[DOI]10.12016/j.issn.2096-1456.202550597

·基础研究·

从遗传关联到临床表型：中性粒细胞胞外诱捕网在头颈部鳞状细胞癌发生发展中的临床意义

李冬[1]，　宋红权[2]
1.哈尔滨医科大学口腔医学院，黑龙江 哈尔滨（150001）；　2.哈尔滨医科大学附属第一医院口腔颌面外科，黑龙江 哈尔滨（150001）

【摘要】　目的　基于孟德尔随机化（MR）评估中性粒细胞胞外诱捕网（NETs）与头颈癌的因果关系，揭示NETs在头颈部鳞状细胞癌（HNSCC）的发生发展中的临床意义。**方法**　从全基因组关联研究（GWAS）数据库的汇总统计数据中获取NETs生物标志物髓过氧化物酶- DNA复合物（MPO-DNA）和头颈癌（包括口腔癌及口咽癌）的相关数据。本研究已通过单位医学伦理委员会审查批准，并获得患者知情同意。纳入哈尔滨医科大学附属第一医院口腔颌面外科HNSCC患者作为研究组，并从同医院的临床体检中心随机选取年龄和性别相匹配的志愿者作为对照组。检测所有受试者NETs标志物MPO-DNA、瓜氨酸化组蛋白H3（CitH3）水平，以及淋巴结转移标志物可溶性黏附因子CD44变体6（CD44v6）和白细胞分化抗原CD109的水平，记录凝血功能指标，包括血浆样本凝血酶原时间（PT）、活化部分凝血活酶时间（APTT）、凝血酶时间（TT）、D二聚体（D-dimer，DD）和纤维蛋白原（FIB）的水平，从而分析NETs与HNSCC的关系和潜在机制。**结果**　孟德尔随机化结果显示NETs与头颈癌之间可能存在因果关系，MR分析结果的逆方差加权法（IVW）结果P值分别为P_1 = 0.037、P_2 = 0.017、P_3 = 0.004、P_4 = 0.023。最终纳入HNSCC患者52例，健康人群20例进行分析。与对照组相比，HNSCC患者组外周血MPO-DNA、CitH3、CD44v6、CD109的水平以及凝血指标FIB、DD均显著上升（P<0.001）。通过对NETs标志物与淋巴结转移标志物、凝血指标进行相关性研究显示：MPO-DNA与DD、FIB、CD44v6、CD109的Pearson相关系数分别为0.686、0.531、0.7、0.5，CitH3与DD、FIB、CD44v6、CD109的Pearson相关系数分别为0.456、0.503、0.525、0.603（P<0.05）。在诊断效果方面，HNSCC的MPO-DNA、CitH3、MPO-DNA+CitH3的AUC分别为0.863、0.892、0.905，三者的受试者工作曲线（ROC）下的面积（AUC）依次增加。HNSCC早期患者MPO-DNA和CitH3分别为（132.4±16.4）ng/mL、（21.3±2.9）ng/mL均低于晚期的HNSCC患者MPO-DNA和CitH3，分别为（199.3±33.1）ng/mL、（26.6±3.7）ng/mL。MPO-DNA高表达组患者的FIB、DD、CD44v6、CD109的血清浓度均比MPO-DNA低表达组患者的血清浓度高，差异具有统计学意义（均P<0.05）。CitH3高表达组患者的FIB、CD44v6、CD109的血清浓度均较CitH3低表达患者高，差异具有统计学意义（均P<0.05）。**结论**　NETs和HNSCC之间可能存在因果关系。NETs相关标志物可能是HNSCC的潜在生物标志物，与HNSCC的高凝状态相关。NETs相关标志物对HNSCC有潜在的诊断作用，并且与肿瘤的进展有关。

【关键词】　中性粒细胞胞外诱捕网；　头颈部鳞状细胞癌；　孟德尔随机化；　全基因组关联研究；　髓过氧化物酶-DNA复合物；　瓜氨酸化组蛋白H3；　凝血功能；　可溶性黏附因子CD44变体6；　白细胞分化抗原CD109
【中图分类号】　R78　**【文献标志码】**　A　**【文章编号】**　2096-1456（2026）04-0338-11
【引用著录格式】　李冬，宋红权. 从遗传关联到临床表型：中性粒细胞胞外诱捕网在头颈部鳞状细胞癌发生发展中的临床意义[J]. 口腔疾病防治, 2026, 34(4): 338-348. doi:10.12016/j.issn.2096-1456.202550597.

微信公众号

From genetic association to clinical phenotype: the clinical significance of neutrophil extracellular traps in the occurrence and development of head and neck squamous cell carcinoma　LI Dong[1], SONG Hongquan[2]. 1.

【收稿日期】2025-12-24；　**【修回日期】**2026-01-26
【基金项目】黑龙江省博士后科研启动金（LBH-Q21143）
【作者简介】李冬，医师，硕士，Email：1797548716@qq.com
【通信作者】宋红权，副教授，博士，Email：007530@hrbmu.edu.cn

School of Stomatology, Harbin Medical University, Harbin 150001, China;　2. Department of Oral Maxillofacial , the First Affiliated Hospital of Harbin Medical University, Harbin 150001, China
Corresponding author: SONG Hongquan, Email: 007530@hrbmu.edu.cn

【Abstract】　Objective　To investigate the causal relationship between neutrophil extracellular traps (NETs) and head and neck squamous cell carcinoma (HNSCC) using Mendelian randomization (MR) methods, and to explore the clinical significance of NETs in the occurrence and development of HNSCC. **Methods**　Data related to NET biomarker myeloperoxidase-DNA complex (MPO-DNA) complex and HNSCC were obtained from the pooled statistical data of the Genome-Wide Association Study database (GWAS). This study was reviewed and approved by the Medical Ethics Committee, and informed consent was obtained from patients. Patients with HNSCC admitted to Department of Oral Maxillofacial, the First Affiliated Hospital of Harbin Medical University were included as the research group, and volunteers matched for age and gender were randomly selected from the Clinical Examination Center as the control group. The levels of MPO-DNA and citrullinated histone H3 (CitH3), two markers of NETs, as well as the levels of soluble adhesion factor CD44 variant 6 (CD44v6) and leukocyte differentiation antigen CD109, markers of lymph node metastasis, were measured in all subjects. Blood coagulation indicators, including plasma prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), D-dimer (DD), and fibrinogen levels (FIB), were recorded to analyze the relationship and potential mechanisms between NETs and HNSCC. **Results**　MR results indicated a possible causal relationship between NETs and HNSCC. The inverse variance weighted P values for the four datasets were P_1 = 0.037, P_2 = 0.017, P_3 = 0.004, and P_4 = 0.023. Ultimately, 52 patients with head and neck squamous cell carcinoma and 20 healthy individuals were included. Compared with the control group, the expression levels of NETs markers MPO-DNA, CitH3, lymph node metastasis markers CD44v6 and CD109, and coagulation indicators FIB and DD were significantly elevated in the group with head and neck squamous cell carcinoma, with statistically significant differences (all P<0.001). In correlation studies between NETs markers and lymph node metastasis markers, as well as coagulation indicators, the Pearson correlation coefficient was 0.686, 0.531, 0.7, and 0.5 for MPO-DNA and DD, FIB, CD44v6, and CD109, respectively, and the Pearson correlation coefficient was 0.456, 0.503, 0.525, and 0.603 for CitH3 and DD, FIB, CD44v6, and CD109, respectively (P<0.05). In terms of diagnostic efficacy, the area under the curve (AUC) for MPO-DNA, CitH3, and MPO-DNA + CitH3 in patients with head and neck squamous cell carcinoma was 0.863, 0.892, and 0.905, respectively, with an increasing AUC of the receiver operating characteristic curve (ROC) in the order mentioned. Levels of MPO-DNA and CitH3 in patients with early-stage head and neck squamous cell carcinoma were (132.4 ± 16.4) ng/mL and (21.3 ± 2.9) ng/mL, respectively, which were lower than those in patients with advanced head and neck squamous cell carcinoma, who had MPO-DNA and CitH3 levels of (199.3 ± 33.1) ng/mL and (26.6 ± 3.7) ng/mL, respectively. The serum concentrations of FIB, DD, CD44v6, and CD109 in patients with high MPO-DNA expression were significantly higher than those in patients with low MPO-DNA expression (all P<0.05). The serum concentrations of FIB, CD44v6, and CD109 in patients with high CitH3 expression were significantly higher than those in patients with low CitH3 expression (all P<0.05). **Conclusion**　The study indicates a potential causal relationship between NETs and HNSCC. NETs-related markers may serve as potential biomarkers for HNSCC, as they correlate with the hypercoagulable state of the cancer. NETs-related markers have potential diagnostic utility for HNSCC and are associated with tumor progression.

