**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 59936

**Manuscript Type:** ORIGINAL ARTICLE

***Retrospective Study***

**Preoperative maximal voluntary ventilation, hemoglobin, albumin, lymphocytes, and platelets predict postoperative survival in esophageal squamous cell carcinoma**

MVV and HALP predict ESCC survival

Shou-Jia Hu, Xue-Ke Zhao, Xin Song, Ling-Ling Lei, Wen-Li Han, Rui-Hua Xu, Ran Wang, Fu-You Zhou, Liang Wang, Li-Dong Wang

**Shou-Jia Hu, Xue-Ke Zhao, Xin Song, Ling-Ling Lei, Wen-Li Han, Rui-Hua Xu, Ran Wang, Li-Dong Wang,** State Key Laboratory of Esophageal Cancer Prevention & Treatment and Henan Key Laboratory for Esophageal Cancer Research of The First Affiliated Hospital, Zhengzhou University, Zhengzhou 450052, Henan Province, China

**Fu-You Zhou,** Department of Thoracic Surgery, Anyang Tumor Hospital, Anyang 455000, Henan Province, China

**Liang Wang,** Department of Tumor Biology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL 33612, United States

**Author contributions:** Wang LD and Hu SJ designed and wrote the paper; Lei LL, Han WL, Xu RH, Wang R, and Zhou FY performed the data collection, interpretation, and follow-up; Hu SJ, Zhao XKand Song X contributed to the data analysis; Zhou FY, Wang L, and Wang LD revised the manuscript; Wang L provided the English editing.

**Supported by** National Natural Science Foundation of China, No. U1301227, No. 81872032 and No. U1804262; Doctoral Team Foundation of the First Affiliated Hospital of Zhengzhou University, No. 2016-BSTDJJ-03.

**Corresponding author: Li-Dong Wang, MD, PhD, Professor,** State Key Laboratory of Esophageal Cancer Prevention & Treatment and Henan Key Laboratory for Esophageal Cancer Research of The First Affiliated Hospital, Zhengzhou University, No. 40 Daxue Road, Zhengzhou 450052, Henan Province, China. ldwang2007@126.com

**Received:** October 13, 2020

**Revised:** December 17, 2020

**Accepted:** December 25, 2020

**Published online:**

**Abstract**

BACKGROUND

Preoperative pulmonary function plays an important role in selecting surgical candidates and assessing postoperative complications. Reduced pulmonary function is associated with poor survival in several cancers, but the prognostic value of preoperative pulmonary function in esophageal squamous cell carcinoma (ESCC) is unclear. Nutritional and systemic inflammation parameters are vital to cancer survival, and the combination of these parameters improves the prognostic value. The hemoglobin, albumin, lymphocytes and platelet (HALP) score is a novel prognostic indicator to reflect the nutritional and inflammation status, but the clinical effects of the HALP score combined with maximal voluntary ventilation (MVV), an important parameter of pulmonary function, have not been well studied in ESCC.

AIM

To investigate the prognostic value of MVV and HALP score for assessing postoperative survival of ESCC patients.

METHODS

Data for a total of 834 ESCC patients who underwent radical esophagectomy with R0 resection were collected and retrospectively analyzed. Preoperative MVV and HALP data were retrieved from medical archives. The HALP score was calculated by the formula: hemoglobin (g/L) × albumin (g/L) × lymphocytes (g/L)/platelets (g/L). The optimal cut-off values of MVV and HALP score were calculated by the receiver operating characteristic curve analysis. The Kaplan-Meier method with log-rank test was used to draw the survival curves for the variables tested. Multivariate Cox proportional hazard regression models were used to analyze the independent prognostic factors for overall survival (OS).

RESULTS

MVV was significantly associated with gender (*P* < 0.001), age at diagnosis (*P* < 0.001), smoking history (*P* < 0.001), drinking history (*P* < 0.001), tumor length (*P* = 0.013), tumor location (*P* = 0.037) and treatment type (*P* = 0.001). The HALP score was notably associated with gender (*P* < 0.001), age at diagnosis (*P* = 0.035), tumor length (*P* < 0.001) and invasion depth (*P* = 0.001). Univariate Cox regression analysis showed that low MVV and low HALP score were associated with worse OS (all *P* < 0.001). Multivariate analysis showed that low MVV and the HALP score were both independent risk factors for OS (all *P* < 0.001). The combination of MVV and HALP score (coMVV-HALP) improved the prediction performance for OS than tumor-node-metastasis. Low coMVV-HALP score was an independent risk factor for poor OS (*P* < 0.001).

CONCLUSION

MVV, HALP score, and their combination are simple and promising clinical markers to predict OS of ESCC patients.

