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Peripheral Monocyte Count as an Independent Prognostic Factor for Patients with Locally Advanced Esophageal Squamous Cell Carcinoma

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Abstract

Introduction: There is no accurate clinicopathological risk model for localized advanced esophageal squamous cell carcinoma (LA-ESCC) that can be used to guide treatment by predicting prognosis. This study aimed to investigate the use of the novel biomarker peripheral absolute monocyte count (AMC) as independent prognostic factor for LA-ESCC with esophagectomy.

Materials and methods: From 2008 to 2017, we retrospectively analyzed LA-ESCC patients (pT3-4aN0M0, pT1-4aN1-3M0) who had AMC testing within a week of an esophagectomy in Sichuan Cancer Hospital & Institute, Chengdu, China. Adjuvant chemotherapy or observation was given postoperatively. Univariate and multivariate Cox regression analyses and Kaplan-Meier curves were calculated for overall survival (OS). Statistical results are presented as hazard ratios (HR), 95% confidence intervals (CI), and P-values.

Results: A total of 1784 patients were enrolled. For all patients, median follow-up, median OS and 5-year OS were 61.2 months, 39.7 months and 42.6%, respectively. In multivariate Cox-regression, high preoperative AMC (>3.90×10^9/L) was significantly related with poor OS (P=0.012). In subanalysis, postoperative adjuvant chemotherapy significantly increased OS in patients with high AMC (P=0.005).

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Conclusions: For LA-ESCC patients with esophagectomy, preoperative AMC was an independent prognostic factor. Postoperative adjuvant chemotherapy was recommended for patients with high AMC.

Keywords: Esophageal squamous cell carcinoma; Absolute monocyte count; Adjuvant chemotherapy; Locally advanced; Esophagectomy.

Abbreviations: LA-ESCC: Locally advanced esophageal squamous cell carcinoma; AMC: Absolute monocyte count; OS: Overall survival; HR: Hazard ratio; CI: Confidence interval; EC: Esophageal carcinoma; ESCC: Esophageal squamous cell carcinoma; KPS: Karnofsky performance status; LN: Lymph node.

Introduction

Esophageal carcinoma (EC) is a major global health issue and the incidence and mortality of EC rank seventh and sixth, respectively, in the worldwide [1]. Multimodal treatment consisting of esophagectomy, postoperative adjuvant chemotherapy and radiotherapy are standard of care for locally advanced esophageal squamous cell carcinoma (LA-ESCC) [2,5]. However, long-term survival varies greatly among patients with the same stage and treatment pattern [6], which indicates that the current clinicopathological risk stratification model is far from satisfactory to predict prognosis and guide treatment precisely. To guide the optimal adjuvant treatment strategy for patients with different risk strata, novel biomarkers beyond the current staging system are urgently needed [7,8]. Peripheral blood represents an ideal sample site due to its easy access to these biomarkers.

The circulating innate immune cells, monocytes, are mononuclear phagocytes that play an important role in the development and progression of cancer [9]. Studies have shown an association between high absolute monocyte count (AMC) in peripheral blood and poor outcome in several solid tumors [10-14] of which only one small-scale retrospective study was performed in EC [14]. This large-scale study aims to investigate the association between preoperative AMC and long-term survival in LA-ESCC patients. The second aim is to clarify the value of preoperative AMC to guide postoperative adjuvant chemotherapy.

Materials and methods

Patient selection: The eligibility criteria were as follows:

(1) Pathologically confirmed resectable LA-ESCC(pT3-4aN0M0, pT1-4aN1-3M0) in TNM classification of AJCC 8th edition [15];

(2) Standard McKeown or Ivor Lewis esophagectomy with curative R0 resection;

(3) Postoperative adjuvant chemotherapy or observation;

(4) Age ≥ 18 years;

(5) Hepatic, renal, and bone marrow function are adequate;

(6) Karnofsky performance status (KPS) score ≥ 70;

(7) Available routine blood test within one week before surgery.

