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Original Article

Circulating levels of adipocytokines omentin-1 and adiponectin in patients with bladder cancer

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Abstract: Bladder cancer (BCa) is one of the leading cancers in urinary system. It is well-known that smoking, occupational exposure as well as obesity are risk factors of BCa. Omentin-1 and adiponectin are adipocytokines abundantly synthesized in adipose tissue. It has been shown that the serum levels of omentin-1 and adiponectin altered not only upon the conditions with insulin resistance, but also associated with neoplastic conditions like prostate cancer and colorectal cancer. Until date, the potential correlation between omentin-1 and adiponectin and BCa is largely unexplored. Therefore, in the present matched case-control study, we evaluated serum levels of omentin-1 and adiponectin in BCa patients. 42 patients newly diagnosed with BCa and 42 healthy controls were recruited in the study. No statistically significant differences were noticed in gender, age, body-mass index (BMI), fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c) and low-density lipoprotein cholesterol (LDL-c) in the paired groups. The circulating levels of omentin-1 and adiponectin in both groups were detected via applying enzyme-linked immunosorbent assays (ELISA). The omentin-1 levels in BCa patients were 1.825 (0, 9.155) ng/mL compared with 5.205 (2.298, 13.153) ng/mL in healthy controls, indicating a dramatic downregulation ($P<0.05$). In addition, the adiponectin levels in healthy controls were 4.05 (3.225, 4.543) μg/mL and increased significantly to 4.545 (4.333, 4.583) μg/mL in BCa patients ($P<0.05$). Subsequently, significant correlations between serum adiponectin levels with age ($r=0.248$, $P=0.023$), HDL-C levels ($r=0.267$, $P=0.014$) and TNM staging ($X^2=15.406$, $P=0.002$) were noticed. In addition, we also found a reverse correlation between serum adiponectin levels and BMI ($r=-0.243$, $P=0.026$). Furthermore, the logistic regression analysis revealed that BCa was the only meaningful influential factor of omentin-1 and adiponectin concentrations were affected by smoking and TC levels. For the future, multi-racial and large cohort-based studies are needed to address the concrete mechanisms underlying the altered circulating levels of omentin-1 and adiponectin and the interactions between BCa and adipose tissues, which efforts may shed novel insights into sensitive diagnosis and effective therapy of BCa.

Keywords: Bladder cancer, circulating biomarkers, omentin-1, adiponectin, ELISA

Introduction

Bladder cancer (BCa) is one of the most common cancers in the world [1]. As it is shown in the recent estimated data of American males, BCa may account for nearly 7% of total newly diagnosed carcinomas and approximately 4% of cancer-associated death [2]. The etiology of BCa is largely in-conclusive. Accumulating studies have demonstrated that genetic alternations and other etiological factors such as smoking, occupationally exposure and affection of schistosome were supposed to comprehensively increase the BCa risk [3]. During the past decades, the potential effect of obesity in cancer initiation and progression has been gradually recognized. Almost 20% of cancer development has been shown to be associated with overweight and relationship between rectal cancer, prostate cancer and renal cancer and obesity has been revealed [4, 5]. Very recently, an evidence based analysis has revealed a potential association between obesity and development of BCa [6]. However, the mechanism underlying the link of cancer development and obesity is largely unexplored.

Several studies have illustrated that insulin resistance, obesity-induced hypoxia, oxidative stress, abnormal insulin-growth factor expression and genetic susceptibility were the general risk factors of obesity-related cancer [7]. Among the different factors, the involvement of adipocytokines from adipose tissue that are currently regarded as a complex endocrine organ in caner development has been proposed recently. It has been suggested the aberrant syntheses of adipocytokines from adipose tissue may result in chronic inflammation in the microenvironment and thereby initiate or promote tumorigenesis [8]. Several biologically active adipocytokines such as omentin, resistin, apelin, adiponectin and leptin have been shown to participate in obesity's association with BCa [9].

