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在线全文

血液标志物对双相情感障碍伴精神病性症状的风险预测价值*

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【摘要】 目的 探究双相情感障碍（bipolar disorder, BD）伴精神病性症状患者基于电子病历的生物标志物，开发具有可解释性的风险预测模型，为识别高危人群和及时临床干预提供决策支持。**方法** 使用医院电子病历系统收集四川大学华西医院收治的2 352名双相情感障碍患者，并在该人群基础上分为双相抑郁（bipolar disorder depression, BDD）和双相躁狂（bipolar disorder mania, BDM）两个亚组。使用逻辑回归（logistic regression, LR）算法训练和验证预测模型，并使用可解释方法分析每个特征对个体的贡献及特征对特定目标预测决策的影响。**结果** 各逻辑回归模型在BD、BDD、BDM三组中表现良好，曲线下面积（area under the curve, AUC）均大于81.6%。核心预测特征包括血小板分布宽度（platelet distribution width, PDW）、纤维蛋白原（fibrinogen, FIB）、大血小板比率（platelet large cell ratio, P-LCR）、活化部分凝血活酶时间（activated partial thromboplastin time, APTT）、凝血酶原时间（prothrombin time, PT）、甘油三酯（triglyceride, TG）。逻辑回归模型提供了良好的可解释性，并结合了列线图进行直观的风险量化和个体化预测。**结论** 通过逻辑回归模型能快速简便筛出伴有精神病性症状的BD患者，双相抑郁组和双相躁狂组血液标志物变化模式的差异丰富了对其潜在病理生理机制的理解，强调了考虑亚型对于干预管理患者的重要性。

【关键词】 双相情感障碍 机器学习 预测模型 生物标志物

Risk Prediction Performance of Blood Biomarkers for Bipolar Disorder With Psychotic Symptoms

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[Abstract] Objective To investigate biological markers associated with psychotic symptoms in patients with bipolar disorder (BD) based on electronic medical records of patients, and to develop an interpretable risk prediction model that supports the identification of high-risk individuals and that facilitates decision-making for providing clinical intervention in a timely manner. **Methods** A total of 2 352 patients diagnosed with BD and admitted to West China Hospital, Sichuan University were enrolled using the electronic medical records system of the hospital. The participants were divided into two subgroups, the bipolar disorder depression (BDD) group and the bipolar disorder mania (BDM) group. The logistic regression algorithm was used to train and validate the prediction model, and interpretability methods were used to analyze the contribution of each feature to individuals and the effect of the features on specific target prediction decisions. **Results** The logistic regression model demonstrated robust predictive performance across the BD, BDD, and BDM cohorts, with areas under the curve (AUC) of the receiver operating characteristic curves always exceeding 81.6%. The core predictive features included platelet distribution width (PDW), fibrinogen (FIB), platelet large cell ratio (P-LCR), activated partial thromboplastin time (APTT), prothrombin time (PT), and triglyceride (TG). The logistic regression model exhibited strong interpretability and was combined with nomograms for intuitive risk quantification and individualized prediction. **Conclusion** The logistic regression model enables rapid and simple screening of BD patients with psychotic symptoms. Distinct patterns of changes observed in blood biomarkers of BDD and BDM subgroups enrich the understanding of the underlying pathophysiological mechanisms and highlight the importance of considering subtypes in the intervention and management of patients.

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双相情感障碍(bipolar disorder, BD)作为重性精神疾病(serious mental illness, SMI),呈现抑郁-躁狂发作特征[1-2],伴76.8%高误诊率[3],是全球疾病负担的十大主要原因之一[4],也是致残或早死的重要风险因素[5-7]。BD精神病性症状很常见,如妄想和幻觉,尤其是在躁狂发作期间,且与高共病率、早发、不良预后显著相关,是BD不良结局和自杀倾向的主要危险因素。研究发现BD患者精神病性症状的点患病率为54%,躁狂发作期精神病性症状的合并点患病率为57%,抑郁发作期精神病性症状的合并点患病率为13%,精神病性症状在BD中可能比既往报道的更常见[8-9]。因此,早期识别双相情感障碍伴精神病性症状(BD with psychotic symptoms, BDPS)有助于临床医生采取干预措施,改善预后并降低不良结局发生的可能性。

