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Original Article

Finding esophageal cancer: could initial blood cell counts tell us?

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Abstract: Background: The endoscope has been the golden criteria in diagnosing esophageal cancer. It lacks, however, some simple screening methods in clinical practice. Blood cell counts are common and accessible clinical evidence. The question remains whether they could assist in diagnosis of a potential esophageal cancer patient. Aim: The goal of this study was to find out whether blood cell counts could be used in screening esophageal cancer. Methods: Clinical data of 1,136 people including 765 patients with esophageal cancer and 371 people without cancer was retrospectively analyzed. Data for the personality traits of non-cancer people only included age and sex. Acidophilic granulocyte and basophilic granulocyte were excluded because of limited quantity. Complete initial blood cell counts were used for analysis. SPSS 22.0 software was employed to analyze the data. Results: Two groups were compared in regard to white blood cells (WBC) and other relevant indicators and WBC, Neutrophils, NE%, lymphocyte, the rate of lymphocyte to WBC (LY%), monocyte, rate of monocyte to WBC (MO%), and rate of neutrophils to lymphocyte (NLR) were different. For red blood cells (RBC) and relevant indicators, hemoglobin (HGB), erythrocyte mean corpuscular volume (MCV), red blood cell specific volume (HCT), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) were significantly different. RBC, or platelets, were not statistically different ($P > 0.05$). Compared to people without cancer, lower levels of HCMC or HCT, were significantly correlated to esophageal cancer and area under curve (AUC) was 0.897 [95% confidence interval (CI) 0.877-0.916] and 0.845 (95% CI 0.822-0.868), respectively. Conclusion: When older people with symptoms of gastrointestinal tract problems (dysphagia and nausea) search for help with results of blood cell counts, HCMC, HCT, etc. could be used to choose high risk patients using endoscopy to exclude esophageal cancer. It is not recommended that people with symptoms but with higher levels of HCMC, HCT, etc. omit endoscopy diagnosis.

Keywords: Esophageal cancer, blood cell counts

Introduction

Esophageal cancer, the 6th most frequent cause of cancer deaths globally, is more common in men [1]. One retrospective study has demonstrated that the incidence and mortality of esophageal cancer in China is the highest worldwide [2].

Currently, endoscopy is used, which is uncomfortable for patients, to diagnose esophageal cancer but we still lack a screening method [NCCN]. Patients of esophageal cancer are often accompanied by symptoms of gastrointestinal tract problems (dysphagia and nausea). If the most common and accessible clinical evidence, such as blood cell counts, is used in combination with these symptoms to find high risk patients with esophageal cancer, these golden criterion could provide meaningful diagnosis and treatment options.

Indicators, such as blood cell counts, were used in some areas. In diagnosis, neutrophils could be used to discover infections caused by bacteria. Different cues within tissues that mediate neutrophils forward and reverse migration in response to injuries or infections and the implications of these mechanisms to human disease are discussed. Neutrophils follow a multitude of signals to reach sites of injury or infection [4, 5]. Higher levels of lymphocytes suggest ALL [6] or accumulated by virus infection [7]. In therapy, patients with cancer using

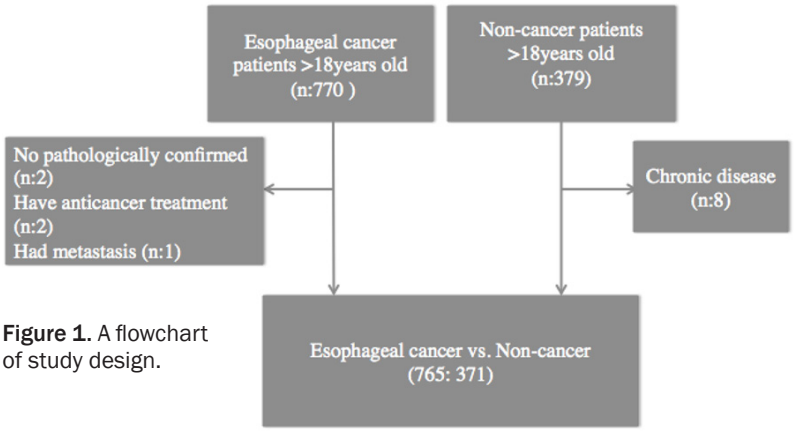

Figure 1. A flowchart of study design.