Omentin-1 is newly identified in human adipose tissue with 34 kDa MW, which adipocytokine is depot-specific and could enhance the activity of insulin but down-regulated by high glucose [10-12]. Adiponectin is a protein that synthesized in white adipose tissue by 244 amino acids. It has been shown that adiponectin plays vital roles in anti-atherosclerosis, anti-insulin resistance [13-18]. Importantly, an inversely correlation between reduced omentin-1 and adiponectin levels and obesity has been reported [11, 19]. In addition, several studies have addressed that altered circulating omentin-1 and adiponectin levels in rectal cancer, prostate cancer and renal cell cancer patients, indicating a potential role with tumorigenesis [12, 20, 22]. However, to our best knowledge, the altered expressions of omentin-1 and adiponectin among BCa patients remain largely unexplored. Therefore, in this current investigation, we assessed the serum omentin-1 and adiponectin levels in BCa patients and matched controls, which will be useful for elucidating the promising diagnostic value of the two adipocytokines for BCa in the future.

Patients and methods

Patients and healthy controls

From July 2014 to July 2015, 42 patients histopathologically diagnosed with BCa at the first affiliated hospital of AHMU were enrolled in this investigation. Informed consent was written by all the candidates and the protocol of our research was checked and approved by ethics committee of the first affiliated hospital of Anhui Medical University (Approval Number: PJ20151008). The following criteria were applied to recruit the patients: no BCa curative medication or bladder operations; no previous malignant history; no diabetes, liver, kidney or acute infectious diseases. Meanwhile, healthy controls were selected when the fitness was confirmed through systematically medical examination. Venous blood samples were drawn from each individual after fasting for 12 hours. Samples were then centrifuged with 8000 rpm at 4°C for 4 minutes and the supernatants were harvested. The serum were divided and stored until detection at -80°C.

Clinical parameters measurements

BMI was calculated following the formula as body weight divided by height squared (kg/m^2). The biochemical parameters such as FBG, TC, TG, HDL-c and LDL-c were detected via the standard protocols by a clinical chemistry analyzer (Shimadzu, cl8000, Japan).

Omentin-1 and adiponectin measurements

Concentrations of omentin-1 and adiponectin were assessed by ELISA based on the manufacturers' protocols (omentin-1: CUSABIO, CSB-E09745h, China; adiponectin: Neobioscience, EHC120, China). The linear ranges of the assay were 1.56 pg/mL-100 pg/mL (omentin-1) and 0.08 ng/mL-10 ng/mL (adiponectin). The intra- and inter-assay coefficients of variation were less than 10% and 9.5%, respectively.

Statistical analysis

Measurement data were presented as mean ± standard error. Kolmogorov-Smirnov test was introduced to check the normally-distribution of data. If the variables were normally-distributed, statistical differences within the group and between groups were estimated by student's t-test. If not, non-parametric Wilcoxon signed ranks test was applied to assess the differences between these paired groups. Later on, Spearman's rank correlation coefficient analyses as well as binary logistic regression were used to address the associations between omentin-1 and adiponectin levels with other biochemical or clinical parameters. Non-parametric Kruskal-Wallis test was lent to address the associations between BCa TNM staging and circulating levels of adipocytokines. All analyses were conducted with SAS software (v. 9.3.1). Statistically significant differences were reached when $P<0.05$.

Table 1. Comparison of the clinical characteristics of included individuals

Variables	Bladder cancer group (*n*=42)	Normal control group (*n*=42)	*T or Z*$^{\Delta}$	*p* value
Gender (Female/Male)	14/28	14/28		1.000
Age (years)	63.52±12.27	62.90±10.34	-0.25	0.803
BMI (kg/m^2)	22.79±2.44	24.04±3.408	1.92	0.059
TG (mmol/L)	1.52±0.81	1.60±1.30	0.33	0.739
TC (mmol/L)	4.30±1.09	4.64±0.75	1.66	0.100
HDL-c (mmol/L)	1.34±0.41	1.33±0.27	-0.12	0.908
LDL-c (mmol/L)	2.49±0.88	2.56±0.59	0.40	0.690
FBG (mmol/L)	5.88±1.60	5.36±0.64	-1.92	0.060
Omentin-1 (ng/mL)	1.825 (0, 9.155)	5.205 (2.298, 13.153)	-2.507$^{\Delta}$	0.012*
Adiponectin (μg/mL)	4.545 (4.333, 4.583)	4.05 (3.225, 4.543)	3.024$^{\Delta}$	0.003*

Abbreviations: BMI, body mass index, TG, triacylglycerol, TC, total cholesterol, HDL-c, high-density lipoprotein cholesterol, LDL-c, low-density lipoprotein cholesterol, FBG, fasting blood glucose; *means statistically significant *P*<0.05, $^{\Delta}$means Z test.

