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ORIGINAL ARTICLE

The effectiveness of postoperative neutrophils to lymphocytes ratio in predicting long-term recurrence after stomach cancer surgery

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Purpose: Immunosuppression is a characteristic of cancer recurrence after curative resection. The neutrophil-to-lymphocyte ratio (NL ratio) in peripheral blood is associated with immune function. However, it is not clear whether the postoperative NL ratio is a predictor for cancer relapse after resection. Thus, we investigated the effectiveness of the short-term postoperative NL ratio in the prediction of disease recurrence within 5 years after stomach cancer surgery by a retrospective chart review. **Methods:** Ninety-three patients with stomach cancer were enrolled. Significant risk factors for cancer recurrence were determined by multivariate Cox regression. Independent variables to increase the NL ratio to >7.7 by postoperative day (POD) 3 were examined by multivariate logistic regression analysis. **Results:** The 5-year risk of cancer recurrence after gastrectomy was 4.2 times higher for patients with a POD3 NL ratio of >7.7 (P = 0.005), 3.4 times higher for normal-weight patients compared with overweight patients (P = 0.008), and 20 times higher for stage III compared with stage 0 according to the tumor-node-metastasis cancer staging system (P = 0.003). The surgical duration (hours) increased the chance of high NL ratio >7.7 (odds ratio, 2.5; P = 0.006). **Conclusion:** The postoperative NL ratio, especially the POD3 NL ratio, predicts long-term recurrence after stomach cancer surgery.

Key Words: Immunosuppression, Lymphocyte, Neoplasm recurrence, Neutrophil

INTRODUCTION

The immune system status is pertinent to both the prevalence [1] and outcomes of various types of cancer [2-4]. Furthermore, it has been suggested that long-term recurrence-free survival after cancer resection can be predicted by evaluating the patient's short term postoperative immunosuppression status [5]. The neutrophil-to-lymphocyte count (NL ratio) is associated with short-term postoperative immune function. The NL ratio is easily calculated from a differential white blood cell count of circulating leukocytes, and it is approved for use in clinical practice as a test to evaluate the cell-mediated immune response to various stresses, including the existence of cancer [6-8]. Previous research has shown that the preoperative NL ratio can be used to predict cancer re-

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currence after curative resection [6, 8-10].

The decline in lymphocyte percentage on postoperative day (POD) 7 is related to recurrence after colorectal cancer surgery [5]. However, to the best of the authors' knowledge, the role of the postoperative NL ratio in predicting cancer recurrence after curative resection has not yet been established. In addition, perioperative factors should also be given consideration when using the postoperative NL ratio as a marker for predicting cancer prognosis because there is an increased variety of factors involved in immunosuppression during and after surgery compared with before surgery [11-13]. In particular, the role of allogenic red blood cell (RBC) transfusion as an immunosuppressive factor should be taken into consideration when interpreting the NL ratio as a predictor of cancer recurrence [12,14].

Thus, in this retrospective study, we sought to evaluate the predictive power of the NL ratio calculated at POD3 and POD7 by multivariate analysis with Cox proportional hazard regression in determining cancer recurrence after gastrectomy. In addition, multivariate logistic regression was used to investigate factors that influence the postoperative NL ratio.

METHODS

After obtaining permission from the local institutional review board, retrospective chart reviews were carried out for 93 adult (34 to 79 years of age) patients of American Society of Anesthesiologists physical status 1 to 3 who underwent regular scheduled operations for complete resection of gastric cancer from January 2004 through July 2009. Laboratory records of preoperative, POD3, and POD7 differential white blood cell (WBC) counts were evaluated. The inclusion criterion was no transfusion within 1 month before surgery. The exclusion criteria were as follows: 1) evidence of adjacent or distant organ metastasis as confirmed by a preoperative test such as multidetector computed tomography, computed tomography (CT), or positron emission tomography-CT; 2) a history of preoperative anticancer chemotherapy or any cancer related surgery; 3) insufficient differential WBC count data up to POD7; 4) preoperative evidence of infection or inflammation when no transfusion was given; e.g., WBC $>12{,}000/mm^2$; 5) perioperative platelet and fresh frozen plasma transfusion; 6) a history of steroid medication; and 7) postoperative infectious complications such as surgical site infection, pneumonia, urinary tract infection, etc.

