The New Journal of Urology
eISSN 3023-6940
doi: https://doi.org/10.33719/nju1829395

RESEARCH ARTICLE

Prognostic Value of Oxidative Stress Markers in Bladder Cancer: A Study of Ceruloplasmin, ADMA, MPO, XO, TAS, and TOS

Murat Demir [1], Muhammed Fatih Keleş [1], Veli Duman [1] *, Halit Demir [2], Canan Demir [3], Recep Eryılmaz [1], Sıddık Keskin [4], Rahmi Aslan [1], Kerem Taken [1]

[1] Department of Urology, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Türkiye
[2] Department of Biochemistry, Faculty of Science, Van Yüzüncü Yıl University, Van, Türkiye
[3] School of Health Services, Van Yüzüncü Yıl University, Van, Türkiye
[4] Department of Biostatistics, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Türkiye

Submitted: *2025-11-25*
Accepted: *2026-07-03*

Corresponding Author;
Veli Duman, MD
Address: Department of Urology, Faculty of Medicine, Van Yüzüncü Yıl University, Van, Türkiye
E-mail: drduman_3366@hotmail.com

ORCID
M.D. 0000-0001-5029-8800
M.F.K. 0000-0001-9996-1693
V.D. 0009-0005-1671-4889
H.D. 0000-0001-5598-2601
C.D. 0000-0002-4204-9756
R.E. 0000-0002-4506-8784
S.K. 0000-0001-9355-6558
R.A. 0000-0002-4563-0386
K.T. 0000-0002-4370-4222

Abstract

Objective: This study aimed to evaluate the oxidant and antioxidant balance in patients with bladder cancer and to investigate the association between oxidative stress markers ceruloplasmin, asymmetric dimethylarginine (ADMA), myeloperoxidase (MPO), xanthine oxidase (XO), total antioxidant status (TAS), and total oxidant status (TOS) with tumor grade and invasion.

Methods: This prospective study included 49 patients with histopathologically confirmed bladder cancer and 49 age- and sex-matched healthy controls. Serum levels of ceruloplasmin, ADMA, MPO, XO, TAS, and TOS were measured using standard biochemical methods.

Results: Compared with the control group, patients with bladder cancer had significantly higher levels of ceruloplasmin, ADMA, MPO, XO, and TOS ($p = 0.001$ for all), while TAS levels were significantly lower ($p = 0.001$). As tumor stage and grade increased, ceruloplasmin, ADMA, and MPO levels significantly increased ($p < 0.05$), whereas XO, TAS, and TOS levels showed no significant differences.

Conclusion: Our findings demonstrate that oxidative stress is markedly increased, while antioxidant defense is impaired in patients with bladder cancer. The disturbed oxidant-antioxidant equilibrium is prominently associated with tumor presence. Furthermore, progressive alterations in ceruloplasmin, ADMA, and MPO may reflect tumor progression and biological aggressiveness, suggesting their potential utility as supportive indicators alongside standard clinical parameters.

Keywords: ADMA, antioxidants, bladder neoplasms, ceruloplasmin, myeloperoxidase, oxidative stress

Cite; Demir M, KeleS MF, Duman V, Demir H, Demir C, Eryilmaz R, Keskin S, Aslan R, Taken K. Prognostic Value of Oxidative Stress Markers in Bladder Cancer: A Study of Ceruloplasmin, ADMA, MPO, XO, TAS, and TOS. New J Urol. 2026;21(3):124–130. **doi:** https://doi.org/10.33719/nju1829395

This work is licensed under a Creative Commons Attribution 4.0 (CC-BY) International License. © *Copyright remains with the authors.*

INTRODUCTION

It can be stated that bladder cancer is one of the most common malignancies of the urinary system, accounting for about 3–4% of all cancer cases and 2–3% of cancer-related deaths. Tobacco use, exposure to aromatic amines, chronic inflammation, prior radiotherapy, and certain analgesic or chemotherapeutic agents are major aetiological factors (1). In recent years, strong evidence has shown that oxidative stress plays a decisive role in the development, progression, and biological behaviour of bladder cancer (2).

