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# Prognostic significance of neutrophil–lymphocyte ratio in resectable pancreatic neuroendocrine tumors with special reference to tumor-associated macrophages

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A B S T R A C T

*Background:* Recent studies have shown that the systemic inflammatory response induced by cancer leads to cancer progression. Neutrophil-to-lymphocyte ratio (NLR) is the most reliable marker to detect systemic inflammation. In this study, we investigated the significance of NLR in patients with well-differentiated pancreatic neuroendocrine tumors (PanNETs) according to the World Health Organization 2017 classification.

*Methods:* We retrospectively collected data for patients with PanNET who underwent pancreatic resection with curative intent between January 2008 and December 2017 at six institutions. Clinicopathological factors, recurrence, and immunohistochemical staining of tumor-associated macrophages (TAMs) were analyzed in a total of 55 patients in this study.

*Results:* High NLR (>3.41) in patients was significantly associated with higher white blood cell count, higher Ki-67 index, higher mitotic count, higher grade, higher incidence of lymph node metastasis, higher incidence of lymphatic and neural invasion, massive blood loss, and a large number of CD163-expressing TAMs. Recurrence-free survival of patients with high NLR was significantly poorer than that of patients with low NLR. Multivariate analysis identified high NLR, NET Grade 2 (G2) or Grade 3 (G3), and synchronous hepatic resection as independent risk factors for recurrence after curative resection.

*Conclusions:* NLR is a promising predictor of recurrence after pancreatectomy that needs to be further investigated and that accumulation of TAMs in the tumor could be one of the causes of NLR elevation.


## Introduction

Pancreatic neuroendocrine neoplasm (PanNEN) is rare, accounting for approximately 3% of all primary pancreatic malignancies [1,2]. PanNEN is associated with good prognosis because of its slow growth rate, but a recent study revealed that there are

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several predictors of poor prognosis. The World Health Organization (WHO) 2017 classification, which is a revision of the 2010 version, is widely used to predict prognosis [3,4]. The grading of well-differentiated pancreatic neuroendocrine tumors (PanNETs) into three categories (G1, G2, and G3) is based on tumor cell proliferation, as assessed by mitotic count and Ki-67 index. The primary therapeutic strategy for well-differentiated PanNETs is surgical resection. Poorly differentiated PanNETs are known as neuroendocrine carcinomas (NECs, which exhibit highly malignant behavior, and a therapeutic strategy for this disease has not yet been established.

Recent studies have shown that the systemic inflammatory response induced by cancer promotes cancer progression. Neutrophil-to-lymphocyte ratio (NLR) is the most reliable marker to detect systemic inflammation. High NLR has been reported to be a predictor of poor survival in many cancers [5–8]. We previously demonstrated that NLR is an important prognostic factor in patients with hepatocellular carcinoma (HCC) after hepatic resection [5] and in patients who have undergone living donor liver transplantation (LDLT) [6,7]. A close relationship between the accumulation of tumor-associated macrophages (TAMs) in HCC [5] and high NLR levels was observed in patients with HCC who had undergone hepatic resection and LDLT [6,7]. TAMs have been shown to have tumor-promoting effects, with a high density of TAMs in the tumor reported to be associated with a poor prognosis [5,6,9–12]. Regarding PanNETs, there are several reports suggesting that a high preoperative NLR was significantly associated with high tumor grade and shorter prognosis after curative surgery [13–18], and additionally that TAMs are a useful biomarker to predict recurrence after surgical resection of non-functional PanNETs [11,12].

Understanding the preoperative risk factor for recurrence in PanNETs is helpful for surgery and follow-up. In this study, we investigated the significance of NLR in patients with well-differentiated PanNETs according to the WHO 2017 classification and the relationship between NLR and TAMs.

