·论著·

血清补体系统激活因子、游离雌三醇及同型半胱氨酸水平对子痫前期的预测价值

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摘要 **目的** 探讨孕早期血清补体系统激活因子、游离雌三醇（uE_3）及同型半胱氨酸（Hcy）水平对子痫前期（PE）的预测价值。**方法** 选取2023年11月至2024年11月间于山东第二医科大学附属医院产前检查并分娩的646例孕妇，于孕11~13^{+6}周常规产前检查时检测血清Hcy、uE_3水平，同时检测补体系统激活因子［补体成分3（C3）和B因子］。根据孕20周后PE发生情况，将研究对象分为PE组（$n = 56$）和对照组（$n = 590$）。比较2组孕妇的一般临床资料、Hcy、uE_3及补体系统激活因子水平，并分析PE的独立危险因素。分析各项指标及联合指标对PE的预测价值，构建列线图预测模型，并进行预测和内部验证。**结果** 2组孕妇年龄、胎龄、生育史及PE史比较无统计学差异（$P > 0.05$）。与对照组相比，PE组收缩压、舒张压、血清Hcy、C3和B因子水平升高，妊娠周期及新生儿体重、uE_3水平降低（均$P < 0.05$）。多因素logistic回归显示，uE_3是PE的独立保护因素（$OR = 0.80$，95%CI：0.71~0.88），Hcy（$OR = 3.531$，95%CI：2.35~5.31）、C3（$OR = 1.04$，95%CI：1.02~1.06）和B因子（$OR = 1.03$，95%CI：1.02~1.05）均为PE的独立危险因素。受试者操作特征曲线分析显示，血清uE_3、Hcy、C3和B因子截断值分别为1.68 ng/mL、7.44 μmol/L、136.25 mg/dL和326.90 mg/L时，预测PE的灵敏度分别为0.66、0.82、0.72和0.85，特异度分别为0.91、0.86、0.75和0.63；上述指标联合预测效能更佳，曲线下面积为0.97，灵敏度为0.90，特异度为0.91。列线图预测模型实际校准曲线与理论参考线及完美拟合线吻合度良好，其一致性统计量达0.97（95%CI：0.65~0.98）。**结论** 孕早期血清Hcy、uE_3以及补体系统激活因子联合检测对PE具有较好的预测价值，构建的PE风险列线图可为临床早期筛查或预测PE提供参考。

关键词 子痫前期；游离雌三醇；同型半胱氨酸；补体系统激活因子；预测价值
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Predictive value of serum complement system activator, unconjugated estriol, and homocysteine levels for preeclampsia

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Abstract **Objective** To explore the predictive value of serum unconjugated estriol (uE_3), homocysteine (Hcy) and complement system activator levels for preeclampsia (PE) during early pregnancy. **Methods** This study included 646 pregnant women who received prenatal care at the Affiliated Hospital of Shandong Second Medical University between November 2023 and November 2024. Serum Hcy and uE_3 levels were measured during routine prenatal examination at 11 to 13^{+6} weeks of gestation, and the complement system activators C3 and factor B were detected. Depending on whether PE occurred after 20 weeks of gestation, women were divided into the PE group ($n = 56$) and control group ($n = 590$). The general clinical data, Hcy, uE_3, and complement system activating factor levels of the two groups were compared, and the independent risk factors for PE were analyzed. Receiver operating characteristic (ROC) curves were used to analyze the predictive value of each index and the combined index for PE. PE risk nomogram prediction model and calibration curves were used for prediction and internal verification, respectively. **Results** There were no significant differences in maternal age, gestational age at detection, reproductive history, or history of PE between the PE and control groups ($P > 0.05$). The systolic and diastolic blood pressure

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measurements in the PE group were significantly elevated compared with that in the control group. Additionally, the gestational age at the time of delivery and neonatal birth weight were notably lower in the PE group than in the control group. Furthermore, serum levels of Hcy, complement component C3, and factor B were significantly higher in the PE group than in the control group. In contrast, the concentration of uE_3 was significantly lower in the PE group. This suggested that uE_3 was an independent protective factor against this condition (*OR* = 0.80, 95%*CI*: 0.71–0.88). In contrast, elevated levels of Hcy, C3, and factor B were identified as independent risk factors for the development of PE (*OR* = 3.53, 95%*CI*: 2.35–5.31; *OR* = 1.04, 95%*CI*: 1.02–1.06; *OR* = 1.03, 95%*CI*: 1.02–1.05, respectively). ROC curve analysis showed that the cutoff values of serum uE_3, Hcy, C3, and factor B were 1.68 ng/L, 7.44 μmol/L, 136.25 pg/dL, and 326.9 mg/L, respectively, and the sensitivity thresholds for predicting PE was 0.66, 0.82, 0.72, and 0.85, respectively, and specificity thresholds were 0.91, 0.86, 0.75, and 0.63. The combined prediction performance of the above indicators was better, the area under the curve was 0.97, sensitivity was 0.90, and specificity was 0.91. Internal validation showed that the calibration curve of the nomogram prediction model was close to the original curve and the ideal curve, and the consistency index was 0.97 (95%*CI*: 0.65–0.98), indicating that the model had a high degree of fit. **Conclusion** A PE risk nomogram based on serum Hcy, uE_3, and complement system activating factors in early pregnancy has a good predictive value, and can be used as a reference for early clinical screening or prediction of PE.

