

Association of Serum YKL-40 and Oxidative Stress Biomarkers with Glioma Grade: A Case-Control Study

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Abstract

Objective

Gliomas are the most common primary malignant brain tumors in adults, and early diagnosis and accurate determination of tumor grade are of great importance for prognosis. This study aimed to evaluate serum levels of YKL-40, total antioxidant status (TAS), total oxidant status (TOS), oxidative stress index (OSI), and malondialdehyde (MDA) in patients with glial tumors and to investigate the association of these biomarkers with tumor grade.

Materials and Methods

This study included 38 patients with histopathologically confirmed glial tumors who underwent surgery at the Department of Neurosurgery, Gaziantep University Faculty of Medicine, between August 2022 and September 2023, and 38 healthy controls. The patient group consisted of 21 low-grade (WHO Grade 1–2) and 17 high-grade (WHO Grade 3–4) glioma patients. Preoperative serum levels of YKL-40, TAS, TOS, and MDA were measured using the ELISA method, while OSI was calculated. Statistical analyses were performed using Student's t-test and the Mann–Whitney U test.

Results

Serum levels of TOS (13.06 ± 6.08 vs. 8.27 ± 3.60 $\mu\text{mol/L}$, $p = 0.001$), OSI (1.11 ± 0.57 vs. 0.67 ± 0.45 , $p = 0.001$), YKL-40 (283.55 ± 136.46 vs. 124.98 ± 53.26 ng/mL , $p = 0.001$), and MDA (22.82 ± 4.84 vs. 17.81 ± 4.71 nmol/mL , $p = 0.001$) were significantly higher in the patient group than in the control group. No significant difference was observed in TAS levels between the groups (1.27 ± 0.37 vs. 1.38 ± 0.38 mmol/L , $p = 0.223$). When low- and high-grade gliomas were compared, only serum YKL-40 levels were significantly higher in high-grade gliomas (400.34 ± 114.94 vs. 189.00 ± 53.83 ng/mL , $p = 0.001$). Although TOS, OSI, and MDA levels were significantly elevated in glioma patients compared to controls, no significant differences in TAS, TOS, OSI, or MDA levels were observed between low- and high-grade tumors.

Conclusion

Serum YKL-40 levels were associated with both the presence of glioma and tumor grade, whereas elevated TOS, OSI, and MDA levels reflected increased oxidative stress in patients with glial tumors. YKL-40 may serve as a potential biomarker for determining glioma grade.

Introduction

Gliomas are the most common primary malignant tumors of the central nervous system and account for approximately 80% of all primary malignant brain tumors in adults (1). Originating from glial cells, these tumors comprise various histopathological subtypes, including astrocytoma, oligodendroglioma, and glioblastoma, and exhibit significant differences in biological behavior and prognosis depending on tumor grade (2). In the 2021 update of the World Health Organization (WHO) classification, molecular markers were incorporated into the diagnostic and grading criteria in addition to histopathological features, aiming to achieve a more accurate classification and a better understanding of glioma biology (3).

Low-grade gliomas (WHO Grade 1–2) generally exhibit slower growth, whereas high-grade gliomas (WHO Grade 3–4) are characterized by rapid proliferation, pronounced angiogenesis, infiltration into surrounding brain tissue, and poor prognosis (4). Glioblastoma (WHO Grade 4), in particular, is the most common malignant primary brain tumor in adults, and despite the combination of surgical resection, radiotherapy, and chemotherapy, the median overall survival remains approximately 15–20 months (5). Therefore, there is an ongoing need for reliable biomarkers that can facilitate early diagnosis, accurate tumor grading, and prognostic prediction in gliomas.

Recent studies have demonstrated that inflammation and oxidative stress play crucial roles in glioma development and progression (6). Oxidative stress is defined as an imbalance between reactive oxygen species (ROS) and antioxidant defense mechanisms, leading to cellular damage (7). Increased oxidative stress contributes to tumor initiation and progression through DNA damage, lipid peroxidation, protein oxidation, and activation of various cellular signaling pathways (8). In rapidly proliferating malignant tumors, oxidative stress has been reported to be elevated and to play a significant role in shaping the tumor microenvironment (9).

