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# Prognosis Value of ISG15 Protein Expression in Bladder Cancer

[1,2]*Lulwah Zeyad Aljumaiah and* [1]*Salina Saddick*

[1]Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia
[2]Department of Biology, Faculty of Science, University of Hail, Saudi Arabia

**Abstract:** Bladder cancer is a primary cause of death globally, and is a genitourinary disease. Compared to 1990, it expanded 10-fold in Saudi Arabia by 2016. Despite recent technical advancements in its identification and care, bladder cancer continues to be a global burden due mostly to high recurrence rates and metastasis. The management of bladder cancer is mostly based on clinicopathological characteristics, which are insufficient to accurately predict patient outcomes. So, it is necessary to identify more robust biomarkers that would more precisely enhance patients' prognoses and outcomes. It is necessary to identify more robust biomarkers that would more precisely enhance patients' prognoses and outcomes. Recent investigations have demonstrated that all cancers exhibit large quantities of the ubiquitin-like Interferon-stimulated gene 15 (ISG15) protein. Nonetheless, the role of ISG15 remains poorly understood, particularly in bladder cancer. Therefore, this study aimed to determine the link between the ISG15 protein expression levels and clinicopathologic features and survival outcomes of Saudi bladder cancer -diagnosed individuals. The level of ISG15 expression was determined in 128 bladder cancer samples by tissue microarray (TMA) and immunohistochemistry (IHC) techniques. Our findings demonstrated an elevation of the ISG15 expression pattern (+2 to +3) in around 40% of our population. Expression level was significantly correlated with lymphovascular invasion (LVI), tumor grade, disease-free survival (DFS), tumor stage, and lymph node (LN) status ($p<0.05$). In Conclusion, our findings point to a possible role for ISG15 as a tumor promoter in bladder cancer, suggesting that it could be a useful marker for diagnosis, prognosis, and therapeutic immunotherapy.

**Key words:** Bladder Cancer · Biomarker ISG15 · Prognosis Value · Survival

## INTRODUCTION

Bladder cancer comes as the 11th most prevalent cancer in males and 12th in females pursuant to the 2020 Cancer Registry Report globally, with a higher incidence in developed countries [1]. Its onset in males is higher than in females by about 4 times as the 6th place common type and 9th most common cause of cancer deaths in men [2]. In Saudi Arabia, bladder cancer incidence increases over time. To illustrate, in 2016 the bladder cancer cases increased 10-fold compared to only 120 cases in 1990 [3]. In addition, bladder cancer incidence is categorized histologically into two forms: Transitional cell carcinoma and non-transitional cell carcinoma. Transitional cell carcinoma represents about 90% of bladder cancer cases and has a good prognosis with a <80% higher 10 years survival rate [4]. The less common histological type of bladder cancer is known as a non-transitional cell carcinoma and includes squamous cell carcinomas, neuroendocrine tumors, adenocarcinomas, and sarcomas [5]. Despite the fact that the etiopathogenesis of bladder cancer is not completely known, many experts believe that mechanical, environmental, and genetic factors, or rather, disposition have an equal impact on the incidence of bladder cancer. As the most primitive grievances of patients are macroscopic hematuria and dysuria, which are not related to infections of the urinary tract. Researchers determined that multiple factors contribute to the occurrence of bladder cancer [6]. The major risk factor of bladder cancer incidence is smoking where carcinogenesis is excreted from cigarettes and remains in constant contact with the urinary tract until eliminated, thus increasing the danger of cancer [7]. Besides, aromatic amines, polycyclic aromatic hydrocarbons, and aniline dyes exposure, such chemicals are often used in different occupations such as textile, paint, plastic, printing, and

**Corresponding Author:** Lulwah Zeyad Aljumaiah, Department of Biological Sciences, Faculty of Science, King Abdulaziz University, Jeddah. Saudi Arabia.

