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·专题研究·

术前中性粒细胞与淋巴细胞比值对胰腺癌手术患者预后价值的Meta分析

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摘　要

背景与目的：胰腺癌是恶性程度极高的实体恶性肿瘤之一，因早期缺乏症状导致多数患者确诊时已处于局部进展期或晚期。因此，探索术前判断预后的标志物对临床制定诊疗策略至关重要。目前，术前中性粒细胞与淋巴细胞比率（NLR）与胰腺癌患者预后的关系尚存在争议。本研究使用Meta分析方法，探讨术前NLR与胰腺癌患者术后生存获益之间的关系及其预后价值。

方法：计算机检索PubMed、Cochrane Library、Web of Science、中国知网、维普及万方数据库收集术前NLR值与胰腺癌患者术后总体生存期（OS）和无病生存期（DFS）关系的研究，检索时限均从建库至2022年3月31日，由两名评价员独立筛选并纳入文献，提取资料并评价纳入研究的偏倚风险后，利用Revman 5.4和Stata 16.0软件对风险比（*HR*）和95%可信区间（*CI*）进行合并，并根据异质性选择对应的效应模型。对纳入研究的文献进行敏感度分析，用Egger回归检验判断纳入文献是否存在显著发表偏倚。

结果：共纳入25项回顾性研究，4 796例研究对象。研究中有24篇文献报道了NLR与术后OS之间的关系，6篇报道了NLR与术后DFS之间的关系。纳入回顾性研究的NLR临界值和样本量分别为2.0~5.0和28~442例，纳入研究NOS评分均在6~9分。Meta分析结果显示，术前高水平NLR的胰腺癌患者术后OS（*HR*=1.24，95% *CI*=1.16~1.33，*P*<0.000 01）与DFS（*HR*=1.39，95% *CI*=1.21~1.60，*P*<0.000 01）均明显缩短；基于不同NLR临界值的亚组分析结果均显示，术前高水平NLR的胰腺癌患者术后缩短的OS与DFS明显有关（均*P*<0.05）。敏感度分析结果如显示，OS和DFS的合并效应量无明显变化；发表偏倚分析结果显示，纳入研究无明显发表偏倚。

结论：术前高水平胰腺癌NLR患者术后OS和DFS较术前低水平NLR患者缩短，术前NLR值是评估胰腺癌患者预后及生存获益的潜在标志物。受研究数量与质量限制，上述结论尚需更多高质量研究予以验证。

关键词　胰腺肿瘤；炎症；预后；Meta分析

中图分类号：R736.7

Meta-analysis of prognostic value of preoperative neutrophil-to-lymphocyte ratio in pancreatic cancer surgery patients

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Abstract

Background and Aims: Pancreatic cancer is one of the highly malignant solid tumors, and most patients are diagnosed at the locally advanced or late stage due to the lack of early symptoms. Therefore, exploring preoperative prognostic markers is crucial for making diagnosis and treatment strategies in clinical practice. Currently, the relationship between preoperative neutrophil-to-lymphocyte ratio (NLR) and the postoperative prognosis of pancreatic cancer patients is still controversial. This study was conducted to investigate the association of preoperative NLR with the postoperative survival benefits of pancreatic cancer patients, as well as its prognostic value through a Meta-analysis.

Methods: The studies concerning the relationship between preoperative NLR values and postoperative overall survival (OS) and disease-free survival (DFS) of pancreatic cancer patients were collected by searching PubMed, Cochrane Library, Web of Science, CNKI, VIP, and Wanfang databases. The search was limited from the inception of the databases to March 31, 2022. Two reviewers independently screened and included the literature, and then extracted data, and assessed the risk of bias in the included studies. Revman 5.4 and Stata 16.0 software were used to combine the hazard ratio (*HR*) and 95% confidence interval (*CI*), and the corresponding effect model was selected based on heterogeneity. Sensitivity analysis was performed on the included studies, and the Egger regression test was used to determine if there was significant publication bias in the included literature.

