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***Retrospective Study***

**Evaluation of the 7th edition of the TNM classification in patients with resected esophageal squamous cell carcinoma**

Wang J *et al.* An assessment from a single institution

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**Abstract**

**AIM:** To evaluate the prognostic factors and tumor stages of the 7th edition TNM classification for esophageal cancer.

**METHODS:** In total, 1033 patients with esophageal squamous cell carcinoma (ESCC) who underwent surgical resection with or without (neo)adjuvant therapy between January 2003 and June 2012 at the Thoracic Surgery Department II of the Beijing Cancer Hospital, Beijing, China were included in this study. The following eligibility criteria were applied: (1) squamous cell carcinoma of the esophagus or gastroesophageal junction identified by histopathological examination; (2) application of esophagectomy plus lymphadenectomy with curative intent; and (3) complete pathologic reports and follow-up data. Patients who underwent non-curative (R1) resections and patients who died in the hospital were excluded. Patients who received (neo)adjuvant therapy were also included in this analysis. All patients were restaged using the 7th edition of the Union for International Cancer Control and the American Joint Committee on Cancer TNM staging systems. Univariate and multivariate analyses were performed to identify the prognostic factors for survival. Survival curves were plotted using the Kaplan-Meier method, and the log-rank test was used to evaluate differences between the subgroups.

**RESULTS:** Of the 1033 patients included in the study, 273 patients received (neo)adjuvant therapy, and 760 patients were treated by surgery alone. The median follow-up time was 51.6 mo (range, 5-112 mo) and the overall five-year survival rate was 36.4%. Gender, “pT” and “pN” descriptors, (neo)adjuvant therapy and the 7th edition TNM stage grouping were independent prognostic factors in the univariate and multivariate analyses. However, neither the histologic grade nor the cancer location was independent prognostic factors in the univariate and multivariate analyses. The 5-year stage-based survival rates were as follows: IA, 84.9%; IB, 70.9%; IIA, 56.2%; IIB, 43.3%; IIIA, 37.9%; IIIB, 23.3%; IIIC,12.9% and IV, 3.4%. There were significant differences between each adjacent staging classification. Moreover, there were significant differences between each adjacent pN and pM subgroups respectively. According to the pT descriptor, there were significant differences between each adjacent subgroups except between pT3 and pT4 (*P* = 0.405). However, there was no significant difference between each adjacent histologic grade subgroup and between each adjacent cancer location subgroup.

**CONCLUSION:** The 7th edition is considered to be valid for patients with resected ESCC. However, the histologic grade and cancer location were not prognostic factors for ESCC.

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**Key words:** Esophageal squamous cell carcinoma; Staging; Prognosis; Surgery; TNM; Survival

**Core tip:** The 7th edition of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) TNM staging system for esophageal and gastroesophageal junction (GEJ) cancer is the first data-driven staging system for esophageal and GEJ cancers. It is based on the Worldwide Esophageal Cancer Collaboration database, which includes 4627 patients from a large multi-institutional collaboration involving of 13 institutions and the data period ranges from the 1970s to 2000s. Therefore, the surgical procedures, pathologic examinations, and patient follow-up can vary greatly between different institutions, resulting in inevitable bias. In this retrospective study, we used a large cohort of patients who have undergone potentially curative surgery for ESCC at a single institution to evaluate the predictive ability of the 7th edition UICC-AJCC TNM staging system.

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**INTRODUCTION**

The present (7th) edition of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) TNM staging system for esophageal cancer was released in late 2009. This edition adopted new factors associated with survival, including the number of cancer-positive lymph nodes, histopathologic cell type, histologic grade and cancer location. The main modifications in the 7th edition are summarized below. (1) T1 is subclassified into T1a (lamina propria or muscularis mucosae) and T1b (submucosa), whereas T4 is subclassified into T4a (pleura, pericardium, diaphragm, or adjacent peritoneum) and T4b (other adjacent structures, *e.g.,* aorta, vertebral body, trachea); (2) N is subclassified according to the number of regional lymph nodes involved (N1, 1 to 2 nodes; N2, 3 to 6 nodes; and N3, ≥ 7 nodes); (3) two new prognostic factors (the histologiic grade and the cancer location) are incorporated; and (4) the stage groups have been adjusted, and separate stage groups are used for squamous cell carcinoma and adenocarcinoma[1,2].