The subjects were divided into two groups: those who were cancer-free 5 years after curative resection, and those who experienced cancer recurrence after surgery. The elapsed time in years from surgery to recurrence was recorded.

The observed data were sex, age, body mass index (BMI), surgical and anesthetic duration, number of allogenic RBC transfusions, age of allogeneic RBCs, and the preoperative, POD3, and POD7 NL ratio. Furthermore, staging of each tumor was conducted in accordance with the tumor-node-metastasis (TNM) system for gastric cancer outlined by the seventh American Joint Committee on Cancer/International Union Against Cancer Classification. Tumor size and evidence of cancer recurrence within 5 years after surgery were also recorded.

The number of allogenic RBC transfusion and the storage time (days) of each unit of RBCs were converted into a single transfusion variable of categorical form: 0, no transfusion; 1, 1 to 3 units of unaged RBC (<14 days in storage); 2, 1 to 3 units of RBCs with at least 1 unit of aged RBCs; 3, 4 or more units of unaged RBCs; 4, 4 or more units of RBCs with at least 1 unit of aged RBCs. The NL ratio was calculated from the differential WBC count preoperatively, on POD3, and POD7.

Statistical analysis was performed using the PASW ver. 18.0 (IBM Co., Armonk, NY, USA). Comparisons of categorical variables were performed using Pearson's chi-square or Fisher's exact test, and an independent t-test was applied for the continuous variables.

For multivariate analysis with Cox hazard proportional regression and logistic regression, the NL ratio, BMI, and tumor size were converted into categorical variables. To transform the NL ratio into a binary categorical variable, the optimal cut-off value of the NL ratio was determined based on the highest area under the receiver operating characteristic (ROC) curve associated with a univariate logistic model of cancer recurrence. The area of tumor mass

was categorized into a binary variable using the median value (9 cm^2). Furthermore, BMI was categorized into two levels: non-overweight (< 24.7 for male or < 22.6 kg/m^2 for female) and overweight (≥ 24.7 for male or ≥ 22.6 kg/m^2 for female) according to the World Health Organization recommended body weight classification system for Asian populations [15] and the results of a previous study that differentiated BMI between overweight male and female subjects [16].

To reveal the factors that influence recurrence-free survival for 5 years after cancer surgery, multivariate analysis was performed with Cox hazard proportional regression: the hazard ratio of the dichotomous cancer recurrence was determined by a backwards stepwise elimination method.

Table 1. Patient's characteristics and univariate analysis for cancer recurrence

Variable	Noncancer recurrence	Cancer recurrence	P-value
Subjects	63	30	
Sex			0.780
Male	38	19	
Female	25	11	
Age (yr)	59.11 ± 9.58	61.20 ± 11.65	0.362
Body mass index (kg/m^2)			0.065
Underweight	10 (15.9)	2 (6.7)	
Normal weight	22 (34.9)	18 (60)	
Overweight	31 (49.2)	10 (33.3)	
Anesthetic duration (hr)	3.80 ± 1.020	4.34 ± 1.70	0.081
Surgical duration (hr)	3.31 ± 1.13	3.82 ± 1.32	0.058
Transfusion variable			0.048
0	33 (52.4)	15 (50)	
1	19 (30.2)	3 (10)	
2	3 (4.8)	4 (13.3)	
3	6 (9.5)	4 (13.3)	
4	2 (3.2)	4 (13.3)	
Preoperative NL ratio ≥ 1.8	20 (31.7)	16 (53.3)	0.046
POD3 NL ratio ≥ 7.7	6 (9.5)	8 (26.7)	0.031
POD7 NL ratio ≥ 5.0	5 (7.9)	8 (26.7)	0.015