**Key Words:** Maximal voluntary ventilation; Hemoglobin, albumin, lymphocytes and platelet score; Nutritional status; Inflammation status; Postoperative survival; Esophageal squamous cell carcinoma

Hu SJ, Zhao XK, Song X, Lei LL, Han WL, Xu RH, Wang R, Zhou FY, Wang L, Wang LD. Preoperative maximal voluntary ventilation, hemoglobin, albumin, lymphocytes and platelets predict postoperative survival in esophageal squamous cell carcinoma. *World J Gastroenterol* 2020; In press

**Core Tip:** Reduced pulmonary function is considered a risk factor for cancer survival. The combination score of hemoglobin, albumin, lymphocytes and platelets (HALP) is a novel prognostic indicator to reflect nutritional and inflammatory status. We demonstrated that preoperative maximal voluntary ventilation (MVV), an important parameter of pulmonary function, and HALP score were independent prognostic factors for patients with esophageal squamous cell carcinoma. The combination of MVV and HALP score (coMVV-HALP) has a better prognostic value than tumor-node-metastasis (TNM) alone. The coMVV-HALP score reflects the status of inflammation, nutrition and pulmonary function simultaneously and may partly compensate for the limitation of TNM staging system.

**INTRODUCTION**

Esophageal cancer is the sixth leading cause of cancer-related death worldwide[1]. Esophageal squamous cell carcinoma (ESCC) is the predominant type of Chinese esophageal cancer. Despite improvements in treatment and clinical management, the prognosis of ESCC is still poor[1]. Surgery remains the preferred method for non-metastatic cancer patients. Although the tumor-node-metastasis (TNM) staging system is well known as a predictive clinical parameter in terms of guiding treatment and clinical prognosis[2], the survival outcomes for esophageal cancer patients with the same TNM stage still vary widely. In addition, accurate TNM stage identification relies on the pathologic result after esophagectomy. Therefore, it is important to identify more effective preoperative clinical factors for early guidance of treatment and for predicting the prognosis of esophageal cancer, particularly in ESCC.

Preoperative pulmonary evaluation is a routine examination used to select potential surgical candidates and assess postoperative respiratory complications[3]. Previous studies have shown that poor pulmonary function is associated with severe postoperative complications in patients undergoing esophagectomy[4-6]. Some studies have reported that reduced pulmonary function is associated with mortality risk in the general population[7,8], lung cancer[9] and gastric cancer[10], while little attention has been given to the correlation between preoperative pulmonary evaluation and the overall survival (OS) of esophageal cancer patients. Forced vital capacity (FVC) and vital capacity (VC) are both important parameters in pulmonary evaluation test. Low FVC has been implicated as a risk prognostic predictor in gastric cancer[10] and low VC also predicts the poor survival in Japanese esophageal cancer[11] in previous limited studies. Maximal voluntary ventilation (MVV) is another important parameter in pulmonary evaluation test and is usually used to reflect respiratory muscle strength and lung capacity. Studies report that MVV reflects dysfunction and airway resistance both in inspiratory and expiratory phases, while FVC and VC reflect only the expiratory phase[12], so MVV may better reflects the real capacity of lung function. However, few studies have examined its effects on esophageal cancer patient survival.

Dysphagia is a typical symptom of esophageal cancer patients and may lead to malnutrition. Numerous studies have demonstrated that the parameters of nutrition and inflammation status, including the levels of hemoglobin and albuminand lymphocyteand plateletcounts, are vital to cancer survival[13-16]. More importantly, some studies have reported that the combination of these parameters such as the neutrophil-lymphocyte ratio[17], platelet-to-lymphocyte ratio[18], and prognostic nutritional index[19] could better predict prognosis than nutritional or inflammatory condition status alone. The combination of hemoglobin, albumin, lymphocytes and platelet (HALP) score with four hematological parameters has been demonstrated as a novel and potential prognostic indicator for several types of malignancies[20-22], but the clinical effects of HALP score combined with other prognostic factors in ESCC patients who underwent esophagectomy have not been well studied.

Thus, to address these issues, we investigated the prognostic value of preoperative pulmonary function (MVV) and HALP score for the long-term survival in this group of ESCC patients.

**MATERIALS AND METHODS**

***Patients***

A total of 834 ESCC patients who underwent radical esophagectomy with R0 resection between 2011 and 2014 from the 500000 esophageal and gastric cardia carcinoma database (1973–2020), established by Henan Key Laboratory for Esophageal Cancer Research of The First Affiliated Hospital, Zhengzhou University (Zhenghou, China), were enrolled in the retrospective study. Patients were selected according to the following criteria: diagnosed with ESCC by postoperative histopathology; had tumors located in the thoracic esophagus; had no other malignant tumors except for ESCC; (received no chemotherapy or/and radiotherapy before surgery; (had no neuromuscular disorders, respiratory diseases, chronic/acute inflammatory disease, autoimmune disease or received glucocorticoid therapy before surgery; and preoperative records of pulmonary evaluation test and HALP parameters were obtained.