KLOIBER等[10-11]的研究中提到,基于精神疾病连续谱理论,BDPS可能呈现精神分裂症及BD的中间表型特征,共享神经发育异常及跨诊断生物标志物。然而,BDPS的准确病因尚不清楚,发病机制涉及多系统交互作用[12]。HEURICH等[13-14]的研究中提到,免疫系统和止血/凝血途径在精神疾病特别是精神分裂症和BD中扮演重要角色。另有研究显示BD等精神疾病患者体内炎症标志物水平升高,提示存在神经炎症反应[15-18]。同时,精神疾病患者凝血功能障碍风险增加[19],止血/凝血途径中的关键成分血小板活化程度在不同精神疾病间存在差异[20]。由于BDPS是BD的一种特定表现,识别与BDPS相关的疾病特异性生物标志物对其预测和机制理解至关重要。目前基于血液标志物BDPS风险预测建模相关的研究较少。因此,本研究通过回顾性分析,探讨BDPS相关的血液标志物并建立预测模型,进一步分析亚组间标志物作用的异同,为其临床诊疗和潜在病理生理机制提供新见解。

1 资料与方法

1.1 研究对象

本研究分析了2011–2024年四川大学华西医院精神卫生中心收治的2 352例BD患者,其中伴有精神病性症状的患者共797例,不伴有精神病性症状的患者共1 555例。纳入患者出院主要诊断符合疾病和有关健康问题的国际统计分类第十次修订本(The International Statistical Classification of Diseases and Related Health Problems, 10th Revision, ICD-10)诊断标准F31.1、F31.2、F31.4、F31.5。排除患有其他神经精神疾病者。本研究由四川大学华西医院生物医学伦理分委会批准(2017年审185号),鉴于系回顾性提取数据,免除患者知情同意。

1.2 BDPS诊断标准及分组

BDPS的诊断标准为:出院时主要诊断符合ICD-10:“当前有精神病症状的躁狂发作型BD”(F31.2)或“当前有精神病症状的重度抑郁发作型BD”(F31.5)。

基于患者当前发作的类型,分为双相抑郁(bipolar disorder depression, BDD)组(F31.4、F31.5),共1 115例,其中双相抑郁伴精神病性症状的患者共296例;双相躁狂(bipolar disorder mania, BDM)组(F31.1、F31.2),共1 237例,其中双相躁狂伴精神病性症状的患者共501例。

1.3 数据收集

通过电子病历系统收集资料,包括社会人口学信息、入院时生命体征及实验室检查和住院基本情况。变量共78个,均为结构化数据,包括56个连续变量和22个离散变量。

1.4 统计学方法

连续变量以$\bar{x}\pm s$或中位数(四分位数)、离散变量以百分比进行统计描述。采用t检验和卡方检验进行组间比较,P<0.05为差异有统计学意义。

使用R 4.0.3和Python 3.8.8软件,样本按7∶3比例随机划分为训练集和测试集。训练集中进行变量筛选:采用卡方检验(离散变量)和t检验/Mann-Whitney U检验(连续变量)并结合单因素逻辑回归(P<0.05)进行初步单变量筛选;随后,采用逐步回归筛选显著性变量(P<0.05),最后,使用随机森林重要性排序筛选核心特征以构建逻辑回归(logistic regression, LR)模型,用于精神病性症状风险预测。用网格搜索法对模型进行超参数优化,通过遍历预定义超参数空间,在训练集上执行10折交叉验证评估每组参数性能(每折验证集独立计算模型准确率),最终以10轮交叉验证的平均准确率作为评价指标,选取平均准确率最高者为最优超参数组合。模型性能通过测试集的曲线下面积(area under the curve, AUC)评估预测能力,并采用Hosmer-Lemeshow检验评估校准度。

2 结果

2.1 基线资料

本研究中,BDPS组与BD不伴精神病性症状组年龄分布差异有统计学意义(P<0.001),BDPS组以<45岁为主(80.2% vs. 70.1%)。住院时间分布差异有统计学意义(P=0.002),BDPS组住院>1个月比例更高(13.2% vs. 8.5%)。BDPS组体温>37.3 ℃(1.8%)、心率>100 min^{-1}(19.7%)、脉搏>100 min^{-1}(19.9%)及舒张压>90 mmHg

