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BRIEF ARTICLE

Prognostic value of preoperative mean corpuscular volume in esophageal squamous cell carcinoma

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Abstract

AIM: To evaluate whether preoperative mean corpuscular volume (MCV) is a prognostic indicator in patients with resectable esophageal squamous cell carcinoma (ESCC).

METHODS: A total of 298 consecutive, prospectively enrolled patients with histologically diagnosed ESCC who underwent surgery with curative intent from 2001 to 2011 were retrospectively evaluated. Patients were excluded if they had previous malignant disease, distant metastasis at the time of primary treatment, a history of neoadjuvant treatment, had undergone non-radical resection, or had died of a non-tumor-associated cause. Survival status was verified in September 2011. Pathological staging was performed based on the 2010 American Joint Committee on Cancer criteria. Preoperative MCV was obtained from blood counts performed routinely within 7 d prior to surgery. Receiver operating characteristic (ROC) curve analysis was used to determine a cutoff for preoperative MCV.

RESULTS: The 298 patients consisted of 230 males and 68 females, with a median follow-up of 30.1 mo. ROC analysis showed an optimal cutoff for preoperative MCV of 95.6 fl. Fifty-nine patients (19.8%) had high (> 95.6 fl) and 239 (80.2%) had low (≤ 95.6 fl) preoperative MCV. Preoperative MCV was significantly associated with gender (P = 0.003), body mass index (P = 0.017), and preoperative red blood cell count (P < 0.001). The predicted 1-, 3- and 5-year overall survival (OS) rates were 72%, 60% and 52%, respectively. Median OS was significantly longer in patients with low than with high preoperative MCV (27.5 mo *vs* 19.4 mo, P < 0.001). Multivariate analysis showed that advanced pT (P = 0.018) and pN (P < 0.001) stages, upper thoracic location (P = 0.010), lower preoperative albumin concentration (P = 0.002), and high preoperative MCV (P = 0.001) were negative prognostic factors in patients with ESCC. Preoperative MCV also stratified OS in patients with T3, N1-N3, G2-G3 and stage Ⅲ tumors.

CONCLUSION: Preoperative MCV is a prognostic factor in patients with ESCC.

Key words: Preoperative markers; Mean corpuscular volume; Prognosis; Resectable; Esophageal neoplasms

Core tip: Elevated mean corpuscular volume (MCV) has been shown to predict the risk of esophageal squamous cell carcinoma (ESCC). We hypothesized that pretreatment MCV could predict prognosis. In analyzing 298 patients with ESCC, we found that the optimal cut-off

for preoperative MCV was 95.6 fl. Multivariate analysis showed that high (> 95.6 fl) preoperative MCV was a negative prognostic factor, along with advanced stage, upper thoracic location and lower preoperative albumin, in patients with ESCC. Median overall survival was significantly longer in patients with low (≤ 95.6 fl) than high preoperative MCV (27.5 mo *vs* 19.5 mo, $P < 0.001$).

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INTRODUCTION

Elevated mean corpuscular volume (MCV) has long been recognized as a biomarker for alcoholic and folate deficient patients[1-3]. Although the nature of the relationship between them remains unclear, recent reports suggested that alcohol-induced folate deficiency can lead to macrocytosis[4]. In addition, MCV was found to be higher in Asian heavy drinkers with inactive aldehyde dehydrogenase-2 (ALDH2)[5,6] and to be a marker for alcohol abuse with inactive heterozygous ALDH2[7,8], suggesting that acetaldehyde is an important contributor to macrocytosis.

Alcohol abuse, and acetaldehyde and folate deficiency, all indicative of poor physical condition, were found to increase susceptibility to esophageal carcinoma[3,9-12], as was macrocytosis[7,13]. In addition, patients with more advanced malignancies frequently present with more severe hematological anomalies[14,15]. These findings led us to hypothesize that pretreatment MCV may predict the prognosis of patients with esophageal carcinoma. We therefore analyzed the association between preoperative MCV and different clinicopathological parameters, as well as the prognostic significance of preoperative MCV in patients with esophageal squamous cell carcinoma (ESCC).