***Clinical data collection and follow-up***

The MVV value was determined and collected from routine preoperative pulmonary evaluation and the values for HALP parameters were obtained from routine blood test before surgery. The HALP score was calculated using the following formula: hemoglobin (g/L) × albumin (g/L) × lymphocytes (g/L)/platelets(g/L). The pathological TNM stage of patients was also collected on the basis of the 7th edition of the TNM staging system from the American Joint Committee on Cancer[2]. The time of diagnosis was the date when patients were confirmed to have ESCC by histopathology. The OS time was the interval from the time of diagnosis to death or the last follow-up. The last follow-up was performed in May, 2020. Of the 834 patients, 799 patients (95.8%) had detailed follow-up data. In the first year after esophagectomy, patients were followed up every 3 mo. Then, follow-up was conducted once a year.

***Statistical analysis***

SPSS software (version 21; IBM, Chicago, IL, United States) and GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, United States) were used to perform the statistical analyses. Two-tailed *P* < 0.05 were considered statistically significant. The optimal cut-off values of MVV and HALP score were calculated by the receiver operating characteristic (ROC) curve analysis. The chi-square test was used to analyze the relationship of clinical features with MVV and HALP score for patients with ESCC. A univariate Cox proportional hazard regression model was used to evaluate the prognostic value of each variable for OS. The Kaplan-Meier method with log-rank test was used to draw the survival curves for the variables tested. Multivariate Cox proportional hazard regression models were used to analyze the independent prognostic factors for OS. Significant prognostic variables in the univariate analysis were chosen for the multivariate analysis.

**RESULTS**

***Patients’ basic clinical characteristics***

From the archived clinical record, we retrieved the baseline clinic parameters for this group of ESCC patients (Table 1). The ratio of males to females was 1.6:1. The median age was 60 years, ranging from 38 to 84 years. In total, 756 patients (90.6%) underwent open esophagectomy by the left approach; 78 patients (9.4%) went through surgery by right approach including 75 patients (9.0%) who were treated with open esophagectomy and 3 patients (0.4%) who were treated with thoracoscopic esophagectomy; and 151 patients (18.1%) had post-operative complications. The median survival time of the ESCC patients was 4.4 years, ranging from 0.19 to 9.5 years. The 1-, 3-, and 5-year survival rates of the total patients were 91.4%, 64.6%, and 42.9%, respectively.

***Association of MVV and HALP score with basic clinical characteristics***

To assess the potential correlation of MVV and HALP score for OS, we first performed ROC analysis using their values in these ESCC patients. We found that the area under the curves (AUCs) of MVV and HALP score were 0.631 and 0.646, respectively, indicating that they were both significant for predicting 5-year OS (all *P* < 0.001; Figure 1). Then we determined the optimal cutoff values of MVV and HALP score as 85.2 and 38.8, respectively, by using the maximal Youden index. Based on the two cutoff values, the ESCC patients were divided into high and low groups for both MVV and HALP score, respectively. We applied the chi-square test to evaluate the potential association of MVV and HALP score with basic clinical factors. We found that MVV was significantly associated with gender (*P* < 0.001), age at diagnosis (*P* < 0.001), smoking history (*P* < 0.001), drinking history (*P* < 0.001), tumor length (*P* = 0.013), tumor location (*P* = 0.037) and treatment type (*P* = 0.001). The association between MVV and overall post-operative complications (*P* = 0.243; Table 2) was not observed, and MVV was not associated with post-operative pulmonary complications (*P* = 0.843). The HALP score was notably associated with gender (*P* < 0.001), age at diagnosis (*P* = 0.035), tumor length (*P* < 0.001), and invasion depth (*P* = 0.001). The association of patients’ clinical features with MVV and HALP score is shown in Table 2.

***Association of MVV and HALP score with OS***

To evaluate the potential association of clinical factors with OS, we performed univariate Cox regression analysis and observed a significant association with age at diagnosis (*P* < 0.001), tumor length (*P* < 0.001), differentiation (*P* < 0.001), invasion depth (*P* < 0.001), lymph node metastasis (*P* < 0.001), and post-operative complications (*P* < 0.001) (Table 3). We also observed an association between survival and MVV (*P* < 0.001) and HALP score (*P* < 0.001) (Table 3). Kaplan-Meier analysis using the log-rank test showed that low MVV (*P* < 0.001, Figure 2) and low HALP score (*P* < 0.001, Figure 2) predicted a worse OS. By adjusting the clinical factors from the multivariate Cox regression analysis, the association of low MVV and low HALP score with poor survival remained significantly with *P* < 0.001 (hazard ratio [HR]: 1.451, 95% confidence interval (CI): 1.208-1.743) and *P* < 0.001 (HR: 1.537, 95%CI: 1.287-1.836) (Table 3), respectively, suggesting that low MVV and HALP score were independent risk factors for OS. Gender, smoking history, drinking history, tumor location, differentiation, surgical approach and treatment type were not independently associated with OS (all *P* > 0.05), whereas age at diagnosis, tumor length, invasion depth, lymph node metastasis, MVV, HALP score and post-operative complications were independent predictive factors for OS (all *P* < 0.05) (Table 3).