Results: A total of 25 retrospective studies with 4 796 subjects were included. Of these, 24 articles reported the relationship between NLR and postoperative OS, and 6 articles reported the relationship between NLR and postoperative DFS. The NLR cutoff values and sample sizes in the included retrospective studies were 2.0−5.0 and 28−442, respectively, and the NOS scores of the included studies were between 6−9. Meta-analysis results showed that pancreatic cancer patients with high preoperative NLR levels had significantly shortened postoperative OS (*HR*=1.24, 95% *CI*=1.16−1.33, *P*<0.000 01) and DFS (*HR*=1.39, 95% *CI*=1.21−1.60, *P*<0.000 01). Subgroup analyses based on different NLR cutoff values also showed that high preoperative NLR levels were significantly associated with shortened postoperative OS and DFS (all *P*<0.05). As revealed by the sensitivity analysis results, the pooled effect sizes for OS and DFS showed no significant changes. Publication bias analysis showed no significant publication bias in the included studies.

Conclusion: Pancreatic cancer patients with high preoperative NLR levels have shortened postoperative OS and DFS compared to those with low preoperative NLR levels. Preoperative NLR value is a potential biomarker for evaluating the prognosis and survival benefits of pancreatic cancer patients. Due to limitations in the number and quality of studies, further high-quality research is needed to verify the above conclusions.

Key words Pancreatic Neoplasms; Inflammation; Prognosis; Meta-Analysis

CLC number: R736.7

胰腺癌是一种进展快、预后差的消化系统恶性肿瘤，疾病初期无特定症状，约50%的患者确诊时已处于局部中晚期或伴有转移灶[1−2]。据2020年GLOBOCAN数据[3−4]显示，胰腺癌已成为全球第12位最常见的恶性肿瘤，第七大癌症死亡原因，整体5年总生存率不足10%。手术切除是胰腺癌最有效的治疗方法之一，但胰腺癌根治术后5年生存率约也低于31%，同时，80%的患者术后出现早期复发和转移[5]。

研究[6−7]表明，肿瘤大小、部位、浸润及分化程度、切缘性质和TNM分期等对于胰腺癌患者预后有重要预测价值。但此类数据高度依赖有创的病理学检查。因此，探索简便、易获取的术前判断预后的标志物对于制定治疗策略至关重要。自

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1863年Virchow提出炎症与肿瘤微环境密切相关以来[8]，多项研究表明炎症反应在肿瘤的发生和进展中发挥至关重要的作用[9]。目前可反应全身炎症反应的指标，如中性粒细胞与淋巴细胞比率（neutrophil to lymphocyte ratio，NLR）、血小板与淋巴细胞比率（platelet to lymphocyte ratio，PLR）等可作为多种恶性肿瘤的诊断及预后标志物[10-11]。但在胰腺癌中，NLR水平与患者生存获益之间的关系尚存在争议，且不同研究探讨的NLR临界值各不相同。本文采用系统评价与Meta分析方法，评估术前NLR与胰腺癌手术患者预后的关系，旨在为临床医生判断胰腺癌预后提供新思路。

1 资料与方法

1.1 文献检索

计算机检索PubMed、Web of science、Cochrane Library、中国知网、万方、维普数据库的中英文文献，搜集术前NLR与胰腺癌患者术后总生存期（overall survival，OS）和无病生存期（disease-free survival，DFS）相关性的研究。检索时限均从建库至2022年3月31日。英文检索词为："Pancreatic Neoplasms" "Pancreatic Neoplasm" "Pancreas Neoplasms" "Cancer of Pancreas" "PDAC" "Pancreatic ductal adenocarcinoma" "PAAD" "Pancreatic adenocarcinoma" "Neutrophils" "Polymorphonuclear Leukocyte" "Polymorphonuclear Neutrophils" "LE Cells" "Neutrophil Band Cells" "Lymphocytes" "Lymphoid Cells" "Neutrophil Lymphocyte Ratio" "Neutrophil-to-Lymphocyte ratio" "Neutrophil-Lymphocyte Ratio" "NLR"等。中文检索词为："胰腺癌""胰腺肿瘤""胰腺腺癌""胰腺导管腺癌""中性粒细胞""淋巴细胞""中性粒细胞与淋巴细胞比值""中性粒细胞淋巴细胞比率"等。

1.2 文献纳入排除标准

纳入标准：(1)研究对象接受外科手术治疗且术后病理诊断为胰腺癌；(2)报告了术前NLR的水平及临界值；(3)报道了术前NLR与胰腺癌患者OS、DFS等预后指标的关系，且报道了风险比（hazard ratio，*HR*）和95%可信区间（confidence interval，*CI*），或可以根据文献数据进行计算获取；(4)研究类型为队列研究或病例-对照研究。排除标准：(1)综述、会议摘要、病例报道、系统评价；(2)患者术前行新辅助治疗；(3)结局指标不符；(4)术前已发现远处转移或合并其他恶性肿瘤疾病；(5)无法获取全文。