Exclusion criteria included the following:

(1) Cervical EC;

(2) Non-Esophageal squamous cell carcinoma;

(3) Non-R0 resection;

(4) Postoperative adjuvant radiotherapy or chemoradiotherapy. In particular, salvage radiotherapy was permitted after disease progression.

We retrospectively collected 2370 patients who received esophagectomy with curative intent at the Sichuan Cancer Hospital in China from January 2008 to December 2017. Finally, 1784 patients were included in the analysis.

Written informed consents were obtained from all patients prior to treatment. This study was approved by the Institutional Review Board of Sichuan Cancer Hospital & Institute (SCCHEC-02-2020-015) and performed in accordance with the principles of Declaration of Helsinki.

Data extraction: A collection of clinicopathological data was obtained from the Department of Pathology's medical records and pathology reports. The clinicopathological factors comprised of histologically verified ESCC, sex, age, KPS, tumor location and size, TNM stage, tumor grade, and the presence of lymphovascular and nerve invasion, as well as the count of lymph nodes dissected. The laboratory results, encompassing complete blood counts such as absolute monocyte count (AMC) and biochemical indices, were procured within a week before the surgical procedure.

Treatment

Esophagectomy: The most common surgical technique was standard McKeown esophagectomy (n=1294, 72%), followed by Ivor Lewis esophagectomy (n=490, 28%). The surgical approach was open (n=997, 56%) or minimally invasive esophagectomy (n=795, 44%). Postoperative adjuvant chemotherapy. 852 patients received postoperative adjuvant chemotherapy. Most patients received platinum plus paclitaxel (n=427, 50%) or platinum plus fluorouracil (n=357, 42%) dual-drug regimens. The paclitaxel plus platinum regimen consisted of paclitaxel 135-175 mg/m^2 (day 1) and cisplatin 75 mg/m^2 (day 1-3) or carboplatin 35 mg/mL/min (day 1) every three weeks. The fluorouracil plus platinum regimen consisted of fluorouracil 750mg/m^2 (day 1-5) and cisplatin 75 mg/m^2 (day 1-3) or carboplatin at an area under the curve of 35 mg/mL/min (day 1) every three weeks. The average chemotherapy cycle is 2.8. Dose adjustment and chemotherapy cycle were decided at the discretion of medical oncologists.

Follow-up: Clinical and laboratory evaluations were routinely conducted following treatment. Computed tomography was the

most prevalent imaging technique. During the first 2 years, follow-up evaluations were conducted every 3 months, every 6 months in the next 3 years, and then annually in the following years. We evaluated treatment response using the Response Evaluation Criteria in Solid Tumors (version 1.1) 16. We collected information on the dates of death through various sources including follow-up telephone calls, clinical medical records, and the central registry of the Chinese Bureau of Population Statistics.

Statistical analysis: The median value of AMC was 3.90×10^9/L. We predefined low and high AMC level as AMC ≤3.90×10^9/L and > 3.90×10^9/L, respectively. The overall survival (OS) refers to the duration between the date of initial diagnosis and the date of either death from any cause or the last follow-up for patients who remain alive at the time of analysis.

Clinicopathological factors of different AMC groups were compared and analyzed by Fisher's exact test or Chi-square test. A multivariate Cox regression analysis was conducted on variables that demonstrated a P-value of less than 0.1 in the univariate analysis. The outcomes of the Cox regression analysis and Kaplan-Meier curve were succinctly presented as the hazard ratio (HR), along with the corresponding 95% confidence interval (CI) and P value. The statistical analysis was conducted using IBM Inc.'s SPSS software (version 22.0), while data visualization was carried out using the ggplot2 package in R software (version 3.3.2, R Foundation for Statistical Computing). P<0.05 was regarded to be statistically significant.

Results

Patient characteristics: Table 1 shows a detailed description of 1784 eligible patients clinicopathological characteristics. The median age was 62 years old, and 1481 (83%) were males. The median follow-up time was 61.2 months. The median OS, 3-year OS, and 5-year OS for all patients were 39.7 (95% CI, 34.8-44.7) months, 51.9%, and 42.6%, respectively (Figure 1A).

