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# **Dynamics of Cancer-Related Proteins in Patients with Bladder Cancer**

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## **Abstract**

Bladder cancer (BC) is the second most common malignancy in the urologic field. Preoperative predictive biomarkers of cancer progression and prognosis are imperative for optimizing appropriate treatment for patients with BC. The prediction of patient outcomes before initial treatment would enable physicians to choose better modalities and avoid unnecessary aggressive treatments. In addition, preoperative molecular markers are expected to be a minimally invasive tool for predicting precise prognosis and progression in patients with BC. The proteins secreted from the tumor cells reflect various states of tumors in real time and at given conditions, and those expression patterns are different from normal cell components. Approximately 20–25% of cellular proteins are in extracellular spaces, and these proteins have important roles in invasion, angiogenesis, regulation of cell-to-cell interactions, and metastasis. It has been suggested that tumor-secreting proteins are a promising source for tumor diagnostic biomarkers. Proteomic analysis was utilized to identify the secreted proteins in sera from patients with BC. Several biomarkers associated with BC are reviewed here.

**Keywords:** bladder cancer, urothelial carcinoma, diagnosis, protein, biomarker

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## **1. Introduction**

Bladder cancer (BC) is one of the most common malignancies of the urinary tract and results in significant morbidity and mortality worldwide. Approximately 75–85% of BC cases are diagnosed as nonmuscle-invasive bladder cancer (NMIBC) at the first diagnosis, and approxi-

mately 70% of cases present as pTa, 20% present as pT1, and 10% present as carcinoma in situ (CIS) lesions [1]. NMIBC has a tendency to recur (50–70%) and may progress (10–20%) to a higher grade and/or muscle-invasive BC (MIBC) in time, which can lead to high cancer-specific mortality [2].

Histological tumor grade is one of the clinical factors associated with outcomes of patients with NMIBC. High-grade NMIBC generally exhibits more aggressive behavior than low-grade NMIBC, and it increases the risk of a poorer prognosis [3, 4]. Due to the unfavorable prognosis of high-grade NMIBC, a differential diagnosis between high-grade and low-grade NMIBC might be crucial for more appropriate follow-up and aggressive treatment. Cystoscopy and urine cytology are commonly used techniques for the diagnosis and surveillance of BC. Cystoscopy can identify the most papillary and solid lesions, but this is highly invasive for the patients; however, urine cytology is limited by examiner experience and low sensitivity. For these reasons, some tumor markers have been investigated (e.g., BTAstat, NMP22), but their sensitivity and specificity are limited [5] and they are unable to predict the clinical outcome of BC patients.

Preoperative predictive biomarkers for cancer progression and prognosis are imperative for optimizing appropriate treatment for patients with BC. The prediction of patient outcomes before initial treatment would enable physicians to choose better modalities and avoid unnecessary aggressive treatments [6, 7]. Various predictive models have been widely investigated to reduce BC-related deaths. One of the challenges is precisely predicting the pathological stage, which is a reliable and established factor connected to disease prognosis [8, 9]. Although preoperative computed tomography and magnetic resonance imaging for BC staging are undergoing development, their accuracy for predicting pathological stage varies between 40% and 90% [10, 11]. To overcome these limitations, preoperative molecular markers are expected to be a minimally invasive tool for predicting precise prognosis and progression in patients with BC.

Numerous efforts have been made to identify tumor markers. In recent years, a vast array of tumor antigens and their products have been identified. Hegele et al. investigated the serum levels of carcinoembryonic antigen (CEA) and carbohydrate-antigen 19-9 (CA19-9) in patients with BC [12]. They concluded that the serum levels of CEA and CA19-9 are associated with tumor invasiveness and pathologic grade. Another study of the serum level of CEA, CA19-9, and soluble cytokeratin 19 fragment (CYFRA21-1) in BC patients indicated that CYFRA21-1 is relatively useful for monitoring BC and predicting its prognosis [13]. These serum materials might be useful for monitoring and staging BC. However, a serum marker that can serve as a reliable detection marker for BC has yet to be identified.

The proteins secreted from the tumor cells reflect various states of the tumor in real time and at given conditions, and those expression patterns are different from normal cell components. Thus, the proteins secreted into body fluids, such as serum, urine, cerebrospinal fluid, tears, and saliva, from tumor cells and conditioned media of cultured tumor cells have been investigated. Approximately 20–25% of cellular proteins are in extracellular spaces, and these proteins have important roles in differentiation, invasion, metastasis, angiogenesis, and regulation of cell-to-cell and cell-to-extracellular matrix interactions [3, 14, 15]. It has been

suggested that tumor-secreting proteins are a promising source for tumor diagnostic biomarkers. Proteomic analysis was utilized to identify the secreted proteins in sera from patients with BC. Several biomarkers and their association with BC are reviewed here [4, 5, 16, 17].

