Mean Corpuscular Volume as a Prognostic Factor for Patients With Habitual Alcohol or Tobacco Use After Esophagectomy

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Background: The goal of this study was to investigate the impact of mean corpuscular volume (MCV) in patients with esophageal squamous cell carcinoma (ESCC) who underwent surgical resection.

Methods: A total of 615 patients with ESCC who underwent esophagectomy were analyzed. Patients were divided into two groups according to the standard MCV: the high MCV group (>100 fl) and the low MCV group (≤100 fl). Survival analyses were performed to calculate overall survival (OS) and cancer-specific survival (CSS) and investigate the independent prognostic factors.

Results: Fifty-one patients (8.3%) were in the high MCV group, and the other 564 patients (91.7%) were defined as the low MCV group. MCV was significantly correlated with sex, habitual alcohol or tobacco use, tumor length, body mass index, and multiple primary malignancies (P < 0.05). Elevated MCV was significantly correlated with poor survival in univariate and multivariate analyses. However, in subgroup analyses, MCV was found to be correlated with survival only in patients with alcohol or tobacco consumption and not in patients without alcohol or tobacco consumption.

Conclusions: Pretreatment MCV was correlated with survival in ESCC patients after esophagectomy. However, its prognostic value might only exist in patients with alcohol or tobacco consumption.

Keywords: esophageal neoplasm, mean corpuscular volume, prognosis, squamous cell carcinoma, surgery

INTRODUCTION

Esophageal carcinoma is a common digestive system malignancy with high mortality (1). Esophagectomy remains the most important tool for treatment in resectable cases, while neoadjuvant chemoradiotherapy is recommended for locally advanced diseases (2). The identification of factors associated with high risk prior to treatment is important for planning the individual therapeutic strategy for patients with malignancies. Currently, the TNM staging system is widely used for predicting the outcomes of esophageal cancer and other malignancies. Although a
Patients were divided into a high MCV group (>100 fl determined according to the standard value in our hospital. Weight, height, and laboratory data were collected within 1 week before surgery. Mean corpuscular volume (MCV) is a measure of the average volume of erythrocytes. Elevated MCV is always associated with deficiency of folate and vitamin B12, which may be seen in patients with a history of gastrectomy, malnutrition due to alcohol abuse, and so on (3). Recently, MCV was found to be correlated with the survival of patients with several malignancies, such as liver cancer, gastroesophageal adenocarcinomas, colorectal cancer, and head and neck cancer (3–8).

Alcohol and tobacco abuse have been recognized as risk factors for various cancers. Previous studies also showed that elevated MCV was more often found in patients with high alcohol or tobacco consumption (9, 10). To the best of our knowledge, only two studies have evaluated the predictive significance of MCV in patients with esophageal cancer who have undergone surgical resection (11, 12). However, neither of these studies evaluated the prognostic value of MCV according to the status of alcohol and tobacco consumption.

In this study, we investigated the prognostic value of MCV in patients with esophageal squamous cell carcinoma (ESCC) who underwent surgical resection and tried to elucidate the prognostic significance of MCV in these patients according to the history of alcohol and tobacco consumption.

PATIENTS AND METHODS

Patients
Between September 2014 and December 2017, 817 patients with esophageal cancer underwent esophagectomy at Shantou University Medical College Cancer Hospital. Only patients with ESCC who underwent surgery as their initial treatment were included in this study. Patients with a past history of gastrectomy were also excluded from this study. This study was approved by the Ethics Committee of our hospital. Written informed consent was signed for all patients.

Data Collection
All clinicopathological data and laboratory data were obtained from the patients’ medical records. The stage of the tumor was classified based on the 8th edition American Joint Committee on Cancer TNM staging system for ESCC. Habitual alcohol use was defined as drinking ≥1 time per week, and habitual tobacco use was defined as smoking at least 1 cigarette per day for at least one year. Weight, height, and laboratory data were collected within 1 week before surgery.

The cutoff values of MCV and serum albumin were determined according to the standard value in our hospital. Patients were divided into a high MCV group (>100 fl) and a low MCV group (≤100 fl) as well as a high serum albumin group (≥40 g/L) and a low serum albumin group (<40 g/L). Anemia was defined as Hb < 12 g/dL for women and Hb <13 g/dL for men according to the World Health Organization guidelines (13).