【Key words】　neutrophil extracellular traps;　head and neck squamous cell carcinoma;　Mendelian randomization;　Genome-Wide Association Study;　myeloperoxidase-DNA complex;　citrullinated histone H3;　coagulation function;　soluble adhesion factor CD44 variant 6;　leukocyte differentiation antigen CD109
J Prev Treat Stomatol Dis, 2026, 34(4): 338-348.
【Competing interests】　The authors declare no competing interests.
This study was supported by the grants from Postdoctoral Scientific Research Developmental Fund of Heilongjiang Province of China (No. LBH - Q21143).

头颈部恶性肿瘤是全球七大常见恶性肿瘤之一，好发部位主要在喉、咽和口腔的黏膜组织，其主要亚类包括口腔鳞状细胞癌、咽鳞状细胞癌和喉鳞状细胞癌等[1]。研究表明，头颈部恶性肿瘤与

多种因素有关，如吸烟、长时间大量摄入酒精及感染人乳头瘤病毒（human papillomavirus，HPV）等[2]。对于头颈部恶性肿瘤的治疗常采取多模式方法，对于晚期患者通常应用化疗、放疗、联合治疗及免疫治疗等疗法。相关研究发现癌症患者血液或肿瘤组织中大量中性粒细胞的存在与不良预后密切相关[3-4]。

在2004年，Brinkmanm等[5]发现中性粒细胞可以在细胞外通过一种DNA-蛋白质复合物杀死病原体，其被Science命名为中性粒细胞胞外诱捕网（neutrophil extracellular traps，NETs）。在一项Ewing肉瘤患者中开展的研究显示，肿瘤组织内部存在NETs现象的病例占比达到25%，在此研究中也发生转移现象。因此NETs与肿瘤二者之间关联性被首次确立发现[6]。后续研究发现，NETs在肿瘤的生长过程、进展阶段及转移过程中也发挥着极其重要的作用[7]。NETs能够在肿瘤微环境（tumor micro-environment，TME）中与免疫细胞相互作用，激活巨噬细胞；促进髓系抑制细胞的免疫抑制作用；并能包裹在肿瘤表面，防止$CD8^+$T细胞和自然杀伤细胞发挥细胞毒性作用[8]。相关文献显示，NETs组成成分髓过氧化物酶-DNA复合物（myeloperoxidase-DNA complex，MPO-DNA）、瓜氨酸化组蛋白H3（citrullinated histone H3，CitH3）作为NETs的特定生物标志物[9-11]。CitH3由肽基精氨酸脱亚氨酶（peptidylarginine deiminases，PADs）对组蛋白H3的翻译后修饰产生[12-13]。CitH3会增强炎症和免疫功能障碍。CitH3既是生物标志物，也是循环因子，当中性粒细胞的炎性细胞死亡时从受伤部位逸出进入血液时，会引发与中性粒细胞的炎性细胞死亡相关的下游损伤。癌症循环中的CitH3激活巨噬细胞、上皮和内皮细胞上的模式识别受体，促进细胞因子释放、内皮功能障碍和微血管血栓形成[9]。髓过氧化物酶（myeloperoxidase，MPO）属于含血红素酶，由于血红素的翻译后修饰[14]，MPO-DNA具有独特的光谱和氧化还原特性，这使得MPO-DNA通过释放氧化性和反应性产物，参与宿主对先天免疫系统的防御，其产物随后用于防御入侵的病原体。MPO-DNA通过支持高突变环境参与肿瘤发生，这是由于MPO-DNA衍生的氧化剂能够氧化和修饰DNA。此外，癌症进展也受MPO-DNA存在的影响，MPO-DNA参与调控肿瘤生长、凋亡、细胞迁移和转移。一些研究还表明，MPO-DNA可能在癌症中调节适应性免疫[15]。然而，中性粒细胞如何影响头颈部鳞状细胞癌（head and neck squamous cell carcinoma，HNSCC）进展的具体机制仍不明确。本研究拟基于孟德尔随机化（Mendelian randomization，MR）评估NETs与头颈癌的因果关系，揭示NETs在头颈部鳞状细胞癌（head and neck squamous cell carcinoma，HNSCC）的发生发展中的临床意义。

1　资料和方法

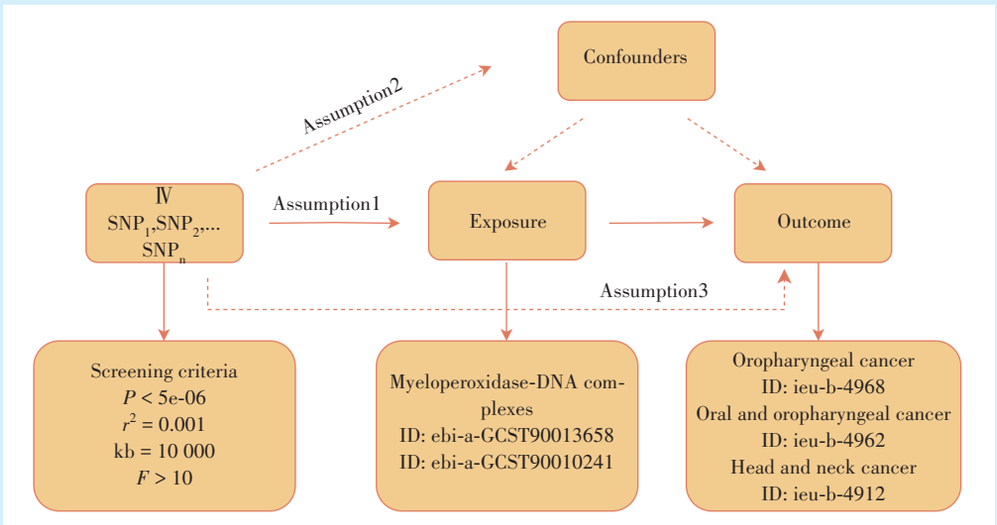
1.1　孟德尔随机化分析

1.1.1　研究设计　孟德尔随机化（Mendelian randomization，MR）是在随机分配的基础上，将遗传变异作为工具，通过此种方式来预估特定结果与某个暴露因素间的因果关系[16]。本研究以“NETs”为暴露因素，“HNSCC”为结局，具体探讨两者之间的因果关系。同时，合适的工具变量（instrumental variable，IV）需满足以下3个基本假设以减少误差存在的可能性：①相关性假设：IVs与NETs相关联；②独立性假设：IVs不能与头颈癌存在共同的原因；③排他性假设：IVs对头颈癌的影响必须仅通过免疫细胞进行介导。本研究设计的具体流程见图1。

