.128	0.056	<0.05	0.880	0.788	0.982
GGT (Normal)						
High	0.166	0.039	<0.05	1.181	1.094	1.275

β: partial regression coefficient; SE: standard error; OR: odds ratio; CI: confidence interval. The other abbreviations are explained in the note to Table 1.

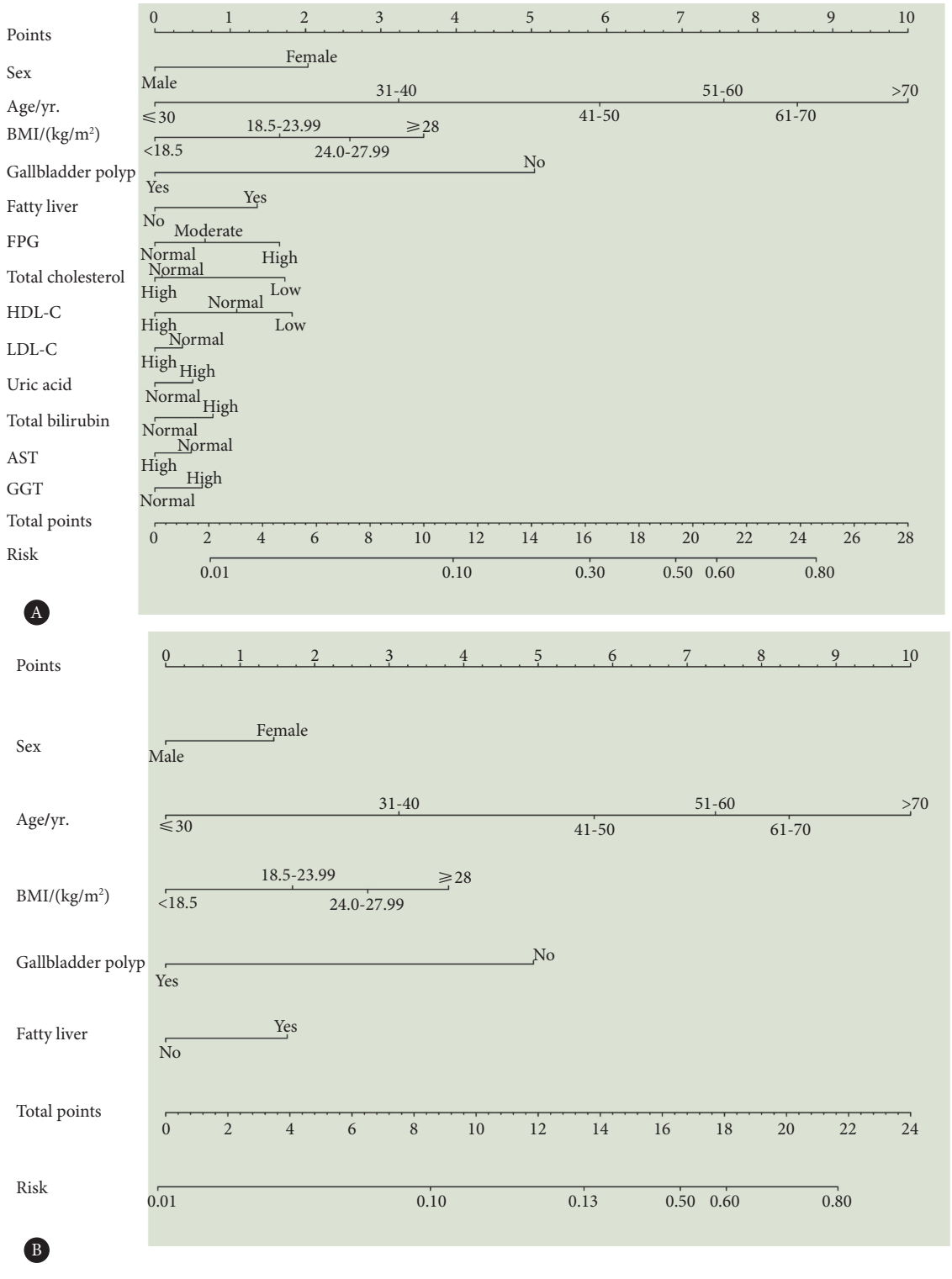

图 2 完全模型（A）与简化模型（B）的列线图

Fig 2 Nomogram of the complete model (A) and the simplified model (B)

The abbreviations are explained in the note to Table 1.