Oxidative stress results from an imbalance between reactive oxygen species (ROS) and antioxidant defence mechanisms, favouring oxidants. Free radicals damage DNA, lipids, and proteins, triggering mutation, oncogenic transformation, and apoptosis dysfunction (3). The body's antioxidant enzymes and molecules attempt to maintain cellular integrity by neutralising these radicals. Disruption of this oxidant-antioxidant balance is considered a key biochemical mechanism in cancer development and progression (2).

Previous studies have shown decreased antioxidant parameters (e.g., superoxide dismutase, glutathione reductase, paraoxonase, arylesterase, glutathione S-transferase) and increased oxidant markers (e.g., xanthine oxidase, protein carbonyl, malondialdehyde) in bladder cancer (4). Demir et al. (2022) reported elevated protein carbonyl levels and reduced activities of arylesterase, paraoxonase-1, and glutathione reductase, especially in high-grade and invasive tumours (2). These findings indicate that increased oxidative stress and weakened antioxidant defence are closely associated with tumour development and progression.

Ceruloplasmin, asymmetric dimethylarginine (ADMA), myeloperoxidase (MPO), and xanthine oxidase (XO) are oxidative stress markers that promote cellular oxidation through distinct biochemical pathways. Ceruloplasmin is a ferroxidase with physiological antioxidant properties that rises as a positive acute phase reactant under oxidative and inflammatory conditions (5), while ADMA inhibits endothelial nitric oxide synthase (eNOS), reducing nitric oxide production and causing endothelial dysfunction and hypoxia, which facilitate tumour proliferation and invasion (6). Furthermore, MPO released from neutrophils generates reactive chlorine compounds such as hypochlorous acid via hydrogen peroxide, promoting DNA and protein damage (7). Concurrently, XO produces superoxide and hydrogen peroxide during purine metabolism, and its increased activity serves as a strong indicator of intracellular ROS accumulation and oxidative damage (8). Together with these specific markers, total antioxidant status (TAS) represents the overall redox defence capacity, while total oxidant status (TOS) reflects the systemic oxidative load (9).

Based on this information, this study aimed to evaluate ceruloplasmin, ADMA, MPO, XO, TAS, and TOS levels in bladder cancer patients and to analyse their association with tumour presence, grade, and invasion level.

MATERIALS AND METHODS

This prospective study was conducted at the Urology Clinic of Van Yüzüncü Yıl University. Eighty patients with suspected bladder tumor were initially evaluated. The study was approved by the Non-Interventional Clinical Research Ethics Committee of Van Yüzüncü Yıl University (Decision No. 04, Date: October 8, 2025). Written informed consent was obtained from all participants, and the study adhered to the Declaration of Helsinki principles.

Inclusion and Exclusion Criteria

The inclusion criteria for the patient group were age over 18 years, histopathologically confirmed primary bladder cancer, and voluntary provision of written informed consent.

The exclusion criteria for both the patient and control groups were strictly defined to eliminate confounding factors that directly alter systemic oxidative stress markers and antioxidant capacity, which could otherwise skew the biochemical analyses. Participants were excluded if they met any of the following criteria: current active smoking (defined as smoking at least one cigarette per day during the past year); habitual alcohol or substance use; a history or current diagnosis of other systemic malignancies; chronic systemic metabolic or vascular diseases (such as diabetes mellitus and hypertension); hepatic or renal failure; and acute or chronic active infectious or inflammatory diseases. After applying these exclusion criteria, 49 patients with bladder cancer were eligible for final evaluation.

The control group comprised 49 age- and sex-matched healthy volunteers who admitted to our outpatient clinic for routine check-ups. These individuals had no history of malignant diseases or chronic systemic illnesses and met the same exclusion criteria as the patient group.

Statistical Analysis

Data distribution was evaluated using the Kolmogorov-Smirnov test. For comparisons between two independent groups (Patient vs. Control and Low-grade vs. High-grade), the Independent Student's t-test or Mann-Whitney U test was used where appropriate. For comparisons among three groups (Ta, T1, and T2 stages), 1-way ANOVA followed by Duncan's post-hoc test (or Kruskal-Wallis test for non-normal data) was applied. Pearson correlation analysis was performed to evaluate the relationships among the continuous variables. Statistical significance was set at $p < 0.05$.