(1 mmHg=0.133 kPa)(14.3%)比例升高(P<0.05); 炎症标志物如白细胞计数, 血小板参数如大血小板比率(platelet large cell ratio, P-LCR)及代谢指标如甘油三酯(triglyceride, TG)升高(P<0.05); 而两组间性别、红细胞计数、肌酐、血糖等的差异无统计学意义。基线资料见网络资源附件表S1。

2.2　模型构建

2.2.1　特征筛选

一共提取了78个特征, 所选取的特征缺失率均在25%以下。对BDPS组与BD不伴精神病性症状组共2 352例患者的单因素分析显示白细胞计数、单核细胞百分比、嗜酸性粒细胞百分比、纤维蛋白原(fibrinogen, FIB)、血小板分布宽度(platelet distribution width, PDW)、白细胞计数、中性粒细胞绝对值、凝血酶原时间(prothrombin time, PT)、活化部分凝血活酶时间(activated partial thromboplastin time, APTT)、淋巴细胞百分比、乳酸脱氢酶等为BDPS的独立危险因素〔比值比(odds ratio, OR)>1, P<0.05〕。单因素逻辑回归结果见网络资源附件表S2。

将单因素分析中差异有统计学意义的变量纳入逐步逻辑回归分析, 经20次迭代筛选出30个变量, 方差膨胀因子均小于10, 排除多重共线性。为了提高血液标志物诊断BDPS的准确性, 使用随机森林重要性排序筛选出核心标志物作为最终的特征子集, 分别是: PDW、FIB、P-LCR、APTT、PT、TG。利用该子集在BD亚组(BDD、BDM)及总BD队列中构建并验证预测模型效能。

2.2.2　模型性能

在逻辑回归模型中, 结果显示(图1, 表1): BD组含训练集1 646例, 测试集706例。AUC为0.816, 准确率为81.3%; PDW、FIB、P-LCR、APTT、PT、TG均具有统计学意义, PT是保护因素, 其他均为风险因素。BDD组中含训练集780例, 测试集335例。AUC为0.930, 准确率为89.8%, PDW和APTT是风险因素, FIB是保护因素。BDM组中含训练集865例, 测试集372例。AUC为0.898, 准确率为86.5%, FIB、P-LCR和TG是风险因素, PT是保护因素。FIB在所有模型中均有显著影响, FIB每增加一个单位, 总BD组患者发生精神病性症状的风险增加132%, BDD组患者发生精神病性症状的风险降低51%, BDM组患者发生精神病性症状的风险增加374%(所有P<0.001)。PDW每增加一个单位, BDD组患者发生精神病性症状的风险增加36%(OR=1.360, P<0.001)。TG每增加一个单位, BDM组患者发生精神病性症状的风险增加

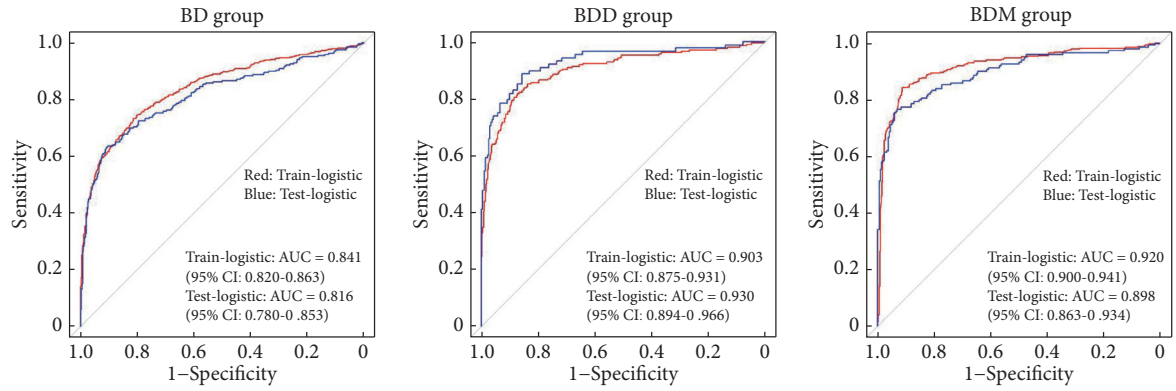

图 1　模型的ROC曲线

Fig 1　ROC curves of the model

ROC: receiver operating characteristic; BD: bipolar disorder; BDD: bipolar disorder depression; BDM: bipolar disorder mania; AUC: area under the curve.