Total oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), and malondialdehyde (MDA), a final product of lipid peroxidation, are among the most commonly used biochemical parameters for assessing oxidative stress (10). TAS reflects the overall antioxidant capacity of the organism, whereas TOS represents the total oxidant burden. OSI, calculated as the ratio of TOS to TAS, provides a more comprehensive assessment of oxidative stress levels (11). MDA, on the other hand, is produced through the oxidation of polyunsaturated fatty acids in cell membranes and is considered a reliable marker of oxidative damage (12). Several studies have demonstrated that oxidative stress biomarkers are elevated in patients with glial tumors compared with healthy individuals (13, 14). However, the relationship between these biomarkers and tumor grade remains controversial.

YKL-40 (chitinase-3-like protein 1, CHI3L1) is a glycoprotein that has recently attracted considerable attention in glioma biology. Initially thought to be associated with inflammation and tissue remodeling, YKL-40 was subsequently shown to be highly expressed in a variety of malignant tumors (15). It has been reported to be involved in cell proliferation, angiogenesis, extracellular matrix remodeling, and tumor invasion (16). In particular, YKL-40 levels have been found to be markedly increased in

glioblastoma tissues and serum samples, and elevated serum YKL-40 levels have been associated with poor prognosis and shorter overall survival (17, 18).

Although YKL-40 expression has been reported to correlate with tumor grade and to be elevated in high-grade gliomas, studies evaluating YKL-40 together with oxidative stress biomarkers are limited (19).

Moreover, the potential utility of serum YKL-40 as a reliable biomarker for glioma grading remains to be elucidated. Therefore, the combined evaluation of YKL-40 and oxidative stress parameters may not only contribute to a better understanding of glioma biology but also facilitate the development of novel diagnostic and prognostic approaches.

In this study, we aimed to compare serum levels of YKL-40, TAS, TOS, OSI, and MDA between patients with histopathologically confirmed glial tumors and healthy controls and to investigate the association of these biomarkers with tumor grade. Furthermore, the potential utility of YKL-40 and oxidative stress biomarkers as diagnostic and grading biomarkers for gliomas was evaluated.

Materials and Methods

This study included 38 patients with histopathologically confirmed intracranial glial tumors who underwent surgery at the Department of Neurosurgery, Gaziantep University Faculty of Medicine, between August 2022 and September 2023, as well as 38 healthy volunteers with similar age and sex characteristics. The study was conducted in accordance with the principles of the Declaration of Helsinki after obtaining approval from the Clinical Research Ethics Committee of Gaziantep University Faculty of Medicine (Approval No: 2022/413, Date: December 21, 2022).

Based on histopathological examination, patients were classified into two subgroups according to the 2021 World Health Organization (WHO) Classification of Central Nervous System Tumors: low-grade glial tumors (WHO Grade 1–2) and high-grade glial tumors (WHO Grade 3–4). Accordingly, 21 patients (55.3%) were classified as having low-grade gliomas, whereas 17 patients (44.7%) had high-grade gliomas. The low-grade glioma group consisted of 10 males and 11 females, while the high-grade glioma group comprised 9 males and 8 females.

The inclusion criteria were as follows: histopathologically confirmed diagnosis of a glial tumor, surgical treatment, availability of preoperative serum samples, and complete clinical and laboratory data. Patients with a history of another malignancy, active infection or inflammatory disease, chronic liver or renal failure, autoimmune disease, previous chemotherapy or radiotherapy, or incomplete clinical or laboratory data were excluded from the study. Healthy volunteers in the control group had no history of malignancy, chronic systemic disease, active infection, or inflammatory disorders.