RESULTS

Among the 49 bladder cancer patients and 49 controls, 35 were male, and 14 were female in each group. The mean age was 61.9 ± 7.0 years in patients and 62.6 ± 6.8 years in controls ($p = 0.61$). Ceruloplasmin, ADMA, MPO, XO, and TOS levels were significantly higher in the bladder cancer group, while TAS levels were higher in controls (all $p = 0.001$) (Table 1).

With increasing T stage, ceruloplasmin, ADMA, and MPO levels rose significantly ($p < 0.05$), whereas XO, TAS, and TOS showed no significant differences (Table 2).

Similarly, as tumour grade increased, ceruloplasmin, ADMA, and MPO levels were elevated, while XO, TAS, and TOS remained unchanged (Table 3).

DISCUSSION

This study indicates that the systemic oxidant-antioxidant balance is profoundly disrupted in bladder cancer patients, and this redox imbalance correlates closely with tumor presence, histological grade, and invasion depth. Our findings revealed that total antioxidant capacity (TAS) was significantly depleted in the bladder cancer group, whereas specific oxidative stress markers, including ceruloplasmin,

Table 1. Comparison of oxidant and antioxidant levels in the patient and control groups

		N	Mean	p
Ceruloplasmin (mg/dL)	Control	49	21.07 ± 0.04	0.001
	Patient	49	42.06 ± 0.03	
	Total	98	31.46 ± 10.54	
ADMA (µmol/L)	Control	49	2.49 ± 0.03	0.001
	Patient	49	4.59 ± 0.18	
	Total	98	3.53 ± 1.06	
MPO (ng/mL)	Control	49	126.82 ± 3.18	0.001
	Patient	49	261.53 ± 4.35	
	Total	98	193.49 ± 67.80	
XO (mU/mL)	Control	49	0.15 ± 0.22	0.001
	Patient	49	0.28 ± 0.27	
	Total	98	0.21 ± 0.07	
TAS (mmol/L)	Control	49	8.57 ± 0.11	0.001
	Patient	49	4.42 ± 0.09	
	Total	98	6.52 ± 2.08	
TOS (µmol/L)	Control	49	5.29 ± 0.07	0.001
	Patient	49	11.19 ± 0.38	
	Total	98	8.21 ± 2.97	

Table 2. Comparison of patient characteristics according to T stage

		N	Mean	p
Ceruloplasmin (mg/dL)	Ta	24	42.04 ± 0.02 b	0.001
	T1	17	42.06 ± 0.03 b	
	T2	8	42.10 ± 0.01 a	
ADMA (µmol/L)	Ta	24	4.51 ± 0.14 b	0.001
	T1	17	4.59 ± 0.18 b	
	T2	8	4.84 ± 0.05 a	
MPO (ng/mL)	Ta	24	260.02 ± 3.8 b	0.001
	T1	17	261.32 ± 4.33 b	
	T2	8	266.54 ± 1.46 a	
XO (mU/mL)	Ta	24	0.28 ± 0.26	0.759
	T1	17	0.29 ± 0.26	
	T2	8	0.28 ± 0.36	
TAS (mmol/L)	Ta	24	4.42 ± 0.10	0.623
	T1	17	4.44 ± 0.09	
	T2	8	4.41 ± 0.06	
TOS (µmol/L)	Ta	24	11.22 ± 0.40	0.751
	T1	17	11.14 ± 0.36	
	T2	8	11.23 ± 0.41	

a, b: The difference between stages with different letters is significant ($p < 0.05$)

Table 3. Comparison of patient characteristics according to grade

		N	Mean	p
Ceruloplasmin (mg/dL)	Low grade	32	42.05 ± 0.02	0.001
	High grade	17	42.08 ± 0.02	
ADMA (µmol/L)	Low grade	32	4.53 ± 0.17	0.001
	High grade	17	4.72 ± 0.16	
MPO (ng/mL)	Low grade	32	260.07 ± 4.13	0.001
	High grade	17	264.29 ± 3.38	
XO (mU/mL)	Low grade	32	0.290 ± 0.02	0.424
	High grade	17	0.28 ± 0.03	
TAS (mmol/L)	Low grade	32	4.42 ± 0.09	0.377
	High grade	17	4.44 ± 0.08	
TOS (µmol/L)	Low grade	32	11.19 ± 0.41	0.937
	High grade	17	11.20 ± 0.33	

Values are presented as Mean ± SD (Standard Deviation).