## Methods

### *Patient characteristics*

We retrospectively collected data for 95 consecutive patients with PanNETs who underwent pancreatic resection with curative intent between January 2008 and December 2017 at six institutions of Gunma University Hospital and its affiliated hospitals. An experienced pathologist (H.I.) diagnosed all cases as well-differentiated PanNETs, and curative resection was defined as complete macroscopic removal of tumor tissue. All patients underwent a surveillance period of more than 2 years. Functional tumors were also included. Patients were excluded if they: (1) had pancreatic cancer or another malignancy; (2) had incomplete laboratory data; (3) had no immunohistochemical data; and (4) were diagnosed with a NEC. The clinicopathological factors, recurrence, and immunohistochemical staining were analyzed in a total of 55 patients. Our institutional review board approved this study (2017-271).

### *Histological examination*

All histological findings were reviewed by an experienced pathologist. Grading was performed based on proliferation according to the criteria of the WHO 2017 classification. NET G1 was defined as mitotic counts <2 per 10 high-power fields (HPFs) and/or Ki-67 index <3, NET G2 as 2–20 mitotic counts per 10 HPFs and/or Ki-67 between 3 and 20%, and NET G3 as >20 mitotic counts per 10 HPFs and/or Ki-67 > 20%. Poorly differentiated PanNETs, namely NECs, were excluded. We also evaluated lymphatic, vessel, and neural invasion.

### *Immunohistochemical staining*

Sections of resected specimens were fixed in 10% buffered formalin, embedded in paraffin, and stained using the Envision + system and DAB kit (DAKO, Grostrup, Denmark). Immunohistochemical staining was performed using CD163 antibody (10D6, 1:200; Novocastra, Danvers, MA). Serial sections were stained according to the previous study [5] and examined by a pathologist (H.I.) without knowledge of patients' clinical information. The total number of CD163-positive cells with cytoplasmic or membrane staining in three HPFs was counted.

### *Follow-up strategy and recurrence pattern*

After discharge, all patients were examined for recurrence by computed tomography every 3 or 6 months. When recurrence was suspected, additional examinations such as magnetic resonance imaging were performed.

### *Statistical analysis*

Associations of continuous and categorical variables with the relevant outcome variables were assessed using Student's *t*-test and $\chi$ [2] test, respectively. Survival outcomes were determined by the Kaplan–Meier method and compared by the log-rank test. Univariate and multivariate analyses were performed using a logistic regression model. To identify prognostic factors, several variables found to be independent in the univariate analysis were included in an overall multivariate Cox proportional model to analyze recurrence-free survival. Ki-67 index and mitotic index were calculated according to the WHO 2017 grading and then were excluded in the multivariate analysis. All analyses were performed with JMP version 12 (SAS Institute, Cary, NC, USA). $P < 0.05$ was considered statistically significant.

## Results

In this study, we selected the patients who have a minimum follow-up of 2 years and the median follow-up period was 1,406 days (range, 371–3,672 days). Eight patients had PanNET recurrence during follow-up (14.5%). Seven patients (12.7%) died, of which five patients died of disease-specific causes.

The best cut-off of NLR was determined for recurrence of PanNET after surgery using a time-dependent receiver operating characteristic curve. According to the area under the curve (0.795), an NLR of 3.41was the best cut-off value for recurrence ($P = 0.015$). All patients were divided into two groups: a low (<3.41) NLR group (n = 41) and a high (≥3.41) NLR group (n = 14).

Table 1 compares the clinicopathological characteristics of the patients with low and high NLRs. High NLR were significantly associated with higher white blood cell count, higher Ki-67 index, higher mitotic count, higher grade, higher incidence of lymph node metastasis, higher incidence of lymphatic and neural invasion, massive blood loss, and a large number of CD163-expressing cells.

Univariate and multivariate analyses of prognostic factors for recurrence-free survival are shown in Table 2. Significant prognostic factors for recurrence-free survival included high NLR, tumor >2 cm in size, non-functional PanNET, NET G2 or G3, synchronous hepatic resection, higher Ki-67 index, mitotic count, higher incidence of lymphatic, vessel, and neural invasion, and massive blood loss.

