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Total Oxidant/Antioxidant Status in Sera of Patients with Esophageal Cancer

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Background: Oxidative stress parameters such as total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI) have been studied in breast, thyroid, and simple esophageal cancers (EC). We evaluated these parameters in patients with EC and analyzed their correlations with treatment outcomes.

Material/Method: Serum TOS, TAS, and OSI in 92 patients with EC at different clinical stages and in 64 healthy people (controls) were measured.

Results: Serum TOS, TAS, and OSI were significantly different between patients with EC and healthy controls (all $p<0.001$); however, there were no significant differences across different clinical stages (all $p>0.05$). These factors are not correlated with smoking or drinking history (all $p>0.05$). Patients with EC with higher TOS and OSI and lower TAS had better responses to chemotherapy and/or radiotherapy, but there was no significant correlation with different responses (all $p>0.05$). In a receiver operating characteristic curve analysis comparing patients with EC with healthy controls, the Youden indices were 0.391, 0.886, and 1, respectively.

Conclusions: Serum TOS, TAS, and OSI were significantly different between patients with EC and healthy controls. In patients with EC, these factors were not correlated with smoking or drinking history or with clinical stage. Patients with EC with higher TOS and OSI and lower TAS had a trend towards better outcomes but it did not reach significance. Serum TOS and OSI are potential diagnostic biomarkers that can be used to identify cases of EC.

MeSH Keywords: Antioxidants • Esophageal Neoplasms • Oxidants • Oxidative Stress

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Background

Esophageal cancer (EC) is a common malignancy worldwide. A global cancer investigative report in 2012 showed that the incidence and mortality age-standardized rates per 100 000 men were 6.4 and 5.2, respectively, in more developed countries, and 10.1 and 9.0, respectively, in less developed countries. For women, the relative statistics were 1.2 and 0.9, and 4.1 and 3.6, respectively [1]. In China in 2015, the total incidence and mortality rates of EC were 477.9 and 375.0 per 100 000 persons, respectively. [2]. The high incidence and mortality rates of EC places a serious burden on society and results in poor quality of life and morbidity of patients. However, the etiology of EC is unclear. A better understanding of the etiology can help monitor and treat EC.

The concept of oxidative stress, which was established by Helmut in 1985, is a condition that occurs when the generation of reactive oxygen species (ROS) exceeds the ability of cells to neutralize and eliminate them [3]. Cellular metabolisms can produce ROS, and many factors can cause ROS to accumulate or be metabolized more slowly, such as disturbances in their production, distribution, or environmental stressors. Excess ROS can damage proteins or DNA, thus affecting signal transduction pathways and normal cellular function [4]. Antioxidants, including natural or synthetic molecules and enzymatic or non-enzymatic compounds, play a role in preventing the harmful consequences of oxidative stress [5]. If ROS and antioxidants are balanced, the body is maintained in a healthy status; if not, the imbalance can result in many diseases, not only cardiovascular and neurodegenerative diseases, but also cancers, along with an accelerated aging process [6].

Oxidative stress plays a key role in the development of cancers. Cancer initiation is characterized by changes in DNA, such as point mutations or chromosomal aberrations [7]. Increased levels of oxidative DNA lesions have been shown to be involved in the etiology of many cancers [8]. Exposure to chemical carcinogens and ionizing radiation are the most common causes of genome integrity loss, and both carcinogens and radiation are potential sources of ROS that have detrimental roles in damaging DNA. ROS can lead to the production of C5-OH and C6-OH adducts of pyrimidines, alkyl radical formations in thymine [9], double- or single-strand breaks by reacting with the sugar moiety of DNA, and protein-DNA cross-links and intra-strand cross-links [10]. Altogether, these effects may lead to chromosomal rearrangements and mutations [11]. Oxidative stress is related to the generation and development of many cancers, such as breast cancer, lung cancer, prostate cancer, and thyroid carcinoma [11–14].

Oxidative stress parameters such as total oxidant status (TOS), total antioxidant status (TAS), and oxidative stress index (OSI) have been studied in breast and thyroid cancers [15–17]. Studies on the function of oxidative stress systems in the generation of EC are limited [18,19]. To address this, we evaluated serum TOS, TAS, and OSI in patients with EC and in healthy controls, and analyzed the correlations of these parameters with treatment outcomes.