Table 1. Baseline characteristics of patients with esophageal cancer (%)

Outcome	Number	Rate
Sum	765	100%
Sex		
Male	581	75.95%
Female	184	24.05%
Age		
> 65	241	31.50%
< 65	524	68.50%
Smoking		
Yes	425	55.56%
No	340	44.44%
Drinking		
Yes	261	34.12%
No	504	65.88%
Other Chronic Disease		
Yes	330	43.14%
No	435	56.86%
T stage		
Tis	2	0.26%
1	130	16.99%
2	149	19.48%
3	439	57.39%
4	45	5.88%
N stage		
0	303	39.61%
1	271	35.43%
2	143	18.69%
3	48	6.27%

chemotherapy agents should check blood cell count data to prevent myelosuppression, avoiding possible danger [8].

Could initial blood cell counts give signs regarding esophageal cancer? On the basis of this premise, a retrospective study was conducted to provide a clinically useful picture of blood cell counts to find a method to differentiate patients with esophageal cancer from normal controls.

Materials and methods

Data collection

Clinical data were collected regarding 765 esophageal cancer patients (including 581 male and 184 female), enrolled from July 2012 to October 2017, in Sun Yat-sen University Cancer Center (SYSUCC). Data was also collected from 371 normal control people from healthy examinations (personality data only included sex and age) as comparator group. The two groups were then compared concerning data of the main initial blood cell counts.

Criteria about inclusion

Patients were eligible for inclusion if they 1) > 18 years old; 2) had pathologically confirmed diagnosis of esophageal cancer; 3) had not received any anti-cancer treatment before blood was drawn for examination; and 4) had no metastasis to bone, liver, spleen, or kidneys.

Individuals without cancer were eligible for inclusion if they were 1) > 18 years old; 2) generally healthy. Hematological parameters were compared between the two groups. A flowchart of study design is shown in **Figure 1**.

Diagnosis of esophageal cancer

All diagnoses of esophageal cancer are based on pathology.

Statistical analysis

Student's t-test was used for continuous variables and Chi-square test or Fisher's exact test were used for categorical variables. Receiver operating characteristic (ROC) curves were constructed to calculate sensitivity and specificity. AUC was used for various cut-off points of indicators of blood cell counts (eg. HCMC, HCT, HCM, HGB). $P < 0.05$ defined statistical significance. All statistical analyses were computed using SPSS Version 22.0.

Table 2. Differences of laboratory indexes between patients with esophageal cancer and normal controls

	EC	Non-EC	T value	*P* value
WBC (× 10^9/L)	7.22 ± 2.07	6.23 ± 1.60	-8.850	< 0.001*
Neutrophils (× 10^9/L)	4.52 ± 1.80	3.63 ± 1.22	-9.830	< 0.001*
NE%	0.61 ± 0.1	0.58 ± 0.08	-6.824	< 0.001*
Lymphocyte (× 10^9/L)	1.96 ± 0.60	2.05 ± 0.61	2.591	0.01*
LY%	0.28 ± 0.09	0.34 ± 0.08	10.288	< 0.001*
Monocyte (× 10^9/L)	0.52 ± 0.22	0.39 ± 0.12	-13.143	< 0.001*
MO%	0.07 ± 0.02	0.06 ± 0.02	-8.513	< 0.001*
NLR	2.56 ± 1.50	1.92 ± 1.15	-7.883	< 0.001*
RBC (× 10^{12}/L)	4.71 ± 1.78	4.68 ± 0.52	-0.304	0.761
HGB (g/L)	138.84 ± 14.14	141.38 ± 14.32	2.826	0.005*
MCV (fL)	91.00 ± 8.73	87.11 ± 6.37	-8.521	< 0.001*
HCT	0.36 ± 0.12	0.40 ± 0.03	5.349	< 0.001*
MCH	30.07 ± 3.31	30.34 ± 2.56	1.492	0.136
MCHC (g/L)	330.05 ± 10.95	348.08 ± 9.59	27.071	< 0.001*
PLT (× 10^9/L)	244.60 ± 72.13	235.16 ± 51.46	-2.529	0.012*

*Means *P* value < 0.05, WBC = white blood cell, NE% = the rate of neutrophils to WBC, LY% = the rate of lymphocyte to WBC, MO% = the rate of monocyte to WBC, RBC = red blood cell, MCV = erythrocyte mean corpuscular volume, HCT = Red blood cell specific volume, HGB = hemoglobin, MCH = mean corpuscular hemoglobin, HCMC = mean corpuscular hemoglobin concentration.