Venous blood samples were obtained from all participants under fasting conditions before surgery. The blood samples were centrifuged under appropriate conditions to separate the serum and stored at -80°C until analysis. Serum YKL-40 levels were measured using commercially available enzyme-linked

immunosorbent assay (ELISA) kits according to the manufacturer's instructions. Total antioxidant status (TAS) and total oxidant status (TOS) were evaluated using the automated colorimetric method developed by Erel. Malondialdehyde (MDA), a final product of lipid peroxidation, was measured using appropriate biochemical methods. The oxidative stress index (OSI) was calculated as the ratio of total oxidant status to total antioxidant status using the following formula:

$$*OSI = TOS (\mu\text{mol H}_2\text{O}_2 \text{ Eq/L}) / TAS (\text{mmol Trolox Eq/L})^*$$

These parameters were compared between patients with glial tumors and healthy controls, as well as between low-grade and high-grade glioma groups.

Statistical analyses were performed using SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). The normality of numerical variables was assessed using the Shapiro-Wilk test. Student's t-test was used to compare normally distributed variables between two groups, whereas the Mann-Whitney U test was used for variables that did not follow a normal distribution. Continuous variables were expressed as mean $\pm$ standard deviation or median (minimum-maximum), and categorical variables were presented as numbers and percentages (%). A p-value of < 0.05 was considered statistically significant in all analyses.

Results

Demographic Characteristics of the Study Population

A total of 76 individuals were included in the study. Of these, 38 (50%) constituted the patient group with histopathologically confirmed glial tumors, while 38 (50%) comprised the healthy control group. Among the patients, 21 (55.3%) were classified as having low-grade glial tumors (WHO Grade 1–2), whereas 17 (44.7%) were classified as having high-grade glial tumors (WHO Grade 3–4). The low-grade glioma group consisted of 10 males and 11 females, while the high-grade glioma group included 9 males and 8 females. The general descriptive characteristics of the study population are presented in Table 1.

Table 1. Demographic characteristics of patients with glioma and healthy controls

	Low-grade glioma (n=21)	High-grade glioma (n=17)	Total glioma (n=38)	Controls (n=38)
Male, n (%)	10 (47.6)	9 (52.9)	19 (50.0)	17 (44.7)
Female, n (%)	11 (52.4)	8 (47.1)	19 (50.0)	21 (55.3)
Total, n (%)	21 (55.3)	17 (44.7)	38 (100)	38 (100)

Comparison of Biochemical Parameters Between the Patient and Control Groups

Comparison of biochemical parameters between the patient and control groups revealed that serum TOS, OSI, YKL-40, and MDA levels were significantly higher in the patient group than in the control group.

The mean serum TOS level was 13.06 ± 6.08 $\mu\text{mol/L}$ in the patient group and 8.27 ± 3.60 $\mu\text{mol/L}$ in the control group ($p=0.001$). Similarly, OSI values were significantly higher in patients than in controls (1.11 ± 0.57 vs. 0.67 ± 0.45 , respectively; $p=0.001$).

Serum YKL-40 levels were measured as 283.55 ± 136.46 ng/mL in the patient group and 124.98 ± 53.26 ng/mL in the control group, indicating a statistically significant increase in patients ($p=0.001$). Likewise, MDA levels were significantly elevated in the patient group compared with the control group (22.82 ± 4.84 vs. 17.81 ± 4.71 nmol/mL, respectively; $p=0.001$). In contrast, no significant difference was observed in TAS levels between the patient and control groups (1.27 ± 0.37 vs. 1.38 ± 0.38 mmol/L, respectively; $p=0.223$). Comparisons of biochemical parameters between the patient and control groups are presented in Table 2.