The large database upon which the 7th edition is based was created by 13 institutions on 3 continents and the data period ranges from the 1970s to 2000s; therefore, the surgical procedures, pathologic examinations, and patient follow-up can vary greatly between different institutions, resulting in inevitable bias[3]. In this retrospective study, we aimed to use a large cohort of patients who have undergone potentially curative surgery, with or without (neo)adjuvant therapy for ESCC, at a single institution to evaluate the predictive ability of the 7th edition UICC-AJCC TNM staging system.

**MATERIALS AND METHODS**

***Patients***

The Institutional Review Board at Peking University Cancer Hospital approved this retrospective study, the requirement for patient consent was waived. All patients who underwent esophagectomy from January 2003 to June 2012 at the Thoracic Surgery Department II of the Beijing Cancer Hospital, Beijing, China, were reviewed (*n* = 1086). The following eligibility criteria were applied: (1) squamous cell carcinoma of the esophagus or gastroesophageal junction identified by histopathological examination; (2) application of esophagectomy plus lymphadenectomy with curative intent; and (3) complete pathologic reports and follow-up data. Patients who underwent non-curative (R1) resections and patients who died in the hospital were excluded. Patients who received neo(adjuvant) therapy were also included in this analysis. Physical examinations, laboratory tests, esophagogastroduodenoscopy, barium esophagography, computed tomography scans from the neck to the upper abdomen, and abdominal and supraclavicular ultrasound scans were routinely performed to preoperatively evaluate the extent of disease. The surgical procedures used a left or right thoracic approach.

Follow-up

Generally, the patients were postoperatively examined at 3-mo intervals for 2 years, 6-mo intervals for an additional 3 years, and 1-year intervals thereafter to monitor disease recurrence and survival. The survival intervals (overall survival) were calculated from the date of the operation to the date of death or last follow-up.

Statistics

All patients were restaged using the 7th edition of the UICC-AJCC TNM staging systems. Survival curves were plotted using the Kaplan-Meier method, and the log-rank test was used to evaluate differences between the subgroups. Univariate and multivariate Cox proportional hazards modeling were used to evaluate the impact of each factor on overall survival. The *P* values for differences were calculated with a significance level of *P* < 0.05. SPSS software (version 16.0; SPSS, Chicago, IL, United States) was used for all analyses.

**RESULTS**

Of the 1033 patients included in the study, 273 patients received (neo)adjuvant therapy, and 760 were treated by surgery alone. Forty-three patients received neoadjuvant chemotherapy and/or neoadjuvant radiotherapy, 255 patients received adjuvant chemotherapy and/or adjuvant radiotherapy, and 25 patients received both neoadjuvant and adjuvant chemotherapy and/or radiotherapy. The patient characteristics and 5-year survival results are summarized in Table 1. The median follow-up time was 51.6 mo (range, 5-112 mo). The overall five-year survival rate was 36.4%.

The 5-year survival rates and the survival curves by pT, pN and pM are shown in Figure 1. With respected to the pN and pM descriptors, there were significant differences between each adjacent subgroups. According to the pT descriptor, there were significant differences between each adjacent subgroups except betweenpT3 and pT4 (*P* = 0.405). The 5-year survival rates and the survival curves by the new incorporated descriptors in the 7th edition, pG (histologic grade) and cancer location are shown in Figure 2. According to the histologic grade and cancer location, there was no significant difference between each adjacent subgroups( With regard to the histologic grade, between G1 and G2, *P* = 0.577, between G2 and G3, *P* = 0.104; With respect to the cancer location, between upper and middle, *P* = 0.075, between middle and lower, *P* = 0.302). The 5-year survival rates and the survival curves by pStage grouping according to the 7th edition of the TNM classification are shown in Figure 3, there were significant differences between each adjacent subgroups.