***Predictive value of the combination of MVV with HALP score for OS***

Since both MVV and HALP score were independent predictive factors, we next explored the cumulative effect of MVV and HALP score (coMVV-HALP) score on OS. We defined the following: the coMVV-HALP score was 0 when patients had both low MVV and HALP score; the coMVV-HALP score was 1 when patients had either low MVV or HALP score; and the coMVV-HALP score was 2 when patients had both high MVV and HALP score. Then, we performed ROC analysis to evaluate the predictive value of the coMVV-HALP score for 5-year OS. We found that the AUC for the coMVV-HALP score was 0.681 (*P* < 0.001; Figure 3), which indicated better prognostic value than TNM (AUC: 0.659), HALP score (AUC: 0.646) or MVV (AUC: 0.631) alone.

Kaplan-Meier analysis using the log-rank test showed that a low coMVV-HALP score predicted poor OS(*P* < 0.001; Figure 4) in ESCC patients. As age at diagnosis, tumor length, invasion depth and lymph node metastasis were independent predictive factors for OS, we then performed further stratification analysis for the ESCC patients according to age, tumor length and TNM to explore the predictive value of the coMVV-HALP score in different groups. Stratification analysis by age at diagnosis and tumor length accordingly showed that patients with coMVV-HALP score = 0 had a worse OS than patients with coMVV-HALP score = 1 or 2 in groups with age < 60 (*n* = 379,*P* < 0.001; Figure 5), age ≥ 60 (*n* = 420,*P* < 0.001, Figure 5), tumor length < 4 cm (*n* = 374,*P* = 0.002; Figure 5) and tumor length ≥ 4 cm (*n* = 425, *P* < 0.001; Figure 5). Stratification analysis by TNM stage showed no significant difference in OS among patients with different coMVV-HALP scores (0, 1, 2) in stage I (*n* = 98, *P* =0.096; Figure 6). However, we found that, among patients in stage II (*n* = 437,*P* < 0.001, Figure 6) and III (*n* = 264, *P* < 0.001, Figure 6), those with coMVV-HALP score = 0 had a worse OS than those with coMVV-HALP score = 1 or 2. Multivariate analysis further showed that a low coMVV-HALP score was an independent risk factor for poor OS (*P* < 0.001; Supplementary Table 1).

**DISCUSSION**

Reliable clinical factors that predict patients’ OS are important for clinicians to make informed treatment decisions. In this study, we investigated the prognostic value of preoperative pulmonary evaluation with MVV and HALP score for predicting the long-term survival of ESCC patients. Our data showed that MVV, HALP score, and their combination were independent prognostic factors. If further validated, this score may be used clinically to overcome some limitations of the TNM staging system in assessing ESCC prognosis.

Numerous studies have focused mainly on the prognostic value of preoperative pulmonary function in lung cancer but rarely in digestive cancers. These studies have clearly shown that preoperative pulmonary evaluation could be used as a predictor for postoperative complications and survival in lung cancer[9,23]. As previously described, FVC and VC have been demonstrated as predictors of post-operative complications and the survival in gastric cancer[10] and Japanese esophageal cancer[11],respectively. In this study, we did not find an association between MVV and post-operative complications, possibly because we had different sources of patients, inclusion and exclusion criteria, as well as sample size. In this study, we found that low MVV was an independent risk factor for the OS of Chinese ESCC patients. Although the mechanism of this association between lung function and cancer prognosis is unclear, multiple studies have demonstrated that impaired lung function is associated with mortality risk in the general population[7,8]. Additionally, Sarkar *et al*[24] elaborated a mechanism by which abnormal function of the respiratory system could lead to the development of hypoxemia and its detrimental consequences. Muz *et al*[25] reported that tumor-hypoxia plays a vital role in cell mobility and metastasis in cancer progression. It was also shown that hypoxia is correlated with poor prognosis in cancer patients[26]. Moreover, pulmonary rehabilitation is important for lung cancer patients to improve pulmonary capacity and quality of life[27]. A previous study suggested that pulmonary rehabilitation benefits cancer patients and should be applied to the entire process of cancer care[28]. Therefore, MVV may influence the capacity of oxygen supply for the body and then further affect the prognosis.