结果也显示了预测模型的良好区分度，山东中心的AUC为71.7%(95%置信区间: 70.6% ~ 72.8%)，天津中心的AUC为75.3%(95%置信区间: 72.7% ~ 77.9%)，开州中心的AUC为72.9%(95%置信区间: 72.5% ~ 73.3%)。简化模型的结果显示在图4中。

所有校准曲线显示了预测和观察概率之间良好的一致性。虽然完全模型和简化模型在内部验证中可能会高估GSD的风险(校准曲线部分在45°对角线以下)，但预测

表 3　训练集简化模型的多因素logistic回归分析

Table 3　Multivariate logistic regression analyses of factors for GSD in the training set (the simplified model)

Variable	β	SE	P	OR	95% CI	
					Lower	Upper
Constant	−3.574	0.111	<0.05			
Sex						
Female	0.396	0.030	<0.05	1.486	1.401	1.576
Age (≤30 yr.)						
31-40 yr.	0.854	0.059	<0.05	2.350	2.093	2.638
41-50 yr.	1.570	0.058	<0.05	4.807	4.292	5.384
51-60 yr.	2.014	0.058	<0.05	7.495	6.684	8.405
61-70 yr.	2.284	0.063	<0.05	9.819	8.676	11.112
>70 yr.	2.730	0.079	<0.05	15.326	13.117	17.907
BMI (<18.5 kg/m^2)						
18.5-23.99 kg/m^2	0.465	0.093	<0.05	1.591	1.327	1.909
24.0-27.99 kg/m^2	0.740	0.095	<0.05	2.097	1.739	2.528
≥28 kg/m^2	1.036	0.104	<0.05	2.819	2.300	3.455
GP (No)						
Yes	−1.348	0.077	<0.05	0.260	0.223	0.302
FLD (No)						
Yes	0.445	0.034	<0.05	1.561	1.461	1.667

The abbreviations are explained in the note to Table 1 and Table 2.

曲线(实线)大致与45°线相符, 预测较为准确。

2.4　完全模型与简化模型的比较

完全模型和简化模型在各中心的区分能力差异列于附表2中。结果显示, 在开州的验证数据集中, 完全模型的准确性高于简化模型。然而, 在山东和天津的外部验证集中并未观察到统计学上的显著差异。此外, DCA结果显示, 使用两个模型进行治疗决策的净收益均大于不治疗或全面治疗所带来的净收益(图中黑色横线代表Treat none, 即不治疗时所有研究对象的净收益均为0, 而斜率为负值的斜线表示Treat all, 即全面治疗时所有对象的净收益, 净收益指治疗决策所带来的预期收益和预期伤害之和), 且两个模型之间的临床实用性差异不大(图5)。最后, 我们基于本研究的结果建立了两个在线预测模型(完全模型: https://wenqianyu.shinyapps.io/Completemodel/, 简化模型: https://wenqianyu.shinyapps.io/Simplified/)用于GSD的风险预测。

3　讨论

本研究根据多中心的96 426名研究对象建立了GSD风险预测模型, 并对模型进行了内部和外部验证, 弥补了现有GSD风险预测模型研究纳入因素不全面、样本量小和缺少外部验证的短板。此外, 还根据列线图结果选择了赋分高且便于获取的变量用于建立简化模型。两种模型都能够明显区分具有和不具有GSD风险的研究对象, 并且校准图提示模型的准确性和可靠性较好, 决策曲线分析表明两种模型均具有较好的临床效用。最后, 我们基于列线图设计了在线风险预测软件, 便于临床应用。