1.1.2　数据来源　MPO-DNA复合体全基因组关联研究（Genome-Wide Association Study，GWAS）数据来源：以NETs生物标志物MPO-DNA复合体的GWAS数据集作为暴露因素，从中筛选可以作为IVs的单核苷酸多态性（single nucleotide polymorphism，SNP）数据。Gilly等于2020年发表的研究，可在EBI Open GWAS数据库（https：//www.ebi.ac.uk/）中公开获取，数据ID号为：ebi-a-GCST90010241。该数据集涵盖了18 221 703个SNP和1 322名欧洲个体。另一数据集来自Donkel等2021年发表的研究，可在EBI Open GWAS数据库（https：//www.ebi.ac.uk/）中公开获取，数据ID号为：ebi-a-GCST90013658。该数据集涵盖了7 254 867个SNP和5 590名欧洲个体。

头颈癌的汇总统计数据来自UKB数据库，该GWAS数据更新于2021年，包括373 122例欧洲个体（病例数=1 106例，对照数=372 016例）。数据ID号为ieu-b-4912。

口咽癌的汇总统计数据来自UKB数据库，该GWAS数据更新于2021年，包括372 510例欧洲个体（病例数= 494例，对照数=372 016例）。数据ID号为ieu-b-4968。



In Mendelian randomization analysis, using single nucleotide polymorphisms as instrumental variable(IV) to assess the causal relationship between exposure (NETs) and outcome (head and neck cancer) requires the satisfaction of three basic assumptions

Figure 1　Mendelian randomization experimental design

图1　孟德尔随机化实验设计

口腔癌和口咽癌的汇总统计数据来自UKB数据库，该GWAS数据更新于2021年，包括372 855例欧洲个体（病例数= 839例，对照数=372 016例）。数据ID号为ieu-b-4962。本研究中所采用的数据集均来自公开可获取的资源平台，且可自由下载获取。

1.1.3　IVs的选择　选取IVs的SNPs用于MR分析中用于探究暴露因素与结局之间因果关系。全基因组水平上，与MPO-DNA及头颈癌存在关联性的SNP通过关联性分析被筛选出来。采用*P*值小于5×10^{-8}这一严格标准，将满足相关性假设的SNP筛选出来。通过数据分析，符合条件可用作分析的工具变量数量较少。为获取更多可用作分析的工具变量，*P*值的筛选范围放大至5×10^{-6}。解决了连锁不平衡所产生的误差后，标准设定r^2 = 0.001且窗口 = 10 000 kb确保SNP的独立性。使用harmonise_data函数消除了回文序列，得到的结果同时提升了遗传变异的可靠性和准确性。然后，利用公式通过β^2/SE^2公式（式中*SE*为标准误）计算*F*值评估IVs的强度，通过将*F* <10作为阈值来删除弱IVs[17]。最后，再通过LDlink网站（https：//ldlink.nih.gov/）进行筛选核查，筛选核查排除可能影响结果的混杂因素（如吸烟、口腔疾病史、不良修复体、常食烫热食物、经常饮酒）。

1.1.4　MR分析　本实验主要通过逆方差加权方法这一策略估计暴露与结果两者之间的初始关联，在无多效性的情况下这是最优的无偏估计[18]。逆方差加权是MR分析中使用非常普遍的一种方法，通过加权单核SNP的Wald占比来估计因果关联[19]。

1.1.5　敏感性分析　对于敏感性分析中SNP之间异质性的评估工作，采用了Cochran's Q检验方法。在水平多效性的检测时，应用了MR-egger截距法及MR-PRESSO法这两种方法。当*P*值显示小于0.05时，表明存在异质性。分析流程中若出现异常值的情况，该异常值的剔除操作需优先完成，再完成MR因果估计的重新计算步骤。留一法分析为每个单核苷酸多态性对总体因果估计的影响进行了系统性考察。

1.1.6　统计学分析　优势比（odds ratio，*OR*）和95%置信区间（95% confidence interval，95%*CI*）表示结果，*P*<0.05为差异有显著性意义。在R软件（版本4.2.3）使用“Two Sample MR”和“MR-PRESSO”进行MR分析。

1.2　临床验证

1.2.1　研究对象　本研究经过哈尔滨医科大学附属第一医院伦理委员会审核批准（伦理号：2025415），所有研究对象均了解研究的相关细节并知情同意。纳入2025年1月至10月在哈尔滨医科大学附属第一医院口腔颌面外科收治的HNSCC

患者52例为研究组，男性31例，女性21例。年龄52~79岁，平均年龄（65.0±8.0）岁。其中包括舌鳞癌16例、腭部鳞癌5例、口底鳞癌7例、颊鳞癌8例、牙龈鳞癌10例、咽鳞癌6例。其中Ⅰ期14例，Ⅱ期19例，Ⅲ期11例，Ⅳ期8例。HNSCC的诊断依据2025年美国国立综合癌症网络（NCCN）头颈癌指南[20]。对照组纳入在同一临床中心体检部门随机选取年龄和性别相匹配的志愿者20例。HNSCC组患者入选标准：①血样本收集时无任何临床抗肿瘤治疗（手术、放化疗等）；②经组织病理学活检确诊为头颈鳞状细胞癌；③一般临床资料完整，包括：年龄、性别、身体质量指数（body mass index，BMI）、血常规检查、病理活检、淋巴结转移、癌症患者病程；排除标准：①合并其他恶性肿瘤；②既往治疗HNSCC或复发；③合并严重自身免疫性疾病；④合并重要脏器病变或严重的系统性疾病等；⑤合并严重感染；⑥过去3个月内静脉或动脉血栓栓塞，以及接受抗凝治疗者；⑦哺乳期、孕期妇女。对照组：纳入哈尔滨医科大学附属第一医院同期健康体检者20例，纳入标准：血常规、血脂、离子、肝肾功能等均在参考范围内，心电图、胸片及心脏彩超未见明显异常。记录所有研究对象的一般临床资料，包括年龄、性别、BMI、糖尿病、高血压以及吸烟和饮酒史等。

1.2.2　ELISA检测血清中NETs标志物以及淋巴结转移标志物水平　ELISA试剂盒选购于杭州市臻优品生物科技有限公司，货号分别为：MPO-DNA（SYP-H069）、CitH3（SYP-H4190）、CD44v6（SYP-H4524）、CD109（SYP-H2650）。早上空腹采取受试者外周静脉血4 mL，将血样于室温下制备血清。采用双抗体夹心ELISA技术定量检测血清中MPO-DNA、CitH3、CD44v6、CD109的浓度水平，MPO-DNA检测样本经100倍梯度稀释、CitH3检测样本经10倍梯度稀释、CD109检测样本经30倍梯度稀释、CD44v6检测样本未进行稀释，实验严格遵循制造商提供的操作流程进行检测，结果以ng/mL为单位表示。通过分光光度法在波长450 nm下测定酶底物反应产生的显色变化，最终以两次平行测定的平均值作为检测值。