AMC as independent prognosis factor: Clinicopathological characteristics, including gender, KPS, tumor location and length, pathological T and N stages, tumor differentiation, count of lymph node resection, lymphovascular invasion, differed significantly among high and low AMC subgroups (*P*<0.05) (Table 1). The effect of variables including female, T3-4a, N1-3, moderate to poor differentiation, count of lymph node resection >15, adjuvant chemotherapy, and AMC on long-term survival were significant in univariate analysis (*P*<0.1) (Table 2). After adjusting for effects of theses significant variables in multivariate analysis,

In both continuous and dichotomous forms, AMC was a significantly independent prognostic factor (*P*<0.05). Patients with high AMC had significantly poor OS (*P*=0.012), comparing with patients with low AMC (Figure 1B).

Chemotherapy improved survival of patients with high AMC: In patients with high AMC, clinicopathological characteristics including age, KPS, tumor location and length differed between chemotherapy and observation subgroups (*P*<0.05) (Supplementary Table S1). There was a strong association between survival in univariate analysis with factors including female, N1-3, count of lymph node resection >15, and adjuvant chemotherapy (P<0.1). (Supplementary Table S2). In patients with high AMC, multivariate analysis demonstrated that adjuvant chemotherapy was independently connected with longer OS (*P*=0.026) (Figure 2A).

Chemotherapy cannot improve survival of patients with low AMC: For patients with low AMC, there were significant differences in characteristics including age, KPS, tumor location, pathological N stage, tumor differentiation, lymphovascular invasion between chemotherapy and observation subgroups (*P*<0.05) (Supplementary Table S1). In univariate and multivariate analyses, variables including female, T3-4a, N1-3, poor differentiation, number of lymph node resection >15, and nerve invasion were independent prognosis factors (*P*<0.05) (Supplementary Table S3). Compared with observation, there was a tendency of improved OS after the addition of adjuvant chemotherapy, but without statistical significance (*P*=0.091) (Figure 2B).

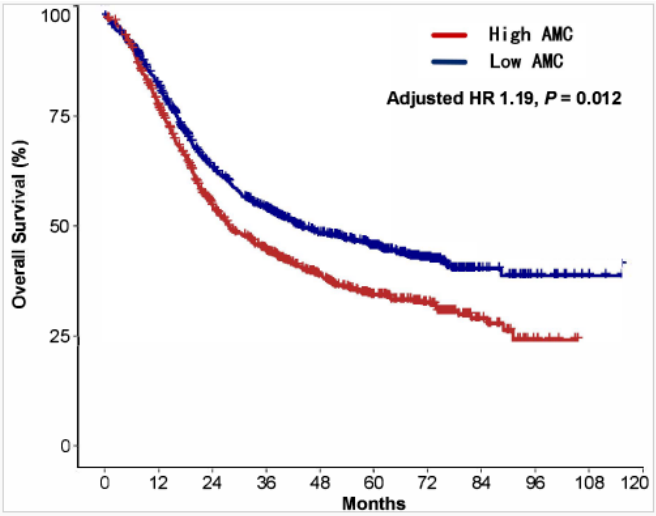

Figure 1: Overall survival.
Kaplan-Meier curves for overall survival in patients with high (red) and low absolute monocyte count (blue).

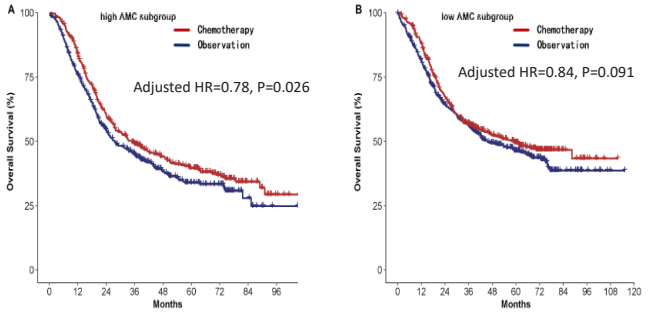

Figure 2: Comparison of overall survival.
Kaplan-Meier curves for overall survival in high **(A)** and low **(B)** absolute monocyte count subgroups with chemotherapy (red) or observation (blue).