尽管GSD在亚洲国家的发病率低于欧洲国家[11, 19], 我国的GSD患病率却逐渐增加, 已成为重大的公共卫生问题[19-20]。GSD的患病风险与遗传、环境和代谢因素有关[10-12]。本研究结果显示, 女性、肥胖和高龄仍是GSD的危险因素[8-9, 13, 21-22], 这可能与雌激素通过上调雌激素受体α和G蛋白偶联受体30来促进胆固醇合成有关[23]。此外, 由于老年人胆囊功能下降, GSD的风险通常随着年龄增长而增加[24]。也有一些研究显示, 胆结石的风险在40 ~ 50岁的人群中最高[25-26]。

既往研究确认了肥胖和高血糖水平是胆结石的危险因素[23, 27]。VICTOR等[28]发现GSD、胰岛素抵抗和肥胖之

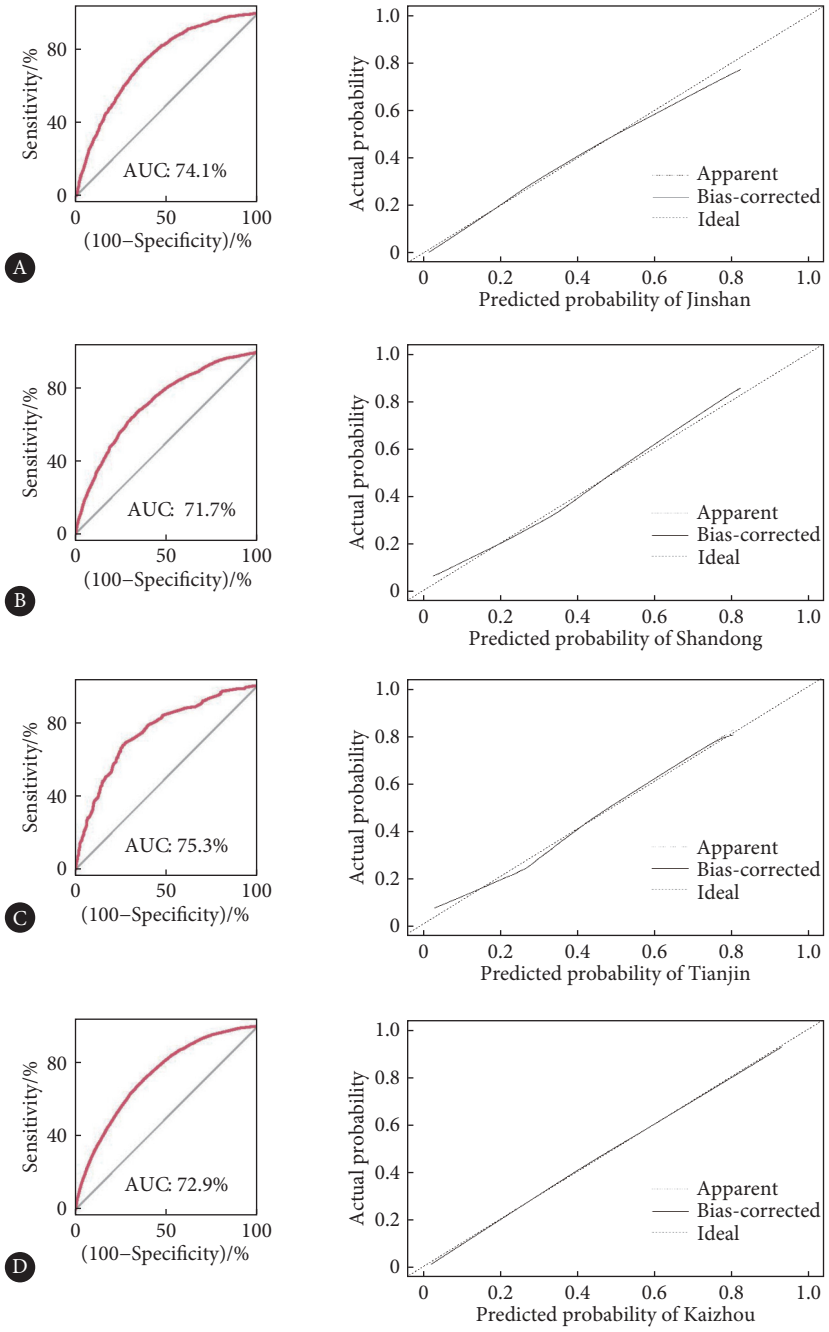

图 3 完全模型的内部与外部验证结果

Fig 3 Internal and external validation results for the complete model

A, Performance of the complete model in the internal validation data set. B, Performance of the complete model in the Shandong external