Keywords preeclampsia; unconjugated estriol; homocysteine; complement system activator; predictive value

子痫前期（preeclampsia，PE）以妊娠期血压异常增高、尿蛋白阳性及组织水肿为主要临床特征，严重时可威胁母体与胎儿生命[1-2]。PE的发病机制尚未阐明，普遍认为涉及多种因素及多重机制[3-4]。同型半胱氨酸（homocysteine，Hcy）是甲硫氨酸循环的代谢产物，其产生的活性氧物质可损伤血管内皮细胞，导致PE等妊娠并发症[5-6]。补体系统的激活可介导血管生成因子异常表达，在PE的发病机制中也起重要作用。妊娠中，胎盘合成分泌游离雌三醇（unconjugated estriol，uE_3）[7]。PE可引起胎盘功能异常，uE_3合成减少[8]。PE的早期预测可改善母胎的生产结局[9]，因此，本研究拟探讨孕早期母体血清uE_3、Hcy及补体系统激活因子水平检测对PE的预测效能，旨在为临床开展PE早期筛查提供科学依据。

1　材料与方法

1.1　一般资料

选取2023年11月至2024年11月间在山东第二医科大学附属医院进行产前检查的孕妇作为研究对象。纳入标准：年龄20~40岁；无与PE相关的症状；孕11~13^{+6}周；临床资料完整；意识正常，无精神类疾病；对本研究知情同意。排除标准：严重的胎儿异常、终止妊娠；生殖器或胎儿畸形；妊娠前患有高血压等心脑血管疾病及糖尿病等；恶性肿瘤；合并内分泌系统疾病、自身免疫性疾病、妇科疾病。

本研究最终共纳入646例孕妇，根据孕20周后是否发生PE，将其分为PE组（n = 56）和对照组（n = 590）。PE诊断标准参照《妊娠期高血压疾病诊治指南（2020）》[10]。本研究已获得山东第二医科大学附属医院医学伦理委员会批准（wyfy-2024-ky-221，KY-2024-M04）。所有患者及家属签署知情同意书。

1.2　方法

1.2.1　资料收集：一般资料包括年龄、孕前体重指数（body mass index，BMI）、胎龄、辅助生殖技术（assisted reproductive technology，ART）使用情况、既往生育史、PE史、妊娠期高血压和糖尿病史，以及分娩时孕周、新生儿出生体重、PE诊断时的收缩压（systolic blood pressure，SBP）和舒张压（diastolic blood pressure，DBP）。实验室检查包括Hcy、uE_3、补体成分3（complement 3，C3）和B因子水平。

1.2.2　血清Hcy、uE_3及补体系统激活因子水平检测：采集所有研究对象2 mL空腹静脉血，分离血清，取上清液冻存于–20 ℃，待检测。通过酶循环法（全自动生化分析仪AU5800，美国Beckman公司）检测Hcy，正常值范围为0~15 μmol/L。通过化学发光法（全自动化学发光免疫分析仪cobas e 601，瑞士Roche公司）检测uE_3，正常值范围为0.5~2.5 ng/mL。通过免疫透射比浊法（全自动生化分析仪AU5800，美国Beckman公司）检测C3和B因子水平，正常值范围为90~180 mg/dL和200~500 mg/L。

1.3　统计学分析

采用SPSS 29.0软件进行统计分析。计量资料以$\bar{x} \pm s$表示，组间比较采用t检验。计数资料以率（%）表示，组间比较采用χ^2检验。采用二元logistic回归

进行多因素分析，绘制受试者操作特征（receiver operating characteristic，ROC）曲线，计算曲线下面积（area under the curve，AUC），评估血清uE_3、Hcy、C3和B因子水平诊断PE的效能。基于R语言构建列线图预测模型，采用校准曲线方法实施内部验证。$P<0.05$为差异有统计学意义。

2　结果

2.1　2组一般资料比较

PE组与对照组孕妇年龄、BMI、胎龄、ART、生育史、妊娠期高血压病史、PE史、糖尿病患病率比较，差异均无统计学意义（$P>0.05$）。PE组孕妇确诊时SBP与DBP均显著高于对照组，分娩孕周及新生儿出生体重均低于对照组（$P<0.05$）。见表1。