1.3 文献筛选与资料提取

由两名评价员独立筛选文献，提取资料并交叉核对，如遇分歧咨询第三方协助判断，缺失资料尽可能联系作者补齐。文献筛选首先去重，之后阅读标题、摘要排除与研究主题明显不相关文献，其次阅读全文以确定最终纳入文献。资料提取内容包括：作者、国家、年份、性别、样本量、NLR截止值、OS、DFS的*HR*和95% *CI*；利用纽约-渥太华量表（Newcastle-Ottawa-Scale，NOS）[12]评估复筛文献质量，总分共9分，包括研究组人群选择（4分），组间可比性（2分）、结果测量（3分），其中6分以上文献可认为是高质量文献。

1.4 数据分析

采用Revman 5.4和Stata 16.0软件进行Meta分析。采用一般逆方差法对各结局指标*HR*及95% *CI*通过计算log *HR*和selog *HR*后进行加权合并以此构建森林图，结合I^2值定量评估研究异质性。I^2<50%选择固定效应模型，反之采用随机效应模型并进行亚组分析。使用Egger漏斗图及Egger线性回归检验来评估发表偏倚[13-14]。进行敏感度分析以评估结果的稳定性。所有统计检验均为双侧检验，*P*<0.05定义为差异有统计学意义。

2 结 果

2.1 文献检索结果

初检共获1 870篇相关文献，去除287篇重复文献后，阅读1 583篇文献的标题、摘要，排除与研究主题明显不相关文献后获得初筛文献389篇，对其阅读全文后获得符合标准的25篇文献[15-39]纳入Meta分析。文献筛选流程图见图1。

2.2 纳入文献基本信息

本次研究纳入25项回顾性研究[15-39]，共计4 796例研究对象，且所有纳入文献均报道了采用Cox回归模型计算的*HR*及95% *CI*。基本信息见表1。纳入研究发表时间在2015—2022年间。其中16项[19,21,24,26,28-39]在中国进行，6项[15-16,20,23,25,27]在

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日本进行，另外 3 项分别在英国[18]、韩国[22]、波兰[17]进行。24 篇[15-28,30-39]文献报道了 NLR 与 OS 的关系，6 篇文献[16,21-22,28-29,32]报道了 NLR 与 DFS 的关系，NLR 临界值和纳入队列的样本量分别为 2.0~5.0 和 28~442 例。基于 NOS 评分量表，所纳入研究得分均在 6 分以上。

2.3　NLR 对 OS 的预测效果 OS 的 Meta 分析

对结局指标为 OS 的 24 篇研究[15-28, 30-39]进行分析，24 篇研究[15-28, 30-39]之间存在明显异质性（I^2=77%），遂采用随机效应模型。Meta 分析结果表明：相较于术前低 NLR 胰腺癌患者，术前高水平 NLR 患者术后 OS 明显缩短（*HR*=1.24，95% *CI*=1.16~1.33，*P*<0.000 01）（图 2）。以 4.0、3.5、3.0、2.65、2.4 对上述研究进行 NLR 临界值分组分析，进一步探究 NLR 预测胰腺癌术后 OS 的取值范围，结果显示，各组均表明术前高水平 NLR 与胰腺癌术后较差的 OS 有关（均 *P*<0.05）（表 2）。