High NLR, NET G2 or G3, and synchronous hepatic resection

**Table 1**
Comparison of the clinicopathological factors between the two groups classified by neutrophil-lymphocyte ratio.

| Variables | NLR<3.41 (n = 41) | NLR≧3.41 (n = 14) | *p*-value |
|---|---|---|---|
| Age | 61.0 ± 13.9 | 61.3 ± 11.8 | 0.95 |
| Male/Female | 16/25 | 7/7 | 0.53 |
| BMI (kg/m2) | 23.2 ± 3.0 | 23.4 ± 3.6 | 0.92 |
| Albumin (g/dl) | 4.2 ± 0.3 | 4.1 ± 0.46 | 0.42 |
| CRP (mg/dl) | 0.29 ± 0.62 | 1.19 ± 3.46 | 0.12 |
| WBC | 5445 ± 1482 | 6525 ± 2271 | 0.04 |
| Platelet count ($10^4$/μl) | 21.3 ± 6.4 | 20.7 ± 5.9 | 0.74 |
| Tumor size (cm) | 2.1 ± 1.5 | 2.9 ± 1.4 | 0.11 |
| Functional/non-functional | 17/24 | 2/12 | 0.10 |
| Ki-67 index | 2.3 ± 2.6 | 21.3 ± 29.6 | <0.01 |
| Mitotic count | 1.5 ± 3.0 | 8.5 ± 11.5 | <0.01 |
| NET G1/G2/G3 | 29/11/1 | 5/6/3 | 0.02 |
| Surgical procedure | | | |
| PDorPPPD/DP/TP/enucleation | 10/20/2/9 | 8/6/0/0 | 0.06 |
| Synchronous hepatic resection | 0 (0%) | 2 (14.3%) | 0.06 |
| Lymph node dissection | 32 (78.1%) | 14 (100%) | 0.09 |
| R1 | 2 (3.0%) | 3 (15.8%) | 0.07 |
| Lymph node metastasis | 4 (9.8%) | 6 (42.8%) | <0.01 |
| ly (+) | 6 (14.6%) | 7 (50.0%) | 0.01 |
| v (+) | 12 (29.3%) | 8 (57.1%) | 0.06 |
| ne (+) | 6 (14.6%) | 7 (50.0%) | 0.01 |
| CD163 cell count | 31.5 ± 40.4 | 100.3 ± 108.1 | <0.01 |
| Operative time (min) | 357 ± 151 | 471 ± 173 | 0.08 |
| Estimated blood loss (g) | 580 ± 681 | 1626 ± 2618 | 0.02 |
| Blood transfusion (+) | 4 (9.8%) | 1 (7.1%) | 0.99 |
| Postoperative complications (+) | 8 (19.5%) | 2 (14.3%) | 0.77 |
| MEN | 5 (12.2%) | 3 (21.4%) | 0.35 |

Data are expressed as means ± standard deviations or number of patients (percentage) as appropriate. NLR:neutrophil-lymphocyte ratio, BMI:body mass index, CRP:C-reactive protein, NET:euroendocrine tumor, PD:pancreatico deuodenectomy, PPPD:Plyrolus preserving PD, DP:distal pancreatectomy, TP:total pancreatectomy, R:residual tumor ly:lymphatic invasion, v:venous invasion, ne:neural invasion, MEN:multiple endocrine neoplasm.