Material and Methods

Subjects

Ninety-two patients with EC and 64 healthy controls were enrolled in the study. The diagnosis of the patients was made based on symptoms, pathological biopsy, computed tomography scan, and gastrointestinal barium examination, and the stage of EC was classified by the standard of clinical staging for non-operative treatment of EC [20]. Patients with other diseases such as hypoglycemia, gout, liver diseases, rheumatoid arthritis, diabetes mellitus, and thyroid disease were excluded because these diseases could be confounding variables. Sixty-nine patients received chemotherapy and/or radiotherapy, and their responses to treatment were collected.

The study was approved by the Medical Ethics Committee of MianYang Central Hospital. All blood draws were obtained with the consent of the patients. Written informed consent from the donors or the next of kin was obtained for use of the blood samples for research purposes.

Blood samples

All of the patients and healthy controls fasted for at least 12 h before blood collection. The next morning, blood was collected and analyzed within 48 h. The blood was collected after their diagnosis but before any treatment. About 5 mL of blood was drawn into a vacuum blood collection tube (Becton-Dickinson, USA) for measurement of TAS and TOS. One hour later, the blood samples were centrifuged for 15 min at 3000 rpm, and the serum samples were stored at -30°C.

TAS determination

The Total Antioxidant Status kit (Randox Laboratories, UK) was used to measure TAS [18]. The serum samples were incubated at 37°C with the chromogen for 10 min, and 600-nm optical density was used to measure the amount of $ABTS^{+}$ formation. The antioxidant concentration in the sample and the decrease in optical density are in a direct ratio. A sample with a known concentration (1.65 mmol/L) was used as the standard for calculation of antioxidant levels. Mmol Trolox equivalent/L was used to express the values of TAS.

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TOS determination

Erle's method was used to measure serum TOS [21]. This method uses xylenol orange to measure ferric ions, which is an oxidized form of ferrous ions in an acidic medium. The results of the assay are expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H2O2 Equiv/L). The method includes 2 reagents, and the volume of serum, reagent 1, and 2 were 10 μL, 200 μL, and 50 μL, respectively. The temperature was 37°C and the reaction time was 10 min. The main and secondary wavelengths were 560 nm and 800 nm, respectively.

Oxidative stress index

OSI is the ratio of TOS to TAS [21,22]. To perform the calculation, the unit of TAC, mmol Trolox equivalent/L, was changed to μmol Trolox equivalent/L and the OSI value was calculated as follows: OSI=(TOS, μmol/L)/(TAC, μmol Trolox equivalent/L)×100.

Statistical analysis

In analysis of the basic characteristics of the participants, ages were compared using Student's t-test. The sex of the patients and their drinking and smoking history were compared using Pearson's chi-square test. The k-s test was performed to determine whether the data were normally distributed. If the data were skewed, the results were expressed as the median (P25–P75) and they were compared using the Kruskal-Wallis test. The results of the comparison are presented as chi-square (χ^2) statistics. If the data were normally distributed, the results were expressed as the mean ± standard deviation and/or as a range (minimum–maximum). The 2 groups were compared using the Student's t-test and multiple sets of comparisons were performed using analysis of variance (ANOVA) were presented as F values. All statistical tests were two-sided and *p* values less than 0.05 were defined as statistically significant. We performed statistical analysis using SPSS 22.0 statistical software (IBM Corp., Armonk, NY, USA). We used MedCalc statistical software (MedCalc, Mariakerke, Belgium) to draw the receiver operating characteristic (ROC) curves.

Results

Demographics and clinical data of patients and healthy controls are summarized in Table 1. The serum TOS in patients with EC was significantly higher than in controls (p<0.001). The serum TAS in healthy controls was significantly higher than in the patients with EC (p=0.001). There were also significant differences between the groups in OSI (p<0.001) (Table 2). There were no significant differences by clinical stage for TOS (p=0.054) and TAS (p=0.365), but there was for OSI (p=0.037) (Table 3). There were also no significant differences in TOS (P=0.296), TAS (P=0.499), or OSI (p=0.207) between cancer patients with and without smoking histories (Table 3). Similarly, there were no significant differences in TOS (p=0.314), TAS (p=0.181), or OSI (p=0.160) between cancer patients with and without drinking histories (Table 3).