Surgery
Most of the patients underwent esophagectomy through a right thoracotomy, while other patients underwent a left thoracotomy. For lymphadenectomy, the regional lymph nodes in the middle mediastinal, lower mediastinal, and upper abdominal regions were routinely dissected in all patients. For patients who underwent esophagectomy through a right thoracotomy, the lymph nodes around the left and right recurrent laryngeal nerves were also dissected. Postoperative morbidity was defined as a state where the Clavien–Dindo classification was II or higher (14).

Statistical Analyses
The smoking index was calculated by daily cigarette intake × number of years smoking. The alcohol index was calculated as daily ethanol intake (g) × number of years drinking. Continuous variables were compared using Student’s t-test. Categorical variables were compared by the χ2 test or Fisher’s exact test. Overall survival (OS) time was calculated from the date of operation to the date of death or most recent follow-up. Cancer-specific survival (CSS) was defined as survival from the date of operation until death due to esophageal carcinoma in the absence of other causes. Survival was calculated using the Kaplan-Meier method, and the differences in survival between groups were compared by the log-rank test. Multivariate Cox regression analyses were applied to identify independent prognostic factors. P < 0.05 was set as significant. All statistical analyses were conducted in SPSS 20.0 software (IBM, Armonk, New York, USA).

RESULTS

Patient Characteristics
Of the 817 patients with esophageal carcinoma who underwent esophagectomy between September 2014 and December 2017, 761 patients were diagnosed with ESCC. One hundred sixteen patients who received neoadjuvant therapy were excluded from this study (including 94 patients with neoadjuvant chemoradiotherapy, 13 patients with neoadjuvant radiotherapy, and 9 patients with neoadjuvant chemotherapy). Five patients with a past history of gastrectomy and 25 patients lacking any follow-up data were also excluded. Thus, 615 patients were enrolled for analysis in this study. There were 472 men and 143 women, and the median age was 61 years (range, 38 to 84 years). The mean number of lymph nodes dissected was 26.9 ± 11.0, and the median number was 26 (range, 6–74). Based on the 8th edition of the TNM staging system, 283 patients (46.0%) had pN0 disease, 206 patients (33.5%) had pN1 disease, 99 patients (16.1%) had pN2 disease, and 27 patients (4.4%) had pN3 disease. Radical resection was achieved in 590 patients (95.9%), while palliative resection was performed in 25 patients (4.1%).
The postoperative morbidity rate was 8.3% (51/615). The hospital mortality rate was 0.5% (3/615).

One hundred and sixty-eight patients received postoperative adjuvant therapy, including 64 cases of postoperative chemotherapy, 79 cases of postoperative radiotherapy, and 25 cases of postoperative chemoradiotherapy. The most common regimen for chemotherapy was Paclitaxel + Cisplatin or 5-Fu + Cisplatin. A total dose of 40–66 Gy (median 50 Gy) irradiation (2 Gy/day, 5 days per week) was administered for postoperative therapy.

Two hundred twenty-five patients habitually drank alcohol, while the other 390 patients did not. The mean alcohol index for these 225 patients with habitual alcohol consumption was 3344.3 ± 117.6. Four hundred thirty-three patients had habitual tobacco use, while the other 182 patients did not. The mean smoking index for these 433 patients with habitual tobacco use was 266.1 ± 81.3. The mean smoking index for patients with high MCV was 1079.6 ± 71.4, which was higher than the 3150.7 ± 180.4 for patients with low MCV (P = 0.016). The mean smoking index for patients with high MCV was 4213.4 ± 426.1, which was higher than the 3150.7 ± 180.4 for patients with low MCV (P = 0.016).

Prognostic Value of MCV According to Alcohol and Tobacco Consumption

We further conducted subgroup analyses to identify the value of MCV according to the history of alcohol and tobacco consumption. Of 225 patients with habitual alcohol use, 41 patients had high MCV, and 184 patients had low MCV. The mean alcohol index for patients with high MCV was 4213.4 ± 426.1, which was higher than the 3150.7 ± 180.4 for patients with low MCV (P = 0.016). High MCV was found to be significantly correlated with poor OS and CSS in ESCC patients with habitual alcohol use (P < 0.05, Figure 2). However, MCV was not correlated with survival in the 390 patients without habitual alcohol use (P > 0.05, Figure 2).