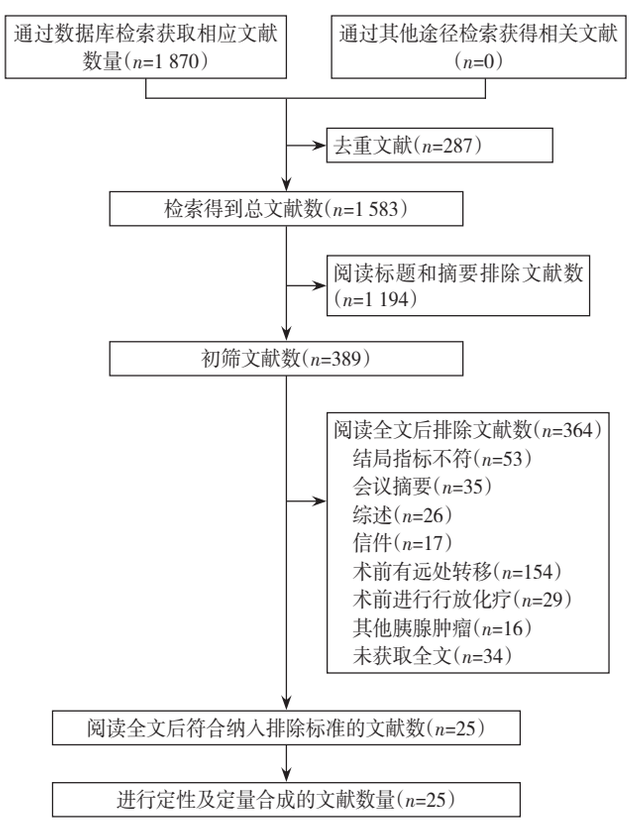

图 1　文献筛选流程图

Figure 1　Flow chart of literature screening

2.4　NLR 对 DFS 的预测效果 DFS 的 Meta 分析

对结局指标为 DFS 的 6 项研究[16, 21-22, 28-29, 32]进行分析，各研究间异质性明显（I^2=83%），遂采用随机效应模型，结果显示，胰腺癌术前高水平 NLR 患者胰腺癌术后的 DFS 短于术前低水平 NLR 患者（*HR*=1.39，95% *CI*=1.21~1.60，*P*<0.000 01）（图 3）。探究 NLR 影响胰腺癌术后 DFS 的临界值范围，结果如示，各组均提示术前高水平 NLR 与术后较差的 DFS 有关（均 *P*<0.05）（表 3）。

表 1　纳入文献基本信息

Table 1　Basic information of the included studies

作者（发表年份）	国家	样本数	性别（男/女）	NLR 临界值	结局指标
Abe，等[15]2018	日本	329	131/198	5.0	OS
Takakura，等[16]2015	日本	28	16/12	5.0	OS、DFS
Sierzega，等[17]2017	波兰	442	260/182	5.0	OS
Bhatti，等[18]2010	英国	84	48/36	4.0	OS
Huang，等[19]2022	中国	48	23/25	3.8	OS
Asari，等[20]2016	日本	184	109/75	3.0	OS
Zhou，等[21]2021	中国	241	136/105	2.9	OS、DFS
Kim，等[22]2019	韩国	198	无具体数据	2.8	OS、DFS
Asaoka，等[23]2015	日本	46	22/24	2.7	OS
Tao，等[24]2016	中国	160	100/60	2.5	OS
Abe，等[25]2021	日本	159	无具体数据	2.5	OS
Xiang，等[26]2020	中国	67	37/30	2.5	OS
Abe，等[27]2018	日本	138	74/64	2.2	OS
Ye，等[28]2018	中国	420	264/156	2.1	OS、DFS
Tian，等[29]2019	中国	185	103/82	2.0	DFS
Cheng，等[30]2016	中国	195	113/82	2.0	OS
Ben，等[31]2015	中国	381	237/144	2.0	OS
叶斯斯，等[32]2015	中国	346	217/129	3.2	OS、DFS
苏子剑，等[33]2016	中国	185	112/73	3.1	OS
董新亚，等[34]2015	中国	74	43/31	2.4	OS
邹文强，等[35]2018	中国	105	59/46	2.4	OS
任瑾，等[36]2020	中国	122	70/52	2.0	OS
李佶松，等[37]2018	中国	143	75/68	2.0	OS
方乐平[38]2018	中国	389	241/148	2.2	OS
唐伟杰[39]2021	中国	127	70/57	2.9	OS

