Am J Transl Res 2026;18(1):455-461
www.ajtr.org /ISSN:1943-8141/AJTR0168529

Original Article

Predictive value of the combined application of oxidative stress indicators and carcinoembryonic antigen for patients with early lung adenocarcinoma

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Received September 2, 2025; Accepted December 10, 2025; Epub January 15, 2026; Published January 30, 2026

Abstract: Objectives: To explore the expression levels of oxidative stress indicators and carcinoembryonic antigen (CEA) in different pathologic types of pulmonary ground-glass nodules (GGN) and their predictive value for early lung adenocarcinoma. Methods: This study was a retrospective analysis. General data were collected from 100 patients diagnosed in The Affiliated Taizhou People's Hospital of Nanjing Medical University from February 2022 to May 2024 with GGN in the lungs. According to pathologic types, they were divided into the glandular prodromal lesion group (n=39) and the lung adenocarcinoma group (n=61). The pretreatment levels of CEA, reactive oxygen species (ROS), superoxide dismutase (SOD), and malondialdehyde (MDA) were compared between the two groups. Risk factors for developing early-stage lung adenocarcinoma were screened by univariate versus multivariate logistic regression analysis. The receiver operator characteristic curve (ROC) was used to evaluate the predictive value of each index for early lung adenocarcinoma. Results: Compared to the glandular prodromal lesion group, the levels of ROS, MDA and CEA in the lung adenocarcinoma group were significantly higher, while the level of SOD was significantly lower ($P<0.05$). Multifactorial logistic regression analysis showed that high MDA (OR=7.205, 95% CI: 1.587-32.704), high ROS (OR=3.553, 95% CI: 1.552-8.136), and high CEA (OR=3.241, 95% CI: 1.343-7.818) were risk factors for developing early-stage lung adenocarcinoma (all $P<0.05$) while elevated SOD levels were a protective factor (OR=0.513, 95% CI: 0.328-0.803, $P<0.05$). ROC curve analysis showed that the combined application of tests had the highest predictive efficacy, with an area under the curve (AUC) of 0.887, both higher than those of the single tests. Conclusions: Oxidative stress indicators and CEA show regular changes in GGN. Combined detection can significantly improve the predictive ability for early lung adenocarcinoma.

Keywords: Ground glass nodules, oxidative stress, carcinoembryonic antigen

Introduction

Lung cancer is one of the most common malignant tumors in the world. It is classified into small cell lung cancer and non-small cell lung cancer (NSCLC). Lung adenocarcinoma is the most frequent NSCLC [1]. According to the WHO lung cancer pathology classification of 2021 [2], lung adenocarcinoma is classified into minimally invasive adenocarcinoma (MIA) and infiltrating adenocarcinoma (I-ADC). Compared to the 2015 WHO lung cancer pathologic classification criteria [3], the new classification classifies lung adenocarcinoma in situ (AIS) and atypical adenomatous hyperplasia (AAH) together, as glandular precursor lesions, while the glandular precursor lesions are no longer classified as lung adenocarcinoma. Both lung adenocarcinoma and glandular precursor lesions can present as focal ground glass nodules on imaging. In recent years, the detection rate of GGN has increased with the widespread application of high-resolution computed tomography (HRCT) [4]. GGN is a local nodular lesion with increased density on HRCT images, but the bronchial vascular bundle within it can still be seen, which is a ground glass density shadow. At present, HRCT is the preferred method for examining GGN, but in pathologic types of lung diseases, its discriminatory value is relatively low. GGN have a high incidence and are difficult to detect in the early stage. GGN are highly occult and lack the corresponding specificity. Thus, feasible and valid predictors are needed for the

https://doi.org/10.62347/ZWFW6679

effective treatment of patients with GGN. Related research has demonstrated that oxidative stress occurs in the body in conjunction with the development of many tumors like breast cancer and head and neck cancer [5]. However, the mechanism of oxidative stress in lung adenocarcinoma is still unclear. In addition, since the discovery of CEA in 1965, some scholars have believed that CEA was closely related to lung adenocarcinoma [6]. However, there are relatively few studies on the correlation between the above biomarkers and GGN. Based on this, the hypothesis was proposed: During the evolution of GGNs to lung adenocarcinoma, oxidative stress indicators and CEA levels undergo significant changes, and the combined detection of these indicators has a good predictive value for early lung adenocarcinoma. This study conducted a retrospective analysis aimed at exploring malondialdehyde (MDA), superoxide dismutase (SOD), and reactive oxygen species expression levels, and correlations of ROS and CEA indicators in different pathologic types of GGN to provide guidance for treatment.