**Table 2**
Cox proportional hazard model of the all clinical characteristics on recurrence-free survival using univariable and multivariable analysis.

| Variables | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | Hazard ratio | *P* | Hazard ratio | *P* |
| Age | 0.87 (0.49, 1.07) | 0.32 | | |
| Gender (male) | 2.18 (0.87, 1.84) | 0.24 | | |
| BMI | 1.79 (0.81, 11.13) | 0.18 | | |
| Albumin (g/dl) | 1.11 (0.51, 11.42) | 0.54 | | |
| WBC | 1.00 (0.99, 1.00) | 0.81 | | |
| NLR>3.41 | 12.62 (2.87, 86.76) | <0.01 | 31.75 (1.93, 382.92) | 0.03 |
| CRP (mg/dl) | 0.92 (0.11, 1.35) | 0.84 | | |
| Tumor size >2 cm | 7.79 (1.37, 146.14) | 0.02 | | |
| Non-functional | 1.14 (1.01, 2.42) | <0.01 | | |
| Lymph node dissection | 1.47 (0.84, 11.85) | 0.07 | | |
| Lymph node metastasis | 4.99 (0.97, 21.82) | 0.05 | | |
| Synchronous hepatic resection | 66.99 (6.25, 146.66) | <0.01 | 13.01 (0.30, 788.79) | 0.04 |
| NET G2orG3 vs NET G1 | 46.62 (7.84, 78.40) | <0.01 | 22.77 (1.78, 182.90) | 0.04 |
| R1 | 3.82(0.20, 21.57) | 0.21 | | |
| Ki-67 index | 1.03 (1.01, 1.05) | <0.01 | | |
| Mitotic count | 1.06 (1.01, 1.11) | <0.01 | | |
| ly (+) | 5.50 (1.25, 24.58) | 0.02 | | |
| v (+) | 7.43 (1.68, 51.38) | 0.02 | | |
| ne (+) | 8.14 (1.96, 40.27) | <0.01 | | |
| CD163 cell count | 1.00 (0.99, 1.01) | 0.61 | | |
| Operative time (min) | 1.00 (0.99, 1.01) | 0.11 | | |
| Estimated blood loss (g) | 1.00 (1.00, 1.00) | 0.01 | | |
| Blood transfusion (+) | 3.50 (0.51, 15.37) | 0.13 | | |
| Postoperative complications (+) | 1.80 (0.32, 33.75) | 0.58 | | |
| MEN | 1.02 (0.05, 6.05) | 0.98 | | |

Values in parentheses are 95% confidence intervals.
BMI:body mass index, NLR:neutrophil-lymphocyte ratio, CRP:C-reactive protein, NET:euroendocrine tumor, R:residual tumor ly:lymphatic invasion, v:venous invasion, ne:neural invasion, MEN:multiple endocrine neoplasm.

were independent risk factors for recurrence after curative resection in the multivariate analysis (Table 2).

The Kaplan–Meier analysis showed differences in recurrence-free survival between the groups with high and low NLRs. As shown in Fig. 1, recurrence-free survival of patients with high NLRs was significantly poorer than that of patients with low NLRs.

Fig. 2 shows the immunohistochemical CD163 staining of a representative tumor specimen (magnification × 200), while CD163-positive cell counts in PanNETs are presented in Fig. 3. CD163-positive cell counts in the high NLR group (Fig. 2A) were

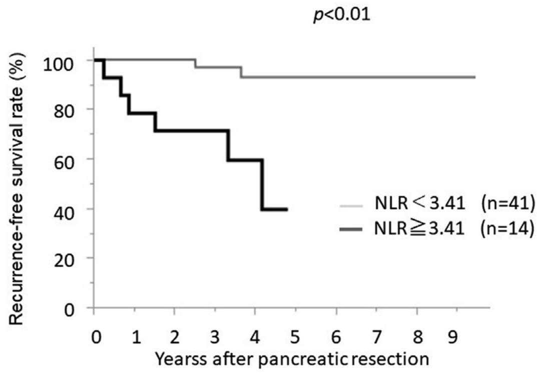


**Fig. 1. Recurrence-free survival of patients who underwent pancreatic resection for PanNET.** Kaplan–Meier analysis showed significant differences in recurrence-free survival between the high and low NLR groups. Recurrence-free survival of patients with high NLRs was significantly poorer than that of patients with low NLRs.