NL ratio, neutrophil-to-lymphocyte ratio; POD, postoperative day.
Values are presented as mean ± SD or number (%).
Body mass index (kg/m^2): underweight, <18.5; normal weight, 18.5 to 24.7 (male) or 18.5 to 22.6 (female); overweight, ≥24.7 (male) or ≥22.6 (female).
Transfusion variable: 0, no transfusion; 1, red blood cell (RBC) 1 to 3 unit without aged RBC (≥14 days); 2, RBC 1 to 3 unit with aged RBC; 3, RBC 4 ≥ without aged RBC; 4, RBC ≥ 4 with aged RBC.
NL ratio, neutrophil-to-lymphocyte ratio; POD, postoperative day.

The independent variables for Cox regression were BMI, size of tumor, sex, cancer stage under the TNM system, categorical transfusion variable, and the preoperative, POD3 and POD7 NL ratio. In addition, multivariate analysis with stepwise logistic regression using backward elimination was conducted to clarify whether perioperative factors were correlated to a higher postoperative NL ratio, which had a significant influence on cancer recurrence in Cox regression analysis. Independent variables of logistic regression were BMI, sex, tumor size, cancer stage under

Table 2. Patient characteristics

Characteristic	Noncancer recurrence	Cancer recurrence	P-value
Subjects	63	30	
Cancer cell differentiation			0.156
Differentiated	33 (52.4)	11 (36.7)	
Undifferentiated	30 (47.6)	19 (63.3)	
Tumor diameter (cm)			0.000
<5.0	48 (76.2)	12 (40.0)	
5.0≥ and 10<	14 (22.2)	10 (33.3)	
10≥	1 (1.6)	8 (26.7)	
Invasion depth[a)]			0.000
T1	35 (55.6)	3 (10.0)	
T2	11 (17.5)	2 (6.7)	
T3	6 (9.5)	12 (40.0)	
T4	11 (17.5)	13 (43.3)	
Lymphovascular invaion			0.000
Absence	48 (76.2)	11 (36.7)	
Presence	15 (23.8)	19 (63.3)	
N stage			0.000
N0	45 (71.4)	2 (6.7)	
N1	8 (12.7)	5 (16.7)	
N2	3 (4.8)	10 (33.3)	
N3	7 (11.1)	13 (43.3)	
Stage (TNM)			0.000
0	16 (25.4)	1 (3.3)	
1	25 (39.7)	2 (6.7)	
2	13 (20.6)	3 (10.0)	
3	9 (14.3)	24 (80.0)	
Total gastrectomy	11 (17.5)	15 (50)	0.006
Subtotal gastrectomy (B1)	43 (68.3)	12 (40)	
Subtotal gastrectomy (B2)	9 (14.3)	3 (10)	
Intraoperative bleeding volume (mL)	657.1 ± 276.3	757.3 ± 351.0	0.138

Values are presented as number (%) or mean ± SD.
TNM, tumor-node-metastasis.
[a)]Invasion of depthis defined by the 7th International Union Against Cancer/American Joint Committee on Cancer tumor-node-metastasis classification: T1, tumor is growing into the submucosa; T2, into the muscularis propria layer; T3, into the subserosa layer; and T4, beyond serosa layer.

the TNM system, anesthetic and surgical duration, categorical transfusion variable, and preoperative NL ratio. In both multivariate analyses, independent variables with P $<$ 0.05 were included in the model, but those with P $>$ 0.1 were removed. Finally, long-term recurrence-free survival was examined by the Kaplan-Meier method using the log-rank test. All statistical results were determined to be significant when P-values $<$ 0.05.