Materials and methods

Case selection

This study was retrospective. We collected information on 100 visits of patients with pulmonary ground glass nodules diagnosed in The Affiliated Taizhou People's Hospital of Nanjing Medical University from February 2022 to May 2024. Patients were classified according to the type of pathology, into a glandular precursor lesion group (including 25 cases of AIS patients and 14 cases of AAH patients, n=39) and lung adenocarcinoma group (Including 33 cases of MIA patients and 28 cases of I-ADC patients, n=61). Inclusion criteria: (1) patients described as having GGN in lung HRCT imaging; (2) patients diagnosed as GGN by pathological examination [7]; (3) without any relevant treatment before the visit. (4) The patient's clinical profile was complete. Exclusion criteria: (1) heart, liver and kidney insufficiency; (2) chronic lung diseases such as asthma and bronchiectasis; (3) various types of cytopenic diseases. This study was approved by the Ethics Committee of The Affiliated Taizhou People's Hospital of Nanjing Medical University.

Data collection

Baseline data of patients included 5 mL of fasting venous blood collected prior to treatment. This was allowed to stand at room temperature, coagulated, and centrifuged at 3000 r/min for 15 min with a centrifugal radius of 10 cm. Serum CEA levels were detected using the fully automatic chemiluminescence immunoassay analyzer (Abbott 12000SR model) produced by Abbott Inc. of the United States and the corresponding ARCHITECT CEA assay kit. The ROS, SOD, and MDA levels of the patients were measured using a fully automated biochemical analyzer 7600 from Hitachi, Japan. Among them, the ROS (Product Number: E004-1-1), SOD (Product Number: A001-1-2), and MDA (Product Number: A003-1-2) detection kits were purchased from Nanjing Jiancheng Bioengineering Company. The main observation indicators were differences in serum CEA, ROS, SOD and MDA levels between the two groups of patients. Secondary observation indicators: The correlations between each indicator and the pathologic type of GGN were determined, as well as the predictive efficacy of the individual and combined detection of the above indicators for early lung adenocarcinoma.

Statistical methods

Data analysis was conducted with SPSS 23.0 statistical software. Measured data were expressed as mean ± SD, and the t-test was used for comparison between groups. One-way analysis of variance (ANOVA) was used for comparisons among multiple groups, and the LSD test was used for pairwise comparisons between groups. Counted data were expressed as [n (%)], and the chi-square test was applied for comparison between groups. Logistic regression was used to analyze the influencing factors for lung adenocarcinoma. The ROC curve was used to analyze the predictive value of a single indicator and combined detection indicators for diseases. The comparison of the areas under different ROC curves was conducted by DeLong test and completed by MedCalc software. $P<0.05$ was a significant difference.

Results

General information

A total of 100 patients with GGN were studied. Among them, there were 61 cases of lung adenocarcinoma and 39 cases of glandular precursor lesions. There was no significant difference between the two groups in gender, age, lesion location, or smoking ($P>0.05$), as shown in **Table 1**.