We observed the effects of chemotherapy and/or radiotherapy in 69 patients with EC, and 20, 34, 3, and 12 patients attained complete response, partial response, stable disease, and progressive disease, respectively. Patients with a higher TOS and OSI and a lower TAS had a trend towards better outcomes, but it did not reach statistical significance for TOS (p=0.222), TAS (p=0.895), or OSI (p=0.233) (3).

The diagnostic significance of TAS, TOS, and OSI for EC was analyzed using ROC curve analysis (Figure 1). The area under the curve (AUC) was calculated and the cutoff values, specificity, p values, sensitivity, and Youden indices (YIs) are detailed in Table 4. Compared to healthy controls, the AUC values of TOS, TAS, and OSI were 0.744 (0.668–0.811), 0.969 (0.928–0.990), and 1.000 (0.977–1.000), respectively, and the YIs were 0.391, 0.886, and 1, respectively. The AUC values for all parameters were >0.7. The optimal cutoff value of serum TOS and OSI has a good sensitivity (90.2% and 100%, respectively) and specificity (98.4% and 100%, respectively) for distinguishing between patients with EC and healthy controls

Discussion

Previous research showed that EC is correlated with decreased antioxidant enzyme activities and increased oxidative stress. However, that study had a small sample size and their test biomarkers were different from ours [23]. In the present study, we found that OSI and TOS were higher in patients with EC than in healthy individuals, and TAS of patients with EC was lower. Previous studies have reported that oxidative stress and oxidative DNA damage is related to the initiation and progression of EC [24]. Mitsuteru found that insulin-like growth factor binding protein 3 can promote EC growth by suppressing oxidative stress in the hypoxic tumor microenvironment [25]. Bile acids and low pH can induce oxidative DNA damage in esophageal tissues and cells. These alterations may underlie tumor progression [26]. Te present study showed that oxidative stress may play a key role in the initiation of EC.

The relationship between oxidative stress parameters and clinical stage has been studied in lung cancer, breast cancer, and prostate cancer [13,15,17]. These studies showed that a higher level of oxidative stress was associated with a more advanced clinical stage. In the present study, TOS and OSI increased with increasing clinical stage in stages I–III, and in stage IV, TOS and OSI decreased and TAS increased. However,

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Table 1. Demographics and clinical data of patients and healthy controls.

	Group A patient (n=92)	Group B control (n=64)	p
Age (years) mean ±SD	63.021±10.366	55.343±12.542	0.001
Sex			0.003
Male	65	30	
Female	27	34	
Smoking		0.001	
Yes	43	12	
No	49	52	
Drinking	0.001		
Yes	42	13	
No	50	51	
Clinical stage			
Stage I	1		
Stage II	29		
Stage III	23		
Stage IV	39		
Response to chemotherapy and/or radiotherapy			
CR	20		
PR	34		
SD	3		
PD	12		
Lost to follow up	23		

Table 2. Serum levels of oxidative stress parameters in patients with esophageal cancer (EC) and healthy controls.

	Patients with EC Median (P25~P75)	Control group Median (P25~P75)	p
TOS	19.100 (14.825~22.225)	14.200 (11.800~17.375)	<0.001
TAS	1.355 (1.220~1.460)	1.770 (1.690~1.880)	<0.001
OSI	1.425 (1.070~1.923)	0.800 (0.640~0.988)	<0.001

TOS, TAS, and OSI were not significantly different in different stages. The reasons for this pattern are not clear and may be related to chance, an insufficient number of few cases, or a reduction of oxidative stress in stage IV.

The relationship between oxidative stress parameters and a history of smoking and drinking is contradictory. A significant rise in oxidative stress and low levels of antioxidants has been observed in breast cancer patients with a smoking history [27]. However, smoking and alcohol consumption did not modify the effect of the oxidative stress-modifying genes in pancreatic cancer [28], and no significant interaction was observed between pack-years of smoking and oxidative stress-related genetic polymorphisms in colorectal cancer [29]. In our study, we found smoking and drinking history had no correlation with the parameters of oxidative stress. Many factors can influence the parameters of oxidative stress, and smoking and drinking are not thought to be the major factors influencing EC.

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Table 3. Serum levels of oxidative stress parameters of in patients with esophageal cancer.