validation data set. C, Performance of the complete model in the Tianjin external validation data set. D, Performance of the complete model in the Kaizhou external validation data set.

间存在双向的病理生理关系：肥胖是胰岛素抵抗和GSD的常见危险因素。脂肪肝(FLD)与GSD之间的关联也可能与胰岛素抵抗和肥胖等代谢因素有关[29]。此外，除了BMI，腹部脂肪积累也可能促进胆结石的发生[28]，脂肪肝的严重程度与胆结石也有关联[30]。

胆囊息肉是胆固醇增加导致巨噬细胞聚集形成的黏膜表面突起，也是一种常见的胆囊疾病。一项队列研究发现，胆囊息肉与胆结石的发生密切相关[26]。本研究发现，胆囊息肉是GSD的保护因素，这可能与胆囊切除术有关，有胆囊息肉的患者很可能已经接受了胆囊切除术，导致GSD发病率显著降低[31]。

本研究还纳入了血清指标，与先前研究一致的是[8-9]，高水平的总胆红素、GGT和尿酸增加了胆结石的风险，过多的胆红素促进了色素结石的形成。GGT作为敏感的胆汁淤积指标，以往也被纳入胆结石相关的预测模型[10, 32]，高尿酸可以通过增加血清胆固醇水平增加患GSD的风险[33]。