Univariate analysis revealed that gender (*P* = 0.046), age (*P* = 0.039), cigarette smoking (*P* = 0.027), (neo)adjuvant therapy (*P* < 0.001) and the “pT” (*P* < 0.001), “pN” (*P* < 0.001) and “pM” (*P* < 0.001) descriptors and the 7th edition TNM stage grouping significantly affected patient survival, but neither histologic grade nor cancer location showed any significance in terms of survival (*P* = 0.130 and *P* = 0.067, respectively). The multivariate Cox regression model was performed by incorporating gender, age, cigarette smoking, (neo)adjuvant therapy, the “pT”, “pN”, “pM” descriptors, histologic grade, cancer location, and the 7th edition TNM stage grouping. Gender, “pT” and “pN” descriptors, (neo)adjuvant therapy and the 7th edition TNM stage grouping remained as independent prognostic factors. However, cigarette smoking and the “pM” descriptor, which were significant prognostic factors in the univariate analysis, did not significantly influence patient survival in the multivariate analysis (Table 2).

Table 3 presents the univariate and multivariate analyses for the 7th edition TNM stage grouping. The multivariate analyses revealed significant differences between each adjacent pStage, except for between pStageIB and IIA (*P* = 0.129). The hazard ratios for stages IB and IIA disease (referred to as pStage IA disease) were 3.013 and 2.368, respectively.

**DISCUSSION**

In Asia, ESCC is one of the most common and aggressive diseases[4]. A robust staging system is important for ESCC patients in terms of planning treatments, estimating prognoses, evaluating the end results of therapy, and providing a standardized nomenclature to facilitate information exchange between treatment centers.

The 7th edition supports the continued use of the accepted T major stages (I, II, III, and IV) in the 6th edition[1]. In our series, which included few pT4 patients, the high prognostic value of the pT1-pT3 subclassification is significantly confirmed. However, the survival of pT4 patients was similar to that of pT3 patients, likely because of the small number of pT4 patients in our study.

Based on the evidence of survival differences, T1 is subclassified as T1a (tumor limited in the mucosa) and T1b (tumor in the submucosa), and T4 is subclassified as T4a (tumor invading adjacent, resectable structures) and T4b (tumor invading adjacent, unresectable structures) in the 7th edition. Rice *et al*[5] and Wijnhoven *et al*[6] reported that T1a patients have a higher survival rate than T1b patients. Moreover, Sepesi *et al*[7] observed differences in the lymph node metastasis rate between T1a and T1b patients. Because treatment strategies for esophageal cancer are based on a precise staging system of esophageal cancer, some of these changes to the descriptors may influence therapy decisions[8].

The refinement of the N classification to N0-N3, which is based on the number of positive regional lymph nodes, is one of the major modifications of the 7th edition[1]. Many investigators have reported that subdividing the “N” classification based on the absolute number of involved lymph nodes may yield better survival stratifications[9,10]. In our analyses of patient prognoses using the pN classification, there were clear differences between each adjacent pN subgroup, which significantly confirmed the high prognostic value of the pN subclassification in the 7th edition.

The M descriptor is a prognostic factor in univariate factor Cox analyses but not in multivariate factor Cox analyses. Because few patients in our study had distant metastases, we cannot exclude the possibility that the discrepancy is caused by the small pM1 sample size.

Male gender, advanced age, cigarette smoking and (neo)adjuvant therapy have been shown to be associated with poor survival[11-16]. In our series, gender and (neo)adjuvant therapy significantly influenced patient survival, as revealed by Univariate and multivariate analyses. However, age and cigarette smoking were shown to be prognostic factors in the univariate factor Cox analyses but not in the multivariate factor Cox analyses, which suggests that age and cigarette smoking were not strong prognostic factors in ESCC patients.

Another major modification of the 7th edition was the incorporation of two new descriptors: histologic grade and cancer location[1]. Working with T, N, and M descriptors, these two new descriptors help to subclassify T2-3N0M0 patients into stages IB, IIA, and IIB. In the 7th edition, patient survival improves as the histologic grade changes from G3 to G1 and/or the cancer location moves from the upper esophagus to the lower esophagus[1,2]. However, according to our analysis, the histologic grade and cancer location are not independent prognostic factors. In fact, the roles of the histologic grade and cancer location in ESCC patient survival were inconsistent among different studies. Although the histologic grade had been shown to be a strong predictor of survival in perijunctional esophagogastric carcinoma[17], Wijnhoven *et al*[6] (2007) and Eloubeidi*et al*[13] (2002) reported that histologic grade is not significantly related to survival. Moreover, many investigators have reported that the histologic grade is not a prognostic factor in ESCC[11,14,18,19].

