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维持性腹膜透析患者并发肺动脉高压危险因素分析及其列线图预测模型的建立与验证

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摘要 目的 探索维持性腹膜透析患者(MPD)并发肺动脉高压(PAH)的危险因素,并构建与验证列线图风险预测模型。**方法** 选取医院肾脏内科 MPD 患者 168 例,人体成分分析仪测量其体液成分,超声心动图检测肺动脉收缩压(PASP)。将所有患者以 1∶1 比例随机分为训练集和验证集,在训练集以 Logistic 多因素回归分析中 $P<0.05$ 的因素纳入并构建列线图模型,验证集验证模型的预测效能。采用 ROC 曲线、校准曲线和决策曲线评价模型的预测准确性和一致性。**结果** 透析龄(*OR*:1.038,95% *CI*:1.008 ~ 1.069,$P=0.012$)、血红蛋白水平(*OR*:0.961,95% *CI*:0.929 ~ 0.994,$P=0.021$)、细胞外液量/细胞内液量(E/I)(*OR*:1.069,95% *CI*:1.024 ~ 1.115,$P=0.002$)是发生 PAH 的独立危险因素。基于上述独立危险因素构建列线图模型,ROC 分析显示训练集和验证集曲线下面积分别为 0.867(95% *CI*: 0.782 ~ 0.953)和 0.808(95% *CI*: 0.714 ~ 0.902),校准曲线见训练集和验证集预测曲线与理想曲线基本重合,表明该列线图风险预测模型预测能力较好。决策曲线结果显示,训练集和验证集在阈值范围 0.13 ~ 0.76 和 0.20 ~ 0.76 的范围内,根据模型的预测概率来干预 MPD 患者临床净收益较高。**结论** MPD 患者的透析龄、血红蛋白水平以及体液负荷 E/I 是发生 PAH 的独立危险因素,基于以上参数构建的列线图预测模型对 MPD 患者发生 PAH 风险具有较好的预测价值。

关键词 维持性腹膜透析;超声心动图;肺动脉高压;成分分析;体液成分;列线图
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肺动脉高压(pulmonary hypertension, PAH)是终末期肾病患者全因死亡率及心血管死亡事件的高危因素[1-2]。根据超声心动图标准评估的终末期肾病患者的 PAH 患病率高达 47%[3],因此早发现及早干预 PAH 尤为重要。已有研究[4]指出维持性腹膜透析(maintenance peritoneal dialysis, MPD)患者 PAH 的发生与容量状态相关。因此,评估 MPD 患者容量状态不仅对短期容量管理重要,且对于 PAH 长期预防也很重要。已有研究[5]证实,透析的慢性肾脏病患者通过多频生物电阻抗法评估的容量超负荷参数与心脏结构及功能的变化密切相关。列线图目前已被广泛运用于疾病预后情况的预测中,通过将多个独立影响因素量化赋值,达到可视化的效果来呈现各个影响因素及其整体对风险事件的预测效能。但目前关于 MPD 患者合并 PAH 的列线图的构建及预测模型验证报道较少。该研究拟通过分析 MPD 患者的容量状态建立有效的列线图,对影响 PAH 发生的危险因素进行量化赋值,数值化预测 PAH 的发生率,以期为临床医护提供便捷的预测方法,为有效避免和降低 MPD 患者 PAH 的发生提供理论指导。

1 材料与方法

1.1 病例资料 选择 2022 年 7 月—2023 年 12 月在安徽医科大学第一附属医院肾脏内科住院且明确诊断为 MPD 的患者 168 例为研究对象。对所有患者采用问卷调查的方法,收集患者资料包括性别、年龄、透析龄、原发病等。依据肺动脉收缩压(pulmonary arterial systolic pressure, PASP)≥35 mmHg[6],分为 PAH 组 72 例,非 PAH 组 96 例。病例纳入标准:① 年龄≥18 岁;② 符合美国肾脏病基金会 K/DOQI 诊断 MPD 标准[7];③ 透析时间≥3 个月且未改变透析方式;④ 心脏射血分数≥50%。排除标准:① 合并先天性心脏病、器质性瓣膜病、心肌病患

