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·临床研究·

肝内胆管癌围手术期外周血NLR和PLR对患者预后的预测价值

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[摘 要] **目的:**探讨肝内胆管癌(intrahepatic cholangiocarcinoma,ICCA)围手术期外周血中性粒细胞与淋巴细胞比率(neutrophil-to-lymphocyte ratio,NLR)和血小板与淋巴细胞比率(platelet-to-lymphocyte ratio,PLR)对患者预后的预测价值。**方法:**收集2015年1月至2018年1月在上海市松江区中心医院接受肝切除术治疗的ICCA患者97例作为ICCA组,选择同期在本院做健康体检的志愿者100例作为正常对照组。检测两组受试者术前1 d、术后3 d和7 d外周血的NLR、PLR,采用单因素、多因素分析ICCA患者术后随访期死亡的危险因素,采用Kaplan-Meier生存曲线分析术后3 d的NLR和PLR对ICCA患者术后生存时间的影响,采用受试者工作特征曲线(receiver operating characteristic curve,ROC)分析术后3 d的NLR和PLR水平对患者术后随访期死亡的预测价值。**结果:**ICCA组患者术前1 d、术后3和7 d外周血的NLR、PLR均高于正常对照组(均P<0.05),术前1 d和7 d外周血NLR、PLR差异无统计学意义(P>0.05),术后3 d外周血NLR、PLR水平最高(P<0.05)。多发肿瘤、合并淋巴结转移、TNM分期Ⅲ~Ⅳ、CA199水平增高、术后3 d的NLR和PLR较高分别是ICCA患者随访期死亡的独立危险因素(均P<0.05)。ROC曲线显示,术后3 d的NLR和PLR高低对ICCA患者术后生存时间具有预测价值。Kaplan-Meier生存曲线显示,低NLR[(50.32±3.69)*vs*(30.12±2.36)个月]和低PLR[(53.6±3.75)*vs*(37.6±2.96)个月]患者生存时间均长于高NLR和PLR的ICCA患者(均P<0.05)。**结论:**ICCA术后3 d的NLR和PLR异常增高是患者肝切除术后死亡的独立危险因素,其对患者生存时间具有早期预测价值。

[关键词] 肝内胆管癌;中性粒细胞和淋巴细胞比率(NLR);血小板和淋巴细胞比率(PLR);生存时间;预后
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Predictive value of peripheral blood NLR and PLR in perioperative period on the prognosis of patients with intrahepatic cholangiocarcinoma

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[Abstract] Objective: To investigate the predictive value of peripheral blood neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in perioperative period on the prognosis of patients with intrahepatic cholangiocarcinoma (ICCA). **Methods:** Ninety-seven cases of ICCA patients underwent liver resection surgery in Songjiang District Central Hospital from January 2015 to January 2018 were chosen as the ICCA group, and 100 healthy volunteers who underwent physical examination in the hospital during the same period were selected as the control group. The NLR and PLR on preoperative day 1, postoperative day 3 and day 7 were compared between the two groups. Univariate and multivariate analyses were performed to determine the risk factors for mortality during postoperative follow-up in patients with ICCA. Kaplan-Meier survival curve was used to analyze the influence of postoperative day 3 NLR and PLR on the survival time of patients with ICCA. ROC curve was used to analyze the predictive value of postoperative day 3 NLR and PLR on the mortality during postoperative follow-up. **Results:** Peripheral blood NLR and PLR in the ICCA group were higher than those in the normal control group on preoperative day 1 and postoperative day 3, 7 (all P<0.05). In the ICCA group, the peripheral blood NLR and PLR on preoperative day 1 and postoperative day 7 showed no statistical difference (P>0.05); however, the levels on postoperative day 3 was the highest (P<0.05). Multiple tumors, lymph node metastasis, TNM staging Ⅲ-Ⅳ, increased carbohydrate antigen 199 (CA199) level and higher NLR and PLR on postoperative day 3 were the independent risk factors of mortality during postoperative follow-up in ICCA patients (all P<0.05). The ROC showed that NLR and PLR on postoperative day 3 had predictive value for the survival time of patients with ICCA. Kaplan-Meier survival curve showed that the survival time of patients in

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low NLR group was longer than those in high NLR group [(50.32±3.69) months *vs* (30.12±2.36) months], and the survival time of patients in low PLR group was longer than those in high PLR group [(53.6±3.75) months *vs* (37.6±2.96) months] (all $P<0.05$). **Conclusion:** Abnormal elevation in NLR and PLR on postoperative day 3 is an independent risk factor for death after liver resection surgery in patients with ICCA, which has early predictive value for patients' survival.