Table 2. Comparison of serum oxidative stress biomarkers and YKL-40 levels between glioma patients and healthy controls

Biomarker	Patients (n=38), Mean $\pm$ SD	Controls (n=38), Mean $\pm$ SD	p value
TAS (mmol/L)	1.27 ± 0.37	1.38 ± 0.38	0.223†
TOS ($\mu\text{mol/L}$)	13.06 ± 6.08	8.27 ± 3.60	0.001*‡
OSI	1.11 ± 0.57	0.67 ± 0.45	0.001*‡
YKL-40 (ng/mL)	283.55 ± 136.46	124.98 ± 53.26	0.001*‡
MDA (nmol/mL)	22.82 ± 4.84	17.81 ± 4.71	0.001*†

Abbreviations: TAS, total antioxidant status; TOS, total oxidant status; OSI, oxidative stress index; YKL-40, chitinase-3-like protein 1; MDA, malondialdehyde.

*Statistically significant ($p < 0.05$). †Student's t-test. ‡Mann–Whitney U test.

Comparison Between Low-Grade and High-Grade Gliomas

When low-grade and high-grade glioma groups were compared in terms of biochemical parameters, only serum YKL-40 levels showed a significant association with tumor grade. The mean serum YKL-40 level was significantly higher in the high-grade glioma group than in the low-grade glioma group (400.34 ± 114.94 ng/mL vs. 189.00 ± 53.83 ng/mL, respectively; $p=0.001$).

In contrast, TAS levels were 1.28 ± 0.37 mmol/L in the low-grade glioma group and 1.26 ± 0.39 mmol/L in the high-grade glioma group, with no statistically significant difference between the groups ($p=0.869$). Similarly, TOS levels were 12.39 ± 6.66 $\mu\text{mol/L}$ in low-grade gliomas and 13.88 ± 5.36 $\mu\text{mol/L}$ in high-grade gliomas ($p=0.220$). OSI values were 1.00 ± 0.48 and 1.24 ± 0.66 in the low-grade and high-grade glioma groups, respectively, with no significant difference observed ($p=0.308$). MDA levels were also

comparable between the two groups, measuring 22.92±4.47 nmol/mL in low-grade gliomas and 22.70±5.40 nmol/mL in high-grade gliomas (p=0.892).

These findings indicate that YKL-40 is associated not only with the presence of glioma but also with tumor grade, whereas TOS, OSI, and MDA reflect increased oxidative stress in glioma patients without significantly discriminating between low- and high-grade tumors. Comparisons of biochemical parameters between low-grade and high-grade glioma groups are summarized in Table 3.

Table 3. Comparison of serum oxidative stress biomarkers and YKL-40 levels between low-grade and high-grade gliomas

Parameter	Low-grade glioma (n=21) Mean ± SD	High-grade glioma (n=17) Mean ± SD	p value
TAS (mmol/L)	1.28 ± 0.37	1.26 ± 0.39	0.869†
TOS (µmol/L)	12.39 ± 6.66	13.88 ± 5.36	0.220‡
OSI	1.00 ± 0.48	1.24 ± 0.66	0.308‡
YKL-40 (ng/mL)	189.00 ± 53.83	400.34 ± 114.94	0.001*‡
MDA (nmol/mL)	22.92 ± 4.47	22.70 ± 5.40	0.892†

*Statistically significant (p < 0.05). †Student’s t-test. ‡Mann–Whitney U test.

Serum YKL-40 levels demonstrated a progressive increase across the study groups, with the highest concentrations observed in patients with high-grade gliomas. The distribution of serum YKL-40 levels among healthy controls, low-grade glioma patients, and high-grade glioma patients is presented in Figure 1.

Figure . Serum YKL-40 levels across study groups.

ROC Analysis of Serum YKL-40

Receiver operating characteristic (ROC) analysis was performed to evaluate the diagnostic performance of serum YKL-40 levels in glioma diagnosis and tumor grading. Serum YKL-40 demonstrated excellent discriminative ability for distinguishing high-grade gliomas from low-grade gliomas, with an area under the curve (AUC) of 0.908 (95% confidence interval [CI]: 0.768–1.000). The optimal cut-off value was determined to be 306.02 ng/mL, yielding a sensitivity of 88.2% and a specificity of 95.2%.