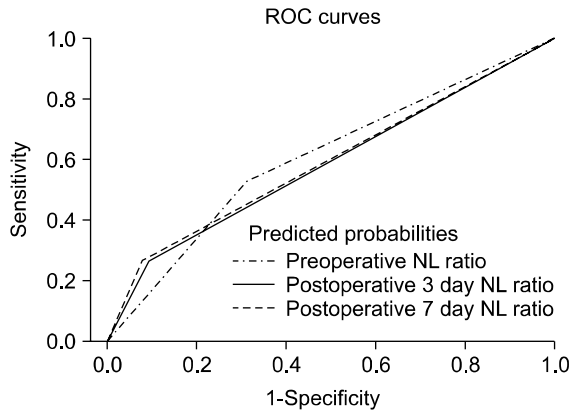

Fig. 1. Receiver operating characteristic (ROC) curves for neutrophil-to-lymphocyte ratio (NL ratio) on pre- and postoperative day 3 and 7 in predicting the probability of a cancer recurrence in all patients.

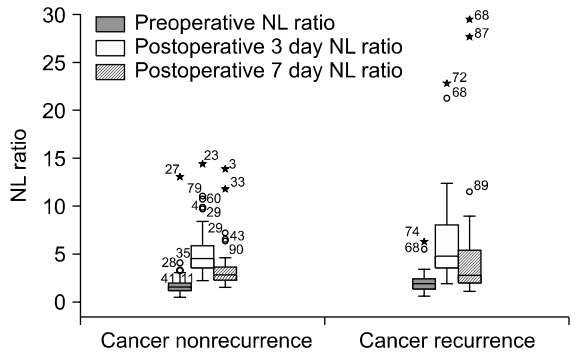

Fig. 2. Box-and-whisker plots showing distributions of neutrophil-to-lymphocyte ratio (NL ratio) values on pre- and postoperative 3 and 7 day for the groups of cancer nonrecurrence (n = 63) and cancer recurrence (n = 30) 5 years after gastrectomy. The bottoms and tops of the boxes are the 25th and 75th percentiles, and the horizontal lines of the boxes are median values. The whiskers represent the lowest and highest value in the 25th percentile minus 1.5 times the interquartile range (IQR) and 75th percentile plus 1.5 IQR regions, respectively. The suspected outliers (o) are 1.5 IQR or more above the 75th percentile, and the outliers (*) are 3 IQR or more above the 75th percentile. The numbers marked on outliers are the registration numbers of patients.

RESULTS

The profile of independent variables for multivariate Cox regression and logistic regression are shown in Table 1 and the clinicopathological features are listed in Table 2.

In our subjects, ROC curve analysis of the preoperative, POD3, and POD7 NL ratio suggested a cut-off of 1.8, 7.7, and 5.0 with an area under the curve of 0.608 (95% confidence interval [CI], 0.483 to 0.733), 0.586 (95% CI, 0.457 to 0.715), and 0.594 (95% CI, 0.464 to 0.723), respectively (Fig. 1). Thus, these values were adopted for the cut-off value of preoperative, POD3, and POD7 NL ratios. And each distribution of NL ratio in recurrence and nonrecurrence cases are showed in Fig. 2. In multivariate analysis with Cox hazard proportional regression, the hazard ratio of cancer recurrence within 5 years after surgery was 4.167 when NL

Table 3. Multivariate analysis for cancer recurrence free-survival using Cox proportional hazard regression using backwards stepwise elimination method

	Variable	Hazard ratio	95% CI	P-value
Step 1	POD7 NL ratio ≥ 5.0	1.144	0.377-3.467	0.813
Step 2	Tumor area ≥ 9 cm^2	0.696	0.240-2.021	0.506
Step 3	Preoperative NL ratio ≥ 1.8	1.327	0.603-2.922	0.482
Step 4	Transfusion variable			
	0 (indicator)			
	1	0.490	0.135-1.779	0.278
	2	2.697	0.821-8.865	0.102
	3	1.718	0.539-5.472	0.360
	4	0.837	0.263-2.670	0.764
Step 5	Sex	2.088	0.746-5.846	0.161
Step 6	POD3 NL ratio ≥ 7.7	4.167	1.550-11.200	0.005
	Body mass index			
	Overweight (indicator)			
	Nonoverweight	3.440	1.378-8.586	0.008
	Cancer stage			
	0 (indicator)			
	I	1.113	0.101-12.288	0.930
	II	3.880	0.402-37.470	0.241
	III	20.706	2.768-154.864	0.003