## 2. Candidates for a serum biomarker in patients with bladder cancer

### 2.1. Uroplakin III

Uroplakin plays a key role in urothelial functions, including participation in the permeability barrier, adjustment of urothelial surface area, stabilization of the urothelial surface, and development of the urinary tract [18]. Because of their specific expression in the urothelium, uroplakin has been investigated as a potential immunohistochemical marker for primary lesions and for identification of the primary cancer in patients with metastases of unknown origin [19]. The uroplakin family comprises a group of four transmembrane proteins, including Ia (27 kDa), Ib (28 kDa), II (15 kDa), and III (47 kDa) [20]. Uroplakin III is the largest protein in the uroplakin family and has been exclusively investigated by immunohistochemical staining. In a previous study, the loss of uroplakin III expression in pathological specimens is associated with biologically aggressive BC and poor prognosis for patients who underwent radical cystectomy [3]. However, the utility of serum uroplakin III (e.g., predictive models of disease outcome) in patients with BC is unknown.

Serum uroplakin III levels were investigated in patients with BC and healthy controls utilizing dot blot analysis to demonstrate the role of preoperative serum uroplakin III levels as a potential biomarker for BC (**Table 1**) [17]. The uroplakin III levels in serum in patients with NMIBC, in those with MIBC, and in healthy controls were 1.3, 2.8, and 0.7, respectively. The serum uroplakin III levels in patients with NMIBC and MIBC were significantly higher than those in healthy controls ( $P = 0.04$  and  $P < 0.001$ , respectively). Comparison of BC groups with the control group yielded the area under the curve-receiver operating characteristics (AUC-ROC) levels for NMIBC and MIBC of 0.62 and 0.88, respectively. The sensitivity and specificity for NMIBC, using a cut-point of 2.1, were 29% and 96%, respectively. The sensitivity and specificity for MIBC, using a cut-point of 2.0, were 67% and 96%, respectively. There was a significantly greater increase in serum uroplakin III levels in patients with MIBC than in those with NMIBC ( $P = 0.003$ ). Preoperative serum uroplakin III levels were significantly higher in patients with positive lymphovascular invasion and pathological grade 3 disease than in those with negative lymphovascular invasion and grade 1 or grade 2 disease. There were no significant differences in other factors, including gender, age, and lymph node status. Survival analysis showed that patients with high serum uroplakin III had a significantly increased probability of cancer-specific death ( $P = 0.04$ ). However, there was no factor associated with an increased risk for cancer-specific death in multivariate Cox proportional hazards regression analysis. These findings suggest that serum uroplakin III is one of the candidates for a predictive biomarker for prognosis of patients with BC.

	N of patients (%)	Serum uroplakin III level		P*
		Median	Range	
Sex				0.41
Male	44 (85)	1.8	0.0–6.9	
Female	8 (15)	1.7	0.02–3.2	
Age (years)				0.72
<65	18 (35)	1.6	0.0–6.9	
≥65	34 (65)	1.8	0.0–6.0	
Pathological stage				0.003
<pT2	28 (54)	1.3	0.66–6.0	
≥pT2	24 (46)	2.8	0.0–6.9	
Pathological grade				0.005
Grade 1 or 2	27 (52)	1.3	0.0–5.4	
Grade 3	25 (48)	2.5	0.25–6.9	
Lymphovascular invasion				0.02
Negative	35 (67)	1.3	0.0–6.9	
Positive	17 (33)	2.5	0.66–6.0	
Lymph node metastases				0.4
Negative	46 (88)	1.7	0.0–6.9	
Positive	6 (12)	2.6	0.74–5.4	

\*Mann-Whitney *U* test.

**Table 1.** Serum uroplakin III levels in patients with bladder cancer.

Other investigators have evaluated the role of the uroplakin family in blood samples from patients with BC [21, 22]. Circulating uroplakin II mRNA-positive cells in blood samples were detected using a nested reverse-transcription polymerase chain reaction assay, as reported by Lu et al. [22]. The detection rate was associated with pathological stage, and positive rates of uroplakin II mRNA were increased with disease extension. Li et al. [21] investigated expression levels of uroplakin II-positive cells in sequential blood samples from patients with metastatic BC. After chemotherapeutic treatment, patients responded well to chemotherapy and uroplakin II-positive cells disappeared. These previous studies showed that uroplakin II in peripheral blood might be used as a biomarker for cancer stage and treatment response.