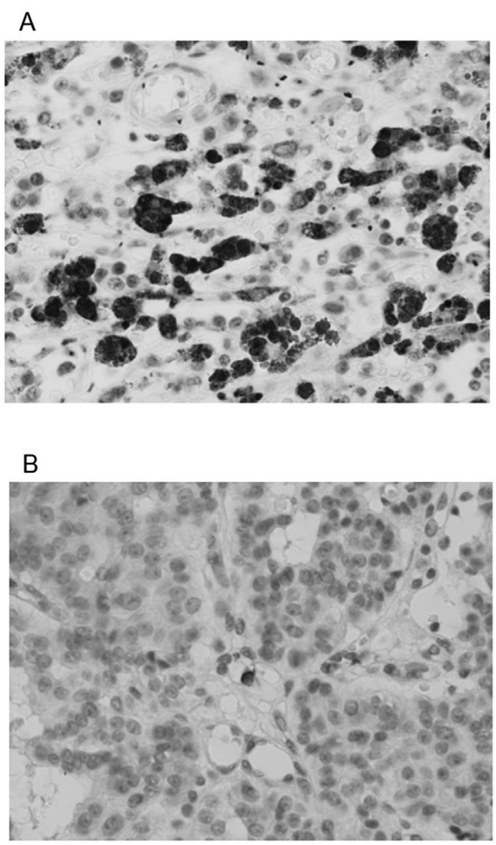


**Fig. 2. Immunohistochemical CD163 staining of a representative PanNET specimen (×200).** A. Representative immunohistochemical staining of CD163 in a high NLR group. B. Representative immunohistochemical staining of CD163 in a low NLR group.

significantly higher compared with those in the low NLR group (Fig. 2B).

## Discussion

In this multi-institutional study, the WHO 2017 classification, NLR, and synchronous hepatic resection were identified as independent prognostic factors in patients with resectable well-differentiated PanNETs. High NLR was associated with the malignant potential of PanNET, as well as higher Ki-67 index, higher

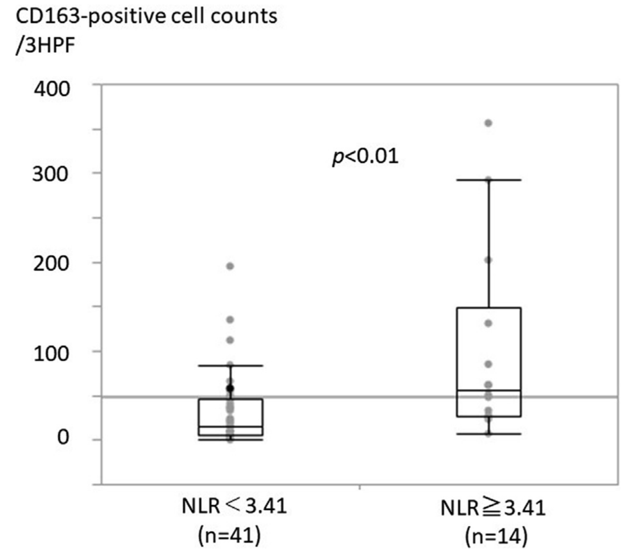


**Fig. 3. CD163-positive cell counts in the low and high NLR groups.** CD163-positive cell counts in the high NLR group were significantly higher compared with those in the low NLR groups ($P < 0.01$). HPF indicates high-power field.

mitotic count, higher grade, lymph node metastasis, and higher incidence of lymphatic and neural invasion. Positive cell counts of CD163, which is a cell surface marker of TAMs, were significantly higher in the high NLR group compared with those in the low NLR group. This is the first report to demonstrate that high NLR is related to poor prognosis and TAMs in resectable well-differentiated PanNET.