CI, confidence interval; POD, postoperative day; NL ratio, neutrophil-to-lymphocyte ratio.
Body mass index (kg/m^2): nonoverweight, $<$24.7 (male) or 22.6 (female) overweight, ≥24.7 (male) or ≥22.6 (female).
Transfusion variable: 0, no transfusion; 1, red blood cell (RBC) 1 to 3 unit without aged RBC (≥14 days); 2, RBC 1 to 3 unit with aged RBC; 3, RBC 4 ≥ without aged RBC; 4, RBC ≥ 4 with aged RBC.

ratio POD3 was >7.7 (P = 0.005) (Table 3). In addition, patients of nonoverweight had a 3.440 fold greater chance of cancer recurrence than those who were overweight (P = 0.008) (Table 3). Later-stage stomach cancers (beyond stage III) were associated with a >20-times increased risk of cancer recurrence after curative resection compared with stage 0 cancers (P = 0.003) (Table 3). However, sex, tumor size, allogenic RBC transfusion, and preoperative and POD3 NL ratios were not predictors for recurrence-free survival in our Cox regression model. The Kaplan-Meire curve also demonstrated a significantly increased incidence of overall cancer recurrence when the POD3 NL ratio was >7.7 (P = 0.009) (Fig. 3).

According to the logistic regression results, the chance of having a POD3 NL ratio of >7.7 was increased by 2.481 times with each 1-hour increase in surgical duration (P = 0.006) (Table 4).

However, allogenic RBC transfusion, cancer stage, BMI, sex, preoperative NL ratio, and anesthetic duration did not play a role in increasing POD3 NL ratio to >7.7 (data not shown).

DISCUSSION

In this retrospective study, we found that the role of the POD3 NL ratio can function as a marker for predicting cancer-free survival for 5 years after curative resection.

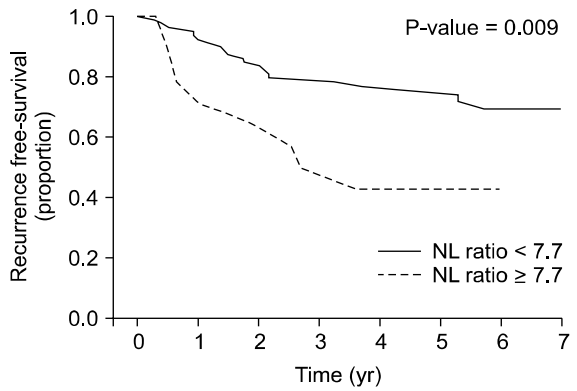

Fig. 3. Kaplan-Meier plot of recurrence free-survival after surgery comparing between neutrophil-to-lymphocyte ratio (NL ratio) at postoperative day 3 less than and above 7.7 in the patients with stomach cancer (log rank test P = 0.009).

Among various perioperative factors, gender and being overweight are assumed to be prognostic factors in predicting recurrence after gastrectomy due to cancer [17,18]. In addition, staging for gastric cancer under the TNM staging system provides significant information about long-term survival after gastrectomy [19]. Moreover, perioperative allogenic RBC transfusion acts to suppress immune function, which increases the risk of postoperative cancer recurrence [12,14]. Finally, animal studies have shown that the age of allogenic RBCs is significantly associated with cancer progression [20].