Although none of the biomarkers detected prognosis for patients with BC, reliable biomarkers will lead to avoidance of unnecessary chemotherapy and radiation and will help physicians choose intensive treatment for the appropriate patients. Expression levels of serum uroplakin III could be used as a predictive biomarker for patients who are at increased risk for worse prognosis. This would help physicians make decisions regarding individual treatment.

## 2.2. Periplakins

The plakin family mediates tissue filaments that represent the cell cytoskeleton in cell-to-cell junctions mediated by cadherin, and it is able to withstand mechanical stimulation and provide integrity of tissues [23, 24]. Dysfunctional plakin proteins show diverse diseases, and autoantibodies (AAb) and mutations perturb their activities with profound consequences. Seven plakin proteins are currently reported. For example, envoplakin, desmoplakin, and periplakin are related to desmosomes in various tissues. A proteomics technique like two-dimensional gel electrophoresis (2-DE) plus immunoblot analysis has been demonstrated to identify tumor-associated proteins for BC [4]. The 195-kDa membrane-associated protein periplakin is involved in cellular movement and attachment [25]. Loss of periplakin expression determined using immunohistochemical staining was associated with biological aggressiveness of BC [26]. In addition, the majority of BC cases showed loss or decreased expression patterns compared with normal or benign lesions on pathological slides. Another study determined whether the dynamics of serum periplakin would detect BC and predict the prognosis of patients with BC (Table 2) [16].

	N of patients (%)	Serum periplakin levels		P*
		Median	Range	
Sex				1
Male	43 (86)	0.23	0.0–4.4	
Female	7 (14)	0.32	0.0–20.5	
Age (years)				0.4
<65	16 (32)	0	0.0–7.0	
≥65	34 (68)	0.51	0.0–20.5	
Pathological stage				0.03
<pT2	27 (54)	0	0.0–4.1	
≥pT2	23 (46)	1.5	0.0–20.5	
Pathological grade				0.4
Grade 1 or 2	26 (52)	0	0.0–7.9	
Grade 3	24 (48)	0.98	0.0–20.5	
Lymphovascular invasion				0.4
Negative	33 (67)	0.043	0.0–7.0	



	N of patients (%)	Serum periplakin levels		P*
		Median	Range	
Positive	17 (33)	0.74	0.0–20.5	0.4
Lymph node metastases				
Negative	44 (88)	0.50	0.0–3.8	
Positive	6 (12)	0.16	0.0–20.5	
*Mann-Whitney <i>U</i> test.				

**Table 2.** Serum periplakin levels in patients with bladder cancer.

The median levels of serum periplakin in patients with BC were significantly less than those of healthy controls (0.3 and 5.7, respectively;  $P < 0.0001$ ). The AUC-ROC level for the comparison between the BC group and the control group was 0.85. The sensitivity and specificity for BC, using a cut-off point of 4.0, were 84% and 73%, respectively. The levels of serum periplakin were higher in patients with MIBC than in those with NMIBC (0 and 1.5, respectively;  $P = 0.03$ ). However, serum periplakin levels were not associated with other factors, including gender, age, pathological grade, lymphovascular invasion, and lymph node status. Survival analyses using the log-rank test showed no significant differences in terms of progression and cancer-specific survival. Using multivariate Cox proportional hazards regression analysis, it was determined that none of the factors was associated with an increased risk for progression or cancer-specific survival.

Recent studies described the biological role of periplakin in cancer. Decreased expression of periplakin was associated with the progression of esophageal squamous cell carcinoma [27, 28]. Cyclin A2-induced upregulation of periplakin was associated with poor prognosis as well as cisplatin resistance in endometrial cancer cells [29]. Periplakin silencing reduced migration and attachment of pharyngeal squamous cancer cells [30]. Periplakin silencing in triple-negative breast cancer cells increased cell growth and reduced cell motility [31]. The loss of periplakin expression determined using immunohistochemical staining was associated with pathological stage and cancer-specific survival in patients with BC [26]. Periplakin is imperative for maintaining epithelial cell barriers, cellular movement, and attachment in normal physiology [23–25].