The HALP score is a new combined index and its prognostic value has been investigated in many cancers, but its role in ESCC patients who underwent esophagectomy has not been studied. Our study showed that the HALP score was an independent factor for OS in this group of ESCC patients. The result is further supported by a study that investigated the role of the HALP score in 39 male ESCC patients receiving platinum-based chemotherapy[29]. The survival association may be explained by the following findings. (1) Studies have shown that anemia affects patients’ disease progression, treatment, quality of life and survival[13,30], and anemia before radiotherapy predicts poor survival for ESCC patients[31]. (2) Low serum albumin levels are common in many advanced cancers and some studies suggest that albumin may be a source of energy for cancer growth[32] and metabolism[33]. Importantly, it has been shown that low albumin is a risk factor for the survival outcome in ESCC[14]. (3) A systemic review has demonstrated that lymphocytes play an important role in mediating tumor suppression and controlling tumor growth[34]. A low preoperative lymphocyte count can serve as a risk factor for a variety of cancers including ESCC[35,36]. (4) Platelets may protect tumor cells from immunosurveillance and mediate cancer metastasis[37]. These studies provide strong evidence showing the prognostic value of the HALP score, which partly reflects the status of inflammation and nutrition.

By combining the MVV and HALP score, we developed a predictive coMVV-HALP score for ESCC survival and it has a better predictive value than TNM. To the best of our knowledge, this study is the first to investigate the value of the combination of MVV and HALP score, which reflects the status of inflammation, nutrition and pulmonary function of ESCC patients. Esophageal cancer is a systemic disease that impacts many systems in the human body. CoMVV-HALP score is based on the routine data from the preoperative blood test and pulmonary evaluation. TNM staging system is well known as the criteria to assess the prognosis of the esophageal cancer patients, but it relies on the complete post-operative pathological information. CoMVV-HALP score may provide a new method to evaluate the prognosis of the patients before surgery. Therefore, the multivariate model integrating MVV with the HALP score may partly compensate for the limitation of the TNM staging system. This score can be easily calculated since individual clinical factors are conveniently available using a less invasive approach. These clinical factors can also be monitored cost-effectively during the course of disease progression.

This study had some limitations. Since it was a retrospective study from a single center involving different pathologists, physicians and technicians, there might be some bias of the uniformity in determining some clinical factors. The sample size was relatively small and included only ESCC with no other types of esophageal cancer. Further prospective studies using a large sample size from more centers are needed to confirm this new finding.

**CONCLUSION**

MVV and HALP score, alone or in combination are simple and promising clinical predictors. Once validated in large cohorts, these clinical factors should be taken into account when assessing the prognosis of ESCC patients.

**ARTICLE HIGHLIGHTS**

***Research background***

Preoperative pulmonary function plays an important role in selecting surgical candidates and assessing postoperative complications. Nutritional and systemic inflammation parameters are vital to cancer survival, and the combination of these parameters improves the prognostic value. The hemoglobin, albumin, lymphocytes and platelet (HALP) score is a novel prognostic indicator to reflect the nutritional and inflammation status.

***Research motivation***

The prognostic values of preoperative pulmonary function and the HALP score for survival in esophageal squamous cell carcinoma (ESCC) are unclear.

***Research objectives***

This study investigated the predictive values of preoperative pulmonary function and the HALP score for survival in ESCC patients.

***Research methods***

The predictive values of preoperative pulmonary function and the HALP score for long-term overall survival (OS) were performed in 834 ESCC patients, who underwent radical esophagectomy.

***Research results***

Low maximal voluntary ventilation (MVV) and the HALP score were both independent risk factors for OS (all *P* < 0.001). The combination of MVV and HALP score (coMVV-HALP) improved the prediction performance for OS than tumor-node-metastasis. And low coMVV-HALP score was an independent risk factor for poor OS (*P* < 0.001).

***Research conclusions***

MVV, HALP score, and their combination are simple and promising clinical markers to predict OS of ESCC patients.

***Research perspectives***

MVV and HALP score, alone or in combination are simple and promising clinical predictors. Once validated in large cohorts, these clinical factors should be taken into account when assessing the prognosis of ESCC patients.

**ACKNOWLEDGEMENTS**

We thank Dr. Yi-Jun Tian (H. Lee Moffitt Cancer Center, United States) for English editing and thoughtful comments for this manuscript; and Professor Xue-Zhong Shi (Department of Epidemiology and Biostatistics, College of Public Health in Zhengzhou University) for help in statistical analysis; and American Journal Experts (AJE) for their professional English language editing services.