Zhou et al. evaluated the association between a hematological inflammatory marker and the prognosis of gastroenteropancreatic neuroendocrine tumors in a systemic review and meta-analysis [13]. Although the number of studies to investigate the predictive value of NLR in PanNET is far fewer than studies of other tumor types, they all revealed that NLR is a remarkable biomarker for predicting poor prognosis. Gaitanidis et al. revealed NLR >2.3 was independently associated with worse progression-free survival in the entire cohort, regardless of whether patients were undergoing surgical treatment [14]. Some reports revealed high NLR predicts liver metastasis or lymph node metastasis in patients who have undergone surgical resection for PanNETs [15–19], but in these studies patients with PanNETs were categorized according to the WHO2 010 classification and not the WHO 2017 classification [18,19].

Chronic systemic inflammation is an important prognostic factor in patients with cancer, and NLR is used as a representative parameter of chronic inflammation in such patients. Although high NLR is thought be associated with systemic inflammation, the cause of this inflammation remains unclear. Neutrophilia as an inflammatory response inhibits the immune system by suppressing the cytotoxic activity of immune cells such as activated T lymphocytes and natural killer cells [20]. Nonetheless, lymphocytes are important in tumor immunity. Several studies reported that the peritumoral infiltration of lymphocytes is associated with better response to cytotoxic treatment and prognosis in cancer patients [21]. Systemic inflammation is induced by local inflammation through several cytokines. Previous studies showed that several cytokines, such as interleukin (IL)-6, −8, and −17, were associated with NLR in colorectal cancer and hepatocellular carcinoma [5,6,22]. IL-6 is a well-known chemotactic factor for neutrophils [23]. Our previous study showed that chronic inflammatory responses in patients with HCC may be due to local accumulation of

M2 macrophages within the tumors [5,6]. Macrophages can assume a range of different phenotypes based on environmental stimuli. The extremes of this range are the M1 phenotype, associated with active microbial killing, and the M2 phenotype, associated with tissue remodeling and angiogenesis [24,25]. M2 phenotype macrophages appear to be the dominant type in tumors, with TAMs characterized by high expression of M2 macrophage antigens such as CD163 and high constitutive expression of IL-6 and IL-10. CD163 is a macrophage-specific scavenger receptor transmembrane protein with a molecular weight of 130 kD and indicates the M2 macrophage phenotype [26]. TAMs and tumor cells also produce IL-10, which effectively blunts the anti-tumor response by cytotoxic T cells. Conversely, CD68-expressing macrophage are ubiquitous.

There are many reports regarding the promotion of distant metastasis of cancer cells by TAMs. Wei et al. revealed TAMs are a useful biomarker to predict recurrence after surgical resection of non-functional PanNETs, although they evaluated CD68 expression as originating from TAMs [12]. In our study, the number of CD163-expressing cells was not a predictor of recurrence. However, further studies in a larger patient population may be required. Recent studies have provided evidence that TAMs produce inflammatory cytokines such as IL-1, tumor necrosis factor, IL-6, IL-8, and IL-17. These cytokines induce inflammation and neutrophilia; namely, elevated NLR is associated with a high infiltration of TAMs and their cytokine production.

Surgical resection is the only curative therapy for PanNETs and detection of the high malignant potential of PanNETs before surgery is crucial. A previous report revealed that WHO classification or lymphatic, vessel, and neural invasion are reported as poor prognostic predictors of PanNETs [27,28]. Preoperative information of PanNET grade should be required. Grading of PanNETs by the highest Ki-67 index in endoscopic ultrasound-fine needle aspiration specimens with adequate cellularity has a high concordance with the grading of resected specimens [29]. NLR is easily obtained before surgery with no invasiveness. Thus, combination of NLR and WHO 2017 grading would predict prognosis before surgery.

Our study had several limitations that must be considered. First, the number of recurrences ($n = 8$) was low, and the multivariate analysis will be affected by the event number. Second, NLR may be affected by many conditions, including chronic inflammatory disease and its duration. Third, the median follow follow-up is relatively short. To overcome this issue, we selected the patients who have a minimum follow-up of 2 years. Finally, there was selection bias due to the low number of patients and the retrospective nature of the study. Therefore, our results could not lead to a definite conclusion.