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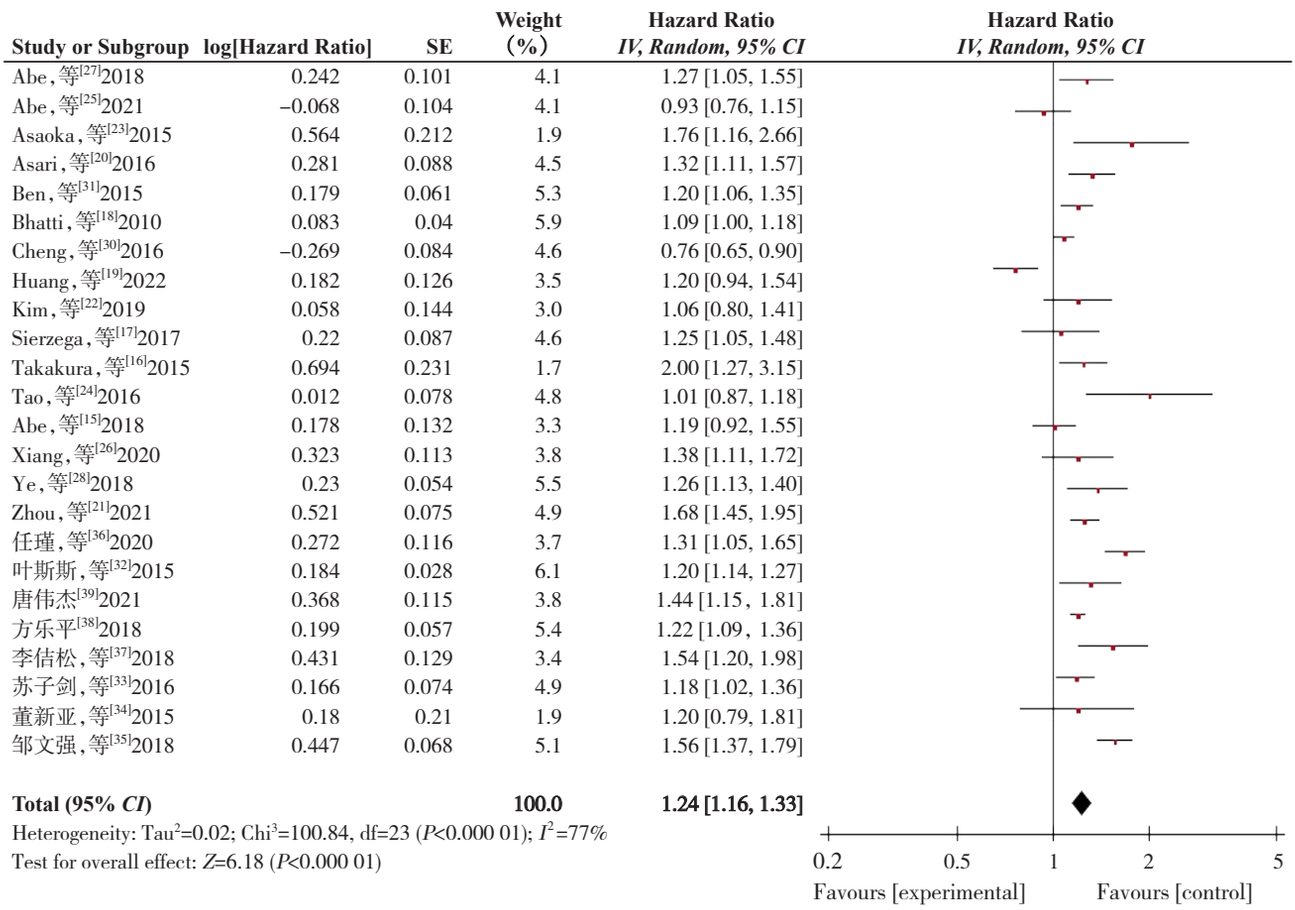

图2 NLR与胰腺癌术后OS的森林图

Figure 2 Forest plot of NLR and postoperative OS in pancreatic cancer

表2 基于不同NLR临界值的NLR与胰腺癌术后OS关系的亚组分析

Table 2 Subgroup analysis of the relationship between NLR and postoperative OS of pancreatic cancer based on different NLR cut-off values

NLR分组	研究数	异质性检验结果		效应模型	Meta分析结果	
		I^2	P		HR(95% CI)	P
>4.00	3	51%	>0.05	随机	1.34(1.07~1.67)	<0.05
≤4.00	21	79%	<0.01	随机	1.23(1.14~1.32)	<0.01
>3.50	5	54%	>0.05	随机	1.21(1.06~1.38)	<0.05
≤3.50	19	80%	<0.01	随机	1.24(1.15~1.35)	<0.01
>3.00	7	42%	>0.05	固定	1.18(1.11~1.27)	<0.01
≤3.00	17	81%	<0.01	随机	1.25(1.13~1.38)	<0.01
>2.65	12	72%	<0.01	随机	1.28(1.18~1.40)	<0.01
≤2.65	12	82%	<0.01	随机	1.19(1.07~1.34)	<0.01
>2.40	16	72%	<0.01	随机	1.28(1.18~1.40)	<0.01
≤2.40	8	86%	<0.01	随机	1.24(1.08~1.42)	<0.01