Abbreviations: ADMA, asymmetric dimethylarginine; MPO, myeloperoxidase; XO, xanthine oxidase; TAS, total antioxidant status; TOS, total oxidant status; N, number of subjects.

Units: mg/dL, milligrams per deciliter; µmol/L, micromoles per liter; ng/mL, nanograms per milliliter; mU/mL, milliunits per milliliter; mmol/L, millimoles per liter.

ADMA, MPO, XO, and total oxidant status (TOS), were prominently elevated compared to healthy controls. Notably, while XO, TOS, and TAS levels were primarily altered by the mere presence of the malignancy, advancements in tumor grade were characterized by further progressive elevations in ceruloplasmin, ADMA, and MPO levels. These results reinforce the understanding that oxidative stress is not merely a bystander effect of carcinogenesis but a driving biochemical mechanism fueling the progression and aggressive biological behavior of bladder cancer.

Our findings align with existing literature documenting a suppressed antioxidant defense system coupled with an escalated oxidative burden in bladder malignancies. For instance, Güneş et al. (4) observed heightened xanthine oxidase activity alongside a concomitant reduction in critical antioxidant enzymes such as glutathione reductase and superoxide dismutase. Similarly, Demir et al. (2) identified elevated protein carbonyl levels alongside depleted paraoxonase-1 and arylesterase activities, particularly within high-grade and invasive tumors. The systemic manifestation of these alterations in our study evidenced by high TOS and low TAS highlights a profound inadequacy in the organism's capability to neutralize reactive oxygen species (ROS) generated during tumor development. This pervasive oxidative load can be directly attributed to the complex interplay of localized hypoxia, accelerated cellular metabolism, chronic intratumoral inflammation, and active immune cell infiltration within the bladder tumor microenvironment.

The individual markers evaluated in this study represent distinct yet highly interconnected biochemical pathways that collectively reinforce this oxidative-nitrosative stress cycle. Xanthine oxidase (XO), a key enzyme in purine catabolism, serves as a primary intracellular source of superoxide anions and hydrogen peroxide, which induce genotoxic stress and DNA damage, thereby promoting oncogenic transformation (10,12). Concurrently, myeloperoxidase (MPO) released predominantly by activated neutrophils infiltrating the tumor stroma utilizes these hydrogen peroxide substrates to generate hypochlorous acid and other highly reactive chlorine derivatives (13). These MPO-derived oxidants exacerbate tissue destruction, lipid peroxidation, and genetic instability, directly facilitating basement membrane degradation and subsequent tumor invasion (14).

Crucially, the pathogenic footprint of MPO and XO is intricately linked to endothelial dysfunction and tissue hypoxia through their negative impact on nitric oxide (NO) bioavailability. This process is further compounded by the marked elevation of asymmetric dimethylarginine (ADMA) observed in our patient cohort. ADMA acts as an endogenous inhibitor of endothelial nitric oxide synthase (eNOS), effectively shutting down NO production (15). While ADMA suppresses NO synthesis, MPO actively scavenges and oxidizes the remaining available NO, leading to severe microcirculatory impairments and localized hypoxia within the tumor bed (13,14). This oxygen-deprived microenvironment serves as a potent biological stimulus for tumor proliferation, angiogenesis, and aggressive invasion, explaining why ADMA and MPO levels were significantly higher in our advanced and high-grade cases, consistent with observations in other solid tumors (16–19).