Table 1: Clinicopathological characteristics.

Variables n (%)	Total (n=1784)	Low AMC (n=935)	High AMC (n=849)	*P*
Age, years				0.516
≤64	1210 (67.8)	645 (69)	565 (66.5)	
65-74	472 (26.5)	240 (25.7)	232 (27.3)	
≥75	102 (5.7)	50 (5.3)	52 (6.1)	
Gender				<0.001
Male	1481 (83.0)	696 (74.4)	785 (92.5)	
Female	303 (17.0)	239 (25.6)	64 (7.5)	
KPS				0.004
70-80	989 (55.4)	549 (58.7)	440 (51.8)	
90-100	795 (44.6)	386 (41.3)	409 (48.2)	
Tumor location				<0.001
Upper	417 (23.4)	245 (26.2)	172 (20.3)	
Middle	946 (53.0)	497 (53.2)	449 (52.9)	
Lower	421 (23.6)	193 (20.6)	228 (26.9)	
Tumor length, cm				<0.001
≤5	1357 (76.2)	767 (82.2)	590 (69.6)	
>5	424 (23.8)	166 (17.8)	258 (30.4)	
Pathological T stage				0.043
T1	50 (2.8)	31 (3.3)	19 (2.2)	
T2	219 (12.3)	127 (13.6)	92 (10.8)	
T3	1382 (77.5)	718 (76.8)	664 (78.2)	
T4a	133 (7.5)	59 (6.3)	74 (8.7)	
Pathological N stage				0.005
N0	620 (34.8)	349 (37.3)	271 (31.9)	
N1	627 (35.1)	325 (34.8)	302 (35.6)	
N2	360 (20.2)	188 (20.1)	172 (20.3)	
N3	177 (9.9)	73 (7.8)	104 (12.2)	
Tumor differentiation				0.002
Good	311 (17.4)	153 (16.4)	158 (18.6)	
Moderate	755 (42.3)	373 (39.9)	382 (45)	
Poor	718 (40.2)	409 (43.8)	309 (36.4)	
Number of LN resection				0.072
≤15	516 (28.9)	288 (30.8)	228 (26.9)	
>15	1267 (71.1)	646 (69.2)	621 (73.1)	
Lymphovascular invasion				0.008
Yes	337 (18.9)	199 (21.3)	138 (16.3)	
No	1447 (81.1)	736 (78.7)	711 (83.7)	
Nerve invasion				0.615
Yes	380 (21.3)	204 (21.8)	176 (20.7)	
No	1404 (78.7)	731 (78.2)	673 (79.3)	
Adjuvant chemotherapy				0.852
No	936 (52.5)	493 (52.7)	443 (52.2)	
Yes	848 (47.5)	442 (47.3)	406 (47.8)	

AMC: Absolute monocyte count; KPS: Karnofsky performance status; LN: Lymph node.

Table 2: Univariate and multivariate analyses of all patients.