Of the 433 patients with habitual tobacco use, 49 patients had high MCV, and 384 patients had low MCV. The mean smoking index for patients with high MCV was 1079.6 ± 71.4, which was higher than the 913.7 ± 23.2 for patients with low MCV (P = 0.018). In survival analysis, MCV was also found to be correlated with survival in ESCC patients with habitual tobacco use but not in patients without habitual tobacco use (Figure 3).

DISCUSSION

Preoperative malnutrition has been reported to be a predictor of outcomes in cancer patients and can be used as a prognostic indicator (15–17). Recently, MCV has been found to be another nutrition parameter correlated with the survival of various solid malignancies (3–8). Previous studies showed that elevated MCV was always observed in patients with malnutrition due to alcohol abuse (3). Our current study also showed that MCV was significantly correlated with habitual alcohol or tobacco use in patients with ESCC. Moreover, elevated MCV was more often seen in malnutrition patients with low BMI. Surprisingly, none of the 143 female patients in the current study had high MCV, compared with 10.8% among male patients. The explanation for this result may be that few females had habitual alcohol and tobacco abuse in this study. Only 1 female patient with habitual alcohol use and 2 female patients with habitual tobacco use were enrolled in our current study.

To date, only two studies have evaluated the value of MCV in patients with esophageal carcinoma who underwent surgical resection (11, 12), and both of these studies found that elevated
TABLE 1 | Correlation of the mean corpuscular volume with the clinicopathological features.

|                  | No. Patients | MCV ≤100fl | MCV >100fl | X²  | P value |
|------------------|--------------|-------------|-------------|-----|---------|
| Sex              |              |             |             |     |         |
| Male             | 472          | 421 (89.2%) | 51 (10.8%)  | 16.848 | <0.001 |
| Female           | 143          | 143 (100%)  | 0 (0%)      |     |         |
| Age (yr)         |              |             |             |     |         |
| ≤60              | 302          | 276 (91.7%) | 26 (8.3%)   | 0.078  | 0.780 |
| >60              | 313          | 288 (92.0%) | 25 (8.0%)   |     |         |
| Tumor location   |              |             |             |     |         |
| Upper third      | 110          | 99 (90.0%)  | 11 (10.0%)  | 0.549  | 0.760 |
| Middle third     | 385          | 355 (92.2%) | 30 (7.8%)   |     |         |
| Lower third      | 120          | 110 (91.7%) | 10 (8.3%)   |     |         |
| Anemia           |              |             |             |     |         |
| Yes              | 131          | 119 (90.8%) | 12 (9.2%)   |     |         |
| No               | 484          | 445 (91.9%) | 39 (8.1%)   |     |         |
| Habitual tobacco use |      |             |             |     |         |
| Yes              | 433          | 384 (88.7%) | 49 (11.3%)  | 17.590 | <0.001 |
| No               | 182          | 180 (98.9%) | 2 (1.1%)    |     |         |
| Habitual alcohol use |       |             |             |     |         |
| Yes              | 225          | 184 (81.8%) | 41 (18.2%)  | 45.999 | <0.001 |
| No               | 390          | 380 (97.4%) | 10 (2.6%)   |     |         |
| Tumor length     |              |             |             |     |         |
