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·临床研究·

# 头颈癌切除游离皮瓣修复患者术后谵妄预测模型的建立与验证

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**【摘要】 目的** 建立并验证头颈部癌(head and neck cancer，HNC)患者游离皮瓣修复术后谵妄(postoperative delirium，POD)的风险预测模型，为临床提供参考。**方法** 本研究已通过单位伦理委员会审查批准，并获得患者知情同意。对2016年1月1日至2022年1月1日在徐州市中心医院头颈肿瘤外科接受头颈癌切除后游离皮瓣重建术患者的相关危险因素和生命体征进行回顾性收集和评估，共纳入241例，其中171例进行预测模型的建立，另外收集70例进行内部验证，采用单因素和多因素Logistic分析，R Studio软件包进行建模统计分析。**结果** 本研究模型最终包含4个风险因素：年龄、输血、术后睡眠障碍、术后疼痛VAS得分；该模型训练集的受试者工作特征曲线下面积(AUC)为0.869(95% *CI*：0.789～0.948)，Youden指数为0.692，预测值为0.215，敏感性为85.3%，特异性为83.9%，Hosmer-Lemeshow拟合优度为10.336($P$ = 0.242)，该模型拟合较好；根据模型对验证集进行验证，C指数为0.827(95% *CI*：0.681～0.973)，模型预测效果较好。**结论** 该模型可应用于头颈部恶性肿瘤切除后游离皮瓣术后谵妄的预测，对入院时HNC-POD的风险具有很高的预测价值，使用该模型可能有助于更好地实施预防性治疗和护理措施。

**【关键词】** 头颈部；恶性肿瘤；危险因素；谵妄；术后；风险预测；睡眠障碍；模型；列线图
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**Development and validation of a postoperative delirium prediction model for patients with head and neck cancer resection and free flap repair**

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**【Abstract】 Objective** To establish and validate a risk prediction model for postoperative delirium (POD) in patients with head and neck cancer (HNC) resection with free flap repair and to provide a reference for clinical practice. **Methods** This study has been reviewed and approved by the Ethics Committee, and informed consent has been obtained from patients. This study retrospectively collected and evaluated the risk factors and vital signs of patients undergoing head and neck cancer free flap reconstruction in the Department of Oromaxillofacial Head and Neck Oncology, Xuzhou Central Hospital from January 1, 2016, to January 1, 2022. A total of 241 cases were included, of which 171 cases were used to establish the prediction model, and 70 cases were collected for internal verification. Univariate and multivariate logistic analyses and the R Studio software package were used for modeling and statistical analysis.

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**Results**　The research model finally included five risk factors: age, blood transfusion, postoperative sleep disorder and postoperative VAS pain value. The area under the working characteristic curve (AUC) of the subjects in the training set of the model was 0.869 (95% *CI*: 0.789-0.948), the Youden index was 0.692, the predictive value was 0.215, the sensitivity was 85.3%, the specificity was 83.9%, and the goodness of fit of the Hosmer Lemeshow test was 10.336 ($P$ = 0.242). The model fit well. The validation set was verified according to the model. The C index was 0.827 (95% *CI*: 0.681-0.973), and the model prediction effect was very good. **Conclusion**　This model may be applied to predict postoperative delirium for patients with head and neck cancer resection and free flap repair, which has a high predictive value for the risk of HNC-POD at admission. The use of this model may help to better implement preventive treatment and nursing measures.

**【Key words】** head and neck; cancer; risk factors; delirium; postopretive; risk prediction; somnipathy; model; nomogram

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术后谵妄(postoperative delirium, POD)是一种急性中枢神经系统病变,术后意识或认知功能障碍综合征,且大多数出现在术后的1～3 d[1-2]。国外研究者对头颈部恶性肿瘤(head and neck cancer, HNC)患者术后谵妄系统研究中发现,POD的发生率为7.5%～33.3%[3-4]。一旦发生POD的患者不仅会延长术后住院时间、增加医疗费用,还可导致患者长期的认知功能障碍,甚至是痴呆[5-6]。各专业的外科手术在POD相关风险方面差异很大,例如,喉切除术患者POD的总发病率为8.7%[7],髋部骨折患者POD发生率为16.02%[8],心脏手术POD发生率为25%～67%[9]等;近几年头颈部恶性肿瘤手术术后也出现了较高的发生率,既往大部分研究显示,POD与年龄、游离皮瓣、手术时间以及输血等危险因素具有相关性[10-11],传统认为POD发生多与麻醉有关,然而研究者发现麻醉方式对髋部骨折的老年患者POD的谵妄类型、发生率及产生的严重程度无显著影响[12],这一研究结果改变了因全麻会导致手术后老年患者的脑功能紊乱的传统观念,同时也为头颈部恶性肿瘤POD防治的临床实践提供了重要指导意义。手术的特异性是POD发生的最强预测因子[13],尽管大型手术POD的研究指南在不断地更新[14-15],但是这些指南中关于HNC-POD常常被忽略。本研究建立HNC-POD的风险预测模型,并采用本院内部头颈部恶性肿瘤游离皮瓣修复患者进行验证,寻找可靠的危险因素来更好地预测HNC-POD,以提高对POD的治疗效果。