rubber industries [8]. Additionally, it has been demonstrated that using specific medicines used in previous cancer treatment and patients who have previously undergone radiation therapy for pelvic and abdominal malignancies. As well as using diabetic medications, infections with bladder schistosomiasis increase the risk of bladder cancer incidence [9, 10]. While the gold standard for bladder cancer diagnosis is the cystoscopic assessment, its invasiveness delays its early utilization, therefore, it requires a non-invasive diagnostic tool [11]. Thus, recently, urine-based noninvasive detection tests using several urinary biomarkers have become the hotspot for diagnosis and follow-up. There are six urine-based biomarkers, which were approved by the FDA and applied for bladder cancer diagnosis in clinics (NMP22 BladderChek, NMP22 BC, BTA TRAK, BTA Stat, uCyt+/ImmunoCyt, and UroVysion) [12]. In addition, many genetic aberrations commonly associated with bladder cancer have been studied and shown effectiveness in bladder cancer diagnosis including TRAP [13], FGFR3 [14], and P16 [15]. Moreover, epigenetic modifications play a key role in the bladder cancer as well and can provide an early warning for tumor induction and progression. DNA methylation is a crucial epigenetic modification that has a substantial impact on the transcriptional control of gene expression. The methylation status of many genes showed an association with bladder cancer initiation, progression, and recurrence [16]. For instance, hypermethylation of PCDH17, POU4F2, PENK, TMEFF2, and GDF15 showed high sensitivity and specificity in bladder cancer detection [17-19]. While the hypermethylated TERT and OTX1 were reported as prognostic biomarkers of bladder cancer [20]. Despite some remarkable results, the majority of the biomarkers do not have sufficient sensitivity or specificity, which makes the discovery of new prognostic biomarkers necessary in order to diagnose and treat bladder cancer more accurately.

Interferon-stimulated gene 15 (ISG15) encodes ISG15 protein that has other names such as UCRP, IMD38, IP17, G1P2, IMD38, and IFI15, which is a 15 kDa ubiquitin-like protein. ISG15 is constructed of two domains including a β-grasp fold containing a five-strand mixed β-sheet into which intercalated a single three-turn α-helix [21]. Intracellularly, ISG15 can be found in its free form, or attached covalently to other target proteins through the process known as ISGylation. The unconjugated intracellular ISG15 was reported to function as a cytokine and can bind noncovalently to intracellular proteins and to regulate their activities, regulate viral replication, and host responses [22]. However, it can be detected extracellularly as free molecule and act as a cytokine to regulate the immune responses [23-26]. Furthermore, in tumor cells, many studies have reported that ISG15 overexpressed in almost all tumors including cervical cancer [27], hepatocellular carcinoma [28], breast cancer [29], colon cancer [30], and esophageal squamous cell carcinoma [31], and stimulated by type I interferons (IFN-α and β) [32]. Interestingly, the role of ISG15 in cancer is still unclear whether it has an oncogenic or tumor-suppressive role [33, 34]. To illustrate, some studies documented that overexpressed ISG15 has an intrinsic feature of human tumors that promotes tumorigenesis and metastasis [35]. Whilst others have reported that free ISG15 high levels correlate with a better outcome for cancer patients [34]. In bladder cancer, as far as we know, ISG15 expression has only been examined in only one study. In that study, they investigated the association between ISG15 levels and the immune responses in bladder cancer [36]. To the best of our knowledge, this is the first research to investigate the correlation between the ISG15 expression in human bladder cancer with the clinicopathological characteristics and survival outcomes of the patients diagnosed with bladder cancer. We analyzed the ISG15 expression in bladder cancer patients using Tissue Microarray (TMA) analysis and immunohistochemistry assay.

## MATERIALS AND METHODS

**Ethical Approval:** The current study was reviewed and approved by Research Ethics Committee (REC) No. (HA-02-J-008) at King Abdulaziz University Hospital, Jeddah (KAUH).

**Patients and Samples:** Patients diagnosed with bladder cancer at the Pathology and Gynecology Departments, King Abdulaziz University Hospital (KAUH) between 1995 and 2014 provided written authorization for the use of 128 FFPE tissues that had been previously processed and stored in formalin. The Tumor Node Metastasis (TNM) classification system was primarily used to categorize the patients based on their diagnoses. After gaining approval from the Institutional Review Board (IRB), we obtained all necessary pathological and clinical data from the medical records of the patients. All research was conducted at the Center of Excellence in Genomic Medicine Research (CEGMR) in Jeddah, Saudi Arabia. Table 1 summarizes the main clinicopathological parameters (including gender, age, stage, grade, lymph node status, and… etc.) as well as follow-up and survival data.

Table 1: The correlation between clinicopathological parameters and ISG15 protein expression patterns (<0 vs >1, Median= 35) of bladder cancer