MATERIALS AND METHODS

Patients selection

This study was a retrospective analysis of a prospectively collected database (2001-2011) of 298 consecutive patients with histologically diagnosed ESCC who underwent surgery with curative intent at the Cancer Center of Sun Yat-Sen University, Guangzhou, China. Patients with previous malignancy, distant metastasis, neoadjuvant treatment, non-radical resection (R1/R2), or non-tumor-associated death were excluded. Tumors were pathologically staged using the American Joint Committee on Cancer (2010) staging system. Patients were followed-up in the outpatient clinic every 3-6 mo during the first 3 years and every 12 mo thereafter. Demography and clinical details were extracted from the database (Table 1). Survival status was verified in September 2011 using the best available methods. The study protocol was approved by the medical ethics committee of the Cancer Center of Sun Yat-Sen University, which waived the requirement for informed consent due to the retrospective nature of the study.

Preoperative MCV

Preoperative MCV was determined from preoperative blood counts, performed routinely within 7 d prior to surgery, using a Beckman Counter blood analyzer (version STKS, Beckman Counter Inc., Fullerton, CA, United States). The cut-off for preoperative MCV was defined by receiver operating characteristic (ROC) curve analysis, with the point maximizing the area under the curve being selected.

Statistical analysis

All statistical analysis were performed using the SPSS 19.0 software package (SPSS, Inc., Chicago, IL, United States). The ROC curve was generated and analyzed using MedCalc statistical software package 11.0.1 (MedCalc Software bvba, Mariakerke, Belgium). Correlations between preoperative MCV and clinicopathological characteristics were assessed using the Pearson's χ^2 test. Overall survival (OS) was defined as the interval from the date of surgery to the date of death, or last follow-up. Multivariate Cox regression analysis was performed for all parameters found to be significant by the univariate analysis. Survival was analyzed using the Kaplan-Meier method, and differences between curves were assessed by the Log-Rank test. Statistical significance was defined as a P value < 0.05.

RESULTS

Patient baseline characteristics and preoperative MCV

The 298 patients consisted of 230 males and 68 females, with a median preoperative MCV of 91.0 fl (range: 61.4-112.4 fl). ROC curve analysis showed that the optimal cut-off point maximizing (0.588) was 95.6 fl ($P = 0.0123$), with a sensitivity of 0.867 and a specificity of 0.324. Using this cut-off, 59 patients (19.8%) had high (> 95.6 fl) and 239 (80.2%) had low (≤ 95.6 fl) preoperative MCV. The correlations between preoperative MCV and clinicopathologic parameters are summarized in Table 1. Preoperative MCV was significantly associated with gender ($P = 0.003$), body mass index (BMI) ($P = 0.017$), and preoperative red blood cell (RBC) count ($P < 0.001$; Figure 1).

Survival and preoperative MCV

Over a median follow-up of 30.1 mo, 102 of the 298 patients (34.2%) died of cancer-related causes, whereas the other 196 (65.8%) survived. The median survival time was 25.8 mo (range: 1.6-116.1 mo), and the predicted 1-, 3- and 5-year OS rates after primary surgery were 72%, 60%, and 52% respectively. Median OS was significantly longer in patients with low than high preoperative MCV (27.5 mo *vs* 19.4 mo, $P < 0.001$; Figure 2).

To determine factors independently prognostic of pa-

Table 1 Clinicopathological parameters and preoperative mean corpuscular volume *n* (%)

Characteristics	Case numbers	Preoperative MCV		*P* value Pearson's χ^2 test
		Low	High	
Age, yr (mean ± SE)	58.2 ± 9.2			
≤ 65	231	184 (79.7)	47 (20.3)	
> 65	67	55 (82.1)	12 (17.9)	0.660
Gender				
Male	230	176 (76.5)	54 (23.5)	
Female	68	63 (92.6)	5 (7.4)	0.003
BMI, kg/m^2 (mean ± SE)	22.3 ± 3.2			
≤ 20	65	46 (70.8)	19 (29.2)	
> 20 and ≤ 25	180	144 (80.0)	36 (20.0)	
> 25	53	49 (92.5)	4 (7.5)	0.017
Smoking index	440.1 ± 483.1			
≤ 400	171	141 (82.5)	30 (17.5)	
> 400	127	98 (77.2)	29 (22.8)	0.257
Preoperative RBC, × 10^{12}/L (mean ± SE)	4.5 ± 0.6			
≤ 4.0[1]	56	31 (55.4)	25 (44.6)	
> 4.0	242	208 (86.0)	34 (14.0)	< 0.001
Preoperative albumin, g/L (mean ± SE)	42.9 ± 4.6			
≤ 43[2]	149	115 (77.2)	34 (22.8)	
> 43	149	124 (83.2)	25 (16.8)	0.191
pT status, UICC^{7th} (mean ± SE)				
T1	33	31 (93.9)	2 (6.1)	
T2	52	44 (84.6)	8 (15.4)	
T3	213	164 (77.0)	49 (23.0)	0.051
N0	138	116 (84.1)	22 (15.9)	
N1	89	67 (75.3)	22 (24.7)	
N2	51	42 (82.4)	9 (17.6)	
N3	20	14 (70.0)	6 (30.0)	0.250
Histologic grade				
G1	94	71 (75.5)	23 (24.5)	
G2	156	127 (81.4)	29 (18.6)	
G3	48	41 (85.4)	7 (14.6)	0.324
pTNM stage (UICC^{7th})				
Stage Ⅰ	37	32 (86.5)	5 (13.5)	
Stage Ⅱ	120	100 (83.3)	20 (16.7)	
Stage Ⅲ	141	107 (75.9)	34 (24.1)	0.191
Tumor location				
Upper	48	37 (77.1)	11 (22.9)	
Middle	150	125 (83.3)	25 (16.7)	
Lower	100	77 (77.0)	23 (23.0)	0.393