The results concerning the cancer location are also controversial. Some investigators have found that survival improves as the tumor moves distally in the esophagus[20]; on the contrary, other researchers have demonstrated that survival is worse in patients whose tumors are located in the lower thoracic portions of the esophagus[13]. Still other investigators have reported that the upper, middle, and lower locations of thoracic esophageal cancer yield similar survival rates[21]. Situ and colleagues explained that one possible reason for this discrepancy is a variation in the experience of the pathologists and endoscopic laboratory doctors from various institutes or the different definitions of tumor segmentation in the 6th edition of the UICC-AJCC cancer staging manual, as the 7th staging system had not yet been published[14]. In addition to the above reasons, we believe that differences in the biological behaviors of ESCC and esophageal adenocarcinoma might also be responsible for the inconsistent results.

In conclusion, our survival characteristics of 1033 patients with resected ESCC in a single institution validated the 7th edition of the UICC-AJCC TNM staging system for esophageal cancer. This edition may clearly differentiate the survival rates between patients in different stages; furthermore, the revised N classification provides prognostic power, and the refinement of the T group may be referenced when determining treatment options. In addition, we demonstrated that gender and (neo) adjuvant therapy are important prognostic factors for patient survival. However, we found that the histologic grade and the cancer location are not important prognostic factors for ESCC patient survival.

**COMMENTS**

***Background***

Esophageal squamous cell carcinoma (ESCC) is one of the most common and aggressive diseases in Asia. The present (7th) edition of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) TNM staging system for esophageal cancer was released in late 2009. This edition adopted new factors associated with survival, including the number of cancer-positive lymph nodes, histopathologic cell type, histologic grade and cancer location.

***Research frontiers***

Nowadays, there are controversal on if the histologic grade and cancer location should be incorporated in the new staging system of easophageal cancer, and some scholars suggested to adopt some other new descriptors into the staging system, such as (neo)adjuvante therapy.

***Innovations and breakthroughs***

Our research is the first retrospective study to use a large cohort of patients with ESCC at a single institution to evaluate the predictive ability of the 7th edition UICC-AJCC TNM staging system for esophageal and gastroesophageal junction cancer.

***Applications***

This results validated the 7th edition staging system for esophageal cancer. Moreover, we demonstrated that gender and (neo) adjuvant therapy are important prognostic factors for patient survival. However, we found that the histologic grade and the cancer location are not important prognostic factors for ESCC patient survival.

***Terminology***

Squamous cell carcinoma (SCC) is the main histopathologic cell type in esophageal cancer in the East, the histopathologic cell type of more than 90% esophageal cancer patient in the East is SCC. Many reports have showed that there are remarkable differences between ESCC and esophageal adenocarcinoma.

***Peer review***

The manuscript is an interesting study, which validated the 7th edition of the TNM classification in patients with this disease.