| Feature | Number of cases (%) | ISG15 expression Median 0 (%) | 1 (%) | (*p*-value) $\chi^2$ |
|---|---|---|---|---|
| Gender | | | | |
| Female | 22 (17%) | 9 (21%) | 13 (15%) | 0.39 |
| Male | 105 (82%) | 33 (79%) | 72 (85%) | |
| Missing | 1 (1%) | | | |
| Age | | | | |
| < 60 | 62 (48%) | 18 (44%) | 44 (52%) | 0.37 |
| > 60 | 63 (49%) | 23 (56%) | 40 (48%) | |
| Missing | 3 (2%) | | | |
| Type | | | | |
| Transitional | 106 (83%) | 35 (85%) | 71 (85%) | 0.90 |
| Non-transitional | 19 (15%) | 6 (15%) | 13 (16%) | |
| Missing | 3 (2%) | | | |
| Tumor Stage | | | | |
| stage I | 41 (32%) | 9 (27%) | 32 (49%) | 0.10 |
| stage II | 31 (24%) | 11 (32%) | 20 (30%) | |
| stage III | 3 (2%) | 1 (3%) | 2 (3%) | |
| stage IV | 25 (20%) | 13 (38%) | 12 (18%) | |
| Missing | 28 (22%) | | | |
| Tumor Stage | | | | |
| Low stage | 72 (56%) | 20 (59%) | 52 (79%) | 0.04 |
| High stage | 28 (22%) | 14 (41%) | 14 (21%) | |
| Missing | 28 (22%) | | | |
| Tumor Grade | | | | |
| Low grade | 55 (43%) | 12 (33%) | 43 (57%) | 0.02 |
| High grade | 57 (45%) | 24 (67%) | 33 (43%) | |
| Missing | 16 (13%) | | | |
| LN status | | | | |
| Negative | 79 (62%) | 22 (71%) | 57 (88%) | 0.05 |
| Positive | 17 (13%) | 9 (29%) | 8 (12%) | |
| Missing | 32 (25%) | | | |
| LVI status | | | | |
| Negative | 81 (63%) | 21 (68%) | 60 (91%) | 0.00 |
| Positive | 16 (13%) | 10 (32%) | 6 (9%) | |
| Missing | 31 (24%) | | | |
| Metastasis | | | | |
| No | 79 (62%) | 26 (81%) | 53 (86%) | 0.60 |
| Yes | 15 (12%) | 6 (19%) | 9 (15%) | |
| Missing | 34 (27%) | | | |
| Smoking Status | | | | |
| No | 16 (13%) | 2 (20%) | 14 (35%) | 0.36 |
| Yes | 34 (27%) | 8 (80%) | 26 (65%) | |
| Missing | 78 (61%) | | | |
| DSS | | | | |
| Living | 37 (29%) | 13 (30%) | 24 (29%) | 0.91 |
| Deceased | 88 (69%) | 30 (70%) | 58 (71%) | |
| Missing | 3 (2%) | | | |
| DFS | | | | |
| None | 91 (71%) | 37 (88%) | 54 (70%) | 0.03 |
| Yes | 28 (22%) | 5 (12%) | 23 (30%) | |
| Missing | 9 (7%) | | | |

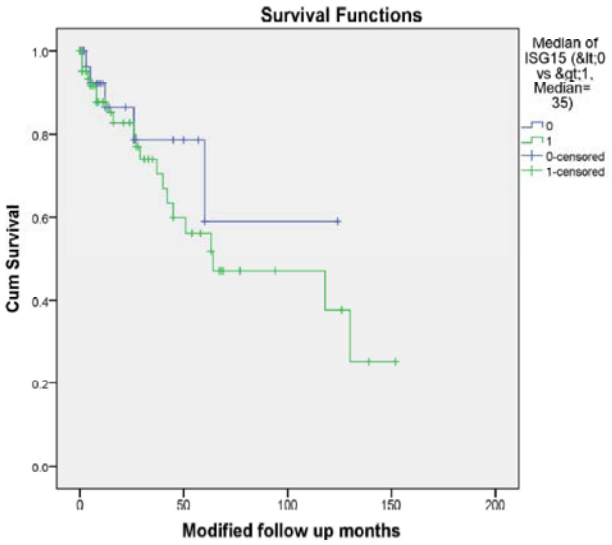


Fig. 1: Disease-specific survival (DSS) for the different levels of Median of ISG15 (<0 vs >1, Median=35) in the overall cohort (Kaplan-Meier curves).

**Tissue Microarray (TMA):** The TMA slides were used for the evaluation and analysis of the expression patterns of ISG15 that were generated in-house from the archived FFPE tumor tissue blocks. The protocol of TMA preparation and validation for 128 bladder cancer samples was followed as described previously by Al-Maghrabi and his colleagues [37]. Moreover, we used a human normal placenta tissue as a positive control with each run (the placenta tissue was provided by Histopathology laboratory, King Abdulaziz University Hospital).

**Statistical Analysis:** The IBM SPSS Statistics (IBM New York, United States of America) programs were used to compile the statistical data (PASW). The Chi-square test and Fischer's exact test were used to determine whether there was a statistically significant relationship between the categorical variables used in the frequency tables. The method of Kaplan-Meier, using the log-rank (Mantel-Cox) test, was used to conduct a univariate survival analysis for the outcome measures (DiseaseSpecific Survival (DSS) and Disease-Free Survival (DFS). A p-value of > 0.05 considered as significant in all tests.