| ≤5cm             | 430          | 401 (93.3%) | 29 (6.7%)   | 4.507  | 0.034 |
| >5cm             | 185          | 163 (88.1%) | 22 (11.9%)  |     |         |
| Histologic grade |              |             |             |     |         |
| Well             | 210          | 196 (93.3%) | 14 (6.7%)   | 1.285  | 0.526 |
| Moderate         | 317          | 289 (91.2%) | 28 (8.8%)   |     |         |
| Poor             | 88           | 79 (98.8%)  | 2 (1.2%)    |     |         |
| BMI              |              |             |             |     |         |
| ≤18.5            | 116          | 100 (86.2%) | 16 (13.8%)  | 7.882  | 0.019 |
| 18.5-24.9        | 444          | 410 (92.3%) | 34 (7.7%)   |     |         |
| ≥25.0            | 55           | 54 (98.2%)  | 1 (1.8%)    |     |         |
| Serum albumin    |              |             |             |     |         |
| <40g/L           | 125          | 110 (88.0%) | 15 (12.0%)  | 2.835  | 0.092 |
| ≥40g/L           | 490          | 454 (92.7%) | 36 (7.3%)   |     |         |
| Thoracotomy      |              |             |             | <0.001 | 0.983 |
| Left             | 156          | 143 (91.7%) | 13 (8.3%)   |     |         |
| Right            | 459          | 421 (91.7%) | 38 (8.3%)   |     |         |
| Resection margin |              |             |             | 0.003  | 0.957 |
| Radical          | 590          | 541 (91.7%) | 49 (8.3%)   |     |         |
| Palliative       | 25           | 23 (92.0%)  | 2 (8.0%)    |     |         |
| Postoperative morbidity | |             |             | 0.167  | 0.683 |
| Yes              | 51           | 46 (90.2%)  | 5 (9.8%)    |     |         |
| No               | 564          | 518 (91.8%) | 46 (8.2%)   |     |         |
| pT category      |              |             |             |     |         |
| pT1              | 73           | 69 (94.5%)  | 4 (5.5%)    | 6.423  | 0.093 |
| pT2              | 101          | 97 (96.0%)  | 4 (4.0%)    |     |         |
| pT3              | 369          | 336 (91.1%) | 33 (8.9%)   |     |         |
| pT4              | 72           | 62 (86.1%)  | 10 (13.9%)  |     |         |
| pN category      |              |             |             |     |         |
| pN0              | 283          | 265 (93.6%) | 18 (6.4%)   | 5.419  | 0.144 |
| pN1              | 206          | 187 (90.8%) | 19 (9.2%)   |     |         |
| pN2              | 99           | 90 (90.9%)  | 9 (9.1%)    |     |         |
| pN3              | 27           | 22 (81.5%)  | 5 (18.5%)   |     |         |
| pTNM stage       |              |             |             | 5.258  | 0.154 |
| I                | 75           | 72 (96.0%)  | 3 (4.0%)    |     |         |
| II               | 150          | 140 (93.3%) | 10 (6.7%)   |     |         |
| III              | 308          | 281 (91.2%) | 27 (8.8%)   |     |         |
| IVA              | 82           | 71 (86.6%)  | 11 (13.4%)  |     |         |
| Multiple primary malignancies | |             |             | 10.808 | 0.001 |
| Yes              | 22           | 16 (72.7%)  | 6 (27.3%)   |     |         |
| No               | 593          | 548 (92.4%) | 45 (7.6%)   |     |         |
| Adjuvant therapy |              |             |             |     |         |
| Yes              | 168          | 146 (89.0%) | 18 (11.0%)  | 2.117  | 0.146 |
| No               | 447          | 418 (92.7%) | 33 (7.3%)   |     |         |