Variable	Univariate Analysis Crude HR (95% CI)	*P**	Multivariate Analysis Adjusted HR (95% CI)	*P*#
Age, years				
≤64	1.00		1.00	
65-74	1.09 (0.95,1.27)	0.226	1.1 (0.94,1.28)	0.225
≥75	1.45 (1.12,1.88)	0.005	1.24 (0.95,1.62)	0.117
Gender				
Male	1.00		1.00	
Female	0.67 (0.55,0.8)	<0.001	0.74 (0.61,0.9)	0.002
KPS				
70-80	1.00			
90-100	1.07 (0.94,1.22)	0.275		
Tumor location				
Upper	1.00			
Middle	1.01 (0.86,1.18)	0.895		
Lower	0.94 (0.78,1.13)	0.508		
Tumor length, cm				
≤5	1.00		1.00	
>5	1.21 (1.05,1.4)	0.01	1.08 (0.93,1.25)	0.34
Pathological T stage				
T1	1.00		1.00	
T2	1.57 (0.95,2.59)	0.075	1.44 (0.88,2.38)	0.15
T3	1.66 (1.04,2.65)	0.034	2.13 (1.33,3.43)	0.002
T4a	2.7 (1.63,4.49)	<0.001	2.79 (1.66,4.68)	<0.001
Pathological N stage				
N0	1.00		1.00	
N1	1.84 (1.55,2.18)	<0.001	2.08 (1.74,2.48)	<0.001
N2	2.96 (2.47,3.55)	<0.001	3.25 (2.68,3.93)	<0.001
N3	3.85 (3.11,4.77)	<0.001	4 (3.17,5.05)	<0.001
Tumor differentiation				
Good	1.00		1.00	
Moderate	1.37 (1.13,1.66)	0.001	1.23 (1.01,1.5)	0.038
Poor	1.56 (1.29,1.9)	<0.001	1.35 (1.1,1.65)	0.004
Number of LN resection				
≤ 15	1.00		1.00	
> 15	0.77 (0.67,0.88)	<0.001	0.64 (0.55,0.73)	<0.001
Lymphovascular invasion				
Yes	1.00		1.00	
No	0.61 (0.53,0.71)	<0.001	0.86 (0.73,1.01)	0.073
Nerve invasion				
Yes	1.00		1.00	
No	0.74 (0.63,0.85)	<0.001	0.9 (0.77,1.05)	0.179
Adjuvant chemotherapy				
No	1.00		1.00	
Yes	0.86 (0.76,0.98)	0.022	0.8 (0.7,0.92)	0.001

AMC				
As continuous variable	1.7 (1.2,2.42)	0.003	1.39 (1.1,2.02)	0.01
As dichotomous variable				
Low, ≤0.39	1.00		1.00	
High, >0.39	1.33 (1.17,1.51)	<0.001	1.19 (1.04,1.36)	0.012

Discussion

As far as we know, this is the first large-scale retrospective study to evaluate the association between preoperative AMC and long-term survival in LA-ESCC patients underwent curative esophagectomy. In LA-ESCC patients, the preoperative AMC is an independent prognostic factor, and high AMC (>3.90×10^9/L) was significantly associated with poor survival. Postoperative adjuvant chemotherapy may rise long-term survival in LA-ESCC patients with high AMC. Currently, TNM stage alone had limited prognostic and predictive values in LA-ESCC. This study provided important evidence supporting the use of AMC in clinical prognostic model beyond TNM stage to guide the application of adjuvant chemotherapy.