[Key words] intrahepatic cholangiocarcinoma (ICCA); neutrophil-to-lymphocyte ratio (NLR); platelet-to-lymphocyte ratio (PLR); perioperative period; prognosis

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肝内胆管癌（intrahepatic cholangiocarcinoma，ICCA）是临床最多见的肝癌类型，该病恶性程度较高，5年生存率仅为30%[1]。研究[1-2]认为，对ICCA患者给予早期肿瘤切除有助于延长生存时间。但随着越来越多的患者接受肝切除术，人们发现患者的生存时间存在较大差异，推测可能存在较多因素影响ICCA手术患者的远期预后。外周血中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）均是反映机体炎症反应程度的指标。王玮等[3]指出，NLR对肝动脉化疗栓塞术（transarterial chemoembolization，TACE）联合微波消融（microwave ablation，MWA）治疗的巨块型原发性肝癌患者生存时间有预测作用。LI等[4]通过荟萃分析显示，PLR可作为评估晚期癌症患者预后的标志物。但通过检测围手术期NLR、PLR评估ICCA患者肝切除术后生存时间尚少有研究。本研究拟探讨围手术期NLR、PLR对ICCA患者肝切除术后生存时间的预测价值，为细化ICCA的治疗措施及预后评估提供便捷可靠的参考指标。

1　资料与方法

1.1　一般资料

收集2015年1月至2018年1月在上海市松江区中心医院接受肝切除术治疗的ICCA患者97例的临床资料。纳入标准：（1）经影像学及病理检查确诊为ICCA；（2）首次确诊并接受根治性R0切除，术前无新辅助化疗；（3）Child-Pugh肝功能分级为A或B级；（4）临床资料完整，本人或家属签署知情同意书。排除标准：（1）围手术期死亡病例；（2）合并肝细胞癌或者其他肝脏良性疾患；（3）合并其他组织器官恶性肿瘤性疾病；（4）随访期失联。97例患者均符合上述纳入及排除标准并作为ICCA组，其中男性51例、女性46例，年龄43~78（65.34±12.06）岁。选取同期在本院进行体检的健康志愿者100例作为正常对照组，纳入标准：（1）临床资料完整、本人签署知情同意书；（2）各项检查结果均在正常范围内；（3）既往无恶性肿瘤病史。排除标准：（1）合并肝脏良性肿瘤、乙肝肝硬化等肝脏病变；（2）肝脏手术史。其中男性53例、女性47例，年龄38~77（65.10±11.73）岁。ICCA组、正常对照组的性别、年龄分布差异均无统计学意义（$P>0.05$），具有可比性。本研究计划获得本院医学伦理委员会审核批准。

1.2　临床资料收集

收集ICCA癌患者的临床资料，包括一般资料及实验室资料。一般资料包括性别、年龄、Child-Pugh肝功能分级、肿瘤数量、最大肿瘤直径、术后是否进行辅助化疗、肿瘤分化程度、淋巴结转移、血管侵犯、TNM分期。实验室资料包括CA199、AFP及围手术期（术前1 d、术后3和7 d）的NLR和PLR。

1.3　术后随访及生存情况

以手术日作为随访起点，采用电话、门诊复诊的方式对患者进行定期随访，术后第1年每隔3个月随访1次、第2年开始每隔6个月随访1次。以2021年1月1日或该时间点之前患者的死亡时间作为随访终点，记录患者的生存情况。