Thus, we included BMI, sex, preoperative staging of stomach cancer, and number and age of allogenic RBC transfusion into the Cox proportional hazard regression model for recurrence-free survival after cancer surgery. The preoperative NL ratio, a marker representing innate immunity [6,8-10], was also included as a variable for survival analysis. There was debate about the age factor. There were significant differences in overall survival of patients ≥75 years of age [21]. However, it is known that the aging process does not impact the risk of disease recurrence in a patient with stomach cancer [17]. Thus, we did not include the effect of age on survival analysis. When all of these previously identified prognostic variables were adjusted in the Cox regression equation, BMI, cancer

Table 4. Risk factors of NL ratio postoperative day 3 above 7.7 on stepwise backward elimination logistic regression analysis

	Variable	Odds ratio	95% CI	P-value
Step 5	Surgical duration (hr)	2.481	1.292-4.763	0.006
	Preoperative NL ratio ≥ 1.8	3.731	0.834-16.688	0.085
	Body mass index	0.180	0.031-1.043	0.056
	Transfusion variable			
	0 (indicator)			
	1	0.172	0.011-2.735	0.212
	2	2.409	0.243-23.872	0.453
	3	2.954	0.455-19.160	0.256
	4	5.004	0.667-37.564	0.117

NL ratio, neutrophil-to-lymphocyte ratio; CI, confidence interval. Body mass index (kg/m^2): nonoverweight <24.7 (male) or 22.6 (female) and overweight ≥24.7 (male) or ≥22.6 (female). Transfusion variable: 0, no transfusion; 1, red blood cell (RBC) 1 to 3 unit without aged RBC (≥14 days); 2, RBC 1 to 3 unit with aged RBC; 3, RBC 4 ≥ without aged RBC; 4, RBC ≥ 4 with aged RBC.

stage, and POD3 NL ratio played significant roles in predicting the risk of cancer recurrence after curative resection. In particular, a patient with a POD3 NL ratio of >7.7 was at an approximately 4-times higher risk of cancer recurrence than a patients with NL ratio of <7.7. Our results are supported by a retrospective study performed by Yoneyama et al. [5], who reported that a lymphocyte percentage of <15% at POD7 is a risk factor for long-term recurrence of colorectal cancer after resection. In addition, Lee et al. [22] reported that peripheral lymphocyte counts after early cervical cancer surgery are important prognostic factors and the patients who showed increased peripheral lymphocyte counts on POD3 also had better disease-free survival. Although they did not discuss neutrophil percentage or NL ratio as a predictor for cancer recurrence, they revealed that the lymphocyte on POD3 and POD7 is an independent prognostic factor for the patients undergoing resection for colorectal and early cervical cancer [5,22].

Surgery-induced immunosuppression has been associated with impaired wound healing, delayed postoperative recovery, an increased incidence of cancer recurrence, and reduced survival [23]. Circulating lymphocyte numbers fall perioperatively [24] because of a decrease in the lymphocyte proliferation rate [25] or a redistribution of lymphocytes from the peripheral blood to the body compartment [26]. POD3, at which point the lymphocyte count and percentage increase, may be the appropriate time to evaluate the immune status. Thus, the NL ratio on POD3 is available to predict long-term recurrence after stomach cancer surgery. Studies of allogenic RBC transfusion have shown evidence of RBC deformity and increased risks associated with transfusion of RBCs stored for >14 days such as increased mortality, postoperative infection, pneumonia, and length of stay for critically ill patients [27-29]. Thus, our study model addressed the effect of the amount of transfused blood and the presence of RBCs that had been stored for >14 days on the predictability of the postoperative NL ratio. However, our findings did not show a correlation between transfusion variables and cancer recurrence.