Table 1. Comparison of general information between the two groups of patients [($\bar{x}$±s), n (%)]

Factor	Lung adenocarcinoma (n=61)	Glandular precursor lesions (n=39)	χ^2/t value	*P* value
Gender				
male	25 (40.98)	18 (46.15)	0.259	0.610
female	36 (59.02)	21 (53.85)		
Age	55.75±12.92	55.90±11.99	0.056	0.956
Lesion location				
Upper lobe of left lung	16 (26.23)	11 (28.21)	0.732	0.947
Lower lobe of left lung	8 (13.11)	7 (17.95)		
Upper lobe of right lung	20 (32.79)	11 (28.21)		
Lower lobe of right lung	9 (14.75)	6 (15.38)		
Middle lobe of right lung	8 (13.11)	4 (10.26)		
Smoking				
yes	41 (67.21)	27 (69.23)	0.045	0.833
no	20 (32.79)	12 (30.77)		

Table 2. Comparison of oxidative stress indexes between two groups of GGN patients

Group	ROS (μg/L)	SOD (U/mL)	MDA (nmol/L)
Lung adenocarcinoma (n=61)	3.27±0.68	10.02±1.34	2.30±0.47
Glandular precursor lesions (n=39)	2.70±0.62	11.01±0.99	1.98±0.36
t value	4.205	3.989	3.615
P value	<0.001	<0.001	<0.001

Note: ROS: reactive oxygen species; SOD: superoxide dismutase; MDA: malondialdehyde.

Table 3. Comparison of CEA levels in the two groups of GGN patients

Group	CEA (ng/mL)
Lung adenocarcinoma (n=61)	2.05±0.73
Glandular precursor lesions (n=39)	1.56±0.64
t value	3.461
P value	<0.001

Note: CEA: carcinoembryonic antigen.

Table 4. Comparison of CEA levels in different types of GGN patients

Group	CEA (ng/mL)
AAH	1.56±0.56
AIS	1.55±0.69
MIA	1.91±0.67
I-ADC	2.22±0.78
F value	5.019
P value	0.003

Note: AAH: Atypical adenomatous hyperplasia; AIS: Adenocarcinoma *in situ*; MIA: Minimally invasive adenocarcinoma; I-ADC: Infiltrating adenocarcinoma.

The oxidative stress indexes were compared between the two groups

ROS and MDA levels were higher in the lung adenocarcinoma group than in the glandular precursor lesion group (*P*<0.05). SOD levels were reduced and were lower than in the pre-glandular lesion group (*P*<0.05), as shown in **Table 2**.

CEA level was compared between the two groups

The differences in CEA levels were significant (P<0.05) between the two groups of patients, as shown in **Table 3**. The two groups of patients were subdivided into four pathologic types. Comparing the CEA levels of the four types, it was observed that patients with I-ADC had higher CEA levels than patients in the MIA, AIS, and AAH groups (*P*<0.05), as shown in **Table 4**.

Logistic regression analysis

The above-mentioned statistically significant variables were included as independent vari-

Table 5. Factor assignment table

Variable	Assignment
MDA	Original value input
SOD	Original value input
ROS	Original value input
CEA	Original value input

Note: ROS: reactive oxygen species; SOD: superoxide dismutase; MDA: malondialdehyde; CEA: carcinoembryonic antigen.

ables (the variable assignment table is shown in **Table 5**), and Logistic regression analysis was conducted with whether it was lung adenocarcinoma as the dependent variable (yes=1, no=0). The results showed that elevated levels of MDA, ROS and CEA were risk factors for the occurrence of lung adenocarcinoma, while elevated levels of SOD were protective factors for the occurrence of lung adenocarcinoma (**Table 6**).

Predictive value of oxidative stress index and CEA level index for GGN

The results of ROC curve analysis showed that the AUC, sensitivity, and specificity of the combined detection were all higher than those of CEA, MDA, ROS and SOD detected separately ($P<0.001$). See **Table 7**. Further, the DeLong test was used to compare the areas under different ROC curves. The results showed that: The AUC value of the combined detection was significantly higher than that of CEA, MDA, ROS, and SOD ($Z=3.826$, 3.786, 3.135, 3.199, $P<0.001$), while there was no significant difference in the AUC values of the other indicators ($P>0.05$). The ROC curve graph is shown in **Figure 1**.

Discussion

Early clinical symptoms of lung cancer are not apparent and difficult to detect. So, patients miss the optimal treatment time and have a low 5-year survival [8]. Studies have shown that GGN had a correlation with early lung cancer [9-11]. Relevant studies have shown that the formation of lung adenocarcinoma generally progresses from atypical adenomatous hyperplasia to adenocarcinoma *in situ*, and eventually transforms into invasive adenocarcinoma [12]. Therefore, how to detect and treat GGN patients in the early stage is of great significance for clinical treatment and early intervention.