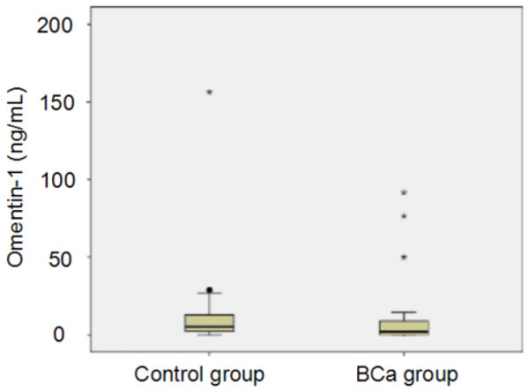

Figure 1. The omentin-1 levels of BCa patients and healthy people (n=42 for each group). The serum omentin-1 levels in each group were shown as median values (25th, 75th percentiles). BCa patients indicated significantly lower omentin-1 expression compared with the healthy people (*P*<0.05).

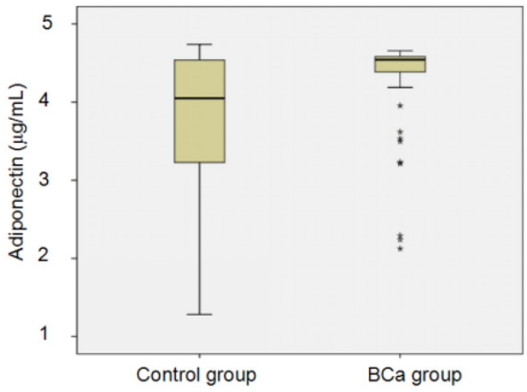

Figure 2. The adiponectin levels of BCa patients and healthy people (n=42 for each group). The serum adiponectin levels in each group were shown as median values (25th, 75th percentiles). BCa patients indicated significantly higher adiponectin expression compared with the healthy people (*P*<0.05).

Results

Characteristics of studied groups

The clinical characteristics consisted of anthropometric and biochemical parameters of BCa patients and healthy controls were listed in **Table 1**. We did not observe statistically significant difference in gender, age and BMI between the paired groups (*P*>0.05). Besides, no any significant differences were found in TG, TC, HDL-C, LDL-C levels and FBG between BCa patients and healthy individuals (*P*>0.05).

Omentin-1 levels in BCa patients and healthy people

The serum omentin-1 and adiponectin levels in each group were shown as median values (25th, 75th percentiles) in **Table 1**. Patients with BCa indicated significantly lower omentin-1 expression compared with the healthy people (**Figure 1**) (*P*<0.05). However, the adiponectin concentrations in patients with BCa were dramatically increased compared with the healthy people (**Figure 2**) (*P*<0.05).

Spearman's correlation analyses of omentin-1 and adiponectin levels with clinical parameters

Subsequently, we analyzed the association between the circulating omentin-1 and adiponectin levels with clinical parameters in BCa, healthy control and whole group, respectively. The result showed that circulating omentin-1 levels were not significantly related to age, BMI, serum TG, total TC, HDL-c, LDL-c and also FBG levels in each group (**Table 2**). Nevertheless,

Table 2. Spearman's correlation analysis of omentin-1 levels with clinical parameters

Variables	Bladder cancer group (*n*=42)		Normal control group (*n*=42)		Whole group (*n*=84)	
	Correlation coefficient (*r*)	*P* value	Correlation coefficient (*r*)	*P* value	Correlation coefficient (*r*)	*P* value
Age (years)	-0.216	0.171	0.117	0.459	-0.067	0.544
BMI (kg/m^2)	-0.026	0.871	-0.151	0.340	-0.049	0.660
TG (mmol/L)	0.034	0.833	-0.141	0.374	-0.060	0.587
TC (mmol/L)	-0.228	0.146	0.151	0.340	0.005	0.961
HDL-c (mmol/L)	-0.022	0.345	0.209	0.183	-0.070	0.524
LDL-c (mmol/L)	-0.095	0.550	0.135	0.396	-0.003	0.982
FBG (mmol/L)	0.105	0.507	-0.078	0.622	0.000	1.000

Abbreviations: BMI, body mass index, TG, triacylglycerol, TC, total cholesterol, HDL-c, high-density lipoprotein cholesterol, LDL-c, low-density lipoprotein cholesterol, FBG, fasting blood glucose.