[1]Normal limit of red blood cell count; [2]Mean value of preoperative hemoglobin. MCV: Mean corpuscular volume; Low: Low preoperative MCV (≤ 95.6 fl); High: High preoperative MCV (> 95.6 fl); BMI: Body mass index; RBC: Red blood cell; UICC: Union for International Cancer Control.

tient survival, we analyzed OS using a Cox proportional hazards model. All parameters found to be potentially significant in univariate analysis were included in a multivariate analysis. We found that pT status ($P = 0.018$), pN status ($P < 0.001$), tumor location ($P = 0.010$), preoperative albumin concentration ($P = 0.002$), and preoperative MCV ($P = 0.001$) were significantly prognostic of survival in this patient cohort (Table 2). When we analyzed the effect of preoperative MCV on OS in patients classified by clinicopathological factors, preoperative MCV was predictive of OS in patients with T3 ($P < 0.001$), N1-N3 ($P < 0.001$), G2-G3 ($P < 0.001$), and stage Ⅲ ($P = 0.001$) tumors (Figure 2 and Table 3).

DISCUSSION

Hematologic parameters have been reported to correlate significantly with prognosis in patients with advanced malignant disease[15-18]. MCV is considered a sensitive indicator of alcohol abuse and folate deficiency[1,2,4,6,19]. Recently, MCV was found to be a biomarker for alcohol abuse accompanied by inactive heterozygous ALDH2, and also allowed for the prediction of ESCC risk[8]. To our knowledge, however, no previous study has assessed the relationship between MCV and the prognosis of patients with ESCC.

Using ROC curve analysis, we found that a cut-off of 95.6 fl was a statistically significant predictor of OS. Moreover, high (> 95.6 fl) MCV was significantly correlated with male gender, lower BMI, and RBC ≤ 4 × 10^{12}/L. Folate deficiency has been shown to inhibit red cell maturation, as well as increasing erythrocyte fragility, resulting in increased hemolysis and lower RBC count, which consequently results in macrocytosis[20]. Lower BMI may accompany poor nutritional status, which was associated with elevated MCV[3,21]. The significant correlation

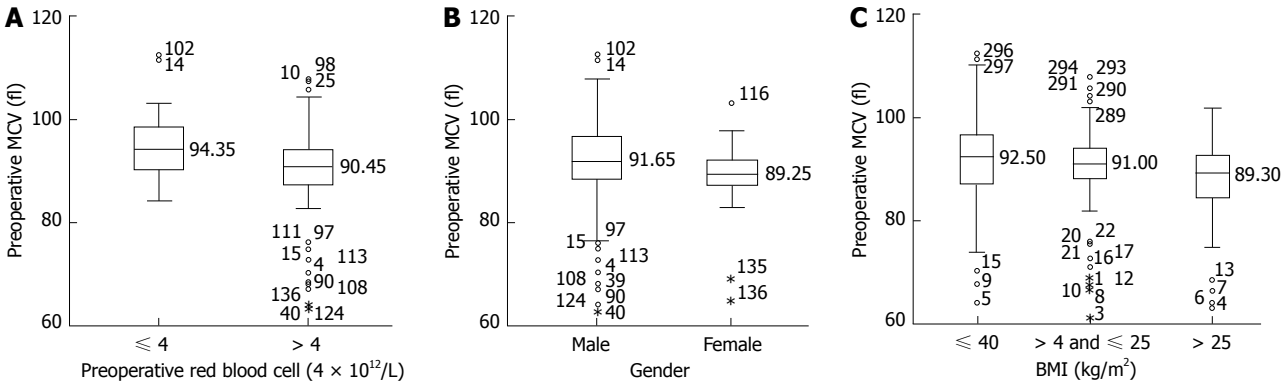

Figure 1 Box plot of preoperative mean corpuscular volume stratified by preoperative red blood cell count (A), gender (B) and body mass index (C). MCV: Mean corpuscular volume; BMI: Body mass index.