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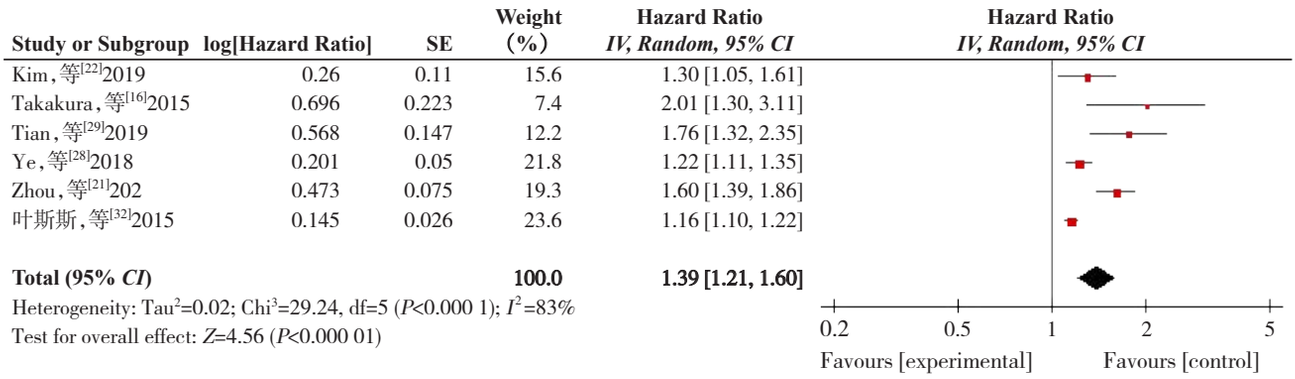

图3　NLR与胰腺癌术后DFS的森林图

Figure 3　Forest plot of NLR and postoperative DFS in pancreatic cancer

表3　基于NLR临界值的NLR与胰腺癌术后DFS关系的亚组分析

Table 3　Subgroup analysis of the relationship between NLR and postoperative DFS in pancreatic cancer based on NLR cutoff value

NLR分组	研究数	异质性检验结果		效应模型	Meta分析结果	
		I^2	P		HR(95% CI)	P
>2.85	3	91%	<0.01	随机	1.48(1.09~1.99)	<0.05
≤2.85	3	83%	<0.01	随机	1.36(1.13~1.63)	<0.01

2.5　敏感度分析

逐一剔除合并的研究进行敏感度分析。结果显示OS和DFS的合并效应量无明显变化，Meta分析结果稳定（图4）。

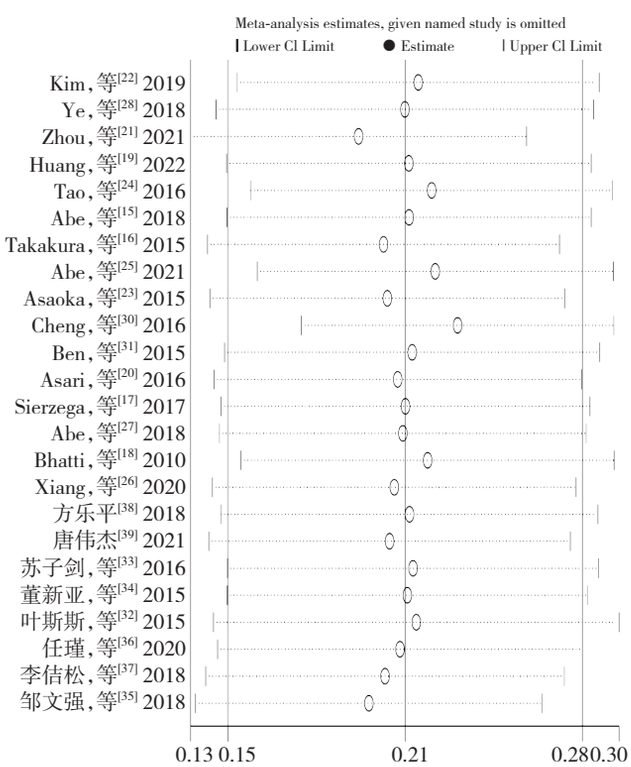

图4　敏感度分析

Figure 4　Sensitivity analysis

2.6　发表偏倚分析

通过Egger漏斗图（图5）及Egger回归检验对NLR与OS相关性研究的24篇文章[15-28, 30-39]进行发表偏倚分析，结果表明不存在明显发表偏倚（P=0.321）。