1.4　统计学处理

采用SPSS20.0统计软件。正态分布的计量资料以均数±标准差表示，两组间比较采用t检验，多组间比较采用F检验；计数资料以例数及百分率表示，两组间比较采用卡方检验。围手术期NLR、PLR对ICCA患者肝切除术后生存时间的影响采用Kaplan-Meier生存曲线分析，对患者术后死亡的预测价值分析采用受试者工作特征（receiver operating characteristic curve，ROC）曲线。以$P<0.05$或$P<0.01$表示差异具有统计学意义。

2　结　果

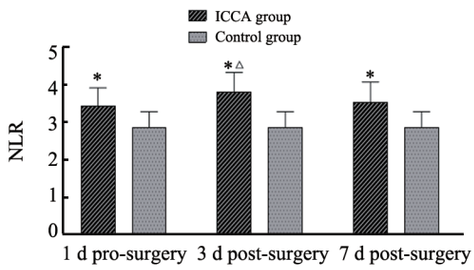
2.1　ICCA患者手术前后NLR、PLR的变化

ICCA组术前1 d、术后3和7 d外周血NLR、PLR均高于正常对照组（均$P<0.05$），ICCA组术前1 d和术后7 d外周血NLR、PLR差异无统计学意义（均$P>0.05$）；术后3 d外周血NLR、PLR最高（均$P<0.05$）。见图1、2。

2.2　ICCA患者随访期病死关联的临床因素

随访时间42~80个月，随访中位数为53.5个月。97例ICCA患者死亡67例（69.07%）作为死亡组，生存30例（30.93%）作为生存组。死亡组和生存组的性别、年龄、Child-Pugh肝功能分级、最大肿瘤直径、术

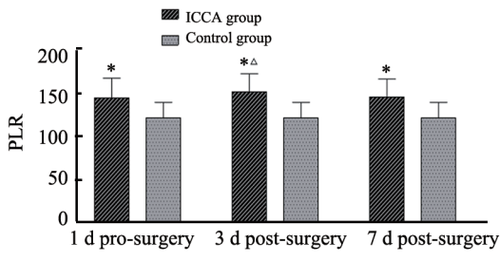
后是否进行辅助化疗、肿瘤分化程度、血管侵犯、AFP、术前及术后7 d的NLR和PLR差异无统计学意义(均 P>0.05)；肿瘤数量、淋巴结转移、TNM 分期、CA199、术后3 d的NLR和PLR差异有统计学意义(均P<0.05)。见表1。



*P<0.05 *vs* Control group, △P<0.05 *vs* 1 d pro-surgery or 7 d post-surgery group

图1 ICCA患者手术前后NLR的变化

Fig.1 Changes in NLR of ICCA patients before and after surgery



*P<0.05 *vs* Control group, △P<0.05 *vs* 1 d post-surgery or 7 d post-surgery group

图2 ICCA患者手术前后PLR的变化

Fig.2 Changes in PLR of ICCA patients before and after surgery

表1 ICCA患者随访期病死的单因素分析(*n*)

Tab.1 Univariate analysis for mortality during follow-up in patients with ICCA (*n*)

Factor	Death group (n=67)	Survival group (n=30)	χ^2	P
Sex				
Male	35	16	0.010	0.921
Female	32	14		
Age (t/a)				
<60	23	12	0.289	0.591
≥60	44	18		
Child-Pugh				
A	29	11	0.374	0.541
B	38	19		
Number of tumors				
Single	11	14	9.911	0.002
Multiple	56	16		
Tumor diameter (d/cm)				
<5	34	18	0.713	0.398
≥5	33	12		
Postoperative adjuvant chemotherapy			3.161	0.075
Yes	25	42		
No	17	13		
Tumor differentiation				
Poorly	2	1	0.008	0.927
Highly	65	29		
Lymph node metastasis				
Yes	49	12	9.747	0.002
No	18	18		
Vascular metastasis				
Yes	37	13	1.173	0.279
No	30	17		
TNM				
Ⅰ~Ⅱ	42	25	4.135	0.042
Ⅲ~Ⅳ	25	5		
CA199 (U/ml)				
<37	7	19	29.540	0.000
≥37	60	11		
AFP [ρ_B/(ng·ml^{-1})]				
<20	4	2	0.017	0.895
≥20	63	28		
NLR				
Preoperative day 1	3.48±0.46	3.43±0.51	0.478	0.634
Postoperative day 3	3.94±0.56	3.57±0.49	3.121	0.002
Postoperative day 7	3.58±0.52	3.50±0.71	0.623	0.535
PLR				
Preoperative day 1	145.27±22.19	144.68±23.40	0.119	0.906
Postoperative day 3	155.45±20.38	146.32±19.39	2.069	0.041
Postoperative day 7	146.02±20.64	145.58±21.37	0.096	0.924

