RESEARCH ARTICLE

Pseudocholinesterase levels and atherogenic indices as indicators of invasive and non-invasive bladder cancer

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ABSTRACT

Background. Bladder cancer (BC) is the most prevalent cancer found in the bladder system and is the tenth most common carcinoma worldwide. Pseudocholinesterase (PChE) is one of the serum proteins. Serum PChE has been recognized as an indicator of outcomes in several cancers; nevertheless, its correlation with oncological results in muscle-invasive bladder cancer (MIBC) and Non-muscle-invasive bladder cancer (NMIBC) remains largely unexamined. The study aims to assess the association of the PChE levels and lipid indices, including the atherogenic index of plasma (AIP), Castelli's risk index II (CRI-II), and the atherogenic coefficient (AC), with the development of MIBC and to use them as indicators of the development of MIBC in the Iraqi population.

Methods: The present case-control research involved 160 patients (80 with NMIBC and 80 with MIBC) from the Central Hospital of Tumor in Najaf Governorate, Iraq. The serum PChE level was determined by enzyme-linked immunosorbent assay (ELISA), while lipid profile parameters were measured using colorimetric assay techniques.

Results: The estimation of demographic and biochemical data revealed significant differences in smoking, PChE, AIP, very low-density lipoprotein (VLDL), high-density lipoprotein (HDL), Triglyceride (TG), and Total cholesterol (TC) in NMIBC patients compared to those in the MIBC group. The logistic regression analysis of AIP, CRI-I, CRI-II, and AC levels revealed a significant association with MIBC at 4, 3, and 1 fold, respectively, while no association was found with PChE levels.

Conclusion: In the present study, the lipid indices' levels of AIP, CRI-II, and AC are associated with the development of MIBC and could be used to help physicians assess and confirm the presence of MIBC, while PChE failed to associate with the development of the disease.

Key words: pseudocholinesterase, MIBC, NMIBC, bladder cancer, AIP

Introduction

Cancer is a cellular illness that originates from genetic mutations in a single cell or a limited cluster of cells. The failure of cellular repair mechanisms will result in the accumulation of genetic changes, ultimately leading to cancer and, over time, metastasis. For cells to become malignant, they must undergo behavioral modifications identified as the 'hallmarks of cancer' (Wanigasekara et al., 2021). In the United States, BC ranks as the second leading cause of cancer-related mortality from the genitourinary system, after prostate cancer, with 81,400 new cases and 17,980 fatalities reported in 2020 (Siegel et al., 2018; Siegel et al., 2019). BC is classified into two distinct clinical types: MIBC and NMIBC, the latter accounting for 75% of BC cases (Knowles & Hurst, 2015; Huang et al., 2021). NMIBC is confined to the mucosa and/or only invades the lamina propria underneath, while MIBC often infiltrates more layers of the bladder, including muscle, the bladder wall, or neighboring tissues (Kirkali, et al., 2005).

About 75% of patients will have illness localized to the mucosa (pTa, Tis) or the lamina propria (pT1), categorizing it as NMIBC. Twenty-five percent of newly diagnosed bladder tumors infiltrate the muscularis propria of the bladder wall (pT2) and are categorized as MIB (Mushtaq et al., 2019). BC mostly affects males, with an expected man-to-woman ratio of 4:1. It was diagnosed in roughly 570,000 persons in 2020, ranking it among the top 10 most frequent malignant tumors globall (Afonso et al., 2023). In Iraq, BC ranks among the four most common malignant tumors in males and the eighth most common in females. BC may affect individuals at a young age, with more than 90% of newly diagnosed cases occurring in those over 55 years (Saginala et al., 2020).

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Several biochemical characteristics have been linked to certain malignancies, including PChE (Li et al., 2017). PChE is an alpha-glycoprotein produced in the liver, present in the nervous system, and found in reduced concentrations in many organs. It is found in human plasma mostly as glycosylated soluble tetramers with a molecular weight of 340 kilodaltons (kDa). Reduced blood PChE levels have been observed in many clinical situations, including hepatic impairment, inflammation, and starvation (Scott & Powers, 1972; Lampón et al., 2012). Serum PChE levels decline in individuals with advanced cancer, independent of liver participation, despite normal results in other liver function test (Ogunkeye & Roluga, 2006). Furthermore, decreased PChE levels have been observed in advanced and metastatic cancer (Klocker et al., 2020). PChE activity has shown a positive connection with blood levels of triglyceride (TG) and cholesterol, in addition to indications of obesity, being overweight, and body fat distribution (Klocker et al., 2020).