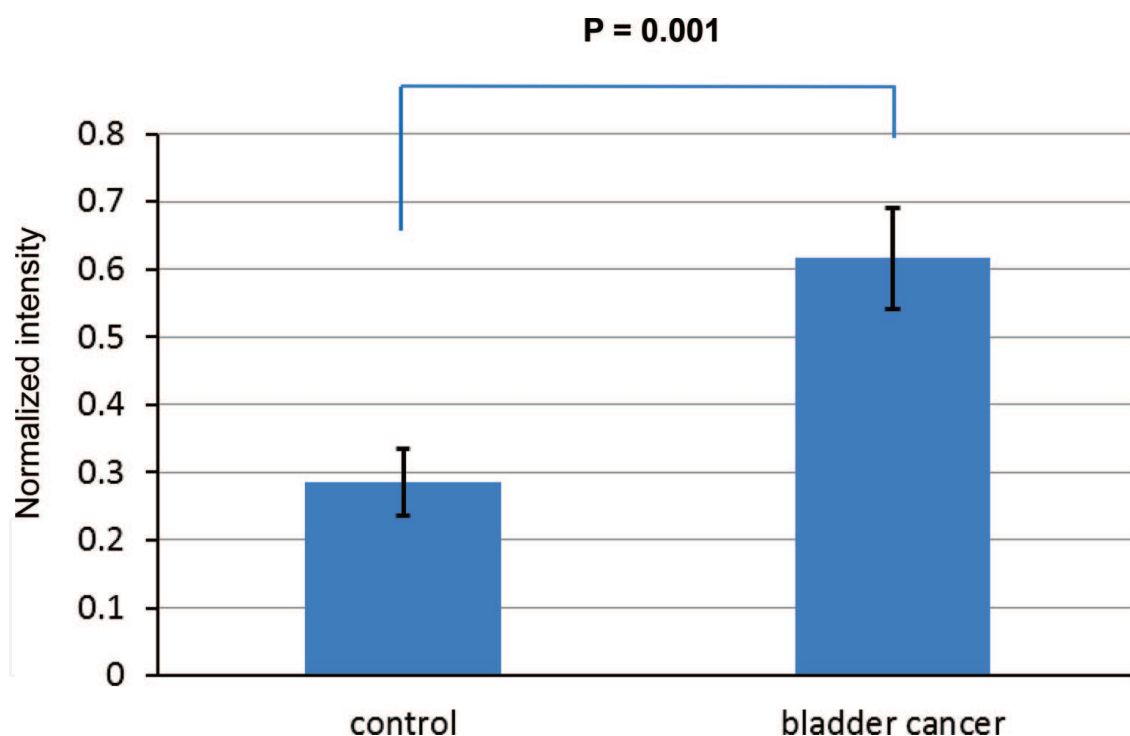
Patients with BC showed significantly decreased expression of serum periplakin protein compared with normal controls. It may be suitable as an adjunct to urine cytology and cystoscopy as a noninvasive diagnostic modality.

**2.3. S100A6**

The S100 protein family contains more than 20 low-molecular-weight  $\text{Ca}^{2+}$ -binding proteins [32]. Most of the genes encoding S100 proteins are located as a cluster on chromosome 1 in the human genome [32, 33]. These proteins are localized in the cytoplasm and nucleus of a wide range of cells and help regulate many cellular processes, such as cell-cycle progression and differentiation [33]. Therefore, the S100 protein family is emerging as a potentially important

group of markers in multiple types of tumors. One of these proteins, S100A6, was reported to regulate the actin cytoskeleton function, ubiquitin ligase action, cell proliferation, and apoptosis [32]. S100A6 overexpression has been frequently reported under stress conditions [34] and in various types of cancers, including melanoma, colon, pancreatic, gastric cancer, and BC [5].

The levels of S100A6 expression in sera of healthy controls and BC patients were investigated [5]. There was a significant difference between BC patients and healthy controls ( $P = 0.001$ ; **Figure 1**). Serum S100A6 expression in NMIBC patients was significantly higher than that of healthy controls ( $P = 0.04$ ). Serum S100A6 in patients with MIBC was significantly higher than that in NMIBC patients ( $P = 0.004$ ). Serum S100A6 in BC patients was associated with pathological grade ( $P = 0.001$ ). However, there was no association between lymph node status and serum S100A6. At a cut-off point of 0.5, the sensitivity and specificity of S100A6 expression as a marker for BC were 48% and 93%, respectively. As a detection marker for MIBC, at a cut-off point of 0.4, the sensitivity and specificity were 80% and 63%, respectively. The AUC-ROC levels were 0.73 and 0.73, respectively.



**Figure 1.** Levels of serum S100A6 in healthy controls and bladder cancer patients. There was statistical significance between groups.