Being overweight [17] and female gender [18] are assumed to be risk factors contributing to a higher prevalence of postoperative recurrence of gastric or colorectal cancer. However, according to our results, nonoverweight patients had a higher incidence rate of cancer relapse than did overweight patients. The exact cause was not disclosed in our study. However, Nobuoka et al. [30] reported the operating times were longer in the overweight group. In addition, Dhar et al. [17] suggested that a higher BMI is closely related to disease recurrence after gastric cancer surgery because of difficulties in dissecting lymph nodes in obese patients. In our report, there were 41 overweight and 54 nonoverweight patients; there were many more overweight patients than in Nobuoka's study (84.6% vs. 15.46%, respectively) [30]. Thus, there may be selection bias effects of too many overweight patients in our study. A previous study suggested that female patients with stomach cancer are at a higher risk than male patients for recurrence after surgery because female patients exhibit a higher NL ratio at POD3 than male patients [18]. However, we did not find a gender effect on incidence of cancer recurrence or even on the postoperative NL ratio.

There are several limitations in our study. Our study was designed retrospectively and involved a small sample of only 93 patients. Therefore, the results were obtained from all patients' prognoses without considering the impact of stage on prognosis. Prognosis is considered to be determined based on the stage. It is too difficult to conclude the importance of the POD3 NL ratio for the postoperative prognosis by these analysis. This is a rare report on the use of the NL ratio as a postoperative prognostic factor in gastric cancer.