In response to this severe localized hypoxia and the overwhelming oxidative-inflammatory cascade, the organism undergoes systemic metabolic adaptations. This is reflected in the marked elevation of ceruloplasmin levels among our bladder cancer patients. Under physiological conditions, ceruloplasmin exerts antioxidant effects by oxidizing toxic free iron (Fe+2 to Fe+3), preventing harmful Fenton reactions (20). However, as a positive acute-phase reactant, its hepatic synthesis is dramatically upregulated by tumor-mediated inflammatory signaling and hypoxia. The parallel rise of ceruloplasmin with advancing tumor stage and grade indicates that it represents a systemic compensatory mechanism attempting to cushion the high oxidative load. Nevertheless, persistent copper ion accumulation associated with prolonged ceruloplasmin elevation may inadvertently transition from a protective response to a pro-oxidant stimulus, potentially fostering angiogenesis and tumor progression within the malignant niche (20,21). Taken together, the synchronized alterations of ceruloplasmin, ADMA, MPO, XO, TAS, and TOS present strong biochemical evidence of a self-sustaining cycle where inflammation, hypoxia, and redox failure converge to dictate the aggressiveness of bladder cancer.

Limitations

Despite its prospective nature and comprehensive evaluation of multiple novel oxidative biomarkers, several limitations of this study must be acknowledged. First, the sample size was

relatively modest and drawn from a single clinical center, which may restrict the immediate generalizability of the findings across broader demographic populations. Second, the single-point baseline measurement of serum biomarkers precludes the assessment of longitudinal variations; evaluating how these oxidant and antioxidant parameters fluctuate following transurethral resection (TUR-BT) or systemic chemotherapy would provide deeper insight into their dynamic monitoring utility. Lastly, because tissue-level expressions of these specific enzymes were not evaluated, the precise intra-tumoral cellular sources and local concentrations of these markers remain inferred through their systemic circulation profiles. Future large-scale, multi-center studies utilizing paired tissue and serum analyses are required to validate the definitive prognostic efficacy of these biomarkers.

CONCLUSION

In conclusion, this study suggests that the systemic oxidant-antioxidant balance is compromised in patients with bladder cancer. The alteration of specific parameters namely ceruloplasmin, ADMA, MPO, XO, and TOS, alongside decreased TAS reflects a disturbed redox equilibrium associated with the presence of the disease. Furthermore, the progressive elevation of ceruloplasmin, ADMA, and MPO in correlation with higher tumor grade and advanced invasion suggests that these biomarkers may reflect tumor biological aggressiveness and clinical progression. While further longitudinal tracking and survival data are required to establish their definitive prognostic value, these interconnected markers hold potential to serve as non-invasive, supportive indicators in the clinical evaluation of bladder cancer.

Conflict of Interest: The authors declare no conflicts of interest.

Funding: The authors received no specific funding for this research.

Informed Consent: Written informed consent was obtained from all participants.

Ethics Approval: The study was approved by the Non-Interventional Clinical Research Ethics Committee of Van Yüzüncü Yıl University (Decision No. 04, Date: October 8, 2025). Written informed consent was obtained from all participants, and the study adhered to the Declaration of Helsinki principles.

Author Contributions: Concept; Murat Demir, Design; Muhammed Fatih Keleş, Data Collection; Veli Duman Analysis; Sıddık Keskin, Canan Demir, Literature Search; Recep Eryılmaz, Kerem Taken, Writing; Murat Demir, Critical Review: Rahmi Aslan, Halit Demir

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424. https://doi.org/10.3322/caac.21492
2. Demir M, Demir C. Oxidative stress has a negative effect on the development and progression of bladder cancer. Turk J Oncol. 2022;37(2). https://doi.org/10.5505/tjo.2022.3538
3. Wigner P, Grebowski R, Bijak M, Saluk-Bijak J, Szemraj J. The interplay between oxidative stress, inflammation and angiogenesis in bladder cancer development. Int J Mol Sci. 2021;22(9):4483. https://doi.org/10.3390/ijms22094483
4. Gecit I, Aslan M, Gunes M, et al. Serum prolidase activity, oxidative stress, and nitric oxide levels in patients with bladder cancer. J Cancer Res Clin Oncol. 2012;138(5):739–43. https://doi.org/10.1007/s00432-011-1137-8
5. Lazar-Poloczek E, Romuk E, Rozentryt P, et al. Ceruloplasmin as redox marker related to heart failure severity. Int J Mol Sci. 2021;22(18):10074. https://doi.org/10.3390/ijms221810074
6. Dowsett L, Higgins E, Alanazi S, et al. ADMA: a key player in the relationship between vascular dysfunction and inflammation in atherosclerosis. J Clin Med. 2020;9(9):3026. https://doi.org/10.3390/jcm9093026
7. Lin W, Chen H, Chen X, Guo C. The roles of neutrophil-derived myeloperoxidase (MPO) in diseases: the new progress. Antioxidants (Basel). 2024;13(1):132. https://