## 1　资料和方法

### 1.1　研究对象

选择2016年1月至2022年1月于徐州市中心医院头颈肿瘤外科接受头颈癌切除游离皮瓣手术的患者作为研究人群进行回顾性研究。所有患者资料由同一名住院医师收集、记录。纳入标准:①年龄≥18岁;②手术期间无其他疾病手术史;③病历档案中患者基本信息、病程记录、检验单、麻醉单、手术记录、护理记录等资料齐全。排除标准:①术前诊断为痴呆和精神病患者,如抑郁症和精神分裂;②先前诊断有神经系统疾病,如帕金森病;③视力、听力功能障碍以及沟通障碍患者。本研究共纳入了发生于口腔、口咽、上颌窦、唾液腺以及颈部等部位,通过结合病史、临床表现和影像学资料及病理确切诊断为头颈部恶性肿瘤的241例患者,平均年龄为(58.6 ± 11.9)岁,男157例,女84例,本研究通过了伦理委员会的批准(批号:XZXY-LK-20211209-047)。

### 1.2　谵妄的诊断标准

选择谵妄评估量表(confusion assessment method, CAM)进行评估[16],并且由同一名神经内科医师依据谵妄诊断量表CAM对所有患者进行评估,CAM包括4个主题内容:①精神状态急性变化或波动;②注意力不集中;③意识水平改变;④思维紊乱。①和②基础上加上③或④其中任意1条,即可

诊断为谵妄。根据患者临床表现，确定谵妄类型（高活动型、低活动型、混合型）。

### 1.3　危险因素

选择既往研究中有争议以及较高危的危险因素作为术前、术中和术后资料进行分析，术前因素：年龄、性别、体重指数（body mass index，BMI）、糖尿病、脑血管疾病、高血压，心脏病、吸烟、酗酒、血钾浓度、血钠浓度；术中因素：手术时间、输血、是否行气管切开；术后因素：术后发热（37.3 ℃以上）、ICU住院时间、术后睡眠障碍、术后疼痛视觉模拟评分（visual analog scales，VAS）值、术后1 d血红蛋白。

### 1.4　统计学分析

通过统计计算得出年龄最佳截断值为65岁，以及复习以往文献中术后谵妄与年龄的相关性将年龄进行分层研究，将患者的年龄值分为4组：年龄＜55、55≤年龄＜65、65≤年龄＜75和年龄≥75。计量资料用平均值±标准差表示，非正态分布的数据用秩和检验的结果表示，计量资料比较采用$t$检验，计数资料比较采用$\chi^2$检验。使用单变量分析评估每个潜在风险因素与HNC-POD之间的关联来开发预测模型，并计算每个变量HNC-POD的$OR$，进行二元逻辑回归分析（纳入$P<0.10$的危险因素），评估各危险因素与谵妄发生的独立关联性，使用受试者工作特征曲线下面积（AUC）估计模型的预后测能力。使用IBM SPSS 25.0分析数据，以Hosmer-Lemeshow拟合优度检验和校准图评价模型的校准度，检验水准$\alpha$=0.05。采用R Studio软件进行建模分析并验证，并制作Nomogram列线图从最终模型中，使用每个变量的回归系数作为权重，推导出HNC-POD的风险方程。