表 1　基于最终变量的多因素逻辑回归结果

Table 1　Multivariate logical regression results based on final variables

Characteristic	BD			BDD			BDM		
	β	OR (95% CI)	P	β	OR (95% CI)	P	β	OR (95% CI)	P
(Intercept)	−6.167	0.002 (0.001-0.008)	0.000	−8.583	0.000 (0.000-0.004)	0.000	−0.186	0.831 (0.077-8.961)	0.878
Activated partial thromboplastin time	0.068	1.071 (1.052-1.09)	0.000	0.084	1.087 (1.056-1.121)	0.000	0.016	1.016 (0.983-1.051)	0.337
Prothrombin time	−0.269	0.764 (0.704-0.828)	0.000	0.094	1.098 (0.907-1.337)	0.342	−0.710	0.492 (0.422-0.568)	0.000
Fibrin	0.839	2.315 (2.038-2.643)	0.000	−0.703	0.495 (0.357-0.677)	0.000	1.557	4.744 (3.858-5.935)	0.000
Triglyceride	0.157	1.17 (1.077-1.276)	0.000	−0.081	0.922 (0.717-1.123)	0.463	0.438	1.550 (1.355-1.782)	0.000
Platelet distribution width	0.171	1.186 (1.128-1.25)	0.000	0.307	1.360 (1.261-1.472)	0.000	−0.027	0.974 (0.868-1.091)	0.642
Large platelet ratio	0.026	1.027 (1.01-1.044)	0.002	0.011	1.011 (0.987-1.035)	0.378	0.043	1.044 (1.008-1.082)	0.015

β: partial regression coefficient; OR: odds ratio; the other abbreviations are explained in the note to Fig 1.

55%(OR=1.550, P<0.001)。在模型效果方面,亚组的表现更佳,模型在测试集上的表现见表2。使用这一组血液标志物能够较好区分精神病性症状,有助于BDPS患者的临床决策和早期干预。

2.3 模型可视化

为使模型更直观和具有可解释性,使用列线图进行可视化分析(图2)。上述6个特征在3个逻辑回归模型中

表 2 LR模型表现及评估

Table 2 Performance and evaluation of LR model

Group	Accuracy	Precision	Recall	F1	AUC
BD	0.813	0.772	0.636	0.697	0.816
BDD	0.898	0.886	0.705	0.785	0.930
BDM	0.865	0.885	0.767	0.821	0.898

AUC: area under the curve; the other abbreviations are explained in the note to Fig 1.