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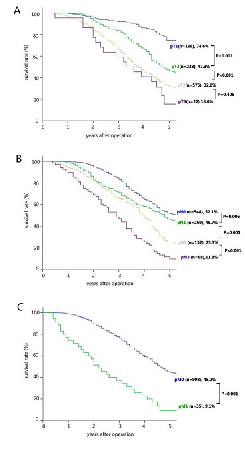
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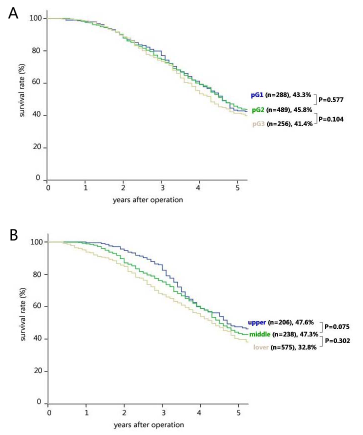
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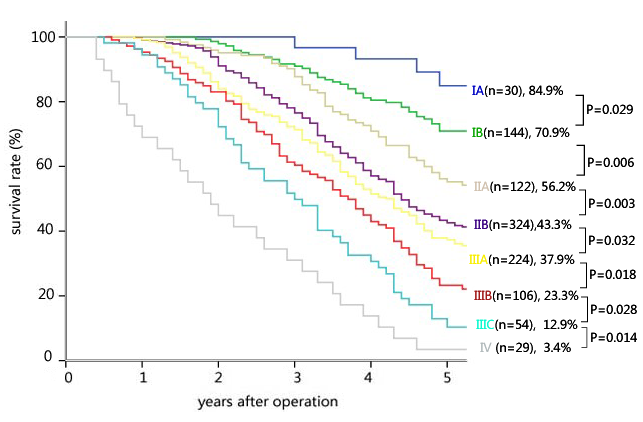
**Figure 1 Survival curves for patient subgroups stratified based on pT, pN and pM descriptors according to the 7th edition, the 5-year survival rate and the number of patients in each subgroup, and the P value between each adjacent subgroup are indicated.** A: With respected to the pT descriptor, there were significant differences between each adjacent subgroups except between pT3 and pT4 (*P* = 0.405); B: With respected to the pN descriptor, there were significant differences between each adjacent subgroups; C: With respected to the pM descriptor, there were significant differences between pM0 and pM1.



**Figure 2 Survival curves for patient subgroups stratified based on pG(histologic grade) and cancer location according to the 7th edition, the 5-year survival rate and the number of patients in each subgroup, and the P value between each adjacent subgroup are indicated.** A: With respected to the pG, there was no significant difference between each adjacent pG classification; B: With respected to the cancer location, there was no significant difference between each adjacent caner location classification.



**Figure 3 Survival curves for patient subgroups stratified according to the 7th edition TNM pStage groupings.** The 5-year survival rate and the number of patients in each subgroup, and the P value between each adjacent subgroupwere indicated. The survival curves showed stepwise deterioration as the pStage increased and there were significant differences between each adjacent pStage group.



**Table 1 Patient demographics and 5-year survival results *n* (%)**

|  |  |  |
| --- | --- | --- |
| **Characteristic** | **Value** | **5-yr survival** |
| Gender  Male  Female | 793 (76.8)  240 (23.2) | 43.1%  47.2% |
| Age, yr  Median (range)  ≤ 60 yr  > 60 yr | 63 (27–81)  688 (66.6)  345 (33.4) | 44.6%  42.9% |
| Cigarette smoking  Yes  No | 544 (52.7)  489 (47.3) | 42.7%  45.5% |
| Alcohol consumption  Yes  No | 272 (26.3)  761 (73.7) | 43.6%  44.1% |
| pT  1  2  3  4 | 198(19.2)  238 (23.0)  575 (55.7)  22(2.1) | 74.6%  47.3%  32.8%  15.6% |
| pN  0  1  2  3 | 544 (52.7)  269 (26.0)  152 (14.7)  68 (6.6) | 52.1%  46.7%  25.3%  11.8% |
| pM  0  1 | 998 (96.6)  35 (3.4) | 45.2%  9.1% |
| Histologic grade  Well differentiated (G1)  Moderately differentiated (G2)  Poorly differentiated (G3) | 288 (27.9)  489(47.3)  256(24.8) | 43.3%  45.8%  41.4% |
| Cancer location  Upper thoracic  Middle thoracic  Lower thoracic + EGJ | 206(19.3)  603 (58.6)  224 (22.2) | 47.6%  44.2%  40.3% |
| Type of Surgical approach  Left thoracic  Right thoracic | 126 (12.2)  907 (87.8) | 40.4%  44.5% |
| Length of tumor  Mean (range)  ≤ Mean  > Mean | 3.4cm（0.4-15.0cm）  689 (66.7)  344 (33.3) | 44.1%  43.9% |
| Stage  ⅠA  ⅠB  ⅡA  ⅡB  ⅢA  ⅢB  ⅢC  Ⅳ | 30 (2.9)  144 (13.9)  122 (11.8)  324 (31.4)  224 (21.7)  106 (10.3)  54 (5.2)  29 (2.8) | 84.9%  70.9%  56.2%  43.3%  37.9%  23.3%  12.9%  3.4% |
| (neo) adjuvant therapy  No  Yes | 760 (73.6)  273 (26.4) | 49.8%  30.3% |