Altered lipid metabolism is a significant metabolic issue in cancer. Indeed, increased production or absorption of lipids promotes the proliferation of cancer cells and the development of tumor (Snaebjornsson et al., 2020). There is widespread agreement that lipid changes may function as potential tumor indicators (Zhao et al., 2015). There are reports that TG levels are negatively linked to PChE and that lipoprotein lipase (LPL) activities suggest that PChE, like LPL, may help break down TG (Crocetto et al. 2022). Both LPL and PChE are essential to lipoprotein metabolism and are involved in lipoprotein interconversions. Consequently, researchers have extensively investigated PChE as a tumor marker (Ghooi et al., 1980). While some biochemical indicators have been linked to certain malignancies, researchers have only had limited luck in establishing them as diagnostic tools. Due to the high recurrence and death rate of BC, appropriate biomarkers for early identification are essential (Shlyapnikov et al., 2021). To our knowledge, the validity of the TG/HDL ratio and PChE level in accurately diagnosing individuals with BC is not well established. Our goal was to examine whether the PChE and lipid indices could be used as biomarkers for MIBC and NMIBC in a group of Iraqis.

Materials and Methods

Subjects

This research recruited BC patients, including 80 with NMIBC and 80 with MIBC. Everyone involved was hospitalized at the National Hospital for Cancer Therapy in Najaf City, Iraq, from September 2022 to February 2023. Invasive and non-invasive BC were diagnosed and differentiated by histopathological biopsy reports (TNM) and radiological examinations (MRI and CT scans). Patients with metastatic BC and other types of cancer, such as liver cancer, hyperlipidemia, hypothyroidism, hepatic diseases, stroke, autoimmune disorders, and endocrine disorders, pregnant women, lactating women, neurological disorders, and patients with TG > 400 mg/dl to fulfill Fredwald's equation were excluded from the study protocol. Blood sampling was taken before operating surgery for muscle-invasive and non-invasive BC. Informed consent was obtained from all participants before their involvement in the research, which was approved by the Institutional Review Board of the University AL-Nahrain (385/2022), following the International Guidelines for Human Research Protection as outlined by the Declaration of Helsinki.

Fasting blood samples were obtained from patients in the early morning. Five milliliters of blood were collected in gel tubes, which were then left undisturbed at room temperature for 20 minutes to allow for coagulation. After coagulation occurred, the samples were subjected to centrifugation for 10 minutes at 1100 x g. After separation, many portions of serum were warehouse at -80°C until measurements were taken. The TC and TG were tested using automated analyzers that use enzymatic colorimetric methods with kits provided by Cobas® (Germany). Serum HDLc was measured enzymatically with kits supplied by Cobas® (Germany). LDLc was measured by the modified precipitation method that involves the use of modified polyethylene glycol methyl ether (PEGME) and polyvinyl sulfonic acid (PVS) with kits supplied by Cobas® (Germany). AIP, CRI-I, CRI-II, and AC were derived from the lipid profile data (Namith, et al., 2022). A standardized ELISA sandwich kit was employed to quantify butyrylcholinesterase (BCHE) (Pars Biochem Co, Nanjing, China). The sensitivities of the kits for BCHE were 0.1 pg/mL. The intra-assay coefficients of variation (precision within an assay) of all assays were less than 10%.

Biostatistical analysis

The data underwent statistical analysis using IBM SPSS Statistics for Windows, version 26.0 (IBM, USA). The normality examination for the variables was performed via the Kolmogorov–Smirnov test. Chi-square tests were applied to examine categorical variables. Normally distributed data are represented as the mean and standard deviation, whereas nonparametric data are displayed as the median and interquartile range (IQR). The Kruskal–Wallis test and the Whitney U test were used to compare the medians of continuous variables within the groups based on the data. Initially, we used univariate logistic regression analysis to investigate possible risk factors for mortality during hospitalization, followed by a multivariate logistic regression model including all relevant variables to compute odds ratios (ORs) with 95% confidence intervals.

Results

Socio-demographic data

The demographic aspects for contributors were given in Table 1. Differences in smoking were significant in the comparison of the NMIBC group with the MIBC group.