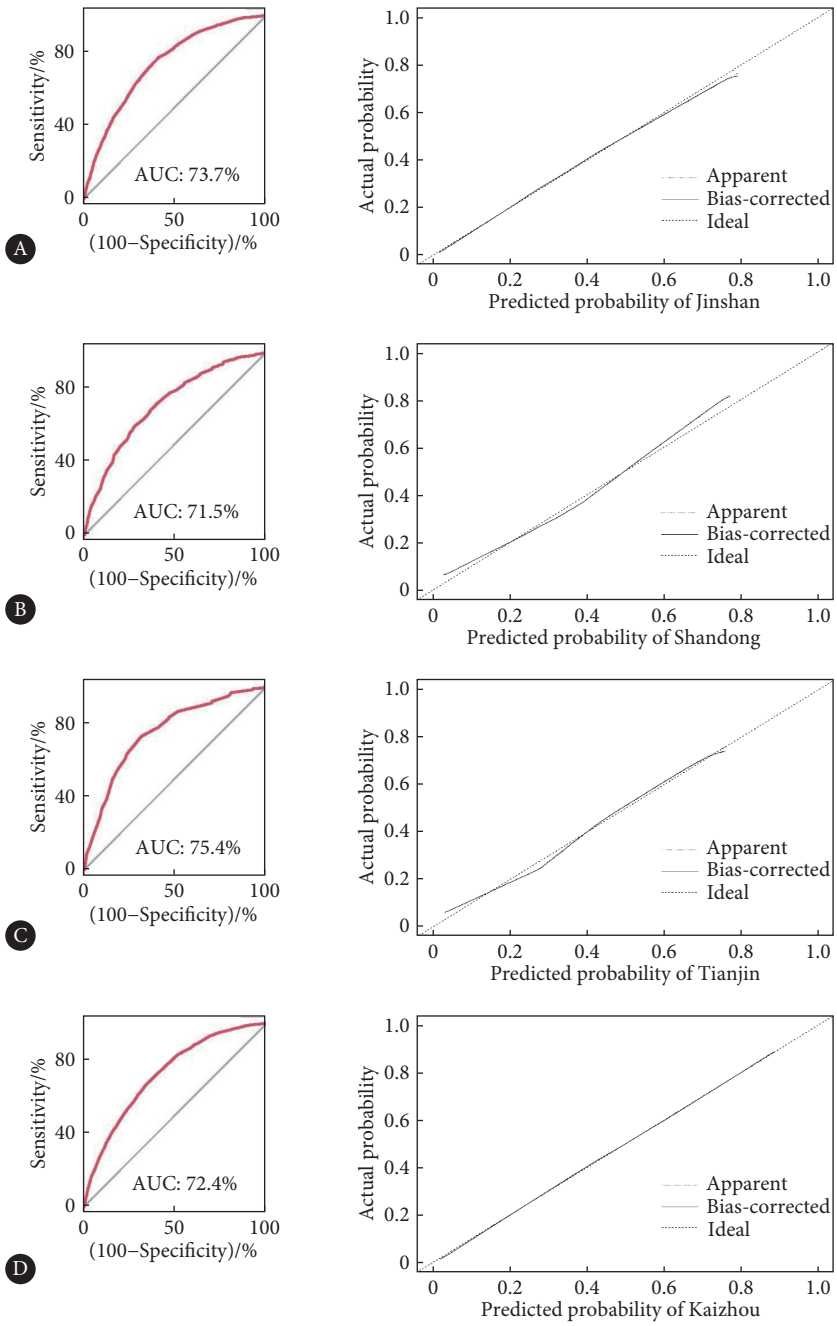

图 4 简化模型的内部与外部验证结果

Fig 4 Internal and external validation results for the simplified model

A, Performance of the simplified model in the internal validation data set. B, Performance of the simplified model in the Shandong external validation data set. C, Performance of the siplified model in the Tianjin external validation data set. D, Performance of the simplified model in the Kaizhou external validation data set.

胆固醇和GSD之间的关系多年来尚未明确。胆固醇水平的增加表现为脂质代谢紊乱，通常导致肝脏合成胆固醇的增加，进一步增加了胆固醇超饱和的风险[34]。然而，我们发现较低的总胆固醇水平增加了GSD的风险，既往的孟德尔随机化研究表示肝脏胆固醇的代偿性分泌和胆汁酸的减少可用来解释该结果[35-36]。此外，我们还发现HDL-C、LDL-C和AST是GSD的独立保护因素。SHANMUGAM等[37]认为HDL-C介导了胆道胆固醇超饱和度的降低。在许多研究的单因素分析中，胆结石患者的LDL-C和AST水平较高，然而，在它们进一步的多因素分析中，这些关联变得无意义[8-10]。因此，LDL-C和AST在胆结石形成中的作用需要进一步研究来探索。

与以往研究相比，本研究建立的胆结石风险预测模型具有一定优势。首先，本研究纳入的变量较既往模型更加全面。COHEN和KADAH等[8-9]利用年龄、GGT等非侵入性变量基于logistic回归建立了胆管结石风险预测模