2.3　ICCA患者随访期病死的独立危险因素

将ICCA患者随访期死亡作为因变量(0=存活,1=死亡),将单因素分析中差异具有统计学意义的指标如肿瘤数量、淋巴结转移、TNM分期、CA199、术后3 d NLR、术后3 d PLR纳入Logistics回归模型进行分析。结果显示,多发肿瘤、合并淋巴结转移、TNM分期Ⅲ~Ⅳ、CA199水平增高、术后3 d NLR较高(高于NLR最佳截断值3.70)、术后3 d PLR较高(高于PLR最佳截断值153.50)等7个因素分别是ICCA患者随访期死亡的独立危险因素(均P<0.05)。见表2。

表2 ICCA患者随访期病死的独立危险因素

Tab.2 Independent risk factors for mortality during follow-up in patients with ICCA

Factor	β	Wald	*OR*	95%CI	*P*
Number of tumors (single *vs* multiple)	1.475	5.182	2.493	1.510~3.071	0.027
Lymph node metastasis (No *vs* Yes)	1.560	6.371	2.645	1.645~3.214	0.021
TNM (Ⅰ~Ⅱ *vs* Ⅲ~Ⅳ)	1.762	8.452	3.102	1.884~3.765	0.012
CA199 (<37 *vs* ≥37)	1.382	4.264	2.173	1.311~2.645	0.038
NLR on postoperative day 3 (<3.70 *vs* ≥3.70)	1.293	3.109	1.963	1.184~2.231	0.045
PLR on postoperative day 3 (<153.50 *vs* ≥153.50)	1.413	4.957	2.310	1.365~2.997	0.031

2.4　术后3 d的NLR、PLR对ICCA患者随访期病死具有一定的预测价值

ROC曲线显示,术后3 d的NLR预测ICCA患者死亡的最佳截断值为3.70,AUC为0.841[95% CI为0.756~0.926],其灵敏度、特异度分别为76.67%、79.10%。术后3 d的PLR预测ICCA患者死亡的最佳截断值为153.50,AUC为0.727[95% CI为0.618~0.836],其灵敏度、特异度分别为63.33%、62.69%,可见术后3 d的PLR和PLR可用于预测ICCA患者死亡。见图3、4。

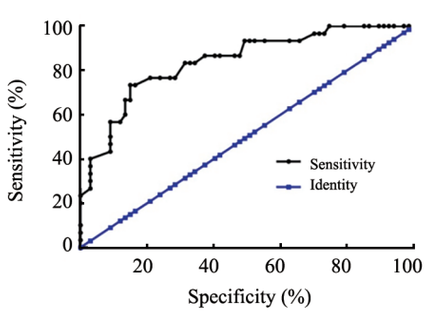


图3 术后3 d的NLR预测ICCA患者死亡的ROC曲线

Fig.3 The ROC curve of NLR on postoperative d3 in predicting the death of patients with ICCA

2.5　术后3 d的NLR、PLR较低ICCA患者的生存期较长

根据ROC曲线所得术后3 d的NLR、PLR最佳截断值,将97例ICCA患者分为高NLR组60例、低NLR组37例;高PLR组63例、低PLR组34例。Kaplan-Meier生存曲线显示,低NLR组ICCA患者半数生存时间长于高NLR组患者[(50.32±3.69) *vs* (30.12±2.36)个月,P<0.05],低PLR组ICCA患者半数生存时间长于高PLR组ICCA患者[(53.6±3.75) *vs* (37.6±2.96)个月,P<0.05]。见图5、6。