Table 3. Spearman's correlation analysis of adiponectin levels with clinical parameters

Variables	Bladder cancer group (*n*=42)		Normal control group (*n*=42)		Whole group (*n*=84)	
	Correlation coefficient (*r*)	*P* value	Correlation coefficient (*r*)	*P* value	Correlation coefficient (*r*)	*P* value
Age (years)	0.261	0.095	0.173	0.275	0.248	0.023*
BMI (kg/m^2)	-0.212	0.177	-0.210	0.182	-0.243	0.026*
TG (mmol/L)	-0.050	0.754	-0.199	0.206	-0.090	0.415
TC (mmol/L)	0.257	0.100	0.117	0.459	0.118	0.287
HDL-c (mmol/L)	0.345	0.025	0.256	0.102	0.267	0.014*
LDL-c (mmol/L)	0.072	0.652	0.115	0.468	0.086	0.436
FBG (mmol/L)	-0.217	0.167	-0.141	0.374	-0.126	0.254

Abbreviations: BMI, body mass index, TG, triacylglycerol, TC, total cholesterol, HDL-c, high-density lipoprotein cholesterol, LDL-c, low-density lipoprotein cholesterol, FBG, fasting blood glucose; *means statistically significant *P*<0.05.

significant correlations between serum adiponectin levels and age (r=0.248, *P*=0.023) and HDL-c (r=0.267, *P*=0.014) in whole group were noticed. In addition, we also found a reverse association between circulating adiponectin levels and BMI (r=-0.243, *P*=0.026) in whole group (**Table 3**).

Multiple-factor binary logistic regression analyses of omentin-1 and adiponectin levels with clinical parameters

Furthermore, multiple-factor binary logistic regression was applied to analyze the correlation between levels of omentin-1 and adiponectin with general clinical parameters in the study. As a result, smoking, BMI, HDL-c, TC, LDL-C and TG did not significantly affect the circulating omentin-1 levels (**Table 4**). Whereas, we noticed that both smoking (95% CI, 0.025-0.629, *P*=0.012) and TC (95% CI, <0.001-0.393, *P*=0.013) significantly affected the circulating adiponectin levels (**Table 5**).

Associations between omentin-1 and adiponectin levels with TNM staging

Finally, we have elucidated no significant correlation between serum omentin-1 levels with TNM staging ($T_{a,1-3}N_0M_0$) was observed (χ^2=1.317, *P*=0.725) (Supplementary Table 1), while a significant association was addressed between circulating adiponectin levels with TNM staging ($T_{a,1-3}N_0M_0$) (χ^2=15.406, P=0.002) in bladder cancer patients (Supplementary Table 2).

Discussion

Bladder cancer is one of the leading cancers in urinary system. During the past a few decades, the bladder cancer incidence dramatically raised worldwide [2]. Importantly, a continuously increased rate of overweight (BMI ranged from 25 kg/m^2 to 29.9 kg/m^2) or obesity (BMI of no less than 30 kg/m^2) has also been observed recently especially in western civilian with a high consumption of animal fat and cholesterol [5]. For instance, the incidence of overweight and obesity is up to 35.5% and 35.8% in America, respectively [23]. The parallel trends may indicate a potential association between BCa and obesity. As a matter of fact, the studies that demonstrated correlation between obesity and BCa have revealed contradictory findings. Previous publication reported that higher BMI was closely cor-

Table 4. Multiple-factor binary logistic regression analysis for omentin-1 levels

Variables	B value	SE value	OR value	95% CI	*P* value
Smoking	-0.137	0.554	0.872	0.294-2.585	0.805
FBG (mmol/L)	0.493	0.794	1.637	0.346-7.756	0.535
BMI (kg/m^2)	-1.126	0.624	0.324	0.095-1.101	0.071
HDL-c (mmol/L)	-0.389	1.092	0.678	0.080-5.756	0.721
TC (mmol/L)	1.851	1.157	6.365	0.659-61.454	0.110
LDL-c (mmol/L)	0.461	0.972	1.586	0.236-10.648	0.635
TG (mmol/L)	0.433	0.847	1.541	0.293-8.102	0.609

Abbreviations: SE, standard error, OR, odds ratio, CI, confidence interval.