## 2　结　果

### 2.1　研究对象的基线资料

共纳入241例行头颈部恶性肿瘤重建术的患者，其中171例作为训练集，术后发生谵妄34例（谵妄组），其中男24例、女10例，平均年龄（65.9 ± 11.6）岁；137例术后未发生谵妄（非谵妄组），其中男84例、女53例，平均年龄（56.4 ± 10.6）岁。将另外70例行头颈部恶性肿瘤切除游离皮瓣重建术的患者作为验证集，术后发生谵妄13例（谵妄组），其中男10例、女3例，平均年龄（66.5 ± 8.9）岁；57例术后未发生谵妄（非谵妄组），男39例、女18例，平均年龄（57.7 ± 11.6）岁。既包括原发性也包括复发性头颈部恶性肿瘤患者；皮瓣类型包括股前外、股前内皮瓣、腓骨游离皮瓣、髂骨肌皮瓣、前臂皮瓣等。

### 2.2　单因素和多因素Logistic回归分析

训练集两组性别、高血压、糖尿病、心脏病、脑血管病、吸烟、$K^+$、$Na^+$、气管切开、术后血红蛋白（Hb）以及重症监护时间等差异无统计学意义（$P>0.05$）。两组在年龄、酗酒、手术时间、输血、术后睡眠障碍、术后VAS疼痛以及术后是否发热方面存在显著差异（$P<0.05$）（表1）。

年龄、输血、术后疼痛VAS值、术后睡眠障碍通过Logistic多变量分析确定为头颈部恶性肿瘤重建术后谵妄的独立危险因素（表2）。

### 2.3　建立与验证HNC-POD预测模型

在对具有统计学意义的风险因素进行二元逻辑回归分析后，最终纳入了4个风险因素：年龄、输血、术后睡眠障碍、术后VAS值以及术后发热，构建了以下HNC-POD预测模型：$\ln[P/(1-P)]$ = 5.71 ×年龄≥65 + 27.52× 年龄≥75 +4.32×输血 + 3.63×术后睡眠障碍 + 1.52×术后VAS值-5.237。C指数0.869（95% $CI$：0.789 ~ 0.948），Youden指数为0.692，预测值为0.215，敏感性为85.3%，特异性为83.9%，Hosmer-Lemeshow拟合优度为10.336（$P$ = 0.242），该模型拟合较好；根据模型对验证集进行验证，C指数为0.827（95% $CI$：0.681 ~ 0.973），该模型拟合较好，当以Youden指数作为截断值时，模型的灵敏度和特异度最高（图1），模型预测谵妄的能力最强。根据公式开发并验证了一种新的Nomogram列线图，得出患者的评分，患者的评分越接近临界值，谵妄的风险越高（图2）。

## 3　讨　论

本研究中发现不同年龄段、手术时间、输血、术后睡眠障碍、术后VAS疼痛值与患者的HNC-POD发展相关。研究结果中表明，年龄在65岁以上时发生POD的一个高危危险因素，高龄的老年患者比年轻患者在生理和心理上更难适应手术后的重大变化，如神经老化、神经炎、神经递质不足和脑网络连接变化等因素，可能导致谵妄的发生[17]。头颈部恶性肿瘤游离皮瓣移植手术操作时间相对较长，当时间达到一定程度时，相应发生POD的风险应该也会增加，长时间手术带来的失血过多、麻醉时间延长、术后炎症反应，以及其他手术相关的因素可能是造成POD的原因；手术中出血量增加和术中、术后需要输血的趋势与POD

**表1**　训练集171例头颈部恶性肿瘤术后谵妄发生的单变量危险因素统计结果

Table 1　Postoperative delirium of head and neck cancer risk factors in the single factor analysis results in 171 cases as training set