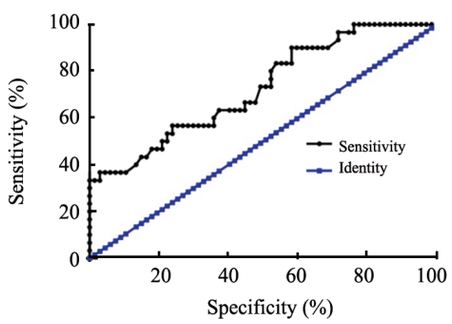


图4 术后3 d的PLR预测ICCA患者死亡的ROC曲线

Fig.4 The ROC curve of PLR on postoperative d3 in predicting the death of patients with ICCA

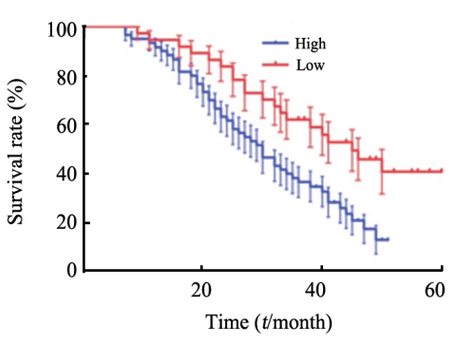


图5 术后3 d不同NLR ICCA患者的生存曲线

Fig.5 Survival curves of ICCA patients with different NLR on postoperative d3

3　讨　论

ICCA患者的病死率很高,符合手术指征的患者即使接受手术治疗,5年生存率也并不理想[5-7],寻找

影响患者生存时间的危险因素并加以干预被认为是优化ICCA患者治疗效果的可靠手段。既往研究中涉及较多的ICCA患者手术预后的影响因素包括临床病理特点、外周血CA199等肿瘤标志物等[8-11]。NLR与PLR均是反映机体炎症程度的有效指标。LEE等[12]研究显示，NLR可用于评估局部浸润性三阴性乳腺癌患者的预后；HIRAHARA等[13]研究显示，NLR与PLR组合可用于预测晚期胃癌化疗患者的预后。

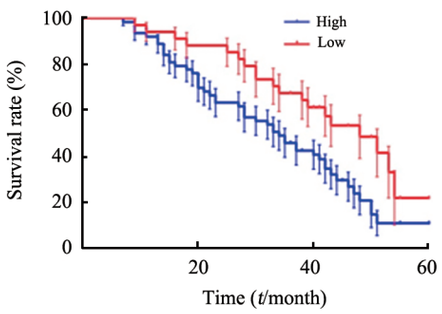


图6 术后3 d不同PLR ICCA患者的生存曲线

Fig.6 Survival curves of ICCA patients with different PLR on postoperative d3

本研究就ICCA患者肝切除术后生存时间的影响因素进行分析，本组患者手术治疗后的生存情况仍不理想，中位随访期53.5个月中97例ICCA患者中死亡67例（69.07%）、生存30例（30.93%），生存率不足1/3。通过分析原因，可能与治疗方案个体化程度不足相关。对不同死亡风险的患者应进一步将治疗方案个体化，以最大程度预防术后复发转移并最终改善预后。通过分析ICCA患者围手术期外周血NLR、PLR与术后生存时间的关系：ICCA患者术前1 d外周血NLR、PLR均高于健康志愿者，提示炎症反应参与疾病的发生发展；单因素和多因素分析显示，术后3 d的NLR、PLR较高是导致ICCA患者肝切除术后早期死亡的独立危险因素，而术前1 d和术后7 d的NLR、PLR对患者生存时间的影响尚不明显。术后早期NLR、PLR较术前增加可能由手术创伤、机体应激反应等多因素所致[14-16]。本组患者术后3 d的NLR、PLR水平均达到峰值，在术后7 d则出现不同程度回落，可能与机体对手术的应激反应在48~72 h达到高峰，随后这种反应逐步消退相关[17-18]。死亡组患者术后3 d的NLR、PLR较存活组更高，提示机体的炎症反应对免疫系统对伤害性刺激的更大，可能间接反映后续抗肿瘤免疫系统功能的变化[19-22]，但关于NLR、PLR具体对患者免疫功能、肿瘤生长等影响有待后续更多直接研究。