1.2.3　记录研究对象的凝血功能指标　早上空腹采取受试者外周静脉血4 mL，送至本院检验科进行血浆样本凝血酶原时间（plasma prothrombin time，PT）、活化部分凝血活酶时间（activated partial thromboplastin tim，APTT）、凝血酶时间（thrombin time，TT）、D二聚体（D-dimer，DD）和纤维蛋白原（fibrinogen，FIB）的检测。冻存的血清样本用于检测外周血中的NETs指标MPO-DNA、CitH3，淋巴结转移指标CD44v6和CD109。所有患者均在治疗前完成血样采集。

1.2.4　诊断效能分析　计算所有受试者工作曲线（receiver operating characteristic curve，ROC）及其曲线下面积（area under curve，AUC），Youden's指数用于最大化敏感性和特异性之间的差异，以个体化每个参数的最佳截断值。

1.2.5　统计学分析　采用SPSS 27、GraphPad Prism9.5软件进行统计分析并作图。HNSCC组与正常对照组性别、糖尿病、吸烟和饮酒史指标组间对比采用卡方检验。HNSCC组与正常对照组的BMI、年龄、PT、APTT、TT、FIB、DD等指标的组间比较采用独立样本t检验。采用Pearson相关性分析对MPO-DNA、CitH3与CD44v6、CD109、PT、APTT、TT、FIB、DD的相关性进行分析。检验水准$\alpha = 0.05$。

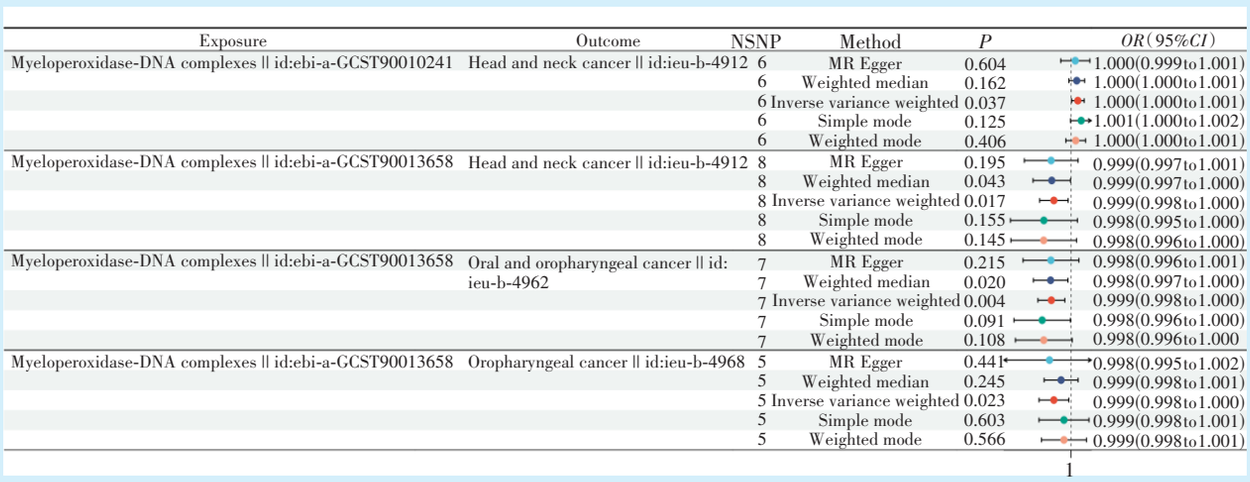
2　结　果

2.1　NETs与头颈癌的因果关系的MR结果

通过逆方差加权法（inverse variance weighted，IVW）、简单模式、加权中位数法、模式加权法以及MR-Egger法5种方法，NETs与头颈癌间因果效应得到确定，IVW结果P值分别为：P_1=0.037、P_2=0.017、P_3=0.004、P_4=0.023（图2）。在5种MR方法中，得到了贝塔估计值方向的一致性，因此可以确保研究结果的稳定性。在敏感性检验中，异质性与水平多效性均未显现（P>0.05，P MR-PRESSO global tests>0.05）（表1）。其中3次MR分析结果显示NETs是头颈癌的保护因素，1次MR分析结果显示NETs是头颈癌的危险因素。补充文件显示，对纳入的SNP进行MR Egger截距检验提示SNP不存在水平多效性。对纳入的SNP进行敏感性分析显示，在去除任一SNP后，剩余SNP对结局影响的效应区间均在无效线右侧并与总体效应区间相似，表明MR结果稳健。

2.2　两组受试者的临床特征和实验室检查结果比较

HNSCC组与对照组受试者间的性别、年龄、BMI、高血压史、糖尿病史、吸烟史、饮酒史、PT、APTT、TT差异均无统计学意义（均为P > 0.05）。与对照组受试者DD、FIB水平分别（0.19±0.05）mg/L、（2.5±0.6）g/L，HNSCC组DD、FIB的表达水平均显



NSNP: number of single nucleotide polymorphisms; *OR*: odds ratio ; *CI*: confidence interval; the illustration demonstrates that a causal relationship exists between the extracellular trap formation of neutrophils and head and neck cancer, as determined by the inverse variance weighted (IVW) method (a ratio >1 indicates a positive correlation, while <1 indicates a negative correlation)

Figure 2　Causality diagram of neutrophil extracellular traps and head and neck cancer

图2　中性粒细胞胞外诱捕网与头颈癌的因果关系图

表1　孟德尔随机化分析：异质性检验、多效性检验及MR-PRESSO

Table 1　Mendelian randomization analysis: heterogeneity test, pleiotropy test, and MR-PRESSO

Exposure	Outcome	Heterogeneity	Pleiotropy	MR - PRESSO Global *P*
MPO-DNA id: ebi-a-GCST90013658	Head and neck cancer id: ieu-b-4912	0.820	0.713	0.741
MPO-DNA id: ebi-a-GCST90013658	Oropharyngeal cancer id: ieu-b-4968	0.251	0.860	0.338
MPO-DNA id: ebi-a-GCST90013658	Oral and oropharyngeal cancer id: ieu-b-4962	0.660	0.972	0.734
MPO-DNA id: ebi-a-GCST90010241	Head and neck cancer id: ieu-b-4912	0.944	0.723	0.948

The MR-PRESSO test indicates significant horizontal multicollinearity in the set of instrumental variables (IV) included when Global $P < 0.05$; when Global $P > 0.05$, it indicates no horizontal multicollinearity of abnormal IV is detected. MPO-DNA: myeloperoxidase-DNA complex

著升高，分别为（0.32±0.13）mg/L、（3.2±0.9）g/L，差异均有统计学意义（均为$P<0.001$）（见表2）。

2.3　NETs相关标志物与凝血功能、淋巴结转移标志物的相关性分析

Pearson相关矩阵分析结果显示MPO-DNA与DD、FIB、CD44v6、CD109的Pearson相关系数分别为0.686、0.531、0.7、0.5，CitH3与DD、FIB、CD44v6、CD109的Pearson相关系数分别为0.456、0.503、0.525、0.603（$P<0.05$）（图3）。

2.4　外周血中的NETs水平对HNSCC的诊断效果

HNSCC患者外周血中MPO-DNA和CitH3浓度分别为（156.8±40.2）ng/mL、（23.2±4.0）ng/mL，对照组MPO-DNA和CitH3浓度分别为（112.4±22.2）ng/mL、（17.8±2.6）ng/mL，两组比较具有显著差异（$P<0.001$）。