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者;② 合并严重心脏衰竭、急性心肌梗死患者;③ 合并慢性阻塞性肺病或肺梗死患者;④ 合并重症感染、腹膜炎患者;⑤ 合并严重胸腔积液、腹腔积液患者。

1.2 肺动脉压测量 使用 PHILIPS 彩超机 Epiq5 检测肺动脉压。双平面 Simpson 法测量左室射血分数、左心房内径、左心室内径、每搏输出量、PASP 等。

1.3 体液成分测量 采用生物电阻抗技术的人体成分分析仪(购自韩国 Biospace 有限公司,型号为 InBody S10)测量体液成分。收集数据包括细胞内液量(intracellular water, ICW)、细胞外液量(extracellular water, ECW)、水负荷(over hydration, OH),并计算 ECW/ICW(E/I)值。

1.4 统计学处理 使用 R 软件(4.3.1)对所有数据进行处理,两组定量资料比较采用 t 检验,定性资料的比较采用 χ^2 检验或者确切概率法。使用 Logistic 回归分析探究影响 MPD 患者发生 PAH 的危险因素。将单因素分析中 $P<0.05$ 的相关因素纳入 Logistic 回归模型。随机按 1∶1 比例将 MPD 患者分为训练集(84 例)和验证集(84 例),采用 R 软件中的 rms、pROC、rmda 程序包构建列线图模型,采用受试者工作特征(receiver operating characteristic curve, ROC)曲线、ROC 曲线下面积(area under curve, AUC)、一致性指数和校准曲线评价模型的预测准确性和一致性。决策曲线分析(decision curve analysis, DCA)反映该模型对患者的净收益。$P<0.05$ 为差异有统计学意义。

2 结果

2.1 MPD 患者 PAH 组与非 PAH 组指标比较 两组间在年龄、性别组成、合并高血压、吸烟、OH、ECW、ICW 和左心房内径水平差异无统计学意义。PAH 组患者透析龄、E/I 及 PASP 高于非 PAH 组,血红蛋白水平和左室射血分数低于非 PAH 组(均 $P<0.05$)。见表 1。

2.2 PAH 组与非 PAH 组中训练集和验证集患者基线指标比较 PAH 组中训练集患者与验证集患者在男性比例、透析龄、吸烟人数、血红蛋白水平、OH、ECW、ICW、E/I、左心房内径、左室射血分数及 PASP 水平差异无统计学意义;训练集患者年龄高于验证集($P=0.019$),患高血压病人数低于验证集($P=0.006$)。非 PAH 组训练集患者与验证集患者在年龄、男性比例、高血压患病率、透析龄、吸烟人数、血红蛋白水平、OH、ECW、ICW、E/I、左心房内径、射血分数及 PASP 水平差异无统计学意义。见表 2。

2.3 列线图模型的构建 训练集中单因素 Logistic 回归分析显示:年龄($OR=1.051$, 95% CI: 1.008 ~ 1.096, $P=0.020$)、透析龄(OR: 1.032, 95% CI: 1.008 ~ 1.057, $P=0.009$)、血红蛋白(OR: 0.964, 95% CI: 0.936 ~ 0.992, $P=0.013$)、ECW(OR: 1.134, 95% CI: 1.009 ~ 1.275, $P=0.035$)、E/I(OR: 1.063, 95% CI: 1.026 ~ 1.101, $P=0.001$)与 PAH 相关。将年龄、透析龄、血红蛋白、ECW、E/I 代入多因素 Logistic 回归分析,分析结果显示透析龄(OR: 1.038, 95% CI: 1.008 ~ 1.069, $P=0.012$)、血红蛋白(OR: 0.961, 95% CI: 0.929 ~ 0.994, $P=0.021$)、E/I(OR: 1.069, 95% CI: 1.024 ~ 1.115, $P=0.002$)是 PAH 的独立危险因素(表 3)。联合上述 3 个指标,建立回归模型并绘制列线图,将各指标于变量轴上查找对应点,从各点向分数轴作垂线获得各指标分

表 1 MPD 患者 PAH 组和非 PAH 组指标比较 ($\bar{x}\pm s$)

Tab. 1 Comparison of clinical parameters between PAH and non-PAH groups in MPD patients ($\bar{x}\pm s$)