**REFERENCES**

1 **Lagergren J**, Smyth E, Cunningham D, Lagergren P. Oesophageal cancer. *Lancet* 2017; **390**: 2383-2396 [PMID: 28648400 DOI: 10.1016/S0140-6736(17)31462-9]

2 **Rice TW**, Blackstone EH, Rusch VW. 7th edition of the AJCC Cancer Staging Manual: esophagus and esophagogastric junction. *Ann Surg Oncol* 2010; **17**: 1721-1724 [PMID: 20369299 DOI: 10.1245/s10434-010-1024-1]

3 **Smetana GW**. Preoperative pulmonary evaluation. *N Engl J Med* 1999; **340**: 937-944 [PMID: 10089188 DOI: 10.1056/NEJM199903253401207]

4 **Ferguson MK**, Celauro AD, Prachand V. Prediction of major pulmonary complications after esophagectomy. *Ann Thorac Surg* 2011; **91**: 1494-1500; discussion 1500-1 [PMID: 21524462 DOI: 10.1016/j.athoracsur.2010.12.036]

5 **Reinersman JM**, Allen MS, Deschamps C, Ferguson MK, Nichols FC, Shen KR, Wigle DA, Cassivi SD. External validation of the Ferguson pulmonary risk score for predicting major pulmonary complications after oesophagectomy†. *Eur J Cardiothorac Surg* 2016; **49**: 333-338 [PMID: 25724906 DOI: 10.1093/ejcts/ezv021]

6 **Goense L**, Meziani J, Bülbül M, Braithwaite SA, van Hillegersberg R, Ruurda JP. Pulmonary diffusion capacity predicts major complications after esophagectomy for patients with esophageal cancer. *Dis Esophagus* 2019; **32** [PMID: 30239639 DOI: 10.1093/dote/doy082]

7 **Mannino DM**, Buist AS, Petty TL, Enright PL, Redd SC. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. *Thorax* 2003; **58**: 388-393 [PMID: 12728157 DOI: 10.1136/thorax.58.5.388]

8 **Godfrey MS**, Jankowich MD. The Vital Capacity Is Vital: Epidemiology and Clinical Significance of the Restrictive Spirometry Pattern. *Chest* 2016; **149**: 238-251 [PMID: 26356330 DOI: 10.1378/chest.15-1045]

9 **Lee SY**, Choi YJ, Seo JH, Lee SY, Kim JS, Kang EJ. Pulmonary function is implicated in the prognosis of metastatic non-small cell lung cancer but not in extended disease small cell lung cancer. *J Thorac Dis* 2019; **11**: 4562-4572 [PMID: 31903245 DOI: 10.21037/jtd.2019.10.77]

10 **Feng F**, Tian Y, Zang Y, Sun L, Hong L, Yang J, Guo M, Lian X, Fan D, Zhang H. Low forced vital capacity predicts poor prognosis in gastric cancer patients. *Oncotarget* 2017; **8**: 28897-28905 [PMID: 28423645 DOI: 10.18632/oncotarget.15953]

11 **Sugawara K**, Mori K, Okumura Y, Yagi K, Aikou S, Uemura Y, Yamashita H, Seto Y. Preoperative Low Vital Capacity Influences Survival After Esophagectomy for Patients with Esophageal Carcinoma. *World J Surg* 2020; **44**: 2305-2313 [PMID: 32123980 DOI: 10.1007/s00268-020-05450-0]

12 **Suh MR**, Kim DH, Jung J, Kim B, Lee JW, Choi WA, Kang SW. Clinical implication of maximal voluntary ventilation in myotonic muscular dystrophy. *Medicine (Baltimore)* 2019; **98**: e15321 [PMID: 31045770 DOI: 10.1097/MD.0000000000015321]

13 **Huang XZ**, Yang YC, Chen Y, Wu CC, Lin RF, Wang ZN, Zhang X. Preoperative Anemia or Low Hemoglobin Predicts Poor Prognosis in Gastric Cancer Patients: A Meta-Analysis. *Dis Markers* 2019; **2019**: 7606128 [PMID: 30719182 DOI: 10.1155/2019/7606128]

14 **Wu N**, Chen G, Hu H, Pang L, Chen Z. Low pretherapeutic serum albumin as a risk factor for poor outcome in esophageal squamous cell carcinomas. *Nutr Cancer* 2015; **67**: 481-485 [PMID: 25706773 DOI: 10.1080/01635581.2015.1004726]

15 **Rho SY**, Hwang HK, Chong JU, Yoon DS, Lee WJ, Kang CM. Association of preoperative total lymphocyte count with prognosis in resected left-sided pancreatic cancer. *ANZ J Surg* 2019; **89**: 503-508 [PMID: 30836428 DOI: 10.1111/ans.15030]

16 **Rachidi S**, Li H, Wallace K, Li Z, Balch C, Lautenschlaeger T. Preoperative platelet counts and postoperative outcomes in cancer surgery: a multicenter, retrospective cohort study. *Platelets* 2020; **31**: 79-87 [PMID: 30744463 DOI: 10.1080/09537104.2019.1573977]

17 **Duan H**, Zhang X, Wang FX, Cai MY, Ma GW, Yang H, Fu JH, Tan ZH, Meng YQ, Fu XY, Ma QL, Lin P. Prognostic role of neutrophil-lymphocyte ratio in operable esophageal squamous cell carcinoma. *World J Gastroenterol* 2015; **21**: 5591-5597 [PMID: 25987784 DOI: 10.3748/wjg.v21.i18.5591]