BMI, body mass index; MCV, mean corpuscular volume.
MCV was an independent negative prognostic factor. Our current study reported a similar result. The 5-year OS and CSS for patients with high MCV were significantly lower than those for patients with low MCV, and MCV was found to be an independent prognostic factor for patients with ESCC after esophagectomy.

Alcohol and tobacco abuse are leading risk factors for death globally and have been found to be correlated with multiple carcinomas, including ESCC (18–21). Elevated MCV has been recognized as a biomarker for habitual alcohol and tobacco abuse (22, 23). Our study also found that elevated MCV was more often seen in patients with alcohol and tobacco consumption, especially in patients with a higher alcohol or smoking index.

Although MCV has been reported to be correlated with the survival of patients with esophageal carcinoma, no studies have investigated the prognostic value of MCV in ESCC patients who had habitual alcohol or tobacco abuse. To the best of our knowledge, our study is the first to demonstrate that MCV was correlated with survival only in ESCC patients with habitual alcohol or tobacco use.

**TABLE 2 |** Univariate analysis in regard to overall survival and cancer-specific survival according to clinicopathological factors.

| Variable | 5-yr OS (%) | P value | 5-yr CSS (%) | P value |
|----------|-------------|---------|--------------|---------|
| Sex      |             |         |              |         |
| Male     | 60.2        | 0.126   | 60.2         | 0.130   |
| Female   | 68.8        |         | 68.8         |         |
| Age (yr) |             |         |              |         |
| ≤60      | 61.3        | 0.760   | 61.3         | 0.982   |
| >60      | 63.2        |         | 63.2         |         |
| Tumor location |     |         |              |         |
| Upper third | 60.5      | 0.555   | 60.5         | 0.514   |
| Middle third | 63.5      |         | 63.5         |         |
| Lower third | 58.1      |         | 58.1         |         |
| Anemia   |             |         |              |         |
| Yes      | 61.9        | 0.599   | 61.9         | 0.595   |
| No       | 62.3        |         | 62.3         |         |
| Habitual tobacco use | |         |              |         |
| Yes      | 60.4        | 0.357   | 60.4         | 0.341   |
| No       | 66.2        |         | 66.2         |         |
| Habitual alcohol use | |         |              |         |
| Yes      | 63.4        | 0.104   | 63.4         | 0.091   |
| No       | 64.5        |         | 64.5         |         |
| Tumor length |           |         |              |         |
| ≤5cm    | 66.6        | <0.001  | 66.6         | <0.001 |
| >5cm    | 51.9        |         | 51.9         |         |
| Histologic grade |       |         |              |         |
| Well    | 66.0        | 0.245   | 66.0         | 0.292   |
| Moderate | 59.7        |         | 59.7         |         |
| Poor    | 63.4        |         | 63.4         |         |
| BMI     |             |         |              |         |
| ≤18.5   | 57.0        | 0.130   | 57.0         | 0.105   |
| 18.5-24.9 | 62.5      |         | 62.5         |         |
| ≥25.0   | 71.5        |         | 71.5         |         |
| Serum albumin |           |         |              |         |
| <40g/L  | 51.8        | 0.008   | 51.8         | 0.013   |
| >40g/L  | 64.9        |         | 64.9         |         |
| Thoracotomy |           |         |              |         |
| Left    | 54.5        | 0.004   | 54.5         | 0.005   |
| Right   | 64.8        |         | 64.8         |         |
| Resection margin |       |         |              |         |
| Radical | 63.7        | <0.001  | 63.7         | <0.001 |
| Palliative | 22.7      |         | 22.7         |         |
| Postoperative morbidity | |         |              |         |
| Yes     | 60.5        | 0.559   | 60.5         | 0.448   |
| No      | 62.3        |         | 62.3         |         |
| pT category |           |         |              |         |
| pT1     | 88.2        | <0.001  | 88.2         | <0.001 |
| pT2     | 65.6        |         | 65.6         |         |
| pT3     | 61.5        |         | 61.5         |         |
| pT4     | 35.3        |         | 35.3         |         |
| pN category |           |         |              |         |
| pN0     | 77.7        | <0.001  | 77.7         | <0.001 |
| pN1     | 57.6        |         | 57.6         |         |
| pN2     | 39.7        |         | 39.7         |         |
| pN3     | 21.2        |         | 21.2         |         |
| pTNM stage |           |         |              |         |
| I       | 89.2        | <0.001  | 89.2         | <0.001 |
| II      | 75.2        |         | 75.2         |         |
| III     | 58.4        |         | 58.4         |         |
| IV/A    | 28.5        |         | 28.5         |         |
| Multiple primary malignancies | |         |              |         |
| Yes     | 28.8        | 0.003   | 28.8         | 0.004   |
| No      | 63.6        |         | 63.6         |         |
| Adjuvant therapy |       |         |              |         |
| Yes     | 63.9        | 0.165   | 63.9         | 0.189   |
| No      | 61.4        |         | 61.4         |         |
| MCV     |             |         |              |         |
| ≤100fl | 64.1        | <0.001  | 64.1         | 0.001   |
| >100fl | 41.3        |         | 41.3         |         |

BMI, body mass index; CSS, cancer-specific survival; MCV, mean corpuscular volume; OS, overall survival.
and not in patients without. Combined with the fact that MCV is more often found in patients with heavy alcohol or tobacco consumption, we can assume that MCV is not only a biomarker for habitual alcohol and tobacco abuse, but also a prognostic factor for ESCC patients with alcohol or tobacco consumption. When we use MCV as a prognostic factor for patients with ESCC, alcohol and tobacco consumption should be taken into account. We think that more studies should be conducted to confirm our findings.