Variable	PAH group ($n=72$)	Non-PAH group ($n=96$)	t/χ^2 value	P value
Age (years)	54.82 ± 11.82	52.15 ± 11.47	1.475	0.142
Male (n)	33	34	1.862	0.204
Hypertension (n)	62	77	1.004	0.410
Dialysis of duration (months)	40.94 ± 35.60	22.63 ± 15.52	4.506	<0.001
Smoking (n)	15	17	0.261	0.691
Hemoglobin (g/L)	93.94 ± 18.57	105.92 ± 18.77	−4.109	<0.001
OH (L)	1.96 ± 3.27	1.13 ± 3.08	1.677	0.095
ECW (L)	16.64 ± 4.81	14.80 ± 4.06	2.684	0.088
ICW (L)	16.12 ± 3.81	16.88 ± 4.31	−1.176	0.241
E/I	1.05 ± 0.32	0.89 ± 0.27	3.346	0.001
Left atrial diameter (cm)	4.18 ± 0.48	4.07 ± 3.31	0.288	0.774
Left ventricular ejection fraction (%)	57.71 ± 7.85	60.78 ± 3.46	−3.417	0.001
PASP (kPa)	5.42 ± 1.16	3.67 ± 0.57	12.827	<0.001

值,并将分值相加所得总分投射于总分轴上,总分对应的风险系数反映 MPD 患者发生 PAH 的概率(图1)。该模型一致性指数及其可信区间为 0.867(0.782, 0.951),提示此模型有较好的预测效能。

2.4 列线图模型的验证 ROC 分析显示模型在训练集和验证集中的 AUC 分别为 0.867(95% *CI*: 0.782~0.953)和 0.808(95% *CI*: 0.714~0.902),表明该模型有较好的预测效能。见图 2A、B。由训练集和验证集的校准曲线可见预测曲线与理想曲线基本重合,该列线图风险预测模型预测能力较好。见图 3A、B。通过对训练集和验证集进行 DCA 分析,其结果显示训练集和验证集在阈值范围 0.13~

表 2 PAH 组和非 PAH 组患者训练集与验证集患者基线资料比较 ($\bar{x} \pm s$)

Tab. 2 Comparison of baseline characteristics between PAH and non-PAH patients in the training and validation sets ($\bar{x} \pm s$)

Variable	PAH group				Non-PAH group			
	Training sets (n=35)	Validation sets (n=37)	t/χ^2 value	P value	Training sets (n=49)	Validation sets (n=47)	t/χ^2 value	P value
Age (years)	58.17±12.77	51.65±10.02	2.418	0.019	51.73±10.90	52.57±12.13	−0.357	0.722
Male (n)	13	20	0.150	0.165	17	17	0.023	1.000
Hypertension (n)	26	36	7.963	0.006	39	10	0.024	1.000
Dialysis duration (months)	40.40±37.18	41.16±34.55	−0.125	0.901	22.14±12.21	23.13±18.48	−0.309	0.158
Smoking (n)	8	7	0.169	0.775	7	10	0.805	0.430
Hemoglobin (g/L)	95.06±18.54	92.89±18.79	0.492	0.624	105.53±16.62	106.32±20.96	−0.205	0.838
OH (L)	1.43±3.36	2.57±3.17	−1.478	0.086	1.24±3.64	1.04±2.34	0.323	0.748
ECW (L)	16.94±3.36	16.41±4.23	0.468	0.641	14.73±3.17	14.94±4.87	−0.241	0.810
ICW (L)	16.94±5.46	16.51±3.68	−0.788	0.433	16.86±4.06	16.94±4.60	−0.089	0.929
E/I	1.09±0.37	1.03±0.16	0.871	0.387	1.00±0.00	1.02±0.33	−0.453	0.652
Left atrial diameter (cm)	4.00±0.59	4.22±0.417	−1.795	0.077	3.71±0.61	4.45±4.45	−1.142	0.256
Left ventricular ejection fraction (%)	59.34±7.19	56.16±8.23	1.742	0.086	61.06±3.44	60.49±3.51	0.806	0.422
PASP (kPa)	5.22±0.76	5.61±1.43	−1.390	0.169	3.67±0.61	3.68±0.3	−0.030	0.976