进一步分析NETs标志物对HNSCC的诊断效果，结果显示，MPO-DNA、CitH3、CitH3+MPO-DNA的ROC的AUC分别为0.863、0.892、0.905，三者的AUC依次增加（表3、图4）。

2.5　不同NETs严重状态下的凝血功能和淋巴结转移标志物特征

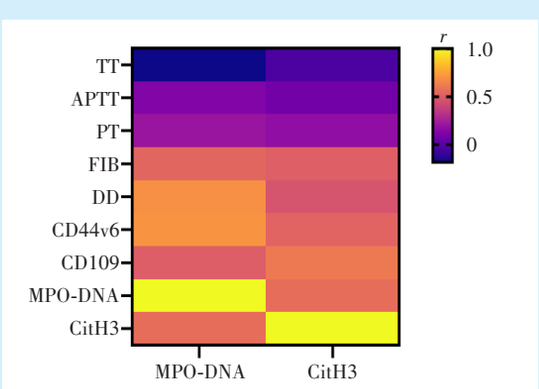
为了检测NETs形成与凝血功能和淋巴结转移标志物的关系，将HNSCC患者分成NETs相关标志物表达量前25%的HNSCC患者（高表达组）和其余病例（低表达组）进行进一步分析。MPO-DNA高表达组患者的FIB、DD、CD44v6、CD109的血清浓度

表2　两组受试者的临床特征和实验室检查结果比较

Table 2　Clinical characteristics and laboratory test results of the two groups of subjects　$\bar{x}\pm s$

Project	Control group (n=20)	HNSCC group (n=52)	t/χ^2	P
Gender (male)	11(55)	31(59.62)	0.1266	0.793
Age/years	62.3±7.1	65.0±8.0	1.313	0.194
BMI/(kg/m^2)	24.3±3.7	23.2±2.5	1.212	0.236
Hypertension[n(%)]	7(35)	18(34.62)	0.0009	>0.999
Diabetes[n(%)]	3(15)	12(23.08)	0.5713	0.534
Smoking[n(%)]	4(20)	21(40.38)	2.648	0.166
Drinking wine[n(%)]	4(20)	13(25)	0.2002	0.764
PT/s	11.8±0.7	11.8±1.3	0.2917	0.772
APTT/s	27.2±2.0	27.4±2.7	0.2818	0.779
DD/(mg/L)	0.19±0.05	0.32±0.13	6.066	<0.001
FIB/(g/L)	2.5±0.6	3.2±0.9	3.542	<0.001
TT/s	17.9±0.8	17.5±0.8	1.868	0.066

HNSCC: head and neck squamous cell carcinoma; BMI: body mass index; PT: Plasma sample prothrombin time; APTT: activated partial thromboplastin time; TT: thrombin time; DD: D-dimer; FIB: fibrinogen



The closer it is to yellow, the greater the correlation; the closer it is to purple, the smaller the correlation. TT: thrombin time; APTT: activated partial thromboplastin time; PT: Plasma sample prothrombin time; FIB: fibrinogen; DD: D-dimer; CD44v6 and CD109 are lymph node metastasis marker characteristics. MPO-DNA: myeloperoxidase-DNA complex; CitH3: citrullinated histone H3

Figure 3　Pearson correlation matrix analysis of neutrophil extracellular traps related biomarkers with coagulation function and lymph node metastasis markers

图3　中性粒细胞胞外诱捕网相关标志物与凝血功能、淋巴结转移标志物的Pearson相关矩阵分析

分别为（3.9±0.5）g/L、（0.46±0.16）mg/L、（151.4±25.6）ng/mL、（55.8±6.1）ng/mL，均比MPO-DNA低表达组患者的血清浓度高，差异具有统计学意义（均P < 0.05）。CitH3高表达组患者的FIB、CD44v6、CD109的血清浓度分别为（3.7±1.1）g/L、（134.7±26.8）ng/mL、（57.8±5.7）ng/mL，较CitH3低表达患者高，差异具有统计学意义（均P < 0.05）。见表4。

2.6　NETs相关标志物与HNSCC临床分期的关系

将HNSCC患者分为早期组（Ⅰ~Ⅱ期）和晚期组（Ⅲ~Ⅳ期），早期患者MPO-DNA和CitH3分别为（132.4±16.4）ng/mL、（21.3±2.9）ng/mL均低于晚期患者MPO-DNA和CitH3，分别为（199.3±33.1）ng/mL、（26.6±3.7）ng/mL，两者差异均有统计学意义（P < 0.05）。

3　讨　论

NETs是以多种酶、多种蛋白为骨架的网状复合体[21-22]。NETs在多种原发肿瘤病程和转移部位中被检测到，作用包括肿瘤细胞脱离、血管渗出、循环肿瘤细胞存活、肿瘤细胞定殖生长[23-24]，同时也发现抑制NETs的形成可产生抗癌效果[25-26]。NETs在肿瘤血管生成中起着重要的作用[27-28]。在胰腺癌中，NETs可直接支持人体内皮细胞的增殖和内皮细胞形成血管样结构，推动新血管生成[29]。在缺血性视网膜病变中，NETs通过清除衰老、功能不佳的视网膜内皮细胞，实现血管重塑[30]。

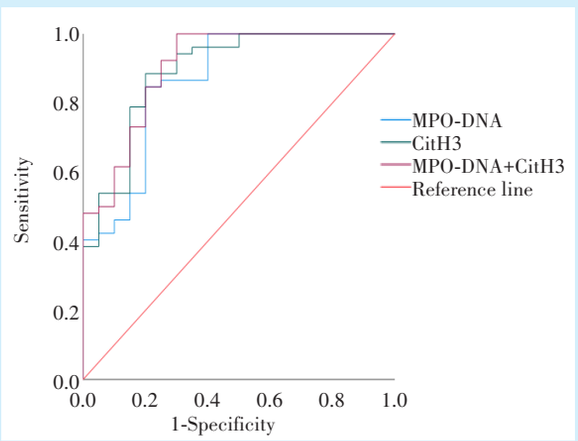
本研究选取CitH3和MPO-DNA水平代表NETs的水平。其中重要组成成分MPO-DNA作为MR分析的暴露因素，本研究尝试使用MR分析将NETs与头颈癌联系起来。在本研究中，MR分析以探索为目的分析NETs与头颈癌之间的关系，证明了NETs与头颈癌之间存在一定的联系。4次MR分析结果中3次结果显示NETs是头颈癌的保护因

表3　髓过氧化物酶- DNA复合物、瓜氨酸化组蛋白H3、髓过氧化物酶- DNA复合物+瓜氨酸化组蛋白H3在头颈部鳞状细胞癌中的诊断效能

Table 3　Diagnostic efficacy of myeloperoxidase-DNA complex, citrullinated histone H3, and myeloperoxidase-DNA complex+citrullinated histone H3 in head and neck squamous cell carcinoma

	Testing indicators	AUC(95% *CI*)	Sensitivity	Specificity	Youden index	Cut-off
Control group- HNSCC group (20-52)	MPO-DNA	0.863 (0.763-0.964)	0.846	0.8	0.646	121.77
	CitH3	0.892 (0.805-0.979)	0.885	0.8	0.685	19.14
	MPO-DNA+CitH3	0.905 (0.823-0.986)	1.000	0.7	0.7	