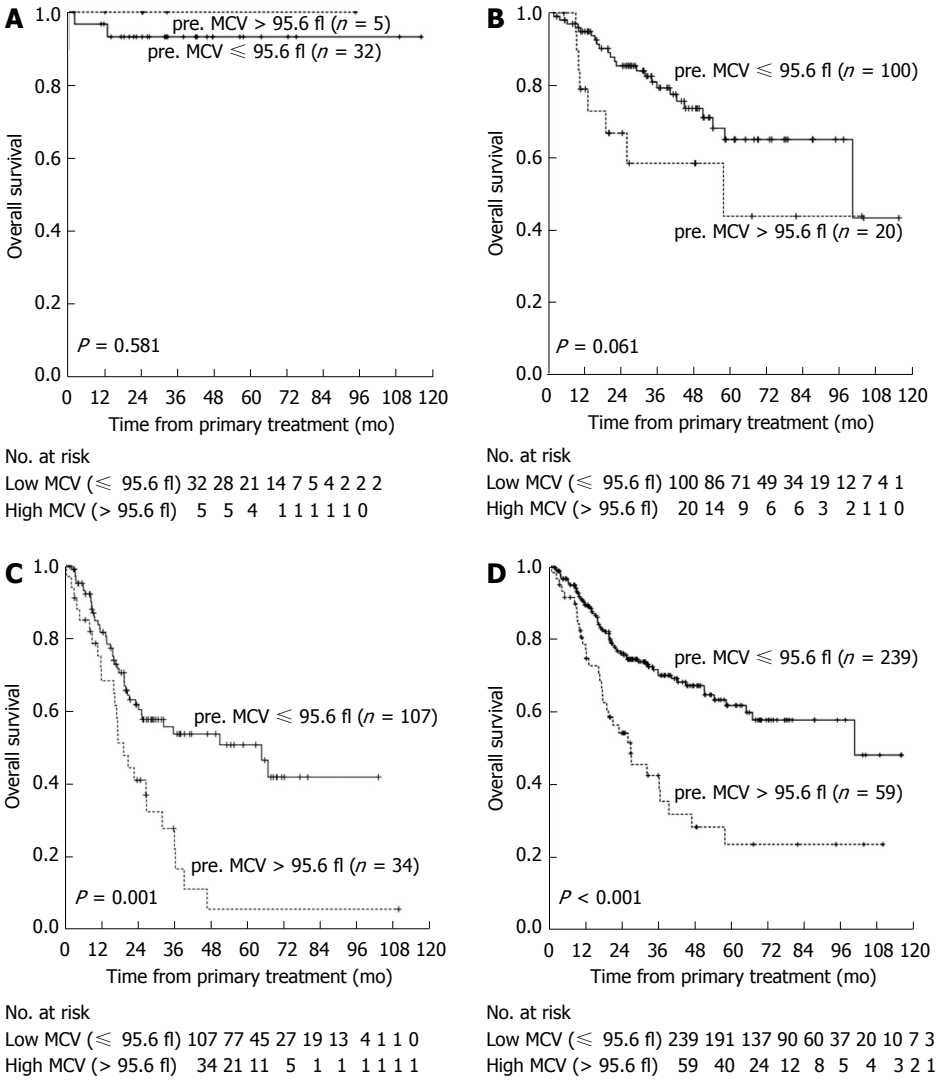

Figure 2 Kaplan-Meier estimates of the probability of overall survival according to preoperative mean corpuscular volume in stage Ⅰ cohort (A), stage Ⅱ cohort (B), stage Ⅲ cohort (C), and all cohorts (D). pre. MCV: Preoperative mean corpuscular volume.

between high MCV and male gender may be related to the association between macrocytosis and alcohol abuse, since overdrinking is much more frequent in males than in females[6-8]. Furthermore, MCV tended to be associated with pT status ($P = 0.051$), consistent with findings showing that preoperative MCV may provide a complementary advantage in assessing tumor invasiveness[17].