**Table 2 Univariate and multivariate analyses of factors**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Univariate** | | | **Multivariate** | | |
|  | **HR** | **95% CI** | ***P*** | **HR** | **95% CI** | ***P*** |
| Gender  Male  Female | 1.000  0.829 | 0.690-0.996 | 0.046 | 1.000  1.333 | 1.091-1.629 | 0.005 |
| Age, yr  ≤ 60 yr  > 60 yr | 1.000  1.183 | 1.009-1.390 | 0.039 | 1.000  0.999 | 0.840-1.190 | 0.995 |
| Cigarette smoking  No  Yes | 1.000  1.190 | 1.019-1.388 | 0.027 | 1.000  0.949 | 0.805-1.119 | 0.537 |
| Alcohol consumption  No  Yes | 1.000  1.070 | 0.903-1.268 | 0.431 |  |  |  |
| (neo) adjuvant therapy  No  Yes | 1.000  1.634 | 1.386-1.927 | < 0.001 | 1.000  1.330 | 1.102-1.606 | 0.003 |
| pT  1  2  3  4 | 1.000  2.487  4.186  5.154 | 1.856-3.331  3.219-5.444  3.015-8.812 | < 0.001  < 0.001  < 0.001 | 1.000  1.982  2.303  1.150 | 1.254-3.132  1.437-3.693  0.518-2.549 | 0.003  0.001  0.732 |
| pN  0  1  2  3 | 1.000  1.294  1.939  3.500 | 1.073-1.560  1.567-2.399  2.650-4.624 | 0.007  < 0.001  < 0.001 | 1.000  0.361  0.290  0.122 | 0.242-0.538  0.145-0.580  0.047-0.314 | < 0.001  < 0.001  < 0.001 |
| pM  0  1 | 1.000  3.392 | 2.359-4.875 | < 0.001 | 1.000  0.789 | 0.231-2.689 | 0.704 |
| Histologic grade  G1  G2  G3 | 1.000  1.054  1.227 | 0.875-1.271  0.995-1.513 | 0.578  0.056 | 1.000  0.917  0.874 | 0.724-1.161  0.681-1.123 | 0.472  0.292 |
| Cancer location  Upper thoracic  Middle thoracic  Lower thoracic + EGJ | 1.000  1.201  1.326 | 0.977-1.476  1.043-1.685 | 1.201  1.326 | 1.000  0.808  1.027 | 0.634-1.031  0.758-1.392 | 0.086  0.862 |
| Type of Surgical approach  Right thoracic  Left thoracic | 1.000  1.149 | 0.912-1.448 | 0.238 |  |  |  |
| Length of tumor  ≤ Mean  > Mean | 1.000  1.075 | 0.916-1.262 | 0.374 |  |  |  |

**Table 3 Univariate and multivariate analyses of the 7th edition of the TNM classification**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Univariate** | | | **Multivariate** | | |
|  | **HR** | **95% CI** | ***P*** | **HR** | **95% CI** | ***P*** |
| Stage  ⅠA  ⅠB  ⅡA  ⅡB  ⅢA  ⅢB  ⅢC  Ⅳ | 1.000  2.919  4.771  7.251  9.062  12.314  18.288  33.720 | 1.059-8.048  1.737-13.103  2.695-19.508  3.359-24.450  4.514-33.591  6.583-50.804  11.799-96.369 | 0.038  0.002  < 0.001  < 0.001  < 0.001  < 0.001  < 0.001 | 1.000  3.013  2.368  6.472  15.152  23.933  89.566  147.116 | 1.065-8.530  0.779-7.198  2.083-20.108  4.282-53.616  4.960-88.354  18.855-425.471  21.759-994.681 | 0.038  0.129  0.001  < 0.001  < 0.001  < 0.001  < 0.001 |