In addition, serum YKL-40 levels showed high diagnostic performance in differentiating glioma patients from healthy controls, with an AUC of 0.902 (95% CI: 0.830–0.962). The optimal cut-off value for this analysis was 173.19 ng/mL, providing a sensitivity of 81.6% and a specificity of 89.5%. The ROC curves for serum YKL-40 are presented in Figure 2.

Figure 2. Receiver operating characteristic (ROC) curves of serum YKL-40 for differentiating high-grade gliomas from low-grade gliomas (A) and glioma patients from healthy controls (B).

Discussion

In this study, serum levels of YKL-40, TAS, TOS, OSI, and MDA were evaluated in patients with glial tumors, and the relationship between these biomarkers and tumor grade was investigated. The most important finding of our study is that serum YKL-40 levels were significantly associated with both the presence of glioma and tumor grade. In contrast, although TOS, OSI, and MDA levels were significantly higher in patients with glial tumors than in healthy controls, these biomarkers did not significantly contribute to distinguishing low-grade from high-grade gliomas.

Gliomas are heterogeneous tumors with diverse biological characteristics, and high-grade gliomas are particularly characterized by aggressive clinical behavior and poor prognosis. Therefore, identifying biomarkers that reflect tumor biology and contribute to tumor grading has become an important area of research. In recent years, YKL-40 has emerged as a promising molecule in glioma biology. YKL-40, encoded by the CHI3L1 gene, is involved in several biological processes, including inflammation, cell proliferation, angiogenesis, extracellular matrix remodeling, and tumor invasion (15,16). It has been demonstrated that YKL-40 is highly expressed in glioblastoma tissues and serum samples and is associated with poor prognosis and shorter survival (17–20).

In the present study, serum YKL-40 levels were significantly higher in the patient group than in the control group (283.55 ± 136.46 ng/mL vs. 124.98 ± 53.26 ng/mL, $p=0.001$). More importantly, serum YKL-40 levels in the high-grade glioma group were approximately two-fold higher than those in the low-grade glioma group (400.34 ± 114.94 ng/mL vs. 189.00 ± 53.83 ng/mL, $p=0.001$). These findings suggest that YKL-40 reflects not only the presence of glioma but also the biological aggressiveness of the tumor.

The findings of previous studies investigating the relationship between YKL-40 and glioma grade support our results. Pelloski et al. reported that high YKL-40 expression was associated with poorer response to radiotherapy and shorter survival in patients with glioblastoma (18). Similarly, Tanwar et al. demonstrated that YKL-40 levels were markedly elevated in malignant gliomas and could serve as a prognostic biomarker (17). Hormigo et al. also reported significantly increased serum YKL-40 levels in patients with high-grade gliomas and suggested its potential utility as a serum biomarker (19). Furthermore, Iwamoto et al. showed that elevated serum YKL-40 levels were associated with poor prognosis and active disease status in patients with anaplastic gliomas and glioblastomas (20). In addition, Nutt et al. identified YKL-40 as an important molecular marker associated with aggressive tumor biology in gene expression profiling studies (21). Consistent with these findings, the significantly higher YKL-40 levels observed in high-grade gliomas in our study suggest that YKL-40 may serve as a potential serum biomarker for glioma grading.

Another important finding of our study is that serum YKL-40 exhibited excellent discriminative ability for both glioma diagnosis and tumor grading in ROC analysis. Serum YKL-40 demonstrated excellent

performance in distinguishing high-grade gliomas from low-grade gliomas, with an area under the curve (AUC) of 0.908 (95% CI: 0.768–1.000), indicating an almost perfect diagnostic performance. In addition, YKL-40 effectively differentiated glioma patients from healthy controls, with an AUC of 0.902 (95% CI: 0.830–0.962). These high AUC values indicate that YKL-40 is strongly associated not only with tumor grade but also with the presence of glioma. Similarly, previous studies have shown that serum YKL-40 levels are associated with disease activity and prognosis and may be useful in predicting survival in patients with glioblastoma (19,20). Taken together, these findings suggest that YKL-40 is a promising biomarker with potential clinical applications in the diagnosis and grading of glial tumors.