| Influencing factor | Delirium ($n$ = 34) | Non delirium ($n$ = 137) | $\chi^2/t$ | $P$ |
|---|---|---|---|---|
| Preoperative variables | | | | |
| Age/years | 65.9 ± 11.6 | 56.4 ± 10.6 | 4.37 | < 0.001 |
| < 55 | 5(14.7) | 55(40.1) | 26.94 | < 0.001 |
| ⩾ 55 | 7(20.6) | 51(37.2) | | |
| ⩾ 65 | 13(38.2)# | 27(19.7) | | |
| ⩾ 75 | 9(26.5)# | 4(2.9) | | |
| Gender | | | 1.01 | 0.316 |
| Male | 24(70.6) | 84(61.3) | | |
| Female | 10(29.4) | 53(38.7) | | |
| BMI/ (kg/m$^2$) | 22.8 ± 2.7 | 23.6 ± 3.4 | 1.20 | 0.233 |
| Hypertension | | | 0.33 | 0.564 |
| Yes | 8(23.5) | 39(28.5) | | |
| No | 26(76.5) | 98(71.5) | | |
| Diabetes | | | 0.66 | 0.417 |
| Yes | 4(11.8) | 24(17.5) | | |
| No | 30(88.2) | 113(82.5) | | |
| Cardiac disease | | | 0.00 | 1.000 |
| Yes | 3(8.8) | 12(8.8) | | |
| No | 31(91.2) | 125(91.2) | | |
| Cerebrovascular disease | | | 0.00 | 1.000 |
| Yes | 3(8.8) | 14(10.2) | | |
| No | 31(91.2) | 123(89.8) | | |
| Smoke | | | 0.72 | 0.397 |
| Yes | 13(38.2) | 42(30.7) | | |
| No | 21(61.8) | 95(69.3) | | |
| Excessivedrinking | | | 1.04 | 0.308 |
| Yes | 13(38.2) | 40(29.2) | | |
| No | 21(61.8) | 97(70.8) | | |
| $K^+$ | 4.1 ± 0.5 | 4.2 ± 2.3 | 0.45 | 0.406 |
| $Na^+$ | 140.3 ± 3.0 | 140.3 ± 2.5 | 0.04 | 0.966 |
| Intraoperative variables | | | | |
| Operation time/min | 521.2 ± 102.9 | 476.2 ± 119.8 | 2.01 | 0.046 |
| Tracheotomy | | | 0.71 | 0.398 |
| Yes | 29(85.3) | 108(78.8) | | |
| No | 5(14.7) | 29(21.2) | | |
| Transfusion | | | 11.75 | 0.001 |
| Yes | 24(70.6) | 52(38.0) | | |
| No | 16(29.4) | 85(62.0) | | |
| Postoperative variables | | | | |
| Haemoglobin | 107.1 ± 18.3 | 107.6 ± 15.7 | 0.16 | 0.875 |
| Intensive care time/d | 1.3 ± 0.6 | 1.2 ± 0.7 | 0.67 | 0.503 |
| VAS | 4.2 ± 2.1 | 2.6 ± 1.5 | 4.92 | < 0.001 |
| Sleep disturbance | | | 9.75 | 0.002 |
| Yes | 23(67.6) | 52(38.0) | | |
| No | 11(32.4) | 85(62.0) | | |
| Fever | | | 0.41 | 0.524 |
| Yes | 25(73.5) | 93(67.9) | | |
| No | 9(26.5) | 44(32.1) | | |

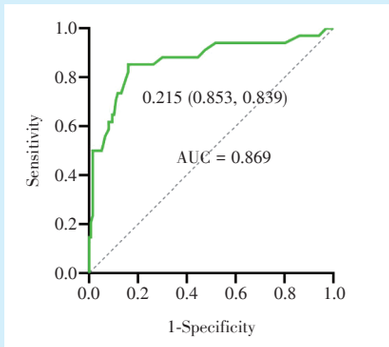
BMI: body mass index; VAS: visual analog scales; #: differences between groups except control group

**表2**　训练集171例头颈部恶性肿瘤重建术后谵妄发生的多因素Logistic回归分析结果

Table 2　Multivariate logistic regression analysis of risk factors for HNC-POD in 171 cases as training set

| | $\beta$ | $SE$ | Wald $\chi^2$ | $P$ | $OR$ | 95%$CI$ |
|---|---|---|---|---|---|---|
| Age/years | | | | | | |
| < 55 | | | | | | |
| ⩾ 55 | 0.27 | 0.67 | 0.16 | 0.691 | 1.31 | 0.35 ~ 4.86 |
| ⩾ 65 | 1.74 | 0.64 | 7.38 | 0.007 | 5.71 | 1.62 ~ 20.08 |
| ⩾ 75 | 3.32 | 0.96 | 11.96 | 0.001 | 27.52 | 4.21 ~ 180.03 |
| Sleep disturbance | | | | | | |
| Yes | 1.29 | 0.51 | 6.37 | 0.012 | 3.63 | 1.33 ~ 9.88 |
| No | | | | | | |
| VAS | 0.42 | 0.13 | 10.79 | 0.001 | 1.52 | 1.18 ~ 1.95 |
| Transfusion | | | | | | |
| Yes | 1.46 | 0.51 | 5.29 | 0.004 | 4.32 | 1.60 ~ 11.69 |
| No | | | | | | |

VAS: visual analog scales; HNC: head and neck cancer; POD: postoperative delirium