Although TNM stage is the best predictor of survival in cancer patients, OS may differ widely in patients with the same TNM stage tumors who receive the same treatment, suggesting that other, as yet undetermined factors may affect prognosis. Since preoperative hematologic parameters have been predictive of patient prognosis[15,22-25], we performed univariate and multivariate analyses of

Table 2 Univariate and multivariate Cox regression analysis for overall survival

Factors	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value[1]	HR (95%CI)	*P* value[1]
Age, yr	1.007 (0.985-1.029)	0.527		
Gender (male *vs* female)	0.744 (0.464-1.196)	0.222		
Smoking index (≤ 400 *vs* > 400)	1.391 (0.940-2.060)	0.099	1.302 (0.874-1.940)	0.194
BMI, kg/m^2 (≤ 20 *vs* > 20; ≤ 25 *vs* > 25)	0.878 (0.638-1.207)	0.422		
Preoperative MCV, fl (≤ 95.6 *vs* > 95.6)	2.495 (1.644-3.787)	< 0.001	2.108 (1.372-3.241)	0.001
Preoperative RBC, × 10^{12}/L (≤ 4 *vs* > 4)	0.685 (0.433-1.082)	0.105	0.835 (0.507-1.350)	0.462
Preoperative albumin, g/L	0.954 (0.919-0.990)	0.012	0.938 (0.900-0.977)	0.002
pT status (pT1 *vs* pT2 and pT3)	1.641 (1.147-2.348)	0.007	1.589 (1.084-2.327)	0.018
pN status (pN0 *vs* pN1, pN2 and pN3)	1.954 (1.603-2.382)	< 0.001	1.957 (1.602-2.392)	< 0.001
Histologic grade (G1 *vs* G2 and G3)	0.961 (0.714-1.293)	0.791		
Tumor location (upper thoracic *vs* middle thoracic and lower thoracic)	0.798 (0.605-1.051)	0.109	0.692 (0.522-0.916)	0.01

[1]Cox proportional hazards model. HR: Hazard ratio; BMI: Body mass index; MCV: Mean corpuscular volume; RBC: Red blood cell.

Table 3 Comparison of prognosis in specified cohort stratified by preoperative mean corpuscular volume

Variable	Case numbers	Overall survival (mo) (mean ± SE)	*P* value Log-Rank test
All cohort			< 0.001
Low	239	33.7 ± 24.7	
High	59	25.8 ± 24.2	
pT status			
T1-T2			0.075
Low	75	39.1 ± 27.1	
High	10	27.6 ± 22.7	
T3			< 0.001
Low	164	31.2 ± 23.2	
High	49	25.4 ± 24.7	
pN status			
N0			0.464
Low	116	40.0 ± 26.0	
High	22	35.5 ± 28.7	
N1-N3			< 0.001
Low	123	27.9 ± 22.0	
High	37	20.0 ± 19.2	
Histologic grade			
G1			0.211
Low	71	32.9 ± 27.6	
High	23	27.4 ± 24.3	
G2-G3			< 0.001
Low	168	34.1 ± 23.4	
High	36	24.8 ± 24.4	
pTNM stage			
Stage Ⅰ			0.581
Low	32	37.9 ± 27.1	
High	5	37.6 ± 32.6	
Stage Ⅱ			0.061
Low	100	39.6 ± 25.4	
High	20	31.1 ± 27.7	
Stage Ⅲ			0.001
Low	107	27.0 ± 21.6	
High	34	20.9 ± 19.8	

Low: Low preoperative mean corpuscular volume (≤ 95.6 fl); High: High preoperative mean corpuscular volume (> 95.6 fl).

factors predictive of OS in patients with ESCC. We found that pathological stage, tumor location, preoperative albumin concentration, and preoperative MCV were prognostic factors in our patient cohort.

We also found that OS was significantly shorter in patients with upper-thoracic cancer than those with middle and lower-thoracic esophageal cancer. A study of 605 patients with ESCC also found that median OS was significantly shorter in patients with upper thoracic cancer than in those with middle and lower thoracic tumors (45.9 mo *vs* 82.2 and 93.8 mo; $P < 0.001$)[26]. Due to their anatomical location, carcinomas of the upper thoracic esophagus often result in early invasion of adjacent structures and extensive lymph node metastasis[27]. The prognostic significance of preoperative albumin concentration may be due to it being a sensitive indicator of nutrition, liver function, and metabolic response to disease; thus patients with lower albumin concentrations may present with poorer physical status, decreasing both their response and tolerance to treatment[28,29]. Similar findings were reported in patients with adenocarcinoma of the gastric cardia[30].