Previous studies found that mononuclear phagocyte system could regulate cancer development and progression [9]. As innate immune cells of the mononuclear phagocyte system, circulating monocytes were related with cancer incidence in healthy population [17] and mortality in cancer patients [10-13]. Per 0.1 × 10^9/L increase of AMC in healthy middle-aged and elderly community-dwelling Danes was independently associated with a HR of 1.12 in tumor incidence [17]. Elevated AMC was also found to be related with disease progression/metastasis and death in many cancer types, including EC [14], diffuse large B-cell lymphoma [10], hepatocellular carcinoma [11], colorectal cancer [12], and cervical cancer [13]. Ding [18] et al. found that AMC remains an independent prognostic factor for patients with esophageal squamous cell carcinoma who receive neoadjuvant chemoradiotherapy followed by surgery. Neoadjuvant chemoradiotherapy, a treatment regimen combining chemotherapy and radiotherapy, plays a dual role: shrinking the tumor before surgery and targeting any potential micrometastases. Currently, there are multiple non-single-factor predictive indicators, such as the lymphocyte/monocyte ratio (LMR) and neutrophil-to-lymphocyte ratio (NLR), which can also serve as predictors of esophageal cancer prognosis. The studies by Wang [19] et al. and Hirahara [20] et al. demonstrated that the LMR is an independent prognostic factor for predicting the outcomes of esophageal cancer patients undergoing solely surgery. In addition, the study [21] shows that the high NLR with better OS. Taking a broader view, we see that the significance of LMR transcends surgery alone. Radiation therapy has played an increasingly important role in the treatment of esophageal cancer. Liu [22] et al. and Li [23] et al. discovered that patients with esophageal cancer after definitive chemoradiotherapy with high LMR group exhibited a better prognosis. Radiotherapy, as a key component in definitive chemoradiotherapy, adds an layer of complexity. It exerts its influence by damaging the DNA of cancer cells, impeding their ability to proliferate and inducing apoptosis. LMR emerges as a promising predictive indicator, wielding its influence across surgical and radiotherapeutic approaches. Similarly, this large-scale cohort study emphasized the significant part of AMC as early prognostic and predictive biomarker in LA-ESCC. But differently, our analysis on high AMC subgroup could further guide the application of chemotherapy.

It has been understood in recent years that monocytes are heterogeneous cells with diverse responses to cancer. In malignancies, different monocyte subsets performed distinct functions, even opponent functions of pro- and antitumoral immunity. A lower peripheral $CD14^+CD16^-$ monocyte count was associated with better survival in pancreatic cancer [24]. In contrast, a higher peripheral $CD14^+CD16^+$ monocyte count indicated better response to anti-CTLA-4 immune checkpoint inhibitor ipilimumab in advanced melanoma [25]. In progressive and advanced stage cancers, protumoral signals from a specific monocyte subset, including angiogenesis, lymphocytes recruitment, tumor microenvironment remodeling, and spin off tumor-associated macrophages might outweigh antitumoral signals from host immune system to restraint cancer growth, such as phagocytosis and secretion of tumoricidal mediators [9]. We do not fully understand the mechanisms that regulate the destiny and differentiation of monocytes into protumoral or antitumoral subsets. Further studies on discrimination of monocyte subsets could offer additional insights in biological heterogeneity in cancer development and precise prediction on tumor response to specific therapies.

The current retrospective study has much strength including a substantial sample size, an extensive follow-up duration, and convenient accessibility to biomarkers. First, compared with similar studies [10-13], significantly more patients were enrolled in our research. The median follow-up was more than 5 years. We tended to believe results of this large-scale, long follow-up cohort were accurate and reliable. Second, the novel biomarker AMC was easily accessed from peripheral blood routine test. No extra examinations were needed to acquire AMC, which would not bring financial burden to insurance or patients. The simple access of AMC facilitated its clinical application in developing countries with high disease burden of EC, such as China.

The study limitations included the lack of research on monocyte subset and bias in retrospective cohort study. First, monocyte was a heterogeneous population of immune cell, and functions of different subsets varied greatly. We only analysed the association between AMC and long-term survival in this study. Monocyte subsets and functions were not distinguished. Further studies should focus on the discrimination of monocyte subsets and their specific functions in cancer progression. Second, there was always bias. Selection bias could not be overlooked in the determination of postoperative adjuvant chemotherapy or observation. Therefore, to avoid effects of biases and confounding factors, multivariate analysis was applied to adjust for effects of theses significant clinicopathological factors. The model utilized in this research to forecast outcomes was derived from data obtained from patients who received adjuvant chemotherapy after surgery. Extrapolating its efficacy to neoadjuvant treatment or adjuvant immunotherapy would be speculative.

Conclusion

In conclusion, our assessment of a large-scale retrospective cohort for LA-ESCC patients with esophagectomy provided high-level evidence that preoperative AMC was an independent prognostic factor and postoperative adjuvant chemotherapy was suggested to implement in patients with high AMC.

Declarations

Conflicts of interest: There are no competing interests declared by the authors.

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