2.2　2组血清Hcy、uE_3、C3及B因子水平比较

与对照组比较，PE组血清Hcy、C3及B因子水平均升高，血清uE_3水平降低（均$P<0.001$）。见表2。

2.3　多因素logistic回归分析

表1　PE组与对照组一般资料比较

Tab.1　Comparison of general data of PE and control groups

Item	Control group (n = 590)	PE group (n = 56)	t/χ^2	P
Age (year)	29.83 ± 4.10	29.41 ± 3.21	0.46	0.74
BMI (kg/m²)	22.84 ± 4.24	22.63 ± 3.19	0.37	0.71
Gestational age (week)	12.03 ± 1.01	11.84 ± 1.04	1.34	0.18
ART [n (%)]	45 (8)	6 (11)	0.67	0.41
Reproductive history [n (%)]	278 (47)	32 (57)	2.06	0.15
History of gestational hypertension [n (%)]	33 (6)	6 (11)	2.37	0.12
Diabetes [n (%)]	32 (5)	4 (7)	0.29	0.59
History of PE [n (%)]	15 (3)	2 (4)	0.21	0.65
Gestational age at delivery (week)	39.94 ± 1.11	36.56 ± 2.45	4.905	<0.001
Neonatal birth weight (kg)	3.33 ± 0.44	3.10 ± 0.76	2.026	0.04
SBP (mmHg)	120.37 ± 10.44	150.04 ± 12.99	−19.846	<0.001
DBP (mmHg)	80.62 ± 6.64	99.39 ± 8.27	−19.759	<0.001

ART, assisted reproductive technology; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure.

表2　PE组与对照组血清Hcy、uE_3、C3及B因子水平比较

Tab.2　Comparison of serum Hcy，uE_3，C3，and factor B levels between PE and control groups

Group	n	uE_3 (ng/mL)	Hcy (μmol/L)	C3 (mg/dL)	Factor B (mg/L)
Control	590	1.85 ± 0.44	6.12 ± 1.35	123.11 ± 22.56	293.85 ± 34.17
PE	56	1.19 ± 0.39	8.43 ± 1.39	145.86 ± 25.40	333.28 ± 36.22
t/χ^2	–	10.71	−12.201	−7.129	−8.208
P	–	<0.001	<0.001	<0.001	<0.001

以是否发生PE（发生PE=1，未发生PE=0）作为因变量，以血清Hcy、uE_3、C3及B因子实测值作为自变量，将其纳入logistic 回归模型。回归方程为$Logit(P)=\ln(P/1-P)=-19.58--0.23\times uE_3+1.26\times Hcy+0.04\times C3+0.03\times B$。结果显示，Hcy、C3和B因子水平均为PE的独立危险因素，uE_3为保护因素。见表3。

2.4　ROC曲线分析

血清uE_3、Hcy、C3和B因子水平截断值分别为1.68 ng/mL、7.44 μmol/L、136.25 mg/dL和326.90 mg/L时，预测PE的灵敏度分别为0.66、0.82、0.72和0.85，特异度分别为0.91、0.86、0.75和0.63，AUC分别为0.87、0.89、0.76、0.79；联合预测AUC为0.97，特异度为0.91，灵敏度为0.90。见图1。

2.5　PE风险列线图预测模型

以uE_3、Hcy、C3及B因子水平作为核心变量，构建PE风险列线图预测模型，见图2A。经内部效度检验，该列线图预测模型的实际校准曲线与理论参考线及完美拟合线均呈现出良好的吻合度，其一致性

表3　多因素logistic回归分析

Tab.3　Multivariate logistic regression analysis results

Variate	β	*SE*	Wald χ^2	*OR*	95%*CI*	*P*
uE_3	−0.23	0.05	21.11	0.80	0.71–0.88	<0.001
Hcy	1.26	0.21	36.84	3.53	2.35–5.31	<0.001
C3	0.04	0.01	12.36	1.04	1.02–1.06	<0.001
Factor B	0.03	0.01	18.409	1.03	1.02–1.05	<0.001