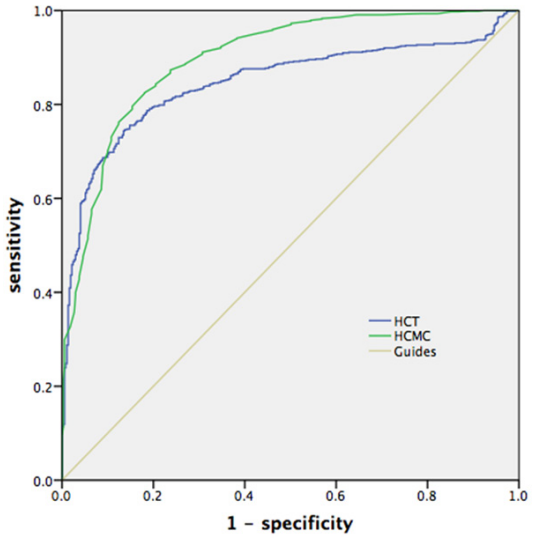

Figure 2. ROC of RBC relevant indicators to negative suggestion of esophageal cancer.

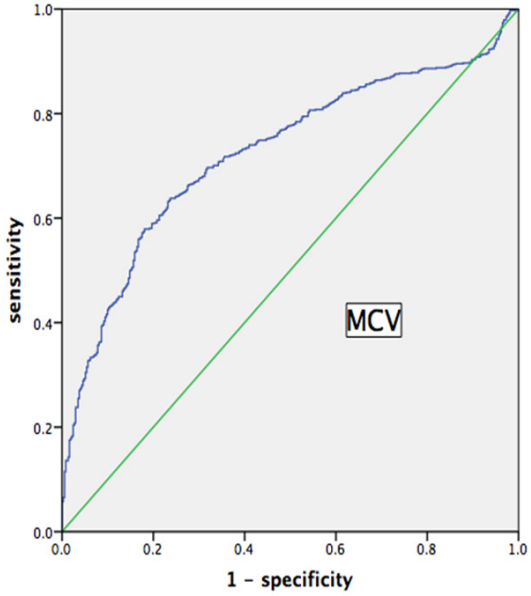

Figure 3. ROC of RBC relevant indicators to postive suggestion of esophageal cancer.

Results

A total of 1,136 people are included in this study, with 765 patients having esophageal cancer and 371 healthy controls. For the comparison group, only data regarding age and sex were available. The two groups were comparable with regard to comparable age and male/female ratio.

In Analysis 1, the differences in esophageal cancer and normal controls was elucidated. **Table 1** illustrates the baseline characteristics of the 765 cases of patients.

Comparing the two groups about WBC and relevant indicators, WBC [(7.22 ± 2.07) × 10^9/L

Table 3. Performance of relevant indicators of RBC in distinguishing patients with esophageal cancer and normal controls

	AUC (95% CI)	*P* value	Cut off	Sensitivity	Specificity
HCT	0.846 (0.823-0.869)	*P* < 0.001*	37.56	74.6%	86.3%
MCHC	0.898 (0.878-0.917)	*P* < 0.001*	339.75	82.5%	80.9%
MCV	0.724 (0.694-0.754)	*P* < 0.001*	90.49	63.8%	76.3%

*Means *P* value < 0.05, MCV = erythrocyte mean corpuscular volume, HCT = Red blood cell specific volume, HCMC = mean corpuscular hemoglobin concentration.

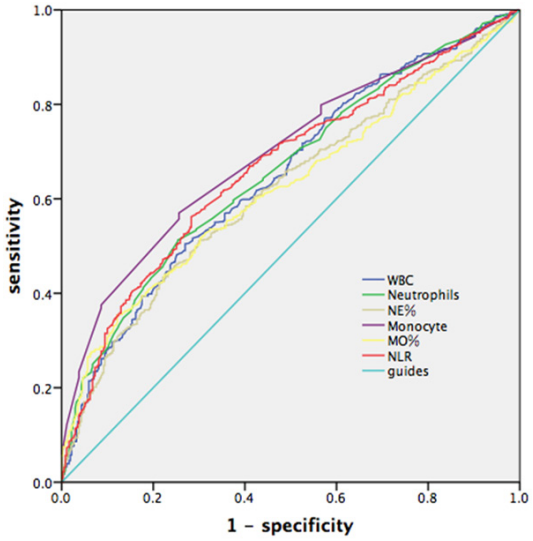

Figure 4. ROC of WBC relevant indicators to postive suggestion of esophageal cancer.