表 3 训练集 PAH 多因素 Logistic 回归分析

Tab. 3 Logistic multivariate analysis of PAH in the training set

Risk factors	*B*	*SE*	*Wals*	*OR* value	95% *CI*	*P* value
Age (years)	0.044	0.026	2.833	1.045	0.993−1.101	0.092
Dialysis duration (months)	0.038	0.015	6.341	1.038	1.008−1.069	0.012
Hemoglobin (g/L)	−0.040	0.017	5.314	0.961	0.929−0.994	0.021
ECW (L)	−0.015	0.089	0.30	0.985	0.828−1.171	0.862
E/I	0.066	0.022	9.265	1.069	1.024−1.115	0.002

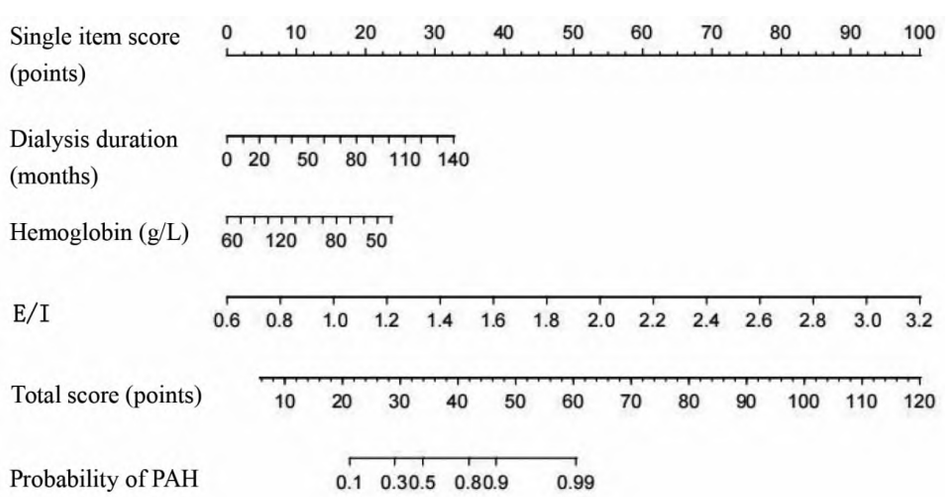

图 1 预测腹膜透析患者并发肺动脉高压的列线图

Fig. 1 Nomogram for predicting pulmonary arterial hypertension in peritoneal dialysis patients

0.76 和 0.20 ~ 0.76 的范围内,根据模型的预测概率来干预腹膜透析患者,临床净收益高于对所有人不进行干预或对所有人进行干预。见图 4A、B。

3 讨论

终末期肾病患者的 PAH 的发生率很高,既往研

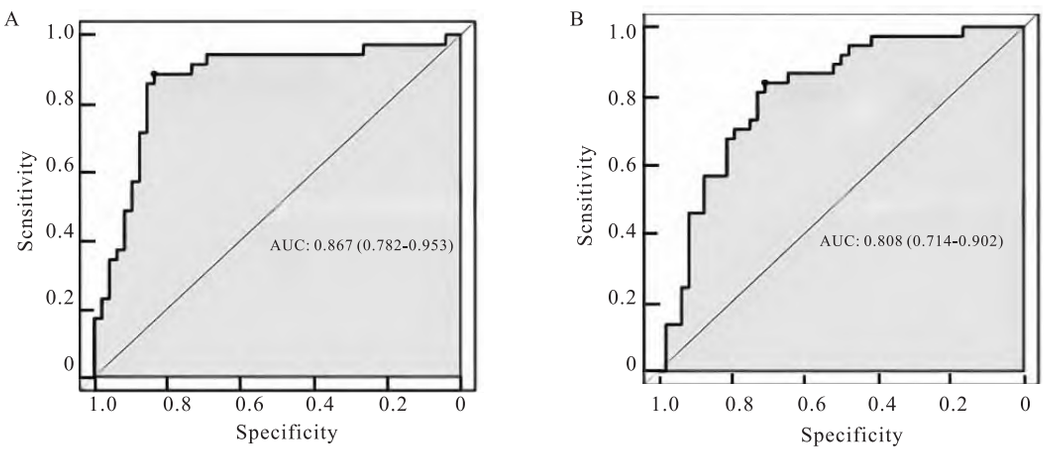

图 2 列线图在训练集(A)和验证集(B)的 ROC 曲线

Fig. 2 ROC curves of the nomogram in the training sets (A) and validation sets (B)