18 **Yodying H**, Matsuda A, Miyashita M, Matsumoto S, Sakurazawa N, Yamada M, Uchida E. Prognostic Significance of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Oncologic Outcomes of Esophageal Cancer: A Systematic Review and Meta-analysis. *Ann Surg Oncol* 2016; **23**: 646-654 [PMID: 26416715 DOI: 10.1245/s10434-015-4869-5]

19 **Xue Y**, Zhou X, Xue L, Zhou R, Luo J. The role of pretreatment prognostic nutritional index in esophageal cancer: A meta-analysis. *J Cell Physiol* 2019; **234**: 19655-19662 [PMID: 31344989 DOI: 10.1002/jcp.28565]

20 **Xu SS**, Li S, Xu HX, Li H, Wu CT, Wang WQ, Gao HL, Jiang W, Zhang WH, Li TJ, Ni QX, Liu L, Yu XJ. Haemoglobin, albumin, lymphocyte and platelet predicts postoperative survival in pancreatic cancer. *World J Gastroenterol* 2020; **26**: 828-838 [PMID: 32148380 DOI: 10.3748/wjg.v26.i8.828]

21 **Peng D**, Zhang CJ, Gong YQ, Hao H, Guan B, Li XS, Zhou LQ. Prognostic significance of HALP (hemoglobin, albumin, lymphocyte and platelet) in patients with bladder cancer after radical cystectomy. *Sci Rep* 2018; **8**: 794 [PMID: 29335609 DOI: 10.1038/s41598-018-19146-y]

22 **Guo Y**, Shi D, Zhang J, Mao S, Wang L, Zhang W, Zhang Z, Jin L, Yang B, Ye L, Yao X. The Hemoglobin, Albumin, Lymphocyte, and Platelet (HALP) Score is a Novel Significant Prognostic Factor for Patients with Metastatic Prostate Cancer Undergoing Cytoreductive Radical Prostatectomy. *J Cancer* 2019; **10**: 81-91 [PMID: 30662528 DOI: 10.7150/jca.27210]

23 **Cho O**, Oh YT, Chun M, Noh OK, Heo JS. Prognostic implication of FEV1/FVC ratio for limited-stage small cell lung cancer. *J Thorac Dis* 2018; **10**: 1797-1805 [PMID: 29707334 DOI: 10.21037/jtd.2018.02.14]

24 **Sarkar M**, Niranjan N, Banyal PK. Mechanisms of hypoxemia. *Lung India* 2017; **34**: 47-60 [PMID: 28144061 DOI: 10.4103/0970-2113.197116]

25 **Muz B**, de la Puente P, Azab F, Azab AK. The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. *Hypoxia (Auckl)* 2015; **3**: 83-92 [PMID: 27774485 DOI: 10.2147/HP.S93413]

26 **Semenza GL**. Defining the role of hypoxia-inducible factor 1 in cancer biology and therapeutics. *Oncogene* 2010; **29**: 625-634 [PMID: 19946328 DOI: 10.1038/onc.2009.441]

27 **Wang H**, Liu X, Rice SJ, Belani CP. Pulmonary Rehabilitation in Lung Cancer. *PM R* 2016; **8**: 990-996 [PMID: 27060645 DOI: 10.1016/j.pmrj.2016.03.010]

28 **Morris GS**, Gallagher GH, Baxter MF, Brueilly KE, Scheetz JS, Ahmed MM, Shannon VR. Pulmonary rehabilitation improves functional status in oncology patients. *Arch Phys Med Rehabil* 2009; **90**: 837-841 [PMID: 19406305 DOI: 10.1016/j.apmr.2008.12.005]

29 **Cong L**, Hu L. The value of the combination of hemoglobin, albumin, lymphocyte and platelet in predicting platinum-based chemoradiotherapy response in male patients with esophageal squamous cell carcinoma. *Int Immunopharmacol* 2017; **46**: 75-79 [PMID: 28268208 DOI: 10.1016/j.intimp.2017.02.027]

30 **Madeddu C**, Gramignano G, Astara G, Demontis R, Sanna E, Atzeni V, Macciò A. Pathogenesis and Treatment Options of Cancer Related Anemia: Perspective for a Targeted Mechanism-Based Approach. *Front Physiol* 2018; **9**: 1294 [PMID: 30294279 DOI: 10.3389/fphys.2018.01294]

31 **Zhang F**, Cheng F, Cao L, Wang S, Zhou W, Ma W. A retrospective study: the prevalence and prognostic value of anemia in patients undergoing radiotherapy for esophageal squamous cell carcinoma. *World J Surg Oncol* 2014; **12**: 244 [PMID: 25085112 DOI: 10.1186/1477-7819-12-244]