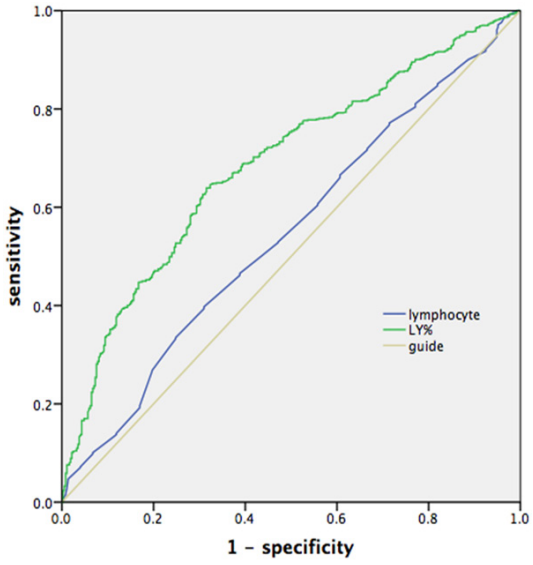

Figure 5. ROC of WBC relevant indicators to negative suggestion of esophageal cancer.

vs. (6.23 ± 1.60) × 10^9/L *P* < 0.001], Neutrophils [(4.52 ± 1.80) × 10^9/L vs. (3.63 ± 1.22) × 10^9/L *P* < 0.001], NE% [0.61 ± 0.1 vs. 0.58 ± 0.08 *P* < 0.001], lymphocyte [(1.96 ± 0.60) × 10^9/L vs. (2.05 ± 0.61) × 10^9/L *P* = 0.01], LY% [0.28 ± 0.09 vs. 0.34 ± 0.08 *P* < 0.001], monocyte [(0.52 ± 0.22) × 10^9/L vs. (0.39 ± 0.12) × 10^9/L *P* < 0.001], MO% [0.07 ± 0.02 vs. 0.06 ± 0.02 *P* < 0.001], and NLR (2.56 ± 1.50 vs. 1.92 ± 1.15 *P* < 0.001) were significantly different (**Table 2**).

For red blood cells (RBC) and relevant indicators, hemoglobin (HGB) [(138.84 ± 14.14) × 10^9/L vs. (141.38 ± 14.32) × 10^9/L *P* = 0.005], MCV (91.00 ± 8.73 fL vs. 87.11 ± 6.37 fL *P* = 0.14), HCT (0.36 ± 0.12 vs. 0.40 ± 0.03 *P* < 0.001), MCH (30.07 ± 3.31 pg vs. 30.34 ± 2.56 pg *P* = 0.136), MCHC (330.05 ± 10.95 g/L vs. 348.08 ± 9.59 g/L *P* < 0.001), and RBC were not statistically different (*P* > 0.05). Platelets [(244.60 ± 72.13) × 10^9/L vs. (235.16 ± 51.46) × 10^9/L *P* = 0.012] were statistically different (**Table 2**).

The most important indicators in differentiating a patient with esophageal cancer are HCMC [AUC 0.898 95% CI (0.878-0.917)], HCT [AUC0.846 95% CI (0.823-0.869)], and HCM [AUC0.724 95% CI (0.694-0.754)] (**Figures 2**, **3**; **Table 3**).

Effects of WBC relevant indicators were weaker than RBC but they were all significantly different between the two groups (**Figures 4**, **5**; **Table 4**).

Conclusion

EBV can be used to screen nasopharyngeal carcinoma and AFP can be used to screen liver cancer. If esophageal cancer could be screened by laboratory blood tests, that would easily assist in diagnosis and help with treatment. Screening for esophageal cancer, however, still lacks an efficient method [3, 9, 10].

Currently, endoscopy is used to diagnose esophageal cancer but for patients it is quite uncomfortable. A good screening method is still lacking. Patients of esophageal cancer are often accompanied with symptoms of gastrointestinal tract discomfort (dysphagia and nausea) but if blood cell counts could assist in find-

Table 4. Performance of relevant indicators of WBC in distinguishing patients with esophageal cancer and normal controls