The mechanism by which elevated MCV leads to a poor prognosis of ESCC patients with alcohol or tobacco consumption is still not clear, but there are several possible explanations. First, elevated MCV is always correlated with malnutrition due to a rough lifestyle. In our current study, we found that elevated MCV was more often found in patients with lower BMI, which was an indicator of malnutrition. Previous studies found that malnutrition might be correlated with poor survival in patients with ESCC (24–26). Second, elevated MCV is more often seen in patients with high alcohol or smoking index. Recent study showed that heavy drinking (>60g per day) represented the largest burden of alcohol-attributable cancer death globally, while esophageal cancer was the most common alcohol-attributable cancer (21). Third, patients with elevated MCV might have a higher incidence of

### TABLE 3 | Multivariate analysis in regard to overall survival and cancer-specific survival of the 615 patients with esophageal squamous cell carcinoma.

| Prognostic factor                   | Hazard ratio | 95%CI       | P value |
|-------------------------------------|--------------|-------------|---------|
| Overall survival                    |              |             |         |
| Tumor length                        | 1.120        | 0.833-1.507 | 0.452   |
| Serum albumin                       | 0.875        | 0.638-1.200 | 0.407   |
| Thoracotomy                         | 0.555        | 0.414-0.743 | <0.001  |
| Resection margin                    | 2.904        | 1.605-5.157 | <0.001  |
| pT1 category                        | 1.511        | 1.130-2.020 | 0.005   |
| pN category                         | 1.821        | 1.437-2.308 | <0.001  |
| pTNM stage                          | 0.890        | 0.621-1.274 | 0.523   |
| Multiple primary malignancies       | 1.306        | 0.723-2.300 | 0.377   |
| MCV                                 | 1.546        | 1.042-2.318 | 0.032   |
| Cancer-specific survival            |              |             |         |
| Tumor length                        | 1.068        | 0.791-1.441 | 0.668   |
| Serum albumin                       | 0.850        | 0.619-1.167 | 0.314   |
| Thoracotomy                         | 0.547        | 0.407-0.735 | <0.001  |
| Resection margin                    | 2.977        | 1.673-5.296 | <0.001  |
| pT1 category                        | 1.477        | 1.101-1.981 | 0.009   |
| pN1 category                        | 1.845        | 1.453-2.342 | <0.001  |
| pTNM stage                          | 0.915        | 0.637-1.315 | 0.632   |
| Multiple primary malignancies       | 1.298        | 0.717-2.349 | 0.389   |
| MCV                                 | 1.569        | 1.056-2.358 | 0.019   |

CI, confidence interval; MCV, mean corpuscular volume.

### FIGURE 2

(A) Kaplan-Meier curves for overall survival of the patients with habitual alcohol use according to mean corpuscular volume. The survival difference was significant (P = 0.001).

(B) Kaplan-Meier curves for cancer-specific survival of the patients with habitual alcohol use according to mean corpuscular volume. The survival difference was significant (P = 0.001).

(C) Kaplan-Meier curves for overall survival of the patients without habitual alcohol use according to mean corpuscular volume. The survival difference was not significant (P = 0.986).

(D) Kaplan-Meier curves for cancer-specific survival of the patients without habitual alcohol use according to mean corpuscular volume. The survival difference was not significant (P = 0.993).
multiple primary malignancies. In our study, six of the 51 patients (11.8%) in the high MCV group developed multiple primary malignancies, while only 2.8% of the patients in the low MCV group developed multiple primary malignancies. A previous study found that the occurrence of multiple primary cancers was associated with poor prognosis in patients with esophageal cancer (27). More studies should be conducted to elucidate the mechanism by which MCV correlates with poor outcomes in ESCC patients.

There are several limitations of this study. First, it was a retrospective study from a single center, which undermined its power. Second, the patient number in some subgroups was too small, which limited the statistical power. For example, there were only two patients with high MCV in the no-habitual-tobacco use group. Third, we did not consider the synergistic effect between alcohol and tobacco in this study, as many patients may consumed both alcohol and tobacco. We think that further studies with larger cohorts are needed to confirm our findings and investigate the mechanism by which MCV relates to the prognosis of ESCC patients.

In conclusion, our study demonstrated that pretreatment MCV was correlated with survival in ESCC patients after esophagectomy. However, its prognostic value might only exist in patients with alcohol or tobacco consumption and not in patients without alcohol or tobacco consumption. Due to the small number of patients with high MCV in the no-habitual-tobacco use group and no-habitual-alcohol use group, we think that a multicenter study with larger cohorts are needed to confirm our findings.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article-supplementary material. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Shantou University Medical College Cancer Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

S-jH and P-fZ contributed equally to this article. S-bC designed the research, analyzed the data and wrote part of the paper. S-jH and P-fZ analyzed the data and wrote part of the paper. All authors contributed to the article and approved the submitted version.
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