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The Urinary Sarcosine/Creatinine Ratio is a Potential Diagnostic and Prognostic Marker in Prostate Cancer

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Manuscript Preparation E
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Background: The aim of this study was to evaluate the role of the urinary sarcosine/creatinine ratio in the diagnosis and prognosis of prostate cancer, using a sarcosine oxidase assay.

Material/Methods: Urine samples were obtained from 203 patients with benign prostate hyperplasia (BPH) and 209 patients with prostate cancer. Levels of urinary sarcosine were measured using the sarcosine oxidase method. The urinary sarcosine/creatinine ratios were compared between the group of patients with BPH and the patients with prostate cancer. In the two patients groups, the urinary sarcosine/creatinine ratio was compared with the measurement of serum prostate-specific antigen (PSA) and the free/total (F/T) PSA ratio. Correlations between of the urinary sarcosine/creatinine ratio and the Gleason grade and stage of prostate cancer were analyzed.

Results: There was a significant difference between the urinary sarcosine/creatinine ratio in the BPH group and prostate cancer group ($P<0.01$), which was independent of serum PSA. The receiver-operating characteristic (ROC) curve, and area under the curve (AUC) for the urinary sarcosine/creatinine ratio was significantly higher compared with the serum PSA and the F/T PSA ratio. There was a significant difference in the urinary sarcosine/creatinine ratio in patients with prostate cancer with Gleason score ≤6, 7, and ≥8, and between patients with metastatic and non-metastatic prostate cancer.

Conclusions: The urinary sarcosine/creatinine ratio was a diagnostic indicator of prostate cancer, for patients with a serum PSA level <10 ng/ml, and correlated with the Gleason score and with the presence of metastases (stage) of prostate cancer.

MeSH Keywords: Diagnosis • Prostate-Specific Antigen • Prostatic Neoplasms • Sarcosine Oxidase

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Background

Worldwide, prostate cancer is a common cancer in men, with an incidence that increases with age, and now ranks as the second most frequent cause of death from male cancer [1]. Although the prevalence of prostate cancer in men in China is lower than that in the United States (US) and other western countries, the incidence has been shown to increase during the recent years [2]. According to the US National Cancer Institute (NCI), the five-year survival rate of localized, non-metastatic, prostate cancer is 100%, is 89% when prostate cancer invades beyond the prostate gland and is 37% when the patient has metastatic prostate cancer (*www.cancer.gov/types/prostate/*). Therefore, screening for prostate cancer and early diagnosis are the key to reduce the mortality rate from prostate cancer. However, early diagnosis is difficult because early-stage prostate cancer lacks specific clinical symptoms and diagnostic imaging markers. Current clinical diagnosis depends on the analysis of serum levels of prostate-specific antigen (PSA) and the histology of the prostate biopsy of suspected cases.

Measurement of serum PSA levels was introduced into clinical use in the 1980s and has significantly improved the early diagnosis of prostate cancer [3]. However, the sensitivity and specificity of the serum PSA test are poor, for several reasons. An elevated serum PSA level is not specific for the presence of prostate cancer, serum PSA levels can be normal in some patients with prostate cancer, and the serum PSA is not an indicator of tumor stage or of prognosis. Therefore, more sensitive and specific markers for the presence of prostate cancer, particularly early-stage prostate cancer, are still required.

In 2009, a metabolomic study conducted by Sreekumar et al. [4] showed that 176 metabolites from 1,126 candidates associated with prostate cancer, among which, sarcosine had the strongest association with the presence of prostate cancer. Sarcosine (N-methylglycine), which is derived from the metabolism of glycine, can be detected in urine. Sarcosine is expressed at very low levels in normal patients or patients with benign prostate hyperplasia (BPH), levels of urinary sarcosine are increased in men with localized prostate cancer, and have been shown to be present at the highest level in the urine of men with metastatic prostate cancer [5]. Since this study was published, several further studies have been undertaken to evaluate the application of measurement of urinary sarcosine in the diagnosis of prostate cancer, but a consensus has been reached, and the study findings have been controversial [6–8].