Although we found that preoperative MCV was prognostic in patients with ESCC, there is no evidence that MCV has a direct effect on tumor progression or patient prognosis. MCV, however, is a marker of internal folate concentration. Folate acts to transfer one-carbon moieties, thus playing a central role in DNA synthesis, replication, repair, and methylation[31]. Folate deficiency leads to aberrant DNA methylation, which has been reported to be a predictor of clinical outcome in patients with esophageal cancer[32]. A recent study of 125 ESCC patients who underwent surgical resection showed that median OS was significantly longer in patients with high than with low/moderate folate intake (4.59 years *vs* 3.06 years; $P = 0.007$)[33]. Similar results were reported in patients with advanced gastric cancer who were treated with chemotherapy[34].

Another factor linking MCV with prognosis in ESCC is macrocytosis, which may be an indicator of malnutrition, a negative prognostic factor in various human cancers[21,35,36]. In addition, crystal osmotic pressure was shown to be a major regulator of red cell volume in internal environments[37]. Dysphagia, a frequently observed symptom in patients with advanced esophageal cancer,

restricts intake, thus reducing serum concentrations of electrolytes, glucose, and amino acids. This, in turn, may decrease crystal osmotic pressure, leading to red cell dilation. Our finding, that preoperative MCV was related to pT stage and BMI, was consistent with results suggesting that increased MCV was associated with tumor invasiveness and nutritional status[3,17]. Thus, taken together, these results suggest that preoperative MCV may be a marker reflecting internal folate concentration, nutritional status, and tumor invasiveness, thus comprehensively predicting prognosis in patients with ESCC. MCV assays are also convenient and inexpensive to perform, allowing for wide clinical application and suggesting that they may be crucial in preoperative assessment.

To further evaluate the prognostic significance of preoperative MCV, we performed subgroup analysis in patients with ESCC. We found that MCV resulted in the stratification of OS in patients with T3, N1-N3, G2-G3, and stage Ⅲ tumors, but not in patients with T1-T2, N0, G1, or stage Ⅰ / Ⅱ tumors. These findings, however, may be due to the small sample size of these subgroups. Moreover, the relatively good prognosis in patients with T1/2, N0, G1, and stage Ⅰ / Ⅱ tumors may mask the significance of preoperative MCV.

This study has limitations and potential biases. Due to its retrospective nature, records of alcohol consumption by patients were incomplete and folic acid concentrations were not tested in most patients. Furthermore, we could not determine whether preoperative MCV was a better predictor of OS than conventional prognostic factors. Finally, our small sample size may reflect a selection bias to some extent.

In conclusion, in patients with resectable ESCC, OS was significantly longer in patients with low (≤ 95.6 fl) than high (> 95.6 fl) preoperative MCV. Additional studies, however, are required to validate our results.

COMMENTS

Background

Surgical resection remains the treatment of choice for patients with localized esophageal carcinoma. Routine preoperative blood tests of red blood cells, white blood cells, and platelet counts can help estimate surgical risk. Significant hematologic variations frequently observed in patients with advanced malignant diseases may predict prognosis.

Research frontiers

Elevated mean corpuscular volume (MCV) has long been recognized as a biomarker for alcohol abuse and folate deficiency. In addition, MCV was reported to be higher in Asian heavy drinkers with inactive aldehyde dehydrogenase-2 (ALDH2), and was found to be a marker of alcohol abuse in individuals with inactive heterozygous ALDH2, suggesting that acetaldehyde may be an important contributor to macrocytosis. A recent study showed that macrocytosis was a risk factor for esophageal carcinoma.

Innovations and breakthroughs

The authors observed a correlation between macrocytosis and prognosis in patients with esophageal carcinoma. Overall survival was significantly shorter in patients with elevated MCV than those with lower MCV. Utilizing receiver operating characteristic curve analysis, the authors determined an optimal cut-off point for MCV, which was both reasonable and objective.

Applications

These results suggest that preoperative MCV may be used to predict prognosis in patients with esophageal cancer. Routine blood tests should be performed shortly before surgery in these patients, and those with elevated MCV, especially greater than 95.6 fl, should be carefully evaluated to assess the risks and feasibility of surgery.

Terminology

MCV, representing the mean volume of a single red blood cell, is determined by indirect calculation. Clinically, this parameter is often used in the differential diagnosis of various type of anemia.

Peer review

This is an article on an unusual topic. The value of MCV has been known up to now as risk factor for esophageal carcinoma, but it is not known as prognostic factor.

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