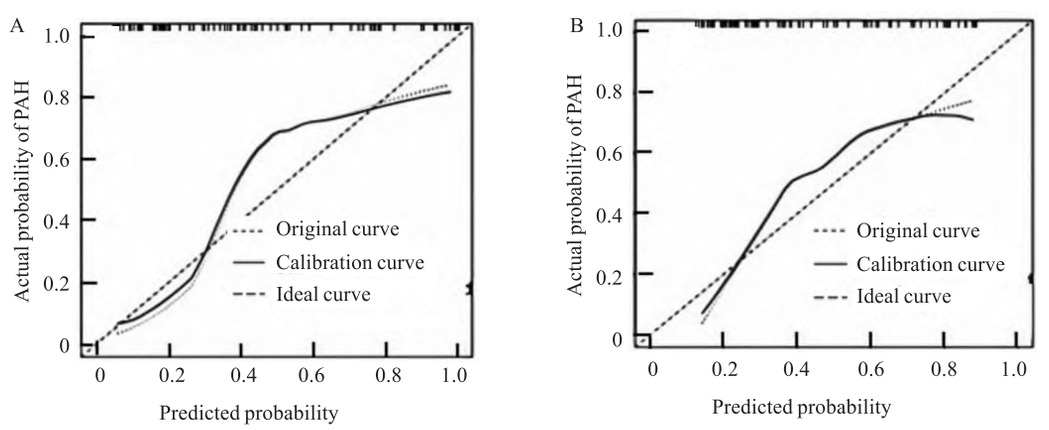

图 3 列线图在训练集(A)和验证集(B)的校准曲线图

Fig. 3 Calibration curves of the nomogram in the training sets (A) and validation sets (B)

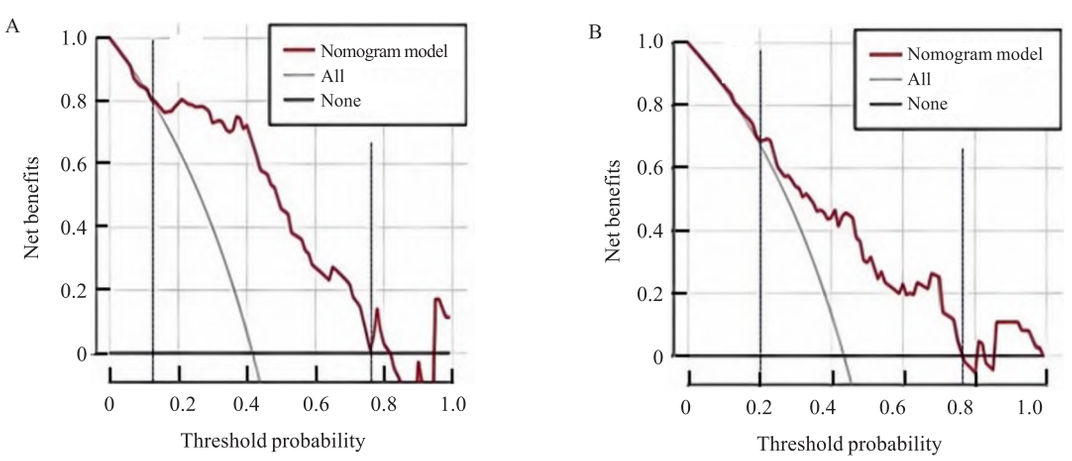

图 4 列线图在训练集(A)和验证集(B)的 DCA 分析

Fig. 4 Decision curve analysis of the nomogram in the training sets (A) and validation sets (B)

究[8]表明在慢性肾脏病5期患者中PAH发病率为9%～39%,血液透析患者中PAH发病率为18.8%～68.8%,MPD患者中发病率为10%～42%。本研究中MPD患者PAH的发病率为42.9%,略高于以前的研究,可能的原因是本研究对象为住院的MPD患者,属于高危亚群,而既往研究多为普通人群或慢性肾脏病早期人群,基线风险不同。