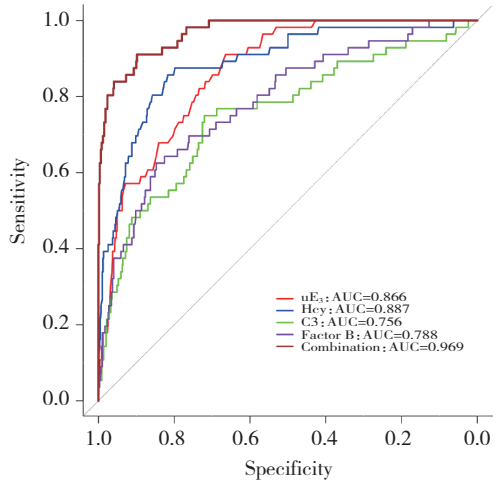


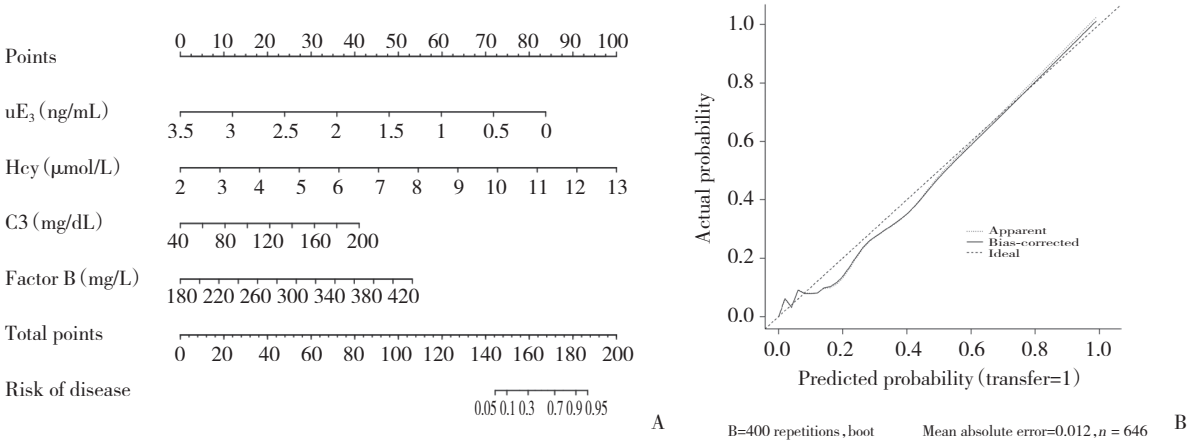
图1　各指标单独及联合预测PE的ROC曲线

Fig.1　ROC curves of each index alone and in combination to predict PE

统计量达0.97(95%*CI*:0.65~0.98),见图2B。

3　讨论

Hcy是心血管疾病的重要独立危险因素。近年来已有研究[11]表明,Hcy在诱发心血管疾病的同时,也是PE的重要相关因素。研究[12]证实,高Hcy血症通过氧化损伤机制与PE的发生密切相关,而通过补充维生素B12和叶酸降低Hcy水平,可有效降低PE的发病风险。本研究结果表明,在妊娠早期阶段孕妇体内的Hcy水平即可出现显著改变。与对照组相比,PE组孕妇的血清Hcy水平明显升高。本研究结果与既往相关文献[13]报道一致,表明Hcy水平与PE发病机制之间具有相关性。



A, the logistic regression prediction model for PE; B, the calibration curve of the logistic regression model for predicting PE.

图2　PE风险列线图预测模型及模型校准曲线

Fig.2　Nomogram prediction model and model calibration curve of PE risk

补体系统的适度激活在维持正常妊娠过程中发挥着重要作用,但过度激活则可能导致靶器官损伤[8]。本研究结果表明,PE组孕妇血清中C3和B因子水平显著高于对照组,且C3和B因子AUC分别为0.76、0.79。提示C3和B因子可能作为预测PE的重要生物标志物。分析其潜在机制可能如下:C3裂解为C3a后,通过激活血管紧张素Ⅱ型受体,刺激可溶性fms样酪氨酸激酶1的释放增加,进而损害血管内皮功能,最终诱发PE[14]。

研究[15]表明,uE_3水平持续下降可提示胎儿发育异常、宫内死亡、先兆子痫等严重并发症的发生。本研究表明,相较于对照组,PE组患者在孕早期即

表现出血清uE_3水平降低的特征，且其预测子痫前期的AUC达0.87，显示出良好的预测效能，提示血清uE_3水平可能成为预测PE的重要生物标志物之一。

当AUC值≤0.5时，诊断价值缺失；>0.5~0.7时，诊断准确性相对有限；>0.7~0.9时，诊断准确性处于中等水平；而>0.9则表明具有较高的诊断准确性[16]。本研究发现，整合血清Hcy、uE_3、C3及B因子4项指标的AUC值显著提升至0.97，同时灵敏度达到90%，较单一指标的诊断效能具有明显优势。此外，本研究构建的PE风险列线图预测模型通过整合Hcy、uE_3、C3及B因子4项指标，显著提高了预测PE的准确性和临床可操作性。同时，该模型的校正曲线与原始曲线及理想曲线高度接近，表明模型具有良好的拟合度和稳定性，该模型有助于改善孕产妇的临床管理和早期干预策略。

综上所述，联合检测孕早期血清uE_3、Hcy、C3和B因子水平，可有效提升预测PE的准确度，并有助于临床早期筛查PE。

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