Oxidative stress is known to play an important role in the development and progression of gliomas. Reactive oxygen species (ROS) contribute to tumorigenesis through DNA damage, cellular proliferation, and angiogenesis (6–9). Therefore, oxidative stress markers have been extensively investigated in glioma research in recent years. In our study, TOS, OSI, and MDA levels were significantly elevated in patients with glial tumors compared with healthy controls, whereas TAS levels did not differ significantly between the two groups.

These findings are consistent with previous studies reporting increased oxidative stress in glioma patients. Yilmaz et al. and Coban et al. demonstrated elevated levels of lipid peroxidation products and oxidative stress markers in patients with glial tumors (13,14). In addition, MDA, the end product of lipid peroxidation, has been recognized as a reliable indicator of oxidative cellular damage and has been shown to be elevated in various malignancies (12). Accordingly, the significantly increased TOS, OSI, and MDA levels observed in our study further support the role of oxidative stress in glial tumor biology.

However, one of the noteworthy findings of our study is that TOS, OSI, and MDA levels did not differ significantly between low-grade and high-grade gliomas. This finding suggests that although oxidative stress contributes to glioma development, these biomarkers may not be sufficiently discriminative for tumor grading. In contrast, the fact that YKL-40 reflects both glioma presence and tumor grade indicates that this biomarker may have greater clinical value.

This study has several limitations. First, it was conducted at a single center with a relatively limited sample size. Second, some clinical variables, such as patient age, were unavailable, preventing the assessment of their potential confounding effects on biomarker levels. Future multicenter studies with larger sample sizes and prospective designs are required to validate our findings.

In conclusion, our study demonstrated that serum YKL-40 levels are associated with both glioma presence and tumor grade. In contrast, TOS, OSI, and MDA reflect increased oxidative stress in patients with glial tumors but do not significantly contribute to distinguishing tumor grades. The high AUC values obtained in ROC analysis suggest that YKL-40 may be a promising biomarker for the diagnosis and grading of gliomas.

Conclusion

This study demonstrated that serum YKL-40 levels are significantly associated with both the presence of glioma and tumor grade. The markedly elevated serum YKL-40 levels observed in high-grade gliomas, together with the high AUC values obtained from ROC analysis, suggest that YKL-40 may serve as a powerful biomarker for the diagnosis and grading of gliomas. In contrast, TOS, OSI, and MDA reflect increased oxidative stress in patients with glial tumors but appear to have limited value in distinguishing tumor grades. These findings indicate that YKL-40 has potential clinical utility for diagnostic and prognostic purposes and should be further validated in larger, prospective studies.

Declarations

Funding:

This study was supported by the Scientific Research Projects Unit of Gaziantep University (Project No: TF.UT.23.14).

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Clinical Research Ethics Committee (Approval No: 2022/413, dated December 21, 2022). Written informed consent was obtained from all participants.

Conflict of Interest:

The authors declare that they have no conflicts of interest.

Author Contributions:

Mustafa Özaslan: Study conception and design, data collection, data analysis, interpretation of data, performance of surgical procedures, manuscript drafting, and critical revision of the manuscript.

Mohammad Alomar: Data collection, statistical analysis, and critical revision of the manuscript.