Table 1. *Demographic characteristics of NMIBC and MIBC patient groups.*

	NMIBC (n= 80)		MIBC (n= 80)		p
	No.	%	No.	%	
Sex:					
Male	60	75	63	78	0.708
Female	20	25	17	22	
Smoking:					
Yes	17	21	63	78	**0.002****
No	36	79	44	22	
Age (years)	59.54 ± 8.75		61.70 ± 13.37		0.228
BMI	21.55 (18.16-27.63)		24.56 (20.54- 29.24)		0.606

*Data presented as number (%), mean ± standard deviation, and median + interquartale range. NMIBC: Non-Muscle-Invasive Bladder Cancer, MIBC: Muscle-Invasive Bladder Cancer, BMI: Body Mass Index, n: Number **P < 0.01.*

Comparison of biomarkers among groups

Table 2 presents the biomarker measures for the study groups. It reveals a significantly higher PChE in the NMIBC groups compared to the MIBC and a significant decrease in AIP, VLDL, HDL, TG, and TC in the NMIBC groups compared to the MIBC patient groups. Furthermore, the levels of CRI-I, CRI-II, and AC were not significantly higher in the NMIBC groups compared to the MIBC patient groups (Figure 1).

Table 2. *Urinary biomarkers and lipid indices of the NMIBC and MIBC patient groups.*

Parameters	NMIBC	MIBC	p
PChE (µg/l)	0.32 (0.22-0.42)	0.23 (0.12-0.32)	**0.003****
AIP	0.55 (0.39-0.63)	0.94 (0.48-1.39)	**0.002****
CRI-I	4.52 (3.16-5.11)	4.15 (3.24-5.11)	0.264
CRI-II	2.29 (1.70-2.99)	2.28 (1.50-3.30)	0.341
AC	3.52 (2.16-4.11)	3.15 (2.24-3.11)	0.273
VLDL (mg/dl)	18.75 (13.40-28.87)	29.54 (24.90-37.13)	**0.040***
LDL (mg/dl)	90.62 (56.10-112.10)	95.63 (69.24-120.68)	0.635
HDL (mg/dl)	53.70 (43.10-56.90)	38.15 (23.97-50.17)	**0.001****
TG (µU/ml)	88.80 (60-132)	147.42 (120.3-185.61)	**0.007****
TC (mg/dl)	162.20 (130.15-168.5)	180.18 (139.4-207.52)	**0.018***

*Data presented as median + interquartile range; NMIBC: Non-Muscle-Invasive Bladder Cancer, MIBC: Muscle Invasive Bladder Cancer, PChE: Pseudocholinesterase, AIP: Atherogenic index of plasma, CRI-I: Castelli's risk Index-I, CRI-II: Castelli's risk index-II, AC: Atherogenic Coefficient, VLDL: Very Low-Density Lipoprotein, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, TG: Triglyceride, TC: Total cholesterol *: p<0.05, **: p<0.01, ***: p<0.001.*

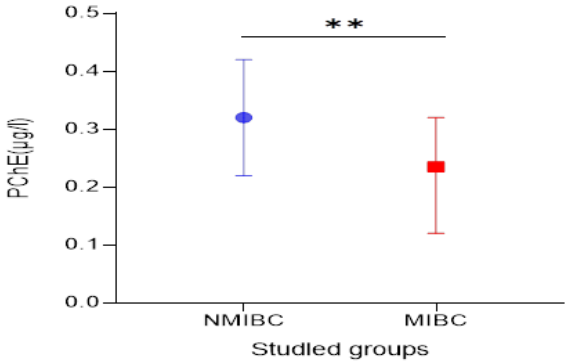

Figure 1. *Concentration of PChE in NMIBC and MIBC patient groups. PChE: Pseudocholinesterase, NMIBC: Non-Muscle -Invasive Bladder Cancer, MIBC: Muscle Invasive Bladder Cancer, The data is presented as the median (interquartile range), **: p<0.001.*

Predictions by the studied urinary biomarker

The PChE and HDL levels failed to show any association with the development of MIBC (OR = 0.81, 95% CI: 0.74-0.88, P<0.003; OR = 1.93, 95% CI: 0.90-0.97, P<0.002, respectively), whereas lipid indices (AIP, CRI-I, CRI-II, AC, TG, and TC) levels increase the risk of developing the disease (OR = 4.17, 95% CI: 2.61-4.66, P<0.0001; OR = 3.44, 95% CI: 3.01-4.51, P<0.002; OR = 1.82, 95% CI: 2.90-3.52, P<0.009; OR = 3.20, 95% CI: 2.07-4.09, P<0.0003; OR = 1.95, 95% CI: 1.02-1.05, P<0.001; OR = 1.53, 95% CI: 1.01-1.05, P<0.004, respectively) as shown in Table 3.