S100A6, a member of the S100 family of calcium-binding proteins, is expressed in BC tissue [35], and immunohistochemical staining of S100A6 showed localization mainly in the cytoplasm of tumor cells [36]. The expression patterns of S100A2 and S100A4, also members of the S100 family, correlated well with pathological stage and prognosis [14]. This finding demonstrated that only one clinical aspect represented postoperative outcomes. It is difficult to



determine which S100 protein is better for BC in terms of biological markers; however, serum markers are potentially useful in clinical practice both preoperatively and postoperatively. Cai et al. reported an association between increased serum S100A6 levels and acute coronary syndrome [37]. S100A6 levels were significantly increased and correlated with tumor necrosis factor (TNF)- $\alpha$  levels in patients with coronary events. They concluded that a close relationship exists between S100A6 and TNF- $\alpha$ -mediated inflammation. Another study reported the expressions of TNF- $\alpha$  and pigment epithelium-derived factor (PEDF), which are highly selective in inhibiting remodeling vessels by inducing apoptosis of endothelial cells in healthy urothelium and in patients with urothelial carcinoma. Decreased PEDF expression and increased TNF- $\alpha$  expression were identified in tumorous tissue compared with healthy urothelium, and the authors concluded that decreased PEDF or increased TNF- $\alpha$  expression is related to differentiation, invasiveness, and angiogenesis of BC [38]. In a study using immunohistochemical staining of 83 patients who underwent radical cystectomy, univariate and multivariate analyses showed that overall survival was significantly greater among patients with lower S100A6 expression [36]. Although the precise mechanism underlying the correlation of S100A6 expression with pathological stage remains to be clarified, serum S100A6 may reveal its role in the biological aggressiveness of BC.

Serum levels of S100A6 in BC patients were significantly higher than in healthy controls. In addition, serum level of S100A6 was associated with pathological stage. By applying this serum marker in clinical practice, patients would benefit from experiencing less invasive examinations and it would allow detection of life-threatening cancer earlier than current modalities.

### 3. Future Potential

BC ranks as one of the most prevalent newly diagnosed cancers. High-risk NMIBC revealed high rates (up to 90%) of recurrence [39]. It is important to diagnose BC accurately and quickly with the help of a simple and cost-effective method. Although histological examination remains the gold standard, urine cytology is helpful as a noninvasive method of early diagnosis of BC [40]. With the currently available modalities, there is no reliable biochemical or molecular examination that can be used as a universal screening tool for BC.

Tumor-associated antigens released into the bloodstream could induce a humoral immune response and generate AAb. The immune response to such antigens generates remarkable biological amplification, although tumor-associated antigens are undetectable in sera during the early stage of tumorigenesis [41]. Therefore, hundreds of tumor-associated antibodies have been identified as potential AAb biomarkers that could be useful for cancer diagnosis [42]. In addition, recent studies based on AAb profiling of cancer patients have suggested diagnostic and prognostic biomarker potential of AAb [43].

Immunoblot analysis combined with 2-DE can identify tumor-associated secreted antigenic proteins that elicit a humoral response in sera of BC patients. By comparing immunoreactive patterns from sera of patients with high-grade and low-grade BC, tumor markers associated with histological grade were obtained. The proteins extracted from culture supernatants of BC

cell lines were separated by 2-DE and transferred onto the polyvinylidene difluoride membranes, and they reacted with mixed sera of patients with high-grade BC or low-grade BC. Results indicated that serum IgG levels of anti-calreticulin (CALR) and matrix metalloproteinase (MMP)-2 AAb were significantly higher in BC patients than in normal controls ( $P < 0.01$ ) [4]. In the ROC analysis for anti-CALR AAb, the diagnostic sensitivity and specificity for BC patients were 64% and 60%, respectively. In terms of anti-MMP AAb, sensitivity and specificity for BC patients were 60% and 62%, respectively. The AUC-ROC levels were 0.65 and 0.59, respectively. AAb against tumor-associated antigens have been identified in sera from patients with various cancers, including BC [4]. The application of the humoral immune response for the detection of cancer biomarkers has great potential [42, 43]. Furthermore, the immune system is especially well adapted for early detection of cancer because AAb can be detected before the appearance of other biomarkers or phenotypic alternations at an early stage of tumorigenesis [41].

Although the prostate-specific antigen test is utilized for the detection of prostate cancer, a diagnosis of BC still relies on imaging modality and cystoscopy because effective and simple screening biomarkers are lacking. Further research is warranted to clarify the availability and limits of the aforementioned serum markers in patients with BC.

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