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Figures

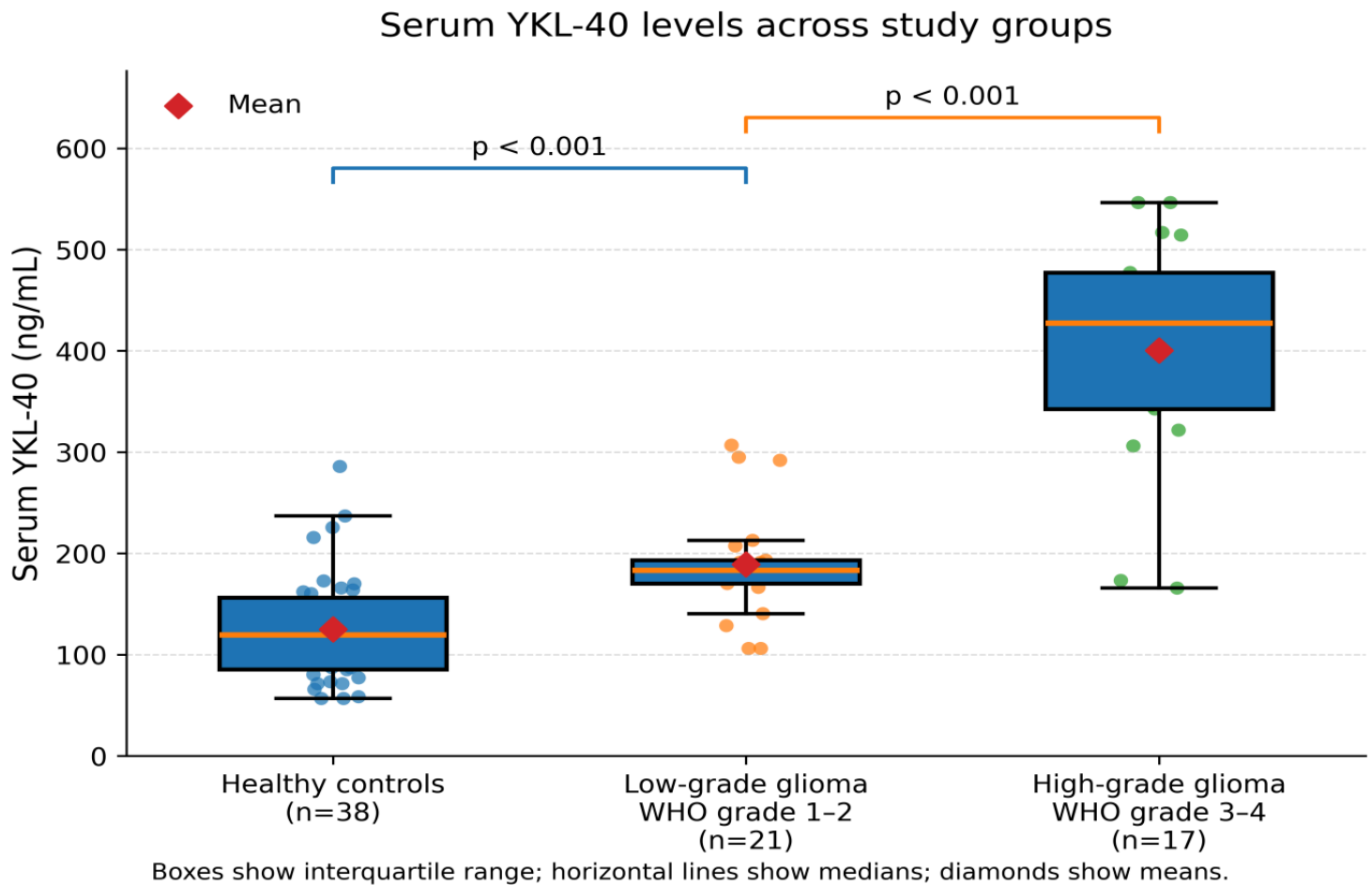


Figure 1

Serum YKL-40 levels across study groups.