The aim of this study was to evaluate the role of the urinary sarcosine/creatinine ratio in the diagnosis and prognosis of prostate cancer, using a sarcosine oxidase assay, to evaluate the potential of this assay in the diagnosis of prostate cancer, and as a prognostic marker, using the known Gleason scores and clinical stage.

Material and Methods

Subjects

This study was approved by the Ethics Committee of Beijing Hospital (Ref: LLKYPJ: 2013030512). The study participants provided written informed consent to participate in this study, which included 209 patients with prostate cancer and 203 patients with benign prostate hyperplasia (BPH). The diagnosis in all participating patients was confirmed histologically by biopsy or from surgical resection specimens. Patients were enrolled in this study between February 2012 and September 2016. Fresh urine and blood samples were collected before the biopsy procedure or surgery. The patients were assigned into groups according to their serum prostate-specific antigen (PSA) test results, as follows: PSA <10 ng/ml, PSA ≥10 ng/ml, and PSA at any other level.

Equipment and reagents

Equipment and reagents included a Beckman AU5400 automatic biochemical analyzer (Beckman, USA), Eppendorf research pipettes (Eppendorf, Germany), an Abbott I4000 automatic immune-analyzer (Abbott Labs, USA), Tris(hydroxymethyl)aminomethane (BDI Pharma, USA), peroxidase (Sangon Biotech, Shanghai, China), 4-amino antipyrine (East China Normal University Chemical Factory), sarcosine oxidase (synthesized in-house), creatinine (Bio Basic, NY, USA), 6N-ethyl-N-(2-hydroxy-3-sulfopropyl)-3-methyl aniline salt (TOOS) (Sigma-Aldrich, St Louis, MI, USA), and a creatinine assay kit (G Cell Technologies).

Specimen collection and processing

Whole blood samples were centrifuged at 2,280×g for 5 min within 2 hours of collection, the serum was added to freezer tubes and stored at –20°C. The urine samples (10–15 ml) were centrifuged at 700×g for 10 min within 2 hours of collection, and the supernatants were added to freezer tubes and stored at –20°C. All specimens were collected before the patients were treated. Gleason scores were assigned by histopathological examination to the specimens of prostate cancer acquired from prostatectomies or prostate biopsies.

Determination of sarcosine, creatinine, and other analytes

The algorithms for the sarcosine oxidase method in the detection of urinary sarcosine were as follows:

1. Sarcosine + H_2O + O_2 → glycine + methanol + H_2O_2 (catalyzed by sarcosine oxidase).
2. H_2O_2 + 4-amino-antipyrine + chromogen → Quinone imine colored substance + H_2O (catalyzed by peroxidase).

Sarcosine was measured using a sarcosine oxidase assay. The target concentration was 2.9 μmol/L for fresh urine specimens,

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Table 1. Characteristics of the groups.

Items		PSA <10ng ml^{-1}			PSA ≥10 ng ml^{-1}			PSA not limited		
		PCa	BPH	P-value	PCa	BPH	P-value	PCa	BPH	P-value
n		97	139	–	112	64	–	209	203	–
Ages mean±SD		64.92±13.73	61.10±16.40	0.062*	65.60±14.93	63.69±15.11	0.417*	65.28±14.35	61.92±16.012	0.25*
Sarcosine/ creatinine ratio Median (range)		0.101 (0.037–0.514)	0.051 (0.014–0.097)	0.000#	0.099 (0.020–0.689)	0.062 (0.020–0.104)	0.000#	0.100 (0.031–0.569)	0.062 (0.020–0.104)	0.000#
PSA (ng ml^{-1}) Median (range)		6.30 (0.48–9.13)	2.92 (0.47–8.25)	0.000#	89.24 (10.78–291.84)	19.70 (10.20–44.45)	0.000#	11.20 (2.12–221.37)	19.70 (10.20–4.45)	0.000#
F/T PSA ratio Median (range)		0.154 (0.093–0.340_)	0.236 (0.129–0.508)	0.006#	0.092 (0.047–0.258)	0.200 (0.071–0.519)	0.000#	0.142±0.075	0.200 (0.071–0.519)	0.000#
Clinical stages	Non-metastatic	76 (78.4%)			83 (74.1%)			159 (76.1%)		
	Mestastatic	21 (21.6%)	–	–	29 (25.9%)	–	–	50 (23.9%)	–	–
	Gleason sorces (≤6)	20 (20.6%)	–	–	17 (12.5%)	–	–	37 (17.7%)	–	–
	Gleason sorces (7)	40 (41.2%)	–	–	51 (45.5%)	–	–	91 (43.5%)	–	–
	Gleason sorces (≥8)	37 (38.1%)	–	–	44 (39.3%)	–	–	81 (38.8%)	–	–