In conclusion, NLR is an easily measurable inflammatory biomarker. Our results show that NLR is a promising predictor of recurrence after pancreatectomy that needs to be further investigated and that accumulation of TAMs in the tumor could be one of the causes of NLR elevation.

## Conflicts of interest

There were no conflicts of interest or financial support

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## References

[1] Fesinmeyer MD, Austin MA, Li CI, De Roos AJ, Bowen DJ. Differences in survival by histologic type of pancreatic cancer. Cancer Epidemiol Biomark Prev 2005;14(7):1766–73.
[2] Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26(18):3063–72.
[3] Bosman FT, Carneiro F, Hruban RH, et al. WHO classification of tumours of the digestive system. fourth ed. Lyon: International Agency for Research on Cancer; 2010.
[4] Lloyd RV, Osamura RY, Klöppel G, Rosai J. WHO classification of tumours of endocrine organs. fourth ed. Lyon: International Agency for Research on Cancer; 2017. p. 355.
[5] Mano Y, Shirabe K, Yamashita YI, Harimoto N, Tsujita E, Takeishi K, et al. Preoperative neutrophil-to-lymphocyte ratio is a predictor of survival after hepatectomy for hepatocellular carcinoma a retrospective analysis. Ann Surg 2013;258(2):301–5.
[6] Motomura T, Shirabe K, Mano Y, Muto J, Toshima T, Umemoto Y, et al. Neutrophil-lymphocyte ratio reflects hepatocellular carcinoma recurrence after liver transplantation via inflammatory microenvironment. J Hepatol 2013;58(1):58–64.
[7] Harimoto N, Shirabe K, Nakagawara H, Toshima T, Yamashita Y, Ikegami T, et al. Prognostic factors affecting survival at recurrence of hepatocellular carcinoma after living-donor liver transplantation: with special reference to neutrophil/lymphocyte ratio. Transplantation 2013;96(11):1008–12.
[8] Tang H, Lu W, Li B, Li C, Xu Y, Dong J. Prognostic significance of neutrophil-to-lymphocyte ratio in biliary tract cancers: a systematic review and meta-analysis. Oncotarget 2017;8(22):36857–68.
[9] Shirabe K, Itoh S, Yoshizumi T, Soejima Y, Taketomi A, Aishima S, et al. The predictors of microvascular invasion in candidates for liver transplantation with hepatocellular carcinoma-with special reference to the serum levels of des-gamma-carboxy prothrombin. J Surg Oncol 2007;95:235–40.
[10] Najafi M, Hashemi Goradel N, Farhood B, Salehi E, Nashtaei MS, et al. Macrophage polarity in cancer: a review. J Cell Biochem 2019;120(3):2756–65.
[11] Krug S, Abbassi R, Griesmann H, Sipos B, Wiese D, Rexin P, et al. Therapeutic targeting of tumor-associated macrophages in pancreatic neuroendocrine tumors. Int J Cancer 2018;143(7):1806–16.
[12] Wei IH, Harmon CM, Arcerito M, Cheng DF, Minter RM, Simeone DM. Tumor-associated macrophages are a useful biomarker to predict recurrence after surgical resection of nonfunctional pancreatic neuroendocrine tumors. Ann Surg 2014;260(6):1088–94.
[13] Zhou Y, Li D, Lin Y, Yu M, Lu X, Jian Z, et al. Pretreatment hematologic markers as prognostic predictors of gastroenteropancreatic neuroendocrine tumors: a systematic review and meta-analysis. OncoTargets Ther 2018;11:2489–96.