	TOS	TAS	OSI
Clinical stages			
I+II (n=1+29)	19.756±6.283	1.345±0.193	1.510±0.585
III (n=23)	22.673±7.178	1.293±0.182	1.813±0.712
IV (n=39)	18.553±6.032	1.363±0.185	1.399±0.550
F	3.012	1.020	3.424
p	0.054	0.365	0.132
Status of smoking			
Smoking history (n=43)	19.291±6.265	1.354±0.188	1.539±0.545
Nonsmoking (n=49)	20.649±6.788	1.327±0.187	1.616±0.677
p	0.296	0.499	0.394
Status of drinking			
Drinking history (n=42)	19.221±6.266	1.368±0.178	1.439±0.557
Non-drinking (n=50)	20.610±6.783	1.315±0.192	1.622±0.664
p	0.314	0.181	0.211
Different responses to chemotherapy and/or radiotherapy			
CR (n=20)	21.795±7.903	1.315±0.181	1.729±0.780
PR (n=34)	19.447±6.217	1.338±0.196	1.510±0.639
SD+PD (n=3+12)	17.906±9.733	1.338±0.187	1.356±0.653
F	1.542	0.111	1.489
p	0.222	0.895	0.478

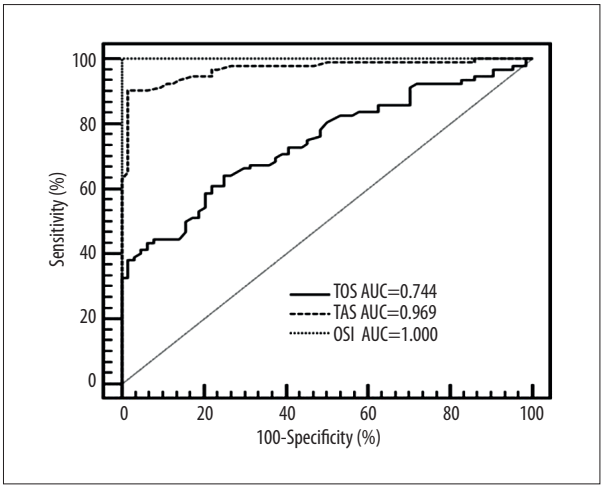

Figure 1. The receiver operating characteristic (ROC) curve analyses of the oxidative stress parameters for esophageal diagnosis. AUC: area under the curve.

Antioxidant enzymes are prognostic factors in Hodgkin lymphoma, prostate cancer, and breast cancer [30–32]. In the present study, we also found that patients with a higher TOS and OSI and a lower TAS had a trend towards better outcomes but it did not reach statistical significance, probably because the number of participants studied was small.

Biomarkers related to oxidative stress can potentially facilitate the development of biomarkers of cancers [38], including prostate cancer and lung cancer [33,34]. In the present study, based on the ROC curve, the optimal cutoff values of serum TOS and OSI had good sensitivity and specificity for EC. This demonstrates that TAS and OSI are potential diagnostic biomarkers that can be used to distinguish patients with EC from healthy individuals. However, additional research is necessary to confirm these findings.

In the present study, compared with healthy controls, serum TAS was significantly lower and TOS and OSI were significantly higher in patients with EC. However, smoking and drinking habits, age, and sex ratio in the EC group were different from those in the healthy controls, which is a limitation of our study. We further analyzed the effects of smoking and drinking habits, age, and sex ratio in the oxidative stress parameters. There were no differences in oxidative stress parameters with regard to age (<60 *vs.* ≥60 years), sex, and smoking or drinking habits (all p>0.05) between patients with EC and healthy controls.

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Table 4. Evaluation of oxidative stress parameters in the diagnosis of esophageal cancer.

	AUC (95%CI)	p	Cutoff	Sensitivity (%)	Specificity (%)	YI
TOS	0.744 (0.668–0.811)	<0.001	17	64.1	75.0	0.391
TAS	0.969 (0.928–0.990)	<0.001	1.56	90.2	98.4	0.886
OSI	1.000 (0.977–1.000)	<0.001	3.44	100	100	1

Conclusions

Serum TOS, TAS, and OSI are significantly different between patients with EC and healthy individuals. However, they do not vary according to clinical stage, smoking history, or drinking history in patients with EC. Patients with higher TOS and OSI and lower TAS had a trend towards better outcomes, but it did not reach the level of statistical significance. The optimal cutoff values of serum TOS and OSI had good sensitivity and specificity for EC. TAS and OSI have the potential to be diagnostic biomarkers that can be used to distinguish patients with EC from healthy individuals.

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