Table 3. *Prediction of the presence of BC by the studied urinary biomarkers and lipid indices.*

	Biomarkers	Coefficient	OR	95% CI	p
Groups (NMIBC versus MIBC)	**PChE**	- 0.20	0.81	0.74-0.88	**0.003**
	AIP	1.42	4.17	2.61-4.66	**<0.001**
	CRI-I	1.86	3.44	3.01-4.51	**0.002**
	CRI-II	2.53	1.82	2.90 -3.52	**0.009**
	VLDLc	0.03	1.02	0.94-1.07	0.921
	LDLc	-0.01	0.98	0.96-1.25	0.632
	HDLc	-0.06	1.93	0.90-0.97	**0.002**
	TG	0.04	1.95	1.02-1.05	**0.001**
	Total cholesterol	0.03	1.53	1.01-1.05	**0.004**

*PChE: Pseudocholinesterase, NMIBC: Non-Muscle-Invasive Bladder Cancer, MIBC: Muscle-Invasive Bladder Cancer, AIP: Atherogenic Index of Plasma, CRI-I: Castelli's Risk Index-I, CRI-II: Castelli's Risk Index-II, AC: Atherogenic Coefficient, VLDL: Very Low-Density Lipoprotein, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, TG: Triglyceride, OR: Odds Ratio, CI: Confidence Interval, **: p<0.01, ***: p<0.001.*

Discussion

Our study revealed a more significant smoking status in MIBC patient groups compared to NMIBC patient groups. Our study results align with those of Jiang X et al., who examined the correlations between smoking cigarettes and BC types at the time of diagnosis. The risks linked to smoking cigarettes were greater for invasive tumors, irrespective of the exposure index considered, whether it be smoking status, daily cigarette consumption, or years of smoking. Certain studies indicate that BC in smokers tends to be more invasive compared to that in nonsmokers (Sturgeon et al., 1994; Hinotsu et al., 2009; Jiang et al., 2020). The precise mechanism of bladder carcinogenesis in smokers is yet to be unidentified. Researchers have identified allelic loss on chromosome 9 as early damage in the progression of BC, which does not differentiate among other tumor subtypes (Knowles, 2006).

The data substantiate the idea that tobacco smoking elevates the risk of all BC subtypes, possibly due to changes in chromosome 9, with invasive tumors showing a stronger correlation (Jiang et al., 2020). In the BC patient groups, the main results of our retrospective study showed that the PChE concentrations and TG/HDL ratio were in inverse correlation. These findings agree with Crocetto et al.'s report. The negative association between TG content and the activities of PChE and LPL indicates that PChE, similar to LPL, may participate in TG breakdown (Crocetto et al. 2022). The TG/HDLc ratio was introduced by Gaziano et al. (2022) as an atherogenic indicator. The TG/HDLc ratio demonstrated a positive connection with the clinical parameters of endometrial cancer, including the stage of the tumor and pathogenic subtype (Luo et al., 2019). The increased conversion of carbohydrates into fatty acids, which are then esterified to accumulate TG, constitutes the metabolic phenotype of BC (Massari et al., 2016). According to our results, MIBC patients showed a lower PChE concentration compared with NMIBC patients. Comparing the findings of the present study with those of prior studies reveals that patients with high-grade BC have decreased PChE levels (Wei et al., 2018). Our results align with Kimura et al. (2018), which demonstrate that reduced PChE levels correlate with shorter recurrence-free survival in patients with NMIBC who have undergone transurethral resection of bladder tumors (TURB) (Kimura et al., 2018). A potential mechanism for the reduction in PChE activity in those with cancer may be secondary anorexia associated with malignancy (Stancu et al., 2022). Systemic inflammation is a common host response to carcinogenesis or cancer advancement, and serum levels of PChE have been shown to reflect the presence of inflammation and various clinical situations (Pavo et al., 2017). The early and correct detection of NMIBC and MIBC is crucial for prompt decisions about appropriate treatment and therapy, which may substantially enhance the survival rates of BC patients (Chen et al., 2019). Interest in analyzing the serum lipid profile in this specific malignancy is growing (Crocetto et al. 2022).

Conclusion

In the present study, the lipid indices' levels of AIP, CRI-II, and AC are associated with the development of MIBC and could be used to help physicians assess and confirm the presence of MIBC, while PChE failed to associate with the development of the disease.

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