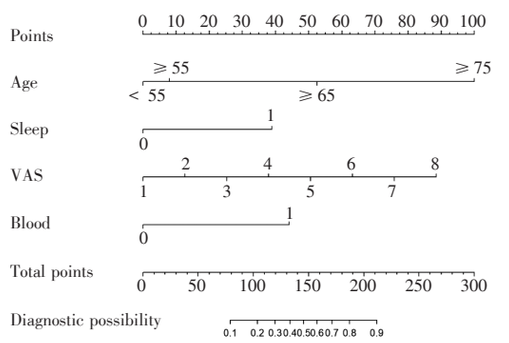



On the ROC curve, the point near the upper left of the coordinate map is the high cutoff value for both sensitivity and specificity. The sensitivity is drawn as the vertical coordinates and (1-specificity) as the horizontal coordinates, and the larger the area under the curve is, the higher the diagnostic accuracy

Figure 1　ROC curve of prediction model in training set

**图1**　训练集预测模型的ROC曲线

的发生密切相关，手术中大量出血可能会造成一系列的身体影响，包括缺氧、低血压、代谢紊乱等，这些影响可能会进一步影响患者的神经系统和精神状态[18]。POD发病前往往伴随着患者的睡眠障碍，睡眠紊乱会导致严重的意识混乱[19]。疼痛也会影响POD的发生，术后疼痛容易产生应激反应，因而能够促使神经炎症进一步发展，引起意识障碍，而且术后镇痛表现出了良好的预防谵妄效果[20]。Imai等[21]对头颈外科手术疼痛的研究表明，使用适当的类固醇激素类药物进行干预疼痛




Sleep (0 = no disorder sleep, 1 = disorder sleep); blood (0 = no blood transfusion, 1 = blood transfusion); HNC: head and neck cancer; POD: postoperative delirium

Figure 2　Nomogram of HNC-POD prediction model

**图2**　HNC-POD预测模型列线图

症状，从而有助于谵妄患者的显著康复，减少了谵妄的发生，术后进行充分的疼痛控制，最好采用最低限度的镇静多模式疼痛管理[22]。

头颈部恶性肿瘤手术与谵妄的发生密切相关[23]，HNC-POD的发病机制和病理生理学尚未完全清楚，可能与术后创伤后应激有关[24]。近几年来关于癌症手术预后预测模型目前也正在研究当中[25]。本研究从不同角度出发，旨在探讨手术与谵妄发生之间的关系，因此并未采用以往的POD预测模型，仅针对大型头颈部恶性肿瘤切除游离皮瓣修复的术后患者，这类患者具有手术时间长、需要游离皮瓣移植以及显微外科血管吻合等特点。本研究模型在更好地理解谵妄方面发挥了重要作用，可作为未来研究的参考，HNC-POD模型具有较高的预测值。

模型所包含的风险因素在各级医院的信息系统中都可以查到，主要是患者的一些病史资料，使得模型被广泛采用成为可能，在开发风险预测模型时，应同时考虑预测效果和各级医院的特点。在本研究中，为了使模型更好地与术后患者的实际情况相吻合，HNC-POD模型仅包含4个危险因素，与其他谵妄预测模型相比更加简洁，更适合临床工作者。本研究包含年龄、手术时间、入院时各种系统疾病、睡眠障碍以及疼痛等会影响谵妄发生的危险因素，与以往研究一致[26]。此外，该模型有助于在HNC患者入院后立即进行分级评估，并提前采取药物或特殊护理预防措施。

POD与长期不良预后相关[27]，谵妄的早期识别和积极干预的开始可以降低谵妄的影响，单独谵妄可以同时提高对急性和严重生理问题的早期迹象的认识[28]。Igwe等[29]提出有必要实施多学科干预，临床医生之间就药物干预的术前和术后护理实践进行合作，以更有效地减少老年人的POD的发生，缩短谵妄持续时间。本研究在开发HNC-POD预测模型时没有考虑药物使用的影响，因为不同的医院更倾向于使用不同的药物。当患者进入病房时，医护人员可以根据最新的生理检查结果、手术记录以及术后的生命体征等结果，完成患者数据的采集。在应用该模型时，医护人员应注意并积极干预评分超过0.215的患者，因为这表明患HNC-POD的风险较高。

本研究开发并验证了针对HNC患者的POD预测模型，该模型具有较高的预测价值，能够及时识别HNC-POD的风险，并且内部验证时拟合度好，使用该模型将有助于在入院早期有针对性地启动预防措施，降低HNC-POD的发生率，同时未来将通过此预测模型对其进行临床药物干预效果、临床护理实践及验证。

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