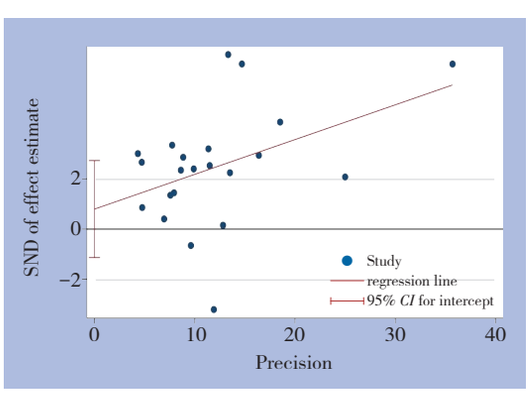

图5　Egger漏斗图

Figure 5　Egger's funnel plot

3　讨　论

3.1　术前NLR与胰腺癌手术患者预后关系

不同于术后获取评估预后的组织学信息，术前血清学指标分析数据简便易得并且创伤性小。本研究比较了术前NLR值与胰腺癌患者术后OS、DFS的相关性。结果表明术前高水平NLR胰腺癌患

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者的术后生存获益时间差于术前低水平NLR患者，将各项研究根据不同NLR临界值亚组分析后得出同样结论，说明术前NLR可作为胰腺癌患者术后预后的有效判断指标。

近期一项针对NLR与不同癌症预后之间关联程度的大样本Meta分析[40]结果显示，癌症患者NLR升高与不良预后之间存在关联。其中，在前列腺癌、非肌层浸润性膀胱癌和鼻咽癌中NLR与OS之间的关联证据最强。另外，研究[41]表明，治疗前高水平NLR值与结直肠癌患者较差的OS及DFS相关，这与本研究结果相一致。但周发权等[42]的Meta分析发现，术前NLR水平对胰腺癌患者预后的DFS并没有预测效果（P>0.05）。分析原因，可能在于其纳入DFS相关文献较少而形成偏倚。Ahmad等[43]的Meta分析结果显示，低NLR胰腺癌患者与高NLR患者的生存差异为2.0~4.3倍，但其纳入人群中包含未手术患者。对此，本研究改进上述研究不足，扩大样本量并明确纳入人群为胰腺癌手术患者。此外，亚组分析结果显示，不同NLR临界值对胰腺癌患者预后的预测结果并没有明显差异。这可能是由于所纳入的研究多数通过受试者工作特征曲线获得诊断实验的临界值，从而导致该值从2.0~5.0不等。虽然该法简化了分析和数据呈现，但也使结果解释复杂化[41]，导致其在临床上推广受限。因此，未来需要进行高质量研究来确定统一的NLR临界值。

3.2 术前NLR可作为预测指标的理论基础

全身炎症与肿瘤间的相关性已逐渐明确。促肿瘤性炎症通过阻断抗肿瘤免疫并通过对上皮细胞和癌细胞施加促肿瘤信号来促进癌症的发生、发展及转移[44]。其中，NLR是外周血中性粒细胞与和淋巴细胞计数为基础并且已证实该值与许多实体瘤中的不良预后相关[45-46]，包括食管癌[47]、胃癌[48]、结直肠癌[41]、肺癌[49]、胆管癌[50]等。但高水平NLR与肿瘤患者不良预后之间相关性的确切机制尚不明确[51]。首先，中性粒细胞能释放基因毒性DNA物质诱导DNA损伤。这在模拟溃疡性结肠炎肠道炎症的体外共培养模型中已得到证实[52]。其次，中性粒细胞通过分泌弹性蛋白酶诱导上皮-间质转化，从而促进胰腺癌侵袭性生长[53]。此外，中性粒细胞分泌基质金属蛋白酶9通过促进内皮细胞迁移主导血管生成或通过血管内皮生长因子间接参与血管生成促进胰腺癌进展及转移[54]。与此同时，淋巴细胞的亚群丰富导致淋巴细胞减少机制更加复杂。研究[55]发现，多种恶性肿瘤过表达程序性死亡配体1，并通过与效应T细胞上的程序性死亡受体1结合导致其功能性无反应，并可使血液调节性T细胞产生免疫抑制功能。有研究[56]通过间接共培养细胞实验发现淋巴细胞可抑制胰腺癌细胞的增殖，并与预后密切相关[57]。此外，$CD4^+$ T淋巴细胞可以通过多种方式增强$CD8^+$细胞毒性T淋巴细胞的肿瘤杀伤能力[58]。有研究[59]显示高外周血$CD3^+$、$CD4^+$ T细胞比例和高CD4/CD8比率与肺癌患者较长OS相关。基于此，NLR代表肿瘤患者全身炎症反应与宿主免疫状态间的平衡，且中性粒细胞增加和（或）淋巴细胞数目减低预示胰腺癌预后不良是合理的。