[14] Gaitanidis A, Patel D, Nilubol N, Tirosh A, Sadowski S, Kebebew E. Markers of systemic inflammatory response are prognostic factors in patients with pancreatic neuroendocrine tumors (PNETs): a prospective analysis. Ann Surg Oncol 2018;25(1):122–30.
[15] Zhou B, Zhan C, Wu J, Liu J, Zhou J, Zheng S. Prognostic significance of preoperative neutrophil-to-lymphocyte ratio in surgically resectable pancreatic neuroendocrine tumors. Med Sci Monit 2017;23:5574–88.
[16] Zhou B, Deng J, Chen L, Zheng S. Preoperative neutrophil-to-lymphocyte ratio and tumor-related factors to predict lymph node metastasis in nonfunctioning pancreatic neuroendocrine tumors. Sci Rep 2017;7(1):17506.
[17] Luo G, Liu C, Cheng H, Jin K, Guo M, Lu Y, et al. Neutrophil-lymphocyte ratio predicts survival in pancreatic neuroendocrine tumors. Oncol Lett 2017;13(4):2454–8.
[18] Arima K, Okabe H, Hashimoto D, Chikamoto A, Nitta H, Higashi T, et al. Neutrophil-to-lymphocyte ratio predicts metachronous liver metastasis of pancreatic neuroendocrine tumors. Int J Clin Oncol 2017;22(4):734–9.
[19] Tong Z, Liu L, Zheng Y, Jiang W, Zhao P, Fang W, et al. Predictive value of preoperative peripheral blood neutrophil/lymphocyte ratio for lymph node metastasis in patients of resectable pancreatic neuroendocrine tumors: a nomogram-based study. World J Surg Oncol 2017;15(1):108.
[20] Petrie HT, Klassen LW, Kay HD. Inhibition of human cytotoxic T lymphocyte activity in vitro by autologous peripheral blood granulocytes. J Immunol 1985;134(1):230–4.
[21] Gooden MJ, de Bock GH, Leffers N, Daemen T, Nijman HW. The prognostic influence of tumour-infiltrating lymphocytes in cancer: a systematic review with meta-analysis. Br J Canc 2011;105(1):93–103.
[22] Chen ZY, Raghav K, Lieu CH, Jiang ZQ, Eng C, Vauthey JN, et al. Cytokine profile and prognostic significance of high neutrophil-lymphocyte ratio in colorectal cancer. Br J Canc 2015;112(6):1088–97.
[23] Rose-John S, Waetzig GH, Scheller J, Grötzinger J, Seegert D. The IL-6/sIL-6R complex as a novel target for therapeutic approaches. Expert Opin Ther Targets 2007;11(5):613–24.
[24] Li YW, Qiu SJ, Fan J, Gao Q, Zhou J, Xiao YS, et al. Tumor-infiltrating macrophages can predict favorable prognosis in hepatocellular carcinoma after resection. J Cancer Res Clin Oncol 2009;135:439–49.
[25] Komohara Y, Hirahara J, Horikawa T, Kawamura K, Kiyota E, Sakashita N, et al. AM-3K, an anti-macrophage antibody, recognizes CD163, a molecule associated with an anti-inflammatory macrophage phenotype. J Histochem Cytochem 2006;54:763–71.
[26] Van Gorp H, Delputte PL, Nauwynck HJ. Scavenger receptor CD163, a Jack-of-all-trades and potential target for cell-directed therapy. Mol Immunol 2010;47(7–8):1650–60.

[27] Chouliaras K, Newman NA, Shukla M, Swett KR, Levine EA, Sham J, et al. Analysis of recurrence after the resection of pancreatic neuroendocrine tumors. J Surg Oncol 2018;118(3):416–21.
[28] Bilimoria KY, Talamonti MS, Tomlinson JS, Stewart AK, Winchester DP, Ko CY, et al. Prognostic score predicting survival after resection of pancreatic neuroendocrine tumors: analysis of 3851 patients. Ann Surg 2008;247(3):490–500.
[29] Hasegawa T, Yamao K, Hijioka S, Bhatia V, Mizuno N, Hara K, et al. Evaluation of Ki-67 index in EUS-FNA specimens for the assessment of malignancy risk in pancreatic neuroendocrine tumors. Endoscopy 2014;46(1):32–8.