Table 5. Multiple-factor binary logistic regression analysis for adiponectin levels

Variables	B value	SE value	OR value	95% CI	*P* value
Smoking	-2.078	0.824	0.125	0.025-0.629	0.012*
FBG (mmol/L)	-1.836	0.994	0.159	0.159-1.118	0.065
BMI (kg/m^2)	-0.258	0.671	0.773	0.207-2.881	0.701
HDL-c (mmol/L)	0.311	0.859	1.365	0.253-7.352	0.717
TC (mmol/L)	-4.408	1.772	0.012	<0.001-0.393	0.013*
LDL-c (mmol/L)	-13.056	446.700	<0.001	<0.001->999.999	0.9767
TG (mmol/L)	-1.038	1.070	0.354	0.044-2.882	0.332

Abbreviations: SE, standard error, OR, odds ratio, CI, confidence interval; *means statistically significant $P<0.05$.

related with an increased BCa risk, which was confirmed by the following study, which illustrated an increased risk of BCa in obese men in America [24, 25]. Conversely, a prospective cohort of BCa patients based on American population revealed that BMI was not associated with BCa, even comparing an extremely higher BMI with a normal BMI [26]. In line with this cohort, other studies demonstrated that overweight or obesity were not associated or even inversely associated with BCa incidence [27-30].

Among the various hypothesis that addressed the link between obesity and tumor development, the impact of adipocytokines on carcinogenesis have been extensively discussed. Aberrant synthesis of adipocytokines results in chronic inflammation in the microenvironment, which may contribute to tumorigenesis and cancer progression [8, 31]. For example, it has been shown that obesity-associated leptin exhibited a tumorigenic role in prostate cancer, which was due to direct effects of leptin on prostatic intraepithelial neoplasia lesions or suppression of apoptosis [32].

Omentin-1 is specifically enriched in human adipose tissue, the concentration of omentin-1 is down-regulated by high glucose concentrations and an inversely association between obesity and omentin-1 was reported [10-12]. Several studies have demonstrated that patients diagnosed with polycystic ovary syndrome often indicated high BMI but exhibited lower omentin-1 concentration than healthy women [33, 34]. More importantly, the altered omentin-1 levels in cancer patients have also been revealed in various studies, indicating a crucial effect of omentin-1 in cancer development. It has been found that omentin-1 levels were significantly higher in colon cancer patients compared with control individuals [12]. In addition, circulating omentin-1 levels in prostate cancer patients were meaningfully higher than older men with benign prostatic hyperplasia [20]. Intriguingly, our previous data indicated a dramatically decreased omentin-1 level in renal cell cancer patients [35].

Similarly, we observed that BCa patients had significantly lower serum levels of omentin-1 at 1.825 (0, 9.155) ng/mL than the healthy control group at 5.205 (2.298, 13.153) ng/mL ($P<0.05$). Furthermore, circulating omentin-1 levels were not significantly associated with all clinical characteristics such as age, BMI, serum TG, total TC, HDL-c, LDL-c levels and FBG. In addition, binary logistic analysis dealing with the influential factors of omentin-1 levels indicated that smoking, BMI, HDL-c, TC, LDL-c and TG did not significantly affect omentin-1 levels, suggesting the altered omentin-1 levels between BCa group and control group were regardless of any clinical characteristics and biochemical parameters. Therefore, we propose that the downregulated concentration of omen-

tin-1 may be an independently biological factor of BCa.

Adiponectin is synthesized in white adipose tissue and exerts function of anti-atherosclerosis, anti-inflammation or anti-insulin resistance [17, 18]. Similar to omentin-1, adiponectin levels are deregulated in obesity patients and altered concentrations of adiponectin have been demonstrated in tumorigenic conditions [19]. It has been shown that low adiponectin levels was related to high colorectal cancer risk [21]. In addition, circulated levels of adiponectin were inversely correlated with renal cancer incidence, which was independent of BMI [22]. In prostate cancer, several studies indicated that concentration of adiponectin in cancer patients was significantly lower than BPH men or healthy population, indicating adiponectin acts as an independent factor of prostate cancer [36-38]. Furthermore, Dalamaga et al. have reported a higher adiponectin levels were associated with risk of pancreas cancer [39].