32 **Stehle G**, Sinn H, Wunder A, Schrenk HH, Stewart JC, Hartung G, Maier-Borst W, Heene DL. Plasma protein (albumin) catabolism by the tumor itself--implications for tumor metabolism and the genesis of cachexia. *Crit Rev Oncol Hematol* 1997; **26**: 77-100 [PMID: 9298326 DOI: 10.1016/s1040-8428(97)00015-2]

33 **Merlot AM**, Kalinowski DS, Richardson DR. Unraveling the mysteries of serum albumin-more than just a serum protein. *Front Physiol* 2014; **5**: 299 [PMID: 25161624 DOI: 10.3389/fphys.2014.00299]

34 **Ostroumov D**, Fekete-Drimusz N, Saborowski M, Kühnel F, Woller N. CD4 and CD8 T lymphocyte interplay in controlling tumor growth. *Cell Mol Life Sci* 2018; **75**: 689-713 [PMID: 29032503 DOI: 10.1007/s00018-017-2686-7]

35 **Hong J**, Chen X, Gao W, Zhu S, Wu J, Huang O, He J, Zhu L, Chen W, Li Y, Fei X, Lin L, Shen K. A high absolute lymphocyte count predicts a poor prognosis in HER-2- positive breast cancer patients treated with trastuzumab. *Cancer Manag Res* 2019; **11**: 3371-3379 [PMID: 31114373 DOI: 10.2147/CMAR.S187233]

36 **Feng JF**, Liu JS, Huang Y. Lymphopenia predicts poor prognosis in patients with esophageal squamous cell carcinoma. *Medicine (Baltimore)* 2014; **93**: e257 [PMID: 25501097 DOI: 10.1097/MD.0000000000000257]

37 **Schlesinger M**. Role of platelets and platelet receptors in cancer metastasis. *J Hematol Oncol* 2018; **11**: 125 [PMID: 30305116 DOI: 10.1186/s13045-018-0669-2]

**Footnotes**

**Institutional review board statement:** This study was reviewed and approved by the Ethics Committee of Zhengzhou University.

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

**Conflict-of-interest statement:** We have no potential conflicts of interest to disclose.

**Data sharing statement:** No additional data are available.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Corresponding Author's Membership in Professional Societies:** International Society for Diseases of the Esophagus; The Chinese Society for Diseases of the Esophagus; American Association for Cancer Research.

**Peer-review started:** October 13, 2020

**First decision:** December 3, 2020

**Article in press:** December 25, 2020

**Specialty type:** Gastroenterology and Hepatology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Cho YS, De Nardi P **S-Editor:** Fan JR **L-Editor:** Filipodia **P-Editor:**

**Figure Legends**

**Figure 1 Receiver operating characteristic curves for 5-year overall survival in esophageal squamous cell carcinoma patients.** A: Receiver operating characteristic (ROC) curve of maximal voluntary ventilation (MVV) for 5-year overall survival; B: ROC curve of hemoglobin, albumin, lymphocytes and platelet (HALP) score for 5-year overall survival. AUC: Area under the curve; CI: Confidence interval.

**Figure 4 Kaplan-Meier curves of overall survival according to the maximal voluntary ventilation and hemoglobin, albumin, lymphocytes and platelet score in esophageal squamous cell carcinoma patients.** coMVV-HALP: MVV and HALP; HALP: Hemoglobin, albumin, lymphocytes and platelets; MVV: Maximal voluntary ventilation.

**Figure 5 Kaplan-Meier curves of overall survival according to the maximal voluntary ventilation and hemoglobin, albumin, lymphocytes and platelet score in subgroups of esophageal squamous cell carcinoma patients with different ages at diagnosis and tumor lengths.** A: Kaplan-Meier curves of overall survival according to maximal voluntary ventilation and hemoglobin, albumin, lymphocytes and platelet (coMVV-HALP) score in group with age < 60; B: Kaplan-Meier curves of overall survival according to coMVV-HALP score in the group with age ≥ 60; C: Kaplan-Meier curves of overall survival according to coMVV-HALP score in the group with tumor length < 4 cm; D: Kaplan-Meier curves of overall survival according to coMVV-HALP score in the group with tumor length ≥ 4 cm.

**Figure 6** **Kaplan-Meier curves of overall survival according to the maximal voluntary ventilation and hemoglobin, albumin, lymphocytes and platelets score in subgroups of esophageal squamous cell carcinoma patients with different tumor-node-metastasis stages.** A: Kaplan-Meier curves of overall survival according to maximal voluntary ventilation and hemoglobin, albumin, lymphocytes and platelets (coMVV-HALP) score in patients with tumor-node-metastasis (TNM) stage I; B: Kaplan-Meier curves of overall survival according to coMVV-HALP score in TNM stage II; C: Kaplan-Meier curves of overall survival according to coMVV-HALP score in TNM stage III.