HNSCC: head and neck squamous cell carcinoma; MPO-DNA: myeloperoxidase-DNA complex; CitH3: citrullinated histone H3



HNSCC: head and neck squamous cell carcinoma; MPO-DNA: myeloperoxidase-DNA complex; CitH3: citrullinated histone H3

Figure 4　Receiver operating characteristic curve of myeloperoxidase-DNA complex, citrullinated histone H3, and myeloperoxidase-DNA complex+citrullinated histone H3 in head and neck squamous cell carcinoma

图4　髓过氧化物酶- DNA复合物、瓜氨酸化组蛋白H3、髓过氧化物酶- DNA复合物+瓜氨酸化组蛋白H3在头颈部鳞状细胞癌中受试者工作曲线

素，1次结果显示NETs的风险因素。结果呈现双向性可能与多个因素有关。首先MR分析的结果依赖SNPs的选择、样本量、混杂因素控制。IVs的*F*统计量、水平多效性、混杂因素都被进行了筛查，但依旧会存在假阳性的结果。其次样本量较小，头颈癌、口腔癌及口咽癌的GWAS数据库样本量与其他常见癌症相比较少，分析时易受随机误差影响。双向性结果可能与NETs在恶性肿瘤中的双重作用机制有关。一方面，NETs可以通过释放中性粒弹性蛋白酶、MPO-DNA等成分直接杀死肿瘤细胞；同时，NETs能捕获循环肿瘤细胞阻止其远处转移[31]。另一方面，在癌症进展期，肿瘤细胞可以诱导中性粒细胞形成促肿瘤性质的NETs，其释放的DNA和组蛋白可激活TLR4信号通路，促进肿瘤细胞增殖和侵袭[32]。本研究还发现MR结果得出的*OR*值接近1，但临床研究显示NETs与HNSCC之间存在显著关联。这是因为多数NETs相关的遗传变异可能为弱效应位点，这导致MR分析结果的SNPs联合构建的遗传风险评估对NETs的调控作用有限，通过遗传预测NETs与头颈癌风险的关联较弱。另外临床中的NETs受多基因以及肿瘤微环境调控并且是水平动态变化的，这些因素对NETs的影响非单一遗传因素决定。本研究首次将MR方法应用于NETs与HNSCC的因果推断，为理解二者关系提供了遗传学层面的新视角。

本研究发现与健康人群相比，HNSCC患者外周静脉血中的CitH3和MPO-DNA水平明显更高。ROC曲线分析显示，MPO-DNA、CitH3及其联合检测对HNSCC均具有良好的诊断效能。ROC分析无论是CitH3、MPO-DNA单一诊断还是CitH3+MPO-DNA联合诊断都可以明显地区分健康人群与HNSCC的患者，这表明NETs标志物有望作为HNSCC辅助诊断的生物标志物。HNSCC患者外周静脉血中的CitH3、MPO-DNA水平与HNSCC患者的肿瘤临床分期存在一定的关联性，特别是在晚期HNSCC患者中这种关联性更加明显。此前研究发现，CitH3与胶质瘤的临床分期相关[33]。Rayes等[34]检测肺癌患者外周血中的MPO-DNA水平，发现晚期（Ⅱ~Ⅲ期）患者高于早期（Ⅰ期）。也有一项关于卵巢癌的研究发现患者外周静脉血CitH3水平与临床分期无相关性[35]。既往研究结果进一步证实了NETs在多种癌症临床分期的关联。

本研究在HNSCC中揭示了NETs与高凝状态标志物的相关性。本研究发现HNSCC患者组和健康人群组年龄、性别、BMI、高血压史、糖尿病史、吸烟饮酒史、部分凝血功能指标（PT、APTT、TT）的差异均无统计学意义。HNSCC患者组DD、FIB水平显著高于健康对照组，且NETs标志物与DD、FIB

表4　不同中性粒细胞胞外诱捕网标志物表达量的头颈部鳞状细胞癌患者的凝血功能和淋巴结转移标志物水平比较

Table 4　Comparison of coagulation function and lymph node metastasis markers in head and neck squamous cell carcinoma patients with different neutrophil extracellular traps marker expression levels　$\bar{x}\pm s$

	MPO-DNA				CitH3			
	Lower (n=39)	Higher (n=13)	t	P	Lower (n=39)	Higher (n=13)	t	P
PT/s	11.6±0.7	12.4±2.4	1.164	0.266	11.7±0.7	12.2±2.4	0.667	0.517
APTT/s	27.1±2.1	28.5±3.9	1.260	0.228	27.3±2.1	27.9±4.1	0.522	0.609
DD/(mg/L)	0.27±0.07	0.46±0.16	4.119	0.001	0.31±0.13	0.36±0.09	1.367	0.178
FIB/(g/L)	2.9±0.9	3.9±0.5	4.859	<0.001	3.0±0.8	3.7±1.1	2.642	0.011
TT/s	17.7±0.9	17.3±0.5	1.717	0.094	17.4±0.9	17.8±0.7	1.323	0.192
CD44v6/(ng/mL)	106.2±24.1	151.4±25.6	5.777	<0.001	111.7±30.9	134.7±26.8	2.394	0.020
CD109/(ng/mL)	47.9±8.1	55.8±6.1	3.212	0.002	47.2±7.4	57.8±5.7	4.710	<0.001

The top 25% of patients with HNSCC with the highest expression levels of NET-related biomarkers (MPO-DNA and CitH3) were classified as the higher group, while the rest are classified as the lower group. MPO-DNA: myeloperoxidase-DNA complex; CitH3: citrullinated histone H3; PT: Plasma sample prothrombin time; APTT: activated partial thromboplastin time; TT: thrombin time; DD: D-dimer; FIB: fibrinogen; CD44v6 and CD109 are lymph node metastasis marker characteristics

呈显著正相关。进一步分层分析显示，NETs高表达组患者DD、FIB显著升高，提示NETs可能通过促进凝血功能异常，参与HNSCC的病程进展过程。相关文献显示，CitH3与癌症相关静脉血栓栓塞症（venous thromboembolism，VTE）生物标志物D—二聚体、可溶性P—选择素、血浆凝血酶原片段1+2和人凝血因子Ⅷ进行比较，发现CitH3水平同样是VTE的强预测因子[36]。MPO-DNA在无凝血酶、低纤维蛋白原浓度条件下介导非传统纤维蛋白原血栓形成[37]。本实验结果与既往研究中NETs促进肿瘤相关血栓形成的结论一致。并且本研究在HNSCC中明确了NETs标志物与具体凝血指标的量化关系，为HNSCC患者血栓风险评估提供了新的生物学靶点。

此外，本研究发现NETs标志物与淋巴结转移标志物CD44v6、CD109也存在显著正相关，且NETs高表达组的CD44v6、CD109水平显著升高。这一结果揭示了NETs可能通过调控淋巴结转移相关分子的表达，促进HNSCC的侵袭转移。NETs在多种肿瘤中被报道通过不同机制促进癌细胞侵袭转移作用。在乳腺癌、肺癌中发现，NETs通过诱导上皮—间质转化（epithelial-mesenchymal transition，EMT）赋予癌细胞侵袭表型[38-39]。在肝细胞癌中，NETs癌细胞来源的白细胞介素-8通过激活TLR4/9-环氧化酶-2；增加组织蛋白酶G、氧化线粒体DNA促进肿瘤侵袭转移[40-41]。在胰腺癌中NETs通过激活白细胞介素-1β/表皮生长因子受体（epidermal growth factor receptor，EGFR）/细胞外调节蛋白激酶（extracellular regulated protein kinases，ERK）通路、抑制$CD8^+$T细胞功能促进癌细胞迁移侵袭[42-43]。在结肠癌中，NETs释放高迁移率族蛋白B1（high mobility group protein B1，HMGB1）并激活TLR9促进癌症增生和转移[44]。这些NETs在不同癌症中的通路机制作用，为理解HNSCC转移机制提供了新线索。