MPD患者发生PAH的机制仍不清楚,这可能归因于患者的容量超负荷、左心室功能障碍、贫血和复发性肺栓塞[9]。本研究中透析龄越长以及血红蛋白水平越低,发生PAH的可能性就越大。终末期慢性肾脏病患者存在慢性炎症已得到充分证实,单核细胞和肥大细胞的增殖、T细胞功能障碍、内皮素-1和血管紧张素Ⅱ等血管收缩物质的过量产生导致氧化应激增加,以及一氧化氮等血管扩张剂合成减少,都会导致肺血管内皮功能障碍,从而导致PAH的发生[10]。随着透析时间的延长,患者长期受血流动力学改变的影响以及多因素作用,使得PAH有可能发生。本研究中MPD患者血红蛋白水平越低越易发生PAH,贫血可导致血黏滞度、外周阻力及运氧能力的下降,从而引起低氧血症,低氧可引起肺动脉压生理性升高,发生低氧性肺血管收缩,而低氧持续存在时,则形成不可逆性的肺血管重构,这也是低氧性PAH发病的重要病理学基础[11]。

多频生物电阻抗测得的E/I反映的是细胞外液与细胞内液的相对分布。ICW减少常见于蛋白质-能量消耗或肌少症[12],ECW增多则提示容量潴留[13]。E/I升高意味着"相对容量过剩和细胞质量下降"的双重失衡。在本研究中合并PAH者的E/I的平均值为1.05,显著高于非PAH组的0.89(P=0.001),且E/I升高是MPD患者发生PAH的独立危险因素。这种差异可能因为长期、相对稳定的容量负荷增高可通过以下途径促成肺血管重塑:① PAH患者右心室长期前负荷增加,引起肺动脉持续张力性扩张,随后肺血管平滑肌细胞肥大、血管壁纤维化,最终肺血管阻力不可逆升高[14];② 细胞外液增加肺间质水肿使肺泡-毛细血管膜总厚度显著增加,氧气从肺泡腔弥散到红细胞的路程延长,弥散系数下降,导致局部肺泡氧分压持续降低。慢性缺氧导致肺动脉平滑肌细胞去极化、电压门控及非选择性阳离子通道上调,使钙离子持续升高,进而触发血管收缩与增殖性重塑[15]。Mai et al[16]研究透析前慢性肾脏病5期患者,ECW%、OH/ECW、ECW/总体水与透析前的PAH风险密切相关,为其独立危险因素。本研究则聚焦已行腹膜透析人群,发现E/I更具预测力。两项研究均使用生物电阻抗技术,但Mai et al[16]研究采用原始ECW/总体水,本研究用E/I排除了总体水波动带来的稀释效应,即不仅是总容量过剩,更关键的是ECW与ICW比例失调,才是触发肺血管重塑的核心。E/I升高可能是连接营养不良、微炎症与肺血管病变的"枢纽表型"。Mai et al[16]与本研究共同说明:无论透析前后,容量分布失衡均是PAH的独立危险因素,将慢性肾脏病患者的容量状态纳入常规监测,不仅可早期识别高危患者,也为个体化容量管理提供了客观依据。

此列线图结合透析龄、血红蛋白水平以及E/I值几个简单的指标,计算出MPD患者发生PAH的概率,在常规随访中可提前发现PAH高危患者。使用人体成分分析设备成本低、无创,可替代昂贵的右心导管筛查,对资源有限地区尤其具有优势。本研究存在以下局限性:① 样本量过小;② 本研究为横断面研究,无法推断体液负荷与PAH发生的因果时序;③ 未对研究对象进行远期预后观察。后续研究可扩大样本量,纳入血液透析、腹透及CKD5期患者,验证E/I在不同透析模式中的预测阈值是否一致。

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Analysis of risk factors for pulmonary artery hypertension in patients with maintenance peritoneal dialysis and establishment and verification of a nomogram