The results of this study showed that the MDA and ROS activities in patients with lung adenocarcinoma were higher than thoseofthe glandular prodromal lesion group, while the SOD level was lower than that of the glandular prodromal lesion group, indicating that there was an oxidative stress response in GGN patients. Oxidative stress is due to an imbalance of the activity of the body's oxidation system and antioxidant system, which leads to lipid peroxidation. Lipid peroxidation can generate a significant number of active and high-toxin intermediates that interfere with the proper function of liver cells [13]. Multivariate logistic regression analysis further confirmed that elevated levels of MDA and ROS were risk factors for lung adenocarcinoma, while elevated levels of SOD were protective factors. Higher levels of MDA and ROS, plus lower levels of SOD, suggest a greater extent of lung infiltration, and a greater risk of lung adenocarcinoma. The possible reason for this is that when the patient's body experiences oxidative stress response, the oxidized fatty acids in the body will gradually decompose into various compounds such as MDA, thereby causing an increase in the patient's MDA level. MDA can indirectly respond to the degree of oxidative damage in the body and is correlated with a wide range of diseases [14-16]. Khalil et al. [17] showed that serum MDA levels were increased in ovarian cancer patients and lipid peroxidation was enhanced in ovarian cancer patients. Ashwaq [18] indicated that MDA levels were greater in breast cancer patients than in normal controls by comparing MDA levels in breast cancer patients with those in normal controls. The results of the present study are similar and suggest that elevated MDA levels lead to oxidative damage, which may be associated with tumorigenesis. As an important oxygen free radical metabolizer, SOD is a key antioxidant enzyme that affects the oxidative system and antioxidant system. It has been discovered that SOD is linked to the occurrence and progression of several diseases [19, 20]. The comparison of this research revealed that the SOD activity in the lung adenocarcinoma group was lower than that of the glandular precursor lesion group. This result is similar to that found by Strycharz-Dudziak [21]. By analyzing the activity of SOD in patients with oropharyn-

Table 6. Logistic regression analysis

Variable	B	SE	Wald	*P*	OR (95% CI)
MDA	1.975	0.772	6.546	0.011	7.205 (1.587-32.704)
SOD	-0.667	0.228	8.531	0.003	0.513 (0.328-0.803)
ROS	1.268	0.423	8.995	0.003	3.553 (1.552-8.136)
CEA	1.176	0.449	6.848	0.009	3.241 (1.343-7.818)
Constant	-2.586	2.968	0.759	-	-

Note: ROS: reactive oxygen species; SOD: superoxide dismutase; MDA: malondialdehyde; CEA: carcinoembryonic antigen.

geal cancer, Strycharz-Dudziak found that the activity of SOD was significantly reduced in patients with oropharyngeal cancer. It was suggested that lung cancer may cause a decrease in SOD activity. As an organ that communicates with the outside world, the lung is highly susceptible to the stimulation of various pollutants in the air to produce ROS. When the level of ROS in the body is too high, it will affect protein and lipid metabolism, cause cell damage, and then induce cancer [22]. In addition, ROS can promote cell division and interfere with the DNA repair system, giving tumor cells a selective proliferation advantage [23]. The results of this research indicated that patients with lung adenocarcinoma had higher ROS levels than the glandular precursor lesion group. Cheung [24] showed that ROS levels are increased in pancreatic ductal adenocarcinoma cells, and pointed out that ROS can promote tumor migration, invasion, and metastasis. The results of the studies were similar, thus suggesting that elevated ROS levels may be correlated with the development of lung cancer.