本研究仅检测了HNSCC患者部分凝血功能指标以及部分淋巴结转移标志物，存在一定的局限性，样本数量较少，造成一定的偏倚并且并未从机制方面探讨NETs影响HNSCC的机制。现已有文献证明了NETs与口腔鳞状细胞癌的关系[45]并且驱动全身炎症增加其促凝活性[46]。NETs的形成与疾病发展过程复杂多样，其在HNSCC干预机制还需在未来更深入地探究。

综上所述，本研究通过MR分析与临床验证相结合，首次揭示NETs与HNSCC之间存在遗传与表型层面的关联。NETs标志物不仅可能作为HNSCC潜在诊断标志物，其水平变化还与肿瘤分期、凝血状态及转移潜能相关，为HNSCC的早期诊断、预后评估及靶向干预提供了新思路。未来还需要进一步大样本的观察性研究和临床试验确定NETs相关标志物在HNSCC发生发展中的诊断、预后和诊断潜能。

【Author contributions】 Li D processed the research, analyzed the data and wrote the article. Song HQ designed the study and revised the article. All authors read and approved the final submitted manuscript.

参考文献

[1] Johnson DE, Burtness B, Leemans CR, et al. Head and neck squamous cell carcinoma[J]. Nat Rev Dis Primers, 2020, 6(1): 92. doi: 10.1038/s41572-020-00224-3.

[2] Chamoli A, Gosavi AS, Shirwadkar UP, et al. Overview of oral cavity squamous cell carcinoma: risk factors, mechanisms, and diagnostics[J]. Oral Oncol, 2021, 121: 105451. doi: 10.1016/j.oraloncology.2021.105451.

[3] Lecot P, Ardin M, Dussurgey S, et al. Gene signature of circulating platelet-bound neutrophils is associated with poor prognosis in cancer patients[J]. Int J Cancer, 2022, 151(1): 138-152. doi: 10.1002/ijc.33991.

[4] Correia BF, Grosa D, Salvador R, et al. Neutrophils matter: new clinical insights on their role in the progression of metastatic breast cancer[J]. Breast Cancer Res, 2025, 27(1): 223. doi: 10.1186/s13058-025-02201-8.

[5] Brinkmann V, Reichard U, Goosmann C, et al. Neutrophil extracellular traps kill bacteria[J]. Science, 2004, 303(5663): 1532-1535. doi: 10.1126/science.1092385.

[6] Berger-Achituv S, Brinkmann V, Abed UA, et al. A proposed role for neutrophil extracellular traps in cancer immunoediting[J]. Front Immunol, 2013, 4: 48. doi: 10.3389/fimmu.2013.00048.

[7] Wang H, Zhang Y, Wang Q, et al. The regulatory mechanism of neutrophil extracellular traps in cancer biological behavior[J]. Cell Biosci, 2021, 11(1): 193. doi: 10.1186/s13578-021-00708-z.

[8] Kaltenmeier C, Yazdani HO, Morder K, et al. Neutrophil extracellular traps promote T cell exhaustion in the tumor microenvironment[J]. Front Immunol, 2021, 12: 785222. doi: 10.3389/fimmu.2021.785222.

[9] Chen Y, Tetz ZA, Zeng X, et al. CitH3, a druggable biomarker for human diseases associated with acute NETosis and chronic immune dysfunction[J]. Pharmaceutics, 2025, 17(7): 809. doi: 10.3390/pharmaceutics17070809.

[10] Barakzie A, van der Steen W, Jansen AJG, et al. Association of NETs markers with clinical and radiological outcomes in patients with acute ischemic stroke undergoing thrombectomy: does heparin treatment modify this? [J]. Transl Stroke Res, 2025, 16(6): 1985-1995. doi: 10.1007/s12975-025-01362-0.

[11] Zuo Y, Yalavarthi S, Shi H, et al. Neutrophil extracellular traps in COVID-19[J]. JCI Insight, 2020, 5(11): e138999. doi: 10.1172/jci.insight.138999.

[12] Wu Z, Li P, Tian Y, et al. Peptidylarginine deiminase 2 in host immunity: current insights and perspectives[J]. Front Immunol, 2021, 12: 761946. doi: 10.3389/fimmu.2021.761946.

[13] Liu X, Arfman T, Wichapong K, et al. PAD4 takes charge during neutrophil activation: impact of PAD4 mediated NET formation on immune-mediated disease[J]. J Thromb Haemost, 2021, 19(7): 1607-1617. doi: 10.1111/jth.15313.

[14] Valadez-Cosmes P, Raftopoulou S, Mihalic ZN, et al. Myeloperoxidase: growing importance in cancer pathogenesis and potential drug target[J]. Pharmacol Ther, 2022, 236: 108052. doi: 10.1016/j.pharmthera.2021.108052.

[15] Liu TW, Gammon ST, Yang P, et al. Myeloid cell-derived HOCl is a paracrine effector that trans-inhibits IKK/NF-κB in melanoma cells and limits early tumor progression[J]. Sci Signal, 2021, 14(677): eaax5971. doi: 10.1126/scisignal.aax5971.

[16] 王晶, 张国燕, 程杉. 孟德尔随机化的良好实践 - 孟德尔随机化分析的常见设计、关键挑战及优化[J]. 首都医科大学学报, 2023, 44(6): 1087-1094. doi: 10.3969/j. issn. 1006-7795. 2023.06.027.
Wang J, Zhang GY, Cheng S. Good practices in Mendelian randomization: common designs, key challenges, and optimization in Mendelian randomization analysis[J]. J Cap Med Univ, 2023, 44(6): 1087-1094. doi: 10.3969/j.issn.1006-7795.2023.06.027.

[17] Wang X, Zhang J, Song XY, et al. Gut microbiota and insomnia: Mendelian randomization and network pharmacology to predict potential intervention with traditional Chinese medicine[J]. Arch Med Sci, 2025, 21(5): 1821-1835. doi: 10.5114/aoms/207509.

[18] Pierce BL, Burgess S. Efficient design for Mendelian randomization studies: subsample and 2-sample instrumental variable estimators[J]. Am J Epidemiol, 2013, 178(7): 1177-1184. doi: 10.1093/aje/kwt084.

[19] Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression[J]. Int J Epidemiol, 2015, 44(2): 512-525. doi: 10.1093/ije/dyv080.

[20] Colevas AD, Cmelak AJ, Pfister DG, et al. NCCN guidelines® insights: head and neck cancers, version 2.2025[J]. J Natl Compr Canc Netw, 2025, 23(2): 2-11. doi: 10.6004/jnccn.2025.0007.

[21] Qiao S, Yuan J, Zhang SC, et al. Neutrophil extracellular traps in central nervous system disorders: mechanisms, implications, and emerging perspective[J]. Front Immunol, 2025, 16: 1602336. doi: 10.3389/fimmu.2025.1602336.