doi.org/10.3390/antiox13010132

8. Saito H, Tanaka K, Iwasaki T, et al. Xanthine oxidase inhibitors are associated with reduced risk of cardiovascular disease. Sci Rep. 2021;11(1):1380. https://doi.org/10.1038/s41598-020-80149-4
9. Ciftci H, Gul HF, Canacik O, et al. The usability of MCP-1, fetuin-A, TAS, and TOS levels in the diagnosis of acute myocardial infarction. Eur Rev Med Pharmacol Sci. 2023;27(10). https://doi.org/10.26355/eurrev_202305_32674
10. Chen MM, Meng LH. The double faced role of xanthine oxidoreductase in cancer. Acta Pharmacol Sin. 2022;43(7):1623–32. https://doi.org/10.1038/s41401-021-00800-7
11. Gunes M, Eryilmaz R, Aslan R, et al. Oxidant-antioxidant levels in patients with bladder tumours. Aging Male. 2020;23(5):1176–81. https://doi.org/10.1080/13685538.2019.1608843
12. Yang YW, Dai CM, Chen XH, Feng JF. The relationship between serum trace elements and oxidative stress of patients with different types of cancer. Oxid Med Cell Longev. 2021;2021(1):4846951. https://doi.org/10.1155/2021/4846951
13. Valadez-Cosmes P, Raftopoulou S, Mihalic ZN, Marsche G, Kargl J. Myeloperoxidase: growing importance in cancer pathogenesis and potential drug target. Pharmacol Ther. 2022;236:108052. https://doi.org/10.1016/j.pharmthera.2022.108052
14. Knaapen AM, Güngör N, Schins RP, Borm PJ, Van Schooten FJ. Myeloperoxidase: a multitalented mediator of inflammation and cancer. Histochem Cell Biol. 2006;125(4):333–48. https://doi.org/10.1007/s00418-005-0045-3
15. Guo Q, Xu J, Huang Z, et al. ADMA mediates gastric cancer cell migration and invasion via Wnt/β-catenin signaling pathway. Clin Transl Oncol. 2021;23(2):325–34. https://doi.org/10.1007/s12094-020-02527-9
16. Avci E, Karabulut A, Alp AG, Baba B, Bilgi C. Crucial markers showing the risk of coronary artery disease in obesity: ADMA and neopterin. J Med Biochem. 2020;39(4):452. https://doi.org/10.5937/jomb0-26658
17. Bednarz-Misa I, Fleszar MG, Zawadzki M, et al. L-Arginine/NO pathway metabolites in colorectal cancer: relevance as disease biomarkers and predictors of adverse clinical outcomes following surgery. J Clin Med. 2020;9(6):1782. https://doi.org/10.3390/jcm9061782
18. Lembas A, Mikula T, Sapula M, et al. The correlation of ADMA with proinflammatory, liver injury and cancer biomarkers in patients with liver dysfunction. Hepatology Forum. 2024;5(4):171. https://doi.org/10.14744/hf.2023.0021
19. Ma M, Liu F, Miles HN, et al. Proteome-wide profiling of asymmetric dimethylated arginine in human breast tumors. J Am Soc Mass Spectrom. 2023;34(8):1692–700. https://doi.org/10.1021/jasms.3c00154
20. Liu Z, Wang M, Zhang C, Zhou S, Ji G. Molecular functions of ceruloplasmin in metabolic disease pathology. Diabetes Metab Syndr Obes. 2022;15:695–711. https://doi.org/10.2147/DMSO.S348046
21 Chen F, Han B, Meng Y, et al. Ceruloplasmin correlates with immune infiltration and serves as a prognostic biomarker in breast cancer. Aging (Albany NY). 2021;13(16):20438–67. https://doi.org/10.18632/aging.203427