鉴于术后3 d的NLR、PLR对ICCA患者术后生存时间存在明确影响，采用ROC曲线分析显示，术后3 d的NLR、PLR对ICCA患者的死亡具有良好的早期预警价值，灵敏度与特异度均超过62%，推测该指标可能在ICCA患者早期死亡风险分层及术后治疗方案指导方面发挥重要作用。根据ROC曲线所得相关截断值对ICCA患者进行分组，Kaplan-Meier生存曲线结果显示，低NLR和低PLR患者的生存时间均更长，再次佐证了术后3 d的NLR、PLR异常增高对患者生存时间的负面影响。

对于术后辅助化疗是否影响ICCA患者的生存时间，业内也存在争议，本研究结果显示，术后辅助化疗不影响ICCA癌患者的生存时间，可能与亚临床病灶影响预后有关[23]。

综上所述，ICCA患者肝切除术后3 d的NLR、PLR异常增高是术后病死的独立危险因素，术后3 d的NLR、PLR较高者预后不佳，对患者的生存时间具有早期预测价值。

[参 考 文 献]

[1] WANG W, FEI Y, LIU J, et al. Laparoscopic surgery and robotic surgery for hilar cholangiocarcinoma: an updated systematic review [J]. ANZ J Surg, 2021, 91(1/2): 42-48. DOI: 10.1111/ans.15948.

[2] BARTOLINI I, RISALITI M, FORTUNA L, et al. Current management of intrahepatic cholangiocarcinoma: from resection to palliative treatments[J]. Radiol Oncol, 2020, 54(3): 263-271. DOI: 10.2478/raon-2020-0045.

[3] 王玮, 杜晓菲, 路运健. 术前NLR水平对TACE联合MWA治疗的巨块型原发性肝癌患者生存时间的影响[J]. 实用肝脏病杂志, 2020, 23(2): 260-263. DOI: 10.3969/j.issn.1672-5069.2020.02.028.

[4] LI B, ZHOU P, LIU Y, et al. Platelet-to-lymphocyte ratio in advanced cancer: review and meta-analysis[J]. Clin Chim Acta, 2018,483(8):48-56. DOI: 10.1016/j.cca.2018.04.023.

[5] RIZVI S, KHAN S A, HALLEMEIER C L,et al. Cholangiocarcinoma evolving concepts and therapeutic strategies[J]. Nat Rev Clin Oncol, 2018,15(2):95-111. DOI: 10.1038/nrclinonc.2017.157.

[6] WANG T, KONG J, YANG X, et al. Clinical features of sarcomatoid change in patients with intrahepatic cholangiocarcinoma and prognosis after surgical liver resection: a propensity score matching analysis[J]. J Surg Oncol, 2020, 121(3): 524-537. DOI: 10.1002/jso.25815.

[7] YUAN M, LI R, ZHANG Y, et al. Enhancement patterns of intrahepatic cholangiocarcinoma on contrast-enhanced ultrasound: correlation with clinicopathologic findings and prognosis[J]. Ultrasound Med Biol, 2019, 45(1): 26-34. DOI: 10.1016/j.ultrasmedbio.2018.08.014.

[8] 汤朝晖, 童焕军, 全志伟. 重视乙肝病毒相关性肝内胆管癌的临床病理学特征及治疗方法[J]. 中华外科杂志，2020，58(4):280-283. DOI: 10.3760/cma.j.cn112139-20200123-00046.

[9] 黄皓川，余杰雄，左超海. 肝内胆管癌的手术治疗的炎症相关性及预后影响因素研究[J]. 黑龙江医学, 2020, 44(1): 62-65. DOI: 10.3969/j.issn.1004-5775.2020.01.025.

[10] HAHN F, MÜLLER L, JUNGMANN F, et al. Survival prediction for patients with non-resectable intrahepatic cholangiocarcinoma undergoing chemotherapy: A retrospective analysis comparing the tumor marker CA199 with cross-sectional imaging[J]. J Cancer Res Clin Oncol, 2020, 146(7): 1883-1890. DOI: 10.1007/s00432-020-03200-2.