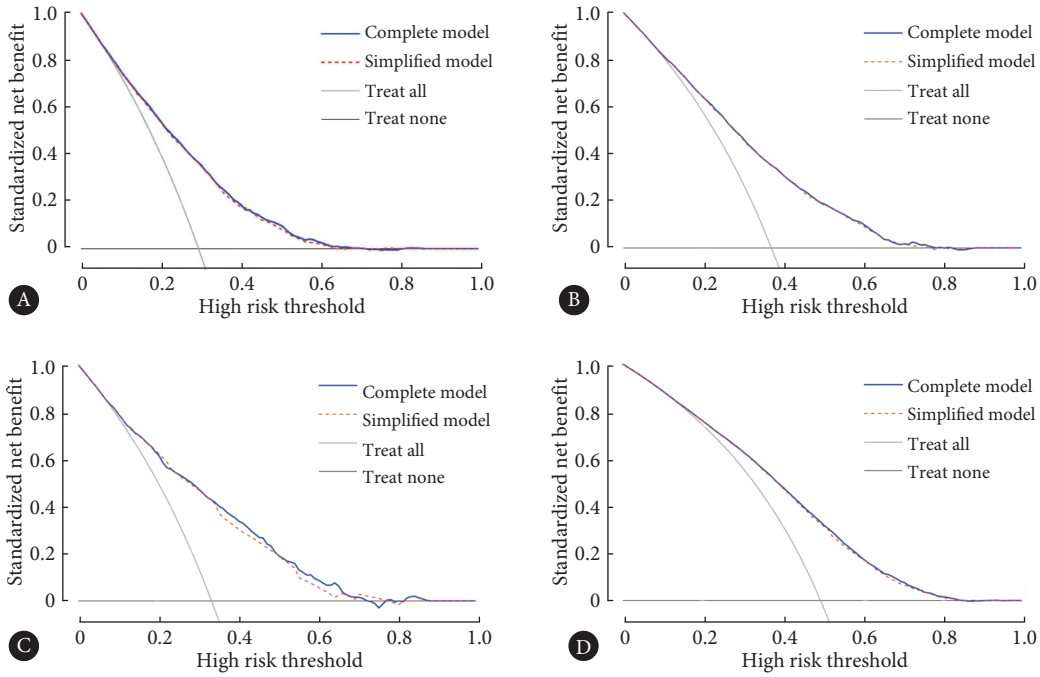

图 5 完全模型与简化模型的决策曲线分析（DCA）结果

Fig 5 DCA results of the complete model and the simplified model

A, DCA of the two models in the internal validation data set. B, DCA of the two models in the external validation data set of Shandong. C, DCA of the two models in the external validation data set of Tianjin. D, DCA of the two models in the external validation data set of Kaizhou.

型。而本研究纳入了研究对象的基本信息、生化指标、生活方式以及疾病信息等多个方面的变量，且最终验证结果表明，无论是完全模型还是简化模型，区分度相比于以往的模型均有所提升。其次，本研究的多中心外部验证表明模型的外推性良好，补足了SANTVOORT等[10]的研究中缺少外部验证的短板。此外，基于列线图结果简化的模型更利于在一般人群中推广使用。本研究通过DeLong检验比较完全模型和简化模型的AUC，发现完全模型的预测性能在一定程度上仍优于简化模型，但这种差异在大样本中并不一定具有统计学意义。与完全模型相比，简化模型的变量较少，预测效果和临床效用类似。因此，我们推荐在实践中使用简化模型以提高筛查高风险人群的效率。使用简化模型有助于增强普通人群的自我防控意识和GSD的早期干预。

然而，作为一项横断面研究，我们仍无法阐明风险因素与GSD之间的因果关系。因此，未来需要前瞻性研究来验证本结果并进一步建立更加完善的GSD风险预测模型。此外，尽管本研究模型的AUC值均达到了70%左右，但预测模型的区分度仍需要进一步提高。

本研究建立的预测模型显示，还需要进一步研究以探讨LDL-C和AST在胆石形成中的作用。包括性别、年龄、BMI、胆囊息肉和脂肪肝在内的GSD风险预测简化模型表现出良好的区分度和临床效果，因此，在一般人群中广泛应用该模型可能有助于快速筛查GSD高风险人群。

* * *

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Declaration of Conflicting Interests All authors declare no competing

interests.

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