In conclusion, this retrospective study revealed the effectiveness of postoperative NL ratio for predicting recurrence-free survival after curative resection of stomach cancer. A POD3 NL ratio of >7.7 was closely related to cancer recurrence after gastrectomy when perioperative factors, especially transfusion-related variables, were considered alongside the postoperative NL ratio. Further investigation may be necessary to build upon this model, adjusting for various perioperative variables, to determine the precise role of the postoperative NL ratio in predicting recurrence-free survival after cancer surgery.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Zhu X, Hu XZ, Ma LL, Tian Y. Level of CD4(+) CD25(high) CD127(low/-) regulatory T cells in transitional cell carcinoma patients and its clinical significance. Zhonghua Yi Xue Za Zhi 2009;89:2269-72.
2. Standish LJ, Sweet ES, Novack J, Wenner CA, Bridge C, Nelson A, et al. Breast cancer and the immune system. J Soc Integr Oncol 2008;6:158-68.
3. Nelson BH. The impact of T-cell immunity on ovarian cancer outcomes. Immunol Rev 2008;222:101-16.
4. Ancuta E, Ancuța C, Zugun-Eloae F, Iordache C, Chirieac R, Carasevici E. Predictive value of cellular immune response in cervical cancer. Rom J Morphol Embryol 2009; 50:651-5.
5. Yoneyama Y, Ito M, Sugitou M, Kobayashi A, Nishizawa Y, Saito N. Postoperative lymphocyte percentage influences the long-term disease-free survival following a resection for colorectal carcinoma. Jpn J Clin Oncol 2011;41:343-7.
6. Sarraf KM, Belcher E, Raevsky E, Nicholson AG, Goldstraw P, Lim E. Neutrophil/lymphocyte ratio and its association with survival after complete resection in non-small cell lung cancer. J Thorac Cardiovasc Surg 2009;137:425-8.
7. Zahorec R. Ratio of neutrophil to lymphocyte counts--rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy 2001;102:5-14.
8. Halazun KJ, Aldoori A, Malik HZ, Al-Mukhtar A, Prasad KR, Toogood GJ, et al. Elevated preoperative neutrophil to lymphocyte ratio predicts survival following hepatic resection for colorectal liver metastases. Eur J Surg Oncol 2008;34:55-60.
9. Bhatti I, Peacock O, Lloyd G, Larvin M, Hall RI. Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus platelet-lymphocyte ratio. Am J Surg 2010;200:197-203.
10. Sharaiha RZ, Halazun KJ, Mirza F, Port JL, Lee PC, Neugut AI, et al. Elevated preoperative neutrophil: lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer. Ann Surg Oncol 2011;18:3362-9.
11. Gottschalk A, Sharma S, Ford J, Durieux ME, Tiouririne M. Review article: the role of the perioperative period in recurrence after cancer surgery. Anesth Analg 2010;110: 1636-43.
12. Snyder GL, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. Br J Anaesth 2010;105:106-15.
13. Ben-Eliyahu S. The promotion of tumor metastasis by surgery and stress: immunological basis and implications for psychoneuroimmunology. Brain Behav Immun 2003;17 Suppl 1:S27-36.
14. Sugita S, Sasaki A, Iwaki K, Uchida H, Kai S, Shibata K, et al. Prognosis and postoperative lymphocyte count in patients with hepatocellular carcinoma who received intraoperative allogenic blood transfusion: a retrospective study. Eur J Surg Oncol 2008;34:339-45.
15. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157-63.
16. Yanai M, Kon A, Kumasaka K, Kawano K. Body mass index variations by age and sex, and prevalence of overweight in Japanese adults. Int J Obes Relat Metab Disord 1997;21:484-8.
17. Dhar DK, Kubota H, Tachibana M, Kotoh T, Tabara H, Masunaga R, et al. Body mass index determines the success of lymph node dissection and predicts the outcome of gastric carcinoma patients. Oncology 2000;59:18-23.
18. Gwak MS, Choi SJ, Kim JA, Ko JS, Kim TH, Lee SM, et al. Effects of gender on white blood cell populations and neutrophil-lymphocyte ratio following gastrectomy in patients with stomach cancer. J Korean Med Sci 2007;22 Suppl: S104-8.
19. Ahn HS, Lee HJ, Hahn S, Kim WH, Lee KU, Sano T, et al. Evaluation of the seventh American Joint Committee on Cancer/International Union Against Cancer Classification of gastric adenocarcinoma in comparison with the sixth classification. Cancer 2010;116:5592-8.
20. Atzil S, Arad M, Glasner A, Abiri N, Avraham R, Greenfeld K, et al. Blood transfusion promotes cancer progression: a critical role for aged erythrocytes. Anesthesiology 2008; 109:989-97.
21. Lee SR, Kim HO, Yoo CH. Impact of chronologic age in the elderly with gastric cancer. J Korean Surg Soc 2012;82: 211-8.
22. Lee YY, Choi CH, Sung CO, Do IG, Hub SJ, Kim HJ, et al. Clinical significance of changes in peripheral lymphocyte count after surgery in early cervical cancer. Gynecol Oncol 2012;127:107-13.
23. Hogan BV, Peter MB, Shenoy HG, Horgan K, Hughes TA. Surgery induced immunosuppression. Surgeon 2011;9: 38-43.
24. Ogawa K, Hirai M, Katsube T, Murayama M, Hamaguchi K, Shimakawa T, et al. Suppression of cellular immunity by surgical stress. Surgery 2000;127:329-36.
25. Ferrero E, Ferrero ME, Marni A, Zocchi MR, Stella L, Rugarli C, et al. In vitro effects of halothane on lymphocytes. Eur J Anaesthesiol 1986;3:321-30.
26. Toft P, Lillevang ST, Tonnesen E, Nielsen CH, Rasmussen JW. The redistribution of granulocytes following E. coli endotoxin induced sepsis. Acta Anaesthesiol Scand 1994;38: 852-7.
27. Tinmouth A, Fergusson D, Yee IC, Hebert PC; ABLE Investigators; Canadian Critical Care Trials Group. Clinical consequences of red cell storage in the critically ill.

Transfusion 2006;46:2014-27.
28. Weinberg JA, McGwin G Jr, Griffin RL, Huynh VQ, Cherry SA 3rd, Marques MB, et al. Age of transfused blood: an independent predictor of mortality despite universal leukoreduction. J Trauma 2008;65:279-82.
29. van de Watering LM, Brand A. Effects of storage of red cells. Transfus Med Hemother 2008;35:359-67.
30. Nobuoka D, Gotohda N, Kato Y, Takahashi S, Konishi M, Kinoshita T. Influence of excess body weight on the surgical outcomes of total gastrectomy. Surg Today 2011;41:928-34.