	AUC (95% CI)	*P* value	Cut off	Sensitivity	Specificity
Leukocyte	0.650 (0.617-0.683)	*P* < 0.001*	6.89	50.5%	73.0%
Neutrophil	0.659 (0.626-0.692)	*P* < 0.001*	4.11	51.2%	74.7%
NE%	0.621 (0.588-0.655)	*P* < 0.001*	0.629	45.8%	75.5%
Lymphocyte	0.546 (0.511-0.581)	*P* = 0.012*	1.68	33.5%	75.2%
LY%	0.686 (0.654-0.718)	*P* < 0.001*	0.304	63.9%	68.5%
Monocyte	0.697 (0.666-0.727)	*P* < 0.001*	0.41	57%	74.4%
MO%	0.624 (0.592-0.657)	*P* < 0.001*	0.079	35.4%	87.9%
NLR	0.666 (0.633-0.698)	*P* < 0.001*	2.819	56.2%	71.7%

*Means *P* value < 0.05, WBC = white blood cell, NE% = the rate of neutrophils to WBC, LY% = the rate of lymphocyte to WBC, MO% = the rate of monocyte to WBC, RBC = red blood cell, MCV = erythrocyte mean corpuscular volume, HCT = Red blood cell specific volume, HGB = hemoglobin, MCH = mean corpuscular hemoglobin, HCMC = mean corpuscular hemoglobin concentration. The effects of WBC relevant indicators are than the RBC, but are all different between two groups.

ing high risk patients with esophageal cancer, they could efficiently be used as the golden criterion.

The results of this study demonstrates that, comparing esophageal cancer patients with healthy people, blood cell counts were different in WBC relevant indicators (total WBC, Neutrophils, NE%, Lymphocyte, LY%, Monocyte, MO %, and NLR), RBC relevant indicators (HGB, HCT, HCMC, and HCM), and platelets.

Some research has proven that varieties of chronic inflammation are related to tumor occurrence and development such as Barrett's esophagus and esophageal cancer, Helicobacter pylori infection and gastric cancer, and chronic pancreatitis and pancreas cancer [11]. The emerging consensus is that multiple pro-inflammatory pathways are fueled by gastroesophageal reflux disease. Barrett's esophagus and obesity are important to the pathogenesis of esophageal adenocarcinoma [13]. Moreover, infections caused by pathogenic microorganisms like human papillomavirus (HPV), Epstein-Barr virus (EBV), and Helicobacter pylori, have been suspected to be associated with esophageal cancer [12]. Some studies have shown that both higher NLRs and PLRs (Platelet-to-Lymphocyte Ratio) are associated with tumor progression and are predictive of poorer survival in patients with esophageal cancer. These ratios may help inform treatment decisions and predict treatment outcomes [14-16]. Therefore, WBC relevant indicators could possibly be different from esophageal patients versus normal controls.

Cancer-related anemia, caused by various mechanisms (cytokine-mediated changes, myelosuppressive effects of chemotherapy, blood loss, and nutritional deficiencies), is a common complication. The most common form of anemia is hypo-proliferative anemia. Cancer-related anemia could result in decreased erythropoietin (EPO) production, decreased response of erythroid progenitors to EPO, and altered iron metabolism, which all affect proliferation of red blood cells [17]. Moreover, cancers are often related to inflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin-1 (IL-1), both linking to proliferation of erythrocytic progenitor cells [18]. Above all, patients with cancer will develop anemia. This is something that could obviously be figured out from the indicators of blood cell counts. Many studies have shown that RBC relevant indicators are associated to the pathological stage of esophageal cancer and cancer-specific survival of patients with esophageal cancer [19, 20].

In this analysis, patients were included with non-organ metastasis (bone, liver, spleen, and kidney). On one hand, metastasis of cancer to bone, liver, or spleen will affect blood cell counts. On the other hand, the results did not suit our original intention of distinguishing patients of esophageal cancer with early stage. MCHC was the most important indicator in blood cell counts in differentiating patients with esophageal cancer and healthy people. AUC was [AUC 0.898 95% CI (0.878-0.917)].

This study is a retrospective study based on large-sample clinical data of 1,136 people. The conclusion is quite convincing but there are still some limitations. The most distinguishing indicator found in our study was HCMC, an indicator associated with anemia. However, evaluation of the relationship of anemia patients with

other diseases and with esophageal cancer could not be determined.

Conclusion

When older people with symptoms of gastrointestinal tract discomfort search for help with results of blood cell counts, HCMC, HCT, etc. could be used to choose high risk patients using endoscopy to exclude esophageal cancer. However, it is not recommended that people with symptoms but higher levels of HCMC, HCT, etc. be omitted from endoscopy.

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Disclosure of conflict of interest

None.

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