ROC analysis of serum YKL-40

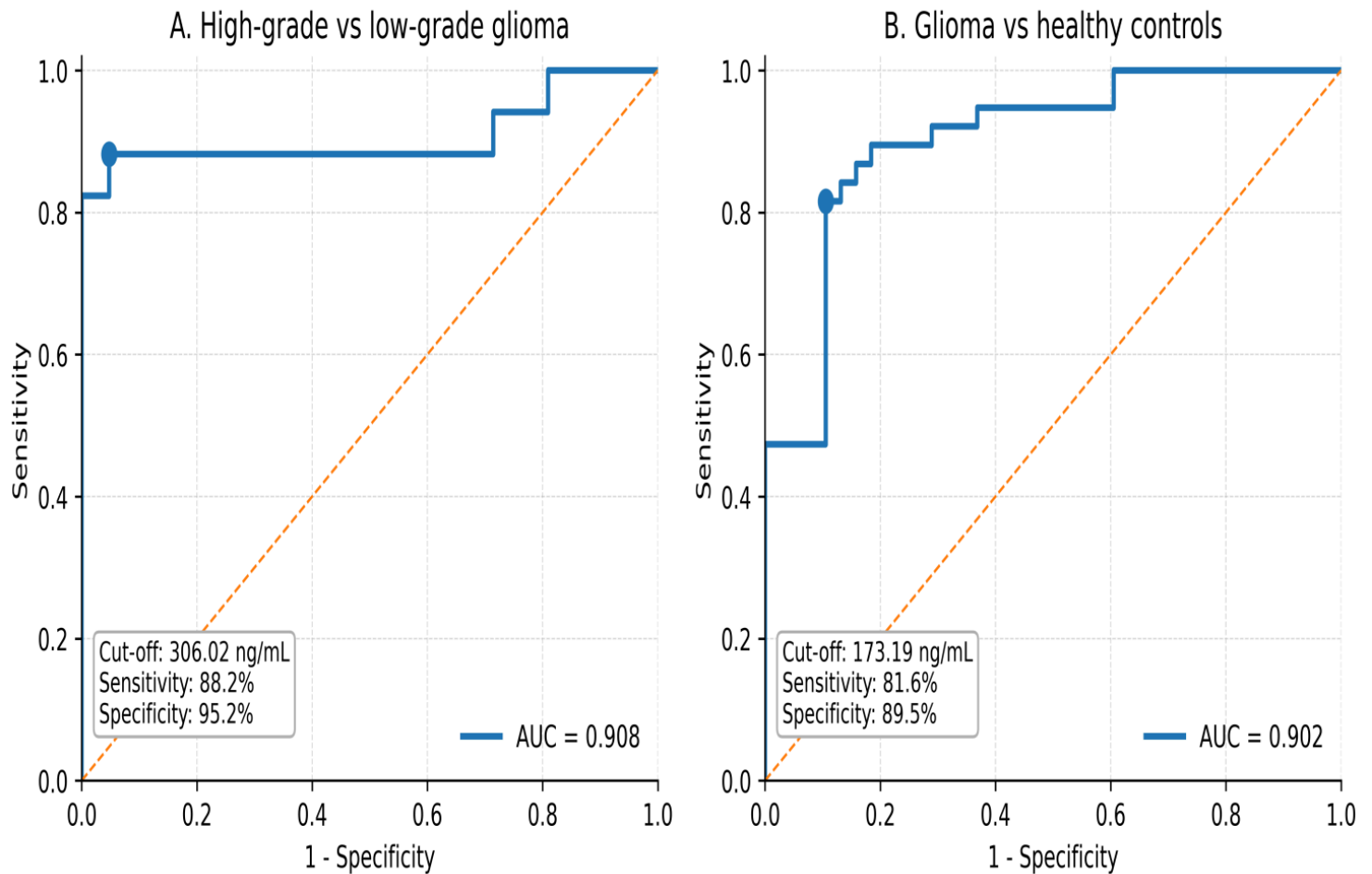


Figure 2

Receiver operating characteristic (ROC) curves of serum YKL-40 for differentiating high-grade gliomas from low-grade gliomas (A) and glioma patients from healthy controls (B).