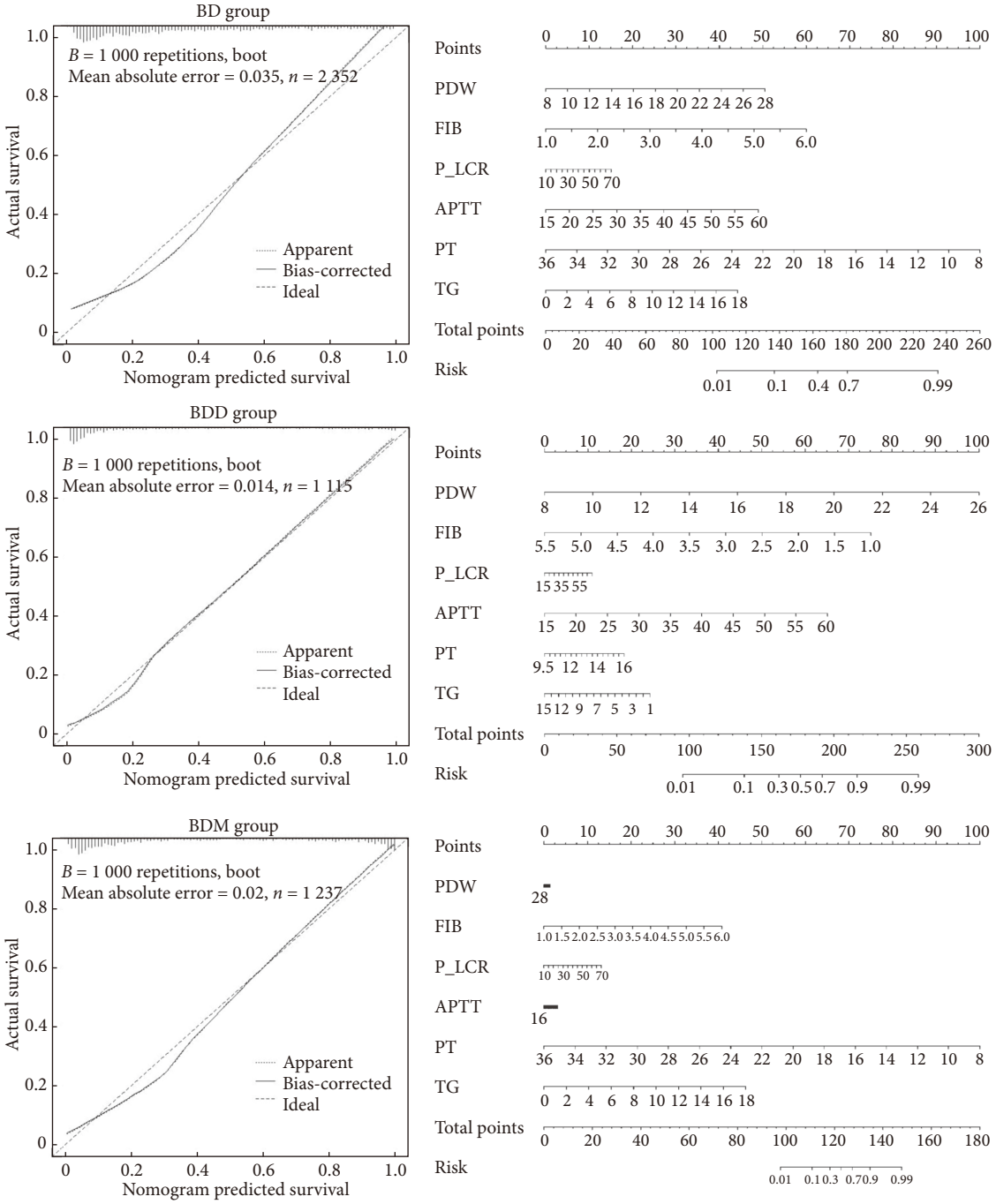

图 2 LR模型的校准曲线和列线图

Fig 2 Calibration curve and nomogram of the LR model

PDW: platelet distribution width; FIB: fibrinogen; P-LCR: platelet large cell ratio; APTT: activated partial thromboplastin time; PT: prothrombin time; TG: triglyceride; the other abbreviations are explained in the note to Fig 1.

贡献性不同。特征贡献性大小在总BD组中依次为PT、FIB、PDW、APTT、TG、P-LCR, BDD组中依次为PDW、FIB、APTT, BDM组中依次为PT、TG、FIB、P-LCR。亚组中, PT的降低、FIB的升高、TG的升高、P-LCR的升高与BDM组中更高的精神病性症状风险相关联; APTT的升高、PDW的升高、FIB的降低与BDD组中更高的精神病性症状相关联。校准曲线显示模型预测概率接近真实概率。

3　讨论

本研究基于电子病历中的血液指标构建了可解释的BDPS风险预测模型, 以实现BDPS患者的早期识别。通过FIB、APTT、PDW、PT、P-LCR、TG六项标志物, 模拟临床决策路径, 优化早期干预。相较于既往基于神经影像或症状量表的模型[21-25], 本研究首次系统性验证血液标志物在BDPS预测中的价值, 揭示其与免疫炎症/止血途径的病理关联及BD不同亚型(BDM与BDD)精神病性症状的异质性病理机制。此外, 逻辑回归模型结合列线图因其直观性及可解释性优势而适用于临床辅助决策。模型在不平衡数据(如总BD组测试集中阳性样本231例, 阴性样本475例)中表现稳健, 无需依赖重采样, 进一步支持其临床实用性。