[11] OHTA S, MORINE Y, IMURA S, et al. Carbohydrate antigen 199 is a prognostic factor which correlates with hdac1 and HIF-1α for intrahepatic cholangiocarcinoma[J]. Anticancer Res, 2019, 39(11): 6025-6033. DOI: 10.21873/anticanres.13808.

[12] LEE J, KIM DM, LEE A. Prognostic role and clinical association of tumor-infiltrating lymphocyte, programmed death ligand-1 expression with neutrophil-lymphocyte ratio in locally advanced triple-negative breast cancer[J]. Cancer Res Treat, 2019, 51(2): 649-663. DOI: 10.4143/crt.2018.270.

[13] HIRAHARA T, ARIGAMI T, YANAGITA S, et al. Combined neutrophil-lymphocyte ratio and platelet-lymphocyte ratio predicts chemotherapy response and prognosis in patients with advanced gastric cancer[J]. BMC Cancer, 2019, 19(1): 672-679. DOI: 10.1186/s12885-019-5903-y.

[14] 音金萍, 岳紫晨, 卓少元. STAT3:慢性炎症介导肝癌进程的关键分子[J]. 临床肝胆病杂志, 2020, 36(4): 948-952. DOI: 10.3969/j.issn.1001-5256.2020.04.054.

[15] NABAVIZADEH R, BOBREK K, MASTER V A. Risk stratification for bladder cancer: biomarkers of inflammation and immune activation [J]. Urol Oncol, 2020, 38(9): 706-712. DOI: 10.1016/j. urolonc. 2020.04.006.

[16] KARAKONSTANTIS S, KALEMAKI D, TZAGKARAKIS E, et al. Pitfalls in studies of eosinopenia and neutrophil-to-lymphocyte count ratio[J]. Infect Dis (Lond), 2018, 50(3): 163-174. DOI: 10.1080/23744235.2017.1388537.

[17] RADAK D, DJUKIC N, TANASKOVIC S, et al. Should we be concerned about the inflammatory response to endovascular procedures? [J]. Curr Vasc Pharmacol, 2017, 15(3): 230-237. DOI: 10.2174/1570161115666170105121900.

[18] 王铖. 中性粒细胞/淋巴细胞比值与高血压关系的研究现状[J]. 右江医学, 2018, 46(4):491-494. DOI: 10.3969/j.issn.1003-1383. 2018.04.030.

[19] LEE H N, KIM Y K, KIM G T, et al. Neutrophil-to-lymphocyte and platelet-to-lymphocyte ratio as predictors of 12-week treatment response and drug persistence of anti-tumor necrosis factor-α agents in patients with rheumatoid arthritis: A retrospective chart review analysis[J]. Rheumatol Int, 2019, 39(5): 859-868. DOI: 10.1007/s00296-019-04276-x.

[20] 雷正清, 司安锋, 杨平华, 等. 肝内胆管癌肝切除术后"教科书式结局"影响因素分析及预测模型建立[J]. 中国实用外科杂志, 2019, 39(10):1071-1076. DOI: 10.19538/j.cjps.issn1005-2208.2019.10.19.

[21] KAMARAJAH S, GIOVINAZZO F, ROBERTS K J, et al. The role of down staging treatment in the management of locally advanced intrahepatic cholangiocarcinoma: Review of literature and pooled analysis[J]. Ann Hepatobiliary Pancreat Surg, 2020, 24(1): 6-16. DOI: 10.14701/ahbps.2020.24.1.6.

[22] MACHAIRAS N, LANG H, JAYANT K, et al. Intrahepatic cholangiocarcinoma: Limitations for resectability, current surgical concepts and future perspectives[J]. Eur J Surg Oncol, 2020, 46(5): 740-746. DOI: 10.1016/j.ejso.2020.01.028.

[23] 胡春秀, 余维, 魏启春. 肝内胆管细胞癌根治术后辅助化疗的价值[J]. 实用肿瘤杂志, 2020, 35(2): 140-144. DOI: 10.13267/j.cnki.syzlzz.2020.02.009.

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