[22] Ibrahim N, Eilenberg W, Neumayer C, et al. Neutrophil extracellular traps in cardiovascular and aortic disease: a narrative review on molecular mechanisms and therapeutic targeting[J]. Int J Mol Sci, 2024, 25(7): 3983. doi: 10.3390/ijms25073983.

[23] Adrover JM, McDowell SAC, He XY, et al. NET working with cancer: the bidirectional interplay between cancer and neutrophil extracellular traps[J]. Cancer Cell, 2023, 41(3): 505-526. doi: 10.1016/j.ccell.2023.02.001.

[24] Hu W, Lee SML, Bazhin AV, et al. Neutrophil extracellular traps facilitate cancer metastasis: cellular mechanisms and therapeutic strategies[J]. J Cancer Res Clin Oncol, 2023, 149(5): 2191-2210. doi: 10.1007/s00432-022-04310-9.

[25] Gazzara E, Adrover JM, Lui A, et al. Targeting neutrophil extracellular traps to inhibit colon cancer tumor necrosis and metastasis [J]. bioRxiv, 2025. doi: 10.1101/2025.05.30.657122.

[26] Han Y, Han M, Wang T, et al. Inhibiting the formation of neutrophil extracellular traps to prevent the recurrence of post-operative glioblastoma[J]. Nat Commun, 2025, 16(1): 10971. doi: 10.1038/s41467-025-65933-3.

[27] Zhan X, Wu R, Kong XH, et al. Elevated neutrophil extracellular traps by HBV-mediated S100A9-TLR4/RAGE-ROS cascade facilitate the growth and metastasis of hepatocellular carcinoma[J]. Cancer Commun (Lond), 2023, 43(2): 225-245. doi: 10.1002/

cac2.12388.

[28] Zhang C, Wu D, Dong B, et al. The scaffold of neutrophil extracellular traps promotes CCA progression and modulates angiogenesis *via* ITGAV/NFκB[J]. Cell Commun Signal, 2024, 22(1): 103. doi: 10.1186/s12964-024-01500-5.

[29] Jung HS, Gu J, Kim JE, et al. Cancer cell-induced neutrophil extracellular traps promote both hypercoagulability and cancer progression[J]. PLoS One, 2019, 14(4): e0216055. doi: 10.1371/journal.pone.0216055.

[30] Zeng J, Wu M, Zhou Y, et al. Neutrophil extracellular traps (NETs) in ocular diseases: an update[J]. Biomolecules, 2022, 12(10): 1440. doi: 10.3390/biom12101440.

[31] Cristinziano L, Modestino L, Antonelli A, et al. Neutrophil extracellular traps in cancer[J]. Semin Cancer Biol, 2022, 79: 91-104. doi: 10.1016/j.semcancer.2021.07.011.

[32] Ren J, He J, Zhang H, et al. Platelet TLR4-ERK5 axis facilitates NET-mediated capturing of circulating tumor cells and distant metastasis after surgical stress[J]. Cancer Res, 2021, 81(9): 2373-2385. doi: 10.1158/0008-5472.CAN-20-3222.

[33] Zhang S, Guo M, Liu Q, et al. Neutrophil extracellular traps induce a hypercoagulable state in glioma[J]. Immun Inflamm Dis, 2021, 9(4): 1383-1393. doi: 10.1002/iid3.488.

[34] Rayes RF, Mouhanna JG, Nicolau I, et al. Primary tumors induce neutrophil extracellular traps with targetable metastasis promoting effects[J]. JCI Insight, 2019, 5(16): e128008. doi: 10.1172/jci.insight.128008.

[35] Dobilas A, Thalin C, Wallen H, et al. Circulating markers of neutrophil extracellular traps (NETs) in patients with ovarian tumors [J]. Anticancer Res, 2022, 42(2): 965-971. doi: 10.21873/anticanres.15556.

[36] Pabinger I, Thaler J, Ay C. Biomarkers for prediction of venous thromboembolism in cancer[J]. Blood, 2013, 122(12): 2011-2018. doi: 10.1182/blood-2013-04-460147.

[37] Barinov NA, Pavlova ER, Tolstova AP, et al. Myeloperoxidase-induced fibrinogen unfolding and clotting[J]. Microsc Res Tech, 2022, 85(7): 2537-2548. doi: 10.1002/jemt.24107.

[38] Dimitrov J, Maddalena M, Terlizzi C, et al. Dynamic roles of neutrophil extracellular traps in cancer cell adhesion and activation of Notch 1-mediated epithelial-to-mesenchymal transition in EGFR-driven lung cancer cells[J]. Front Immunol, 2024, 15: 1470620. doi: 10.3389/fimmu.2024.1470620.

[39] Martins-Cardoso K, Almeida VH, Bagri KM, et al. Neutrophil extracellular traps (NETs) promote pro-metastatic phenotype in human breast cancer cells through epithelial-mesenchymal transition[J]. Cancers (Basel), 2020, 12(6): 1542. doi: 10.3390/cancers12061542.

[40] Yang LY, Luo Q, Lu L, et al. Increased neutrophil extracellular traps promote metastasis potential of hepatocellular carcinoma *via* provoking tumorous inflammatory response[J]. J Hematol Oncol, 2020, 13(1): 3. doi: 10.1186/s13045-019-0836-0.

[41] Guan X, Lu Y, Zhu H, et al. The crosstalk between cancer cells and neutrophils enhances hepatocellular carcinoma metastasis *via* neutrophil extracellular traps-associated cathepsin G component: a potential therapeutic target[J]. J Hepatocell Carcinoma, 2021, 8: 451-465. doi: 10.2147/JHC.S303588.

[42] Jin W, Xu HX, Zhang SR, et al. Tumor-infiltrating NETs predict postsurgical survival in patients with pancreatic ductal adenocarcinoma[J]. Ann Surg Oncol, 2019, 26(2): 635-643. doi: 10.1245/s10434-018-6941-4.

[43] Zhang Y, Chandra V, Riquelme Sanchez E, et al. Interleukin-17-induced neutrophil extracellular traps mediate resistance to checkpoint blockade in pancreatic cancer[J]. J Exp Med, 2020, 217(12): e20190354. doi: 10.1084/jem.20190354.

[44] Tohme S, Yazdani HO, Al-Khafaji AB, et al. Neutrophil extracellular traps promote the development and progression of liver metastases after surgical stress[J]. Cancer Res, 2016, 76(6): 1367-1380. doi: 10.1158/0008-5472.CAN-15-1591.

[45] 杨圣锋, 顾欣, 张瑞, 等. 中性粒细胞胞外诱捕网与口腔鳞状细胞癌关系的研究进展[J]. 口腔疾病防治, 2024, 32(11): 894-900. doi: 10.12016/j.issn.2096-1456.202330441.
Yang SF, Gu X, Zhang R, et al. Research progress on the association between neutrophil extracellular traps and oral squamous cell carcinoma[J]. J Prev Treat Stomatol Dis, 2024, 32(11): 894-900. doi: 10.12016/j.issn.2096-1456.202330441.

[46] Li B, Liu Y, Hu T, et al. Neutrophil extracellular traps enhance procoagulant activity in patients with oral squamous cell carcinoma [J]. J Cancer Res Clin Oncol, 2019, 145(7): 1695-1707. doi: 10.1007/s00432-019-02922-2.

（编辑　周春华）