CEA is a macromolecular glycoprotein, which is mainly produced by colorectal cancer tissue. As an antigen, CEA can stimulate the body's immune response. Previous studies have indicated that CEA is a tumor marker closely associated with lung adenocarcinoma [25]. CEA increases with lymph node involvement and is associated with advanced stage and poor prognosis [26], implying that CEA does not increase significantly in early-stage lung adenocarcinoma. However, this research revealed higher CEA levels in the lung adenocarcinoma group than in the glandular precursor lesion group. This result is different from the view mentioned earlier that elevated CEA is associated with advanced tumors. Related research has compared CEA according to the pathologic subtypes of lung adenocarcinoma and noted that CEA levels increased with local tumor infiltration [25, 27]. This indicates that CEA levels may be an indicator of tumor invasion in lung adenocarcinoma. In this research, by comparing different pathologic subtypes, we discovered that CEA levels were higher in the I-ADC group compared to other patients and increased with the degree of infiltration. These results suggest that serum CEA has a tendency to increase gradually with the deepening of lung adenocarcinoma invasion. Furthermore, multivariate logistic regression analysis further confirmed that elevated CEA levels are a risk factor for the occurrence of lung adenocarcinoma. This indicates that the higher the CEA level, the deeper the degree of lung infiltration, and the greater the risk of lung adenocarcinoma. The changes of CEA level in GGN patients before treatment provided the possibility for clinical dynamic observation of early lung adenocarcinoma, detection of malignant lesions and timely intervention.

Based on the ROC curve analysis in this study, it was found that the AUC of the combined detection was higher than that of the individual detections of MDA, ROS, CEA and SOD. This suggests that the combined detection of MDA, ROS, CEA and SOD levels ican evaluate the patient's condition, and is of great significance for early intervention and treatment.

Advantages and limitations

This research investigated the oxidative stress indicators and CEA levels in patients with different types of ground glass nodules, and explored the changes in their levels and clinical significance. Because the samples in this research were mostly from the same region and the sample size was small, the analysis results were limited. In subsequent studies, multicenter, prospective research is needed to confirm the predictive value of oxidative stress indicators and CEA for conversion to lung adenocarcinoma in patients with ground glass nodules.

Conclusion

Oxidative stress and CEA levels begin to change in early lung adenocarcinoma, even at the stage of glandular precursor lesions. The deep-

Table 7. ROC curve analysis

Variable	AUC	Sensitivity (%)	Specificity (%)	95% CI	*P* value
MDA	0.696	59.02	76.92	0.596-0.784	<0.001
SOD	0.743	67.21	79.49	0.646-0.825	<0.001
ROS	0.747	63.93	82.05	0.650-0.829	<0.001
CEA	0.683	75.41	58.97	0.583-0.773	<0.001
Combined detection	0.887	72.13	94.87	0.808-0.942	<0.001

Note: ROS: reactive oxygen species; SOD: superoxide dismutase; MDA: malondialdehyde; CEA: carcinoembryonic antigen.

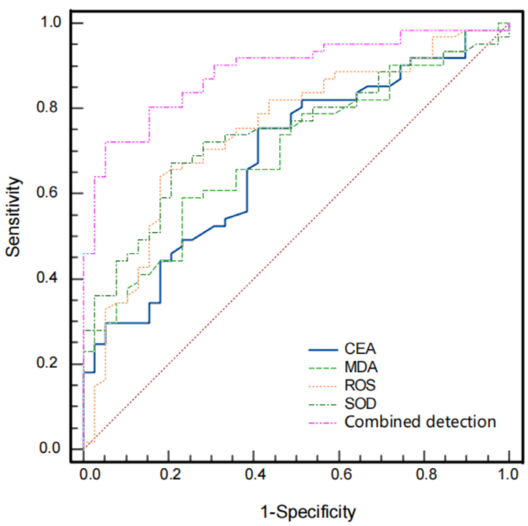

Figure 1. ROC curve analysis of different indicators. *Note:* CEA: carcinoembryonic antigen; ROS: reactive oxygen species; SOD: superoxide dismutase; MDA: malondialdehyde.

ening of lung adenocarcinoma infiltration results in a subsequent increase in MDA, ROS, and CEA levels and a decrease in SOD levels. The combined detection of oxidative stress indexes and CEA levels can effectively improve the sensitivity and specificity of clinical prediction of ground glass nodules transforming into lung adenocarcinoma, which is important for the treatment of GGN and early detection and intervention for lung adenocarcinoma.

Disclosure of conflict of interest

None.

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