Herein, the circulating adiponectin levels of 4.545 (4.333, 4.583) μg/mL were obviously higher within BCa patients than compared with the healthy people of 4.05 (3.225, 4.543) μg/mL ($P<0.05$). Furthermore, serum adiponectin levels were reversely associated with BMI in whole group, which supported the previous investigations that revealed an increased adiponectin values after weight loss in obese subjects [40, 41]. Nevertheless, correlations between serum adiponectin levels and HDL-c in whole group were also noticed. The similar findings have been demonstrated in several studies, which indicated adiponectin accelerated HDL synthesis by upregulation of the proteins related to reverse cholesterol transport [42, 43]. The binary logistic regression analysis indicated that except for BG, BMI, HDL-c, LDL-c and TG, smoking and TC were the factors that associated with adiponectin levels, which is consistent with previous reports [44-46].

To our best knowledge, the mechanisms underlying the role of omentin-1 and adiponectin in tumorigenesis were largely unexplored. A recent study indicated a suppressive role for omentin-1 in prostate cancer, which was related to the differential histone acetylation of transcription factors [47]. Previous report has demonstrated that omentin-1 could decrease p53 deacetylation and thereby increase the protein stability to accelerate apoptosis for preventing liver cancer [48]. Together with previous reports and our findings of reduced levels of omentin-1, we propose that omentin-1 may exert a tumor suppressive role via enhancing the down streaming effects of various transcription factors with anti-tumorigenic function in BCa. Meanwhile, it has been reported that adiponectin may inhibit IL-18-mediated endothelial cell death through an AMP-activated protein kinase (AMPK)-associated mechanism, it can also promote AMPK phosphorylation and endothelial nitric oxide generation, which may finally enhance the cell proliferation and even tumor development and progression [49, 50]. These conclusions were supported by several previous publications regarding the angiogenic process, which is related to tumorigenesis. For instance, adiponectin pre-treatment could enhance endothelial progenitor cell proliferation, indicating it is crucial for angiogenesis [51]. This conclusion was further supported by the similar investigation in adiponectin-deficient mouse model with lischemic hind-limb [52]. Besides, we observed an increased level of adiponectin in BCa patients, which indicated a potential pro-oncogenic function of adiponectin in BCa. Nevertheless, other studies suggest that adiponectin may exert anti-tumorigenic effects via stimulating receptor-mediated signaling pathways or regulating inflammatory responses and influencing tumor angiogenesis. For instance, adiponectin may suppress the growth of rectal cancer cell via AdipoR1- and -R2-mediated pathway and inhibit the proliferation of breast cancer cell by cAMP/Protein Kinase-A pathway [53, 54]. Thus, more comprehensive researches would be needed to explore the concrete roles of adipocytokines in BCa.

In conclusion, we have found significantly decreased omentin-1 levels and increased adiponectin levels in patients with BCa, which were independent of most of the clinical parameters. Our results indicated adipocytokines might play some crucial roles in the tumorigenesis of BCa via mechanisms that were active in the association of obesity and BCa. In the future, larger cohort-based researches will be needed to illuminate the comprehensive mechanisms underlying the deregulated adipocytokines levels and the interactions between adipose tissues with BCa, such efforts could shed novel insights into effective BCa therapy.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Non-parametric Kruskal-Wallis test on omentin-1 levels with BCa status

BCa TNM staging	N	Mean rank	X^2	df	Asymp. Sig.
$T_aN_0M_0$	8	17.50	1.317	3.000	0.725
$T_1N_0M_0$	24	22.90			
$T_2N_0M_0$	7	21.07			
$T_3N_0M_0$	3	22.00			

Asymp. Sig. asymptotic significance.

Supplementary Table 2. Non-parametric Kruskal-Wallis test on adopinectin levels with BCa status

BCa TNM staging	N	Mean rank	X^2	df	Asymp. Sig.
$T_aN_0M_0$	8	31.88	15.406	3.000	0.002*
$T_1N_0M_0$	24	22.85			
$T_2N_0M_0$	7	11.79			
$T_3N_0M_0$	3	5.67			

Asymp. Sig. asymptotic significance, bold value is statistically significant; *means statistically significant $P<0.05$.