凝血指标中, BDM组PT缩短提示高凝状态与精神病性症状风险正相关(P<0.05), 符合精神疾病患者静脉血栓及心血管事件风险升高的循证依据[26-28]; BDD组精神病性症状风险升高伴随APTT的延长, 其机制可能涉及选择性5-羟色胺再摄取抑制剂(SSRI)药物不良反应[29]。对于精神病性症状高风险患者, FIB也呈现亚型特异性双向表达, BDM组呈促炎-症状高风险正相关, BDD组则表现出血风险-症状高风险正相关。值得注意的是, FIB在所有模型中均显示为精神病性症状的显著预测因子, 而在亚组分析提示其作用方向存在异质性, 这种反向效应导致总BD组的"显著影响"实质是双向作用在聚合分析中产生的净效应, 因此未来研究区分疾病时相构建预测模型意义重大。PDW在BDD组、P-LCR在BDM组中分别与症状风险显著正相关, 印证精神疾病患者血小板活化增强及低度炎症特征[30]。脂质代谢方面, TG在BDM组呈现血栓形成与症状高风险的正向关联, 提示脂质代谢通路在亚型间存在差异调控[31-32]。上述发现表明, 精神病性症状发生涉及凝血-免疫-代谢交互作用网络, 且BD亚型间存在显著病理生理异质性。

研究揭示了凝血-免疫-代谢轴在BDPS中的差异化调控机制。①亚组表型异质性: BDM组呈促凝-促炎症表型, BDD组为出血/低凝风险表型, 提示亚型特异性病理通路激活。②方法学突破: 通过亚组解析了总BD组中PT与APTT的矛盾关联, 表明传统未分类表型可能掩盖生物学异质性。③机制假说: BDD组的异常出血风险可能涉及双重机制——SSRI类药物通过5-HT转运体抑制引发获得性血小板功能障碍[29, 33], 或独立于药物的固有纤溶亢进表型。④过往争议讨论: 针对既往PDW研究结论冲突[20, 34], 本研究发现PDW与BDD组精神病症状显著相关, 提示表型解构可提升生物标志物特异性。

本研究存在以下方法学局限: ①未纳入药物暴露数据, 无法排除药效动力学混杂因素的影响, 限制生物学解释的准确性; ②病例纳入受限于ICD-10分类框架, 未覆盖混合发作亚型, 导致表型异质性分析不完整, 需通过研究领域标准(Research Domain Criteria, RDoC)框架扩展多维表型采集。目前定义BD的同质亚组也是个性化精神病学的研究热点[35], 建议未来采用多组学方法深入解析亚型特异性生物标志物网络, 为精准分型诊疗提供依据, 并通过前瞻性队列验证亚型特异性干预靶点。

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作者贡献声明　倪子钧负责正式分析、调查研究、验证、可视化、初稿写作和审读与编辑写作, 尹俊平和王小英负责论文构思、研究方法、研究项目管理和监督指导, 周宇亭负责论文构思、数据审编、研究方法和监督指导, 莫贤负责论文构思、监督指导和审读与编辑写作, 孙璐负责数据审编、正式分析、软件、验证和可视化, 张伟负责论文构思、经费获取、研究项目管理、提供资源和监督指导。所有作者已经同意将文章提交给本刊, 且对将要发表的版本进行最终定稿, 并同意对工作的所有方面负责。

Author Contribution　NI Zijun is responsible for formal analysis, investigation, validation, visualization, writing--original draft, and writing--review and editing. YIN Junping and WANG Xiaoying are responsible for conceptualization, methodology, project administration, and supervision. ZHOU Yuting is responsible for conceptualization, data curation, methodology, and supervision. MO Xian is responsible for conceptualization, supervision, and writing--review and editing. SUN Lu is responsible for data curation, formal analysis, software, validation, and visualization. ZHANG Wei is responsible for conceptualization, funding acquisition, project administration, resources, and supervision. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

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