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Abstract ***Objective*** To identify the risk factors for pulmonary arterial hypertension (PAH) in maintenance peritoneal dialysis (MPD) patients and to develop and validate a nomogram-based risk-prediction model. ***Methods*** A total of 168 hospitalized MPD patients from the Department of Nephrology were enrolled. Body-fluid composition was measured by bioelectrical impedance analysis, and pulmonary-artery systolic pressure (PASP) was assessed by echocardiography. Patients were randomly allocated into a training set and a validation set at 1∶1 ratio. Variables with $P<0.05$ in multivariable Logistic regression in the training set were incorporated to construct a nomogram. The validation set was used to test the model's predictive performance. ROC curves, calibration curves, and decision-curve analysis were applied to evaluate accuracy, consistency, and clinical usefulness of the model. ***Results*** Dialysis vintage (*OR*: 1.038, 95% *CI*: 1.008 – 1.069, $P=0.012$), hemoglobin level (*OR*: 0.961, 95% *CI*: 0.929 – 0.994, $P=0.021$), and extracellular water/intracellular water ratio (E/I) (*OR*: 1.069, 95% *CI*: 1.024 – 1.115, $P=0.002$) were independent risk factors for PAH. ROC analysis yielded area under curve as 0.867 (95% *CI*: 0.782 – 0.953) and 0.808 (95% *CI*: 0.714 – 0.902) in the training and validation sets, respectively. Calibration plots showed that the predicted curves for both the training and validation sets closely overlapped with the ideal reference line, indicating that the nomogram risk-prediction model had good predictive performance. Decision-curve analysis demonstrated that, within threshold ranges of 0.13 – 0.76 (training set) and 0.20 – 0.76 (validation set), clinical net benefit was substantial when interventions were guided by the nomogram. ***Conclusion*** Dialysis vintage, hemoglobin level, and fluid-overload index (E/I) are independent risk factors for PAH in MPD

patients. The nomogram based on these parameters reliably predicts PAH risk and may aid clinical decision-making.

Key words maintenance peritoneal dialysis; echocardiography; pulmonary hypertension; constituent analysis; fluid compartments; nomograms

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Evaluation of brain aging in patients with type 2 diabetes mellitus by structural magnetic resonance-driven machine learning model

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Abstract ***Objective*** To explore the brain-predicted age difference (Brain-PAD) in patients with type 2 diabetes mellitus (T2DM) by a machine learning prediction model based on structural magnetic resonance (sMRI) in the Southwest University Adult Lifespan Dataset (SALD), and to reveal the relationship between Brain-PAD and duration of T2DM and cognition. ***Methods*** Group comparisons about demographic variables and cognitive function were conducted respectively in local database of 104 T2DM patients and 83 healthy controls (HC). The prediction model *via* Gaussian process regression (GPR) was constructed by training sMRI data of 329 healthy volunteers in SALD, then its performance was validated and evaluated. Furthermore, Brain-PAD (predicted age-chronological age) in the local database was calculated. Group comparisons of Brain-PAD between T2DM patients and HCs were conducted by Mann-Whitney *U* test. Finally, Pearson correlation coefficient (r) was calculated between Brain-PAD and duration of disease and cognition. ***Results*** Poor performance in auditory verbal learning test (AVLT)-delayed recall, AVLT-recognition, symbol digital modalities test (SDMT) ($P<0.05$), and increased Brain-PAD were observed in T2DM patients, compared with HCs [1.619(−4.001, 8.272) years *vs* −1.289(−4.128, 4.134) years, $Z=2.056$, $P=0.034$]. Notably, the median of Brain-PAD in T2DM group was positive, indicating that the brain of T2DM patient maybe relatively "older" than his chronological age. Brain-PAD in T2DM group was associated with performance in AVLT-immediate recall ($r=0.291$, $P=0.003$), AVLT-delayed recall ($r=0.248$, $P=0.011$), SDMT($r=0.376$, $P=0.001$) and trail making test (TMT)-A ($r=-0.206$, $P=0.036$). However, the relationships between Brain-PAD and duration of T2DM were not explored. ***Conclusion*** Decreased cognitive function in patients with T2DM is demonstrated in this study. The machine learning prediction model based on sMRI supports the identification of brain aging objectively in patients with T2DM.

Key words diabetes; magnetic resonance imaging; machine learning; brain age; cognition; aging

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