## RESULTS

**Patients Overview:** As shown in Table (1), our cohort consisted of 128 cases where 82% of them were males.

Furthermore, most of our cohort diagnosed with bladder cancer at low stage (56%), smokers represented 26.6% of the cohort. Surprisingly, despite most of our patients showed a less aggressive tumor; negative lymph node and lympho-vascular invasion in 62% and 63% of them respectively, and 62% with no distant metastasis cancer cells, 69% of them were deceased.

Despite there being no significant association, Kaplan–Meier analysis showed a clear trend of association between ISG15 expression with disease-specific survival (DSS), where patients with high expression of ISG15 live longer (Fig. 1).

## DISCUSSION

Bladder cancer is a genitourinary disorder and represents one of the most prevalent cancers with a significant fatality rate globally. Treatment outcomes vary amongst people. Several criteria, including tumor grade, tumor stage, lymph node status and lymphovascular invasion are addressed during the treatment. The status of various mutations is now a well-known prognostic factor that influences the oncologist's decision regarding treatment alternatives. It has been shown that patients with the same stage of bladder cancer may experience different results. Many efforts are assumed to understand the etiology, prognosis, and predictive aspects in order to improve and personalize the treatment.

Given the fact that ISG15 was reported as an overexpressed protein marker in almost all tumors involving breast cancer [29], hepatocellular carcinoma [28], cervical cancer [27], colon cancer [30] and esophageal squamous cell carcinoma [31], and stimulated by type I interferons (IFN-$\alpha$ and $\beta$) [32]. A number of studies have demonstrated that overexpressed ISG15 enhances tumorigenesis and metastasis in human malignancies [35]. While others have indicated that elevated levels of free ISG15 correspond with a better prognosis for cancer patients.

ISG15 is a secreted cytokine and post-translational protein modulator. Despite the fact that ISG15 was once believed to serve as both a tumor-suppressor and an oncogene, each of these functions has been linked to the development of cancer [40]. Cancer chemotherapy was shown to increase ISGylation, indicating that ISG15 has a role in tumor suppression. The carcinogenic potential of ISG15 was highlighted by the significant correlation between carcinogenesis and deregulated overexpression of ISG15 gene and increased ISGylation [35, 41, 42]. Furthermore, ISG15 is also a target of the tumor-suppressor gene TP53 [43].

In HBV-related hepatocellular carcinoma, ISG15 functions as a powerful prognostic marker and contributes to tumor invasion and metastasis [28]. Some of the proteins that ISG15 is targeting are also involved in cellular processes that take place in the nucleus, such as chromatin remodeling and polymerase II transcription [44].

There are little data on ISG15 and bladder cancer, only few studies have examined ISG15 expression in bladder cancer. Interestingly, one previous study was conducted on bladder cancer and reported that immunohistochemistry staining revealed that ISG15 was shown to be mainly present in the nuclei of cancer cells, which was found to be associated with an advanced stage of tumor development [41].

Immunohistochemistry staining method, which is a simple method that has few requirements and is accessible to most laboratories across the world was applied in the current study. Our findings revealed that 40% of the population had an increased (+2 to +3) expression pattern for ISG15. Expression level was correlated significantly ($p<0.05$) with lymphovascular invasion (LVI), tumor grade, disease-free survival (DFS), tumor stage, and lymph node (LN) status. Our findings point to a possible role for ISG15 as an oncogene in bladder cancer, suggesting that it could be a useful marker for diagnosis, prognosis, and therapeutic immunotherapy. These findings are in agreement with previous researches, which reported that ISG15 was highly expressed in HBV-related hepatocellular carcinoma [45], colorectal cancer (CRC) tissues [46] and Endometrial carcinoma (EC) [47]. ISG15 is overexpressed in CRC compared to non-neoplastic tissue and has been linked to factors that are associated with a good prognosis. ISG15 overexpression is associated with longer overall survival in patients with colorectal cancer [46]. ISG15 enhanced the G1/S transition in endometrial cancer (EC) cell cycle. In addition, ISG15 enhanced the progression of EC via activating the MYC proto-oncogene signaling pathway. In addition, ECs with high levels of ISG15 possessed a more robust immune evading capacity, as indicated not only by significantly fewer invading CD8+ T cells, but also by a higher expression of T cell inhibitory factors such as programmed death ligand 1. These results imply that ISG15 plays a tumor-promoting function in EC and may be a viable biomarker for diagnosis, prognosis, and therapeutic immunotherapy [47].

In conclusion, in a large and representative cohort of patients with bladder cancer, we demonstrated for the first time the prognostic value of ISG15 in terms of survival outcome. An interesting and potentially beneficial independent prognostic factor.

We recommend that further studies using larger cohorts are required to deeply investigate the molecular functions of ISG15 and its effects on bladder cancer pathogenesis.

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