3.3 比较NLR与其他可能预测预后的血清学指标

除外周血NLR之外，基于C-反应蛋白（C-reactive protein，CRP）和白蛋白的全身炎症指标如格拉斯哥预后评分（Glasgow prognostic score，GPS）、C反应蛋白与白蛋白比率（C-reactive protein to albumin ratio，CAR）、纤维蛋白原与白蛋白比率（fibrinogen to albumin ratio，FAR）以及基于血细胞计数的血小板-淋巴细胞比（platelet to lymphocyte ratio，PLR）、单核细胞与淋巴细胞比率（monocyte to lymphocyte ratio，MLR）、系统免疫炎症指数（systemic immune-inflammation index，SIII）也是预测包括胰腺癌在内的多种肿瘤的预后因素[60-65]。然而，哪种血清学指标组合最能准确预测胰腺癌患者的预后目前尚无定论。Fang等[63]发现，NLR与可切除胰腺癌患者术后的生存获益无显著相关性，但FAR、MLR、NLR、PLR是预测局部进展或转移性胰腺癌患者预后的相关指标，且FAR预测效果优于MLR、NLR和PLR。Iwai等[65]研究发现NLR是不可切除胰腺癌患者的独立预后因素，且优于GPS、PLR、CAR。Taniai等[66]研究显示CRP联合NLR（C-NLR）预测胰腺癌患者术后生存获益的效果优于两者单独预测效果。此外，近期研究[67]表明基于白蛋白和淋巴细胞的预后营养指数（prognostic nutrition index，PNI）评分是预测胰腺导管腺癌患者根治术后的OS的独立危险因素，且优于GPS、CAR、NLR。综合来看，代表胰腺癌患者炎症、免疫、营养的多个预后标志物各有优劣。因此，将术前NLR值添加到其他综合预后评分中进行联合评估能对临床决策及预测治疗结果提供更多信息。

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3.4　局限性

本 Meta 分析的局限性在于：首先，由于研究对象、手术方式、NLR 临界值并不统一，可能是研究显著异质性的主要原因。例如，部分研究纳入的样本量少且绝大多数患者为亚洲人群，主要集中于中国。因此这可能为结果显著异质性的原因之一，并且分析结果对亚洲以外人群可能不具有普适性。此外，胰腺癌患者的手术方式通常包括根治性手术和姑息性手术，其中根治性手术又可分为胰十二指肠切除术、保留幽门的胰十二指肠切除术等，同时可通过开腹或腹腔镜方式进行，不同术式对患者预后生存期可能会产生重要影响。术前 NLR 值对 OS、DFS 的预测价值在不同术式之中是否都有意义还有待进一步高质量研究证实。其次，纳入研究的患者有部分在术后接受化疗，且化疗方式没有统一标准，例如，目前针对胰腺癌化疗方案主要有吉西他滨联合卡培他滨、mFOLFIRINOX、吉西他滨联合替吉奥等。不同化疗方式同样可能对患者预后生存期产生影响，没有足够数据评估这些治疗在研究内部及研究间是否存在不同。第三，纳入的研究全部为回顾性研究，可能也是本研究异质性的来源之一。因此，今后需要更多大样本、高质量的研究来验证术前 NLR 值在预测胰腺癌患者预后的价值。

总之，术前高 NLR 值与胰腺癌患者术后不良预后有关，作为反应全身炎症指标，NLR 为临床医生预测胰腺癌患者预后提供了新见解。

利益冲突：所有作者均声明不存在利益冲突。

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