* Independent sample *t* test; # Mann-Whitney U-test. Clinical stages are classified in the PCa group only.

with a total error of <14%. At sarcosine concentrations of 6.35 µmol/L and 9.8 µmol/L, the total error levels were <10%. In the sarcosine oxidase assay, the Limit of Blank (LoB), Limit of Detection (LoD), and Limit of Quantitation (LoQ) were the smallest concentrations that could be reliably measured by the analytical method. The LoB was approximately 0.35 µmol/L, the LoD was 1.18 µmol/L, and the LoQ was 2.05 µmol/L. The linear range of the sarcosine oxidase assay was 2.05–125.65 µmol/L. At concentrations of added sarcosine from 2–20 µmol/L, recoveries were between 65.3–90.5%.

Urinary creatinine concentrations were measured using an enzymatic assay and a Beckman AU 5400 analyzer (Beckman, Brea, CA, USA). Serum PSA and free PSA concentrations were measured using a chemiluminescence immunoassay and an Abbott I4000 automatic immune analyzer (Abbott Labs, USA). Detection of serum PSA and the urinary sarcosine/creatinine ratio was conducted in a double-blind manner, and the concentrations of sarcosine and creatinine of each sample were randomly recorded along with the corresponding levels of PSA and the free PSA levels were measured so that the free/total (F/T) PSA ratio could be calculated. All urinary sarcosine values were divided by the corresponding creatinine values to obtain the urinary sarcosine/creatinine ratio for each patient in the two patient groups.

Statistical analysis

Statistical analysis was performed using SPSS version 17.0 software. The normal distribution of data was tested using the Kolmogorov-Smirnov method. When comparing the differences between each group, the t-test was used to analyze normally distributed data. The Mann-Whitney U test and the Kruskal-Wallis test were used to analyze non normally distributed data. The Spearman rank correlation test was performed to determine the relationships between clinicopathological features and the data for the urinary sarcosine/creatinine ratio, concentrations of serum PSA and the F/T PSA ratio. The receiver-operating characteristic (ROC) curve analysis was used to evaluate the applicability of the urinary sarcosine/creatinine ratio for the diagnosis of prostate cancer. P<0.05 indicated a statistically significant difference.

Results

Patient characteristics

The clinical data of the patients in the two groups in this study, patients with prostate cancer and patients with benign prostate

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Table 2. ROC curves for differential diagnosis.

Items	PSA <10 ng/ml			PSA ≥10 ng/ml			PSA not limited		
	AUC	95%CI	P-value	AUC	95%CI	P-value	AUC	95%CI	P-value
Sarcosine/ creatinine ratio	0.855	0.802–0.908	0.000	0.816	0.753–0.879	0.000	0.841	0.802–0.881	0.000
PSA	0.743	0.678–0.808	0.000	0.740	0.669–0.811	0.000	0.728	0.680–0.776	0.000
F/T PSA ratio	0.745	0.678–0.813	0.000	0.805	0.738–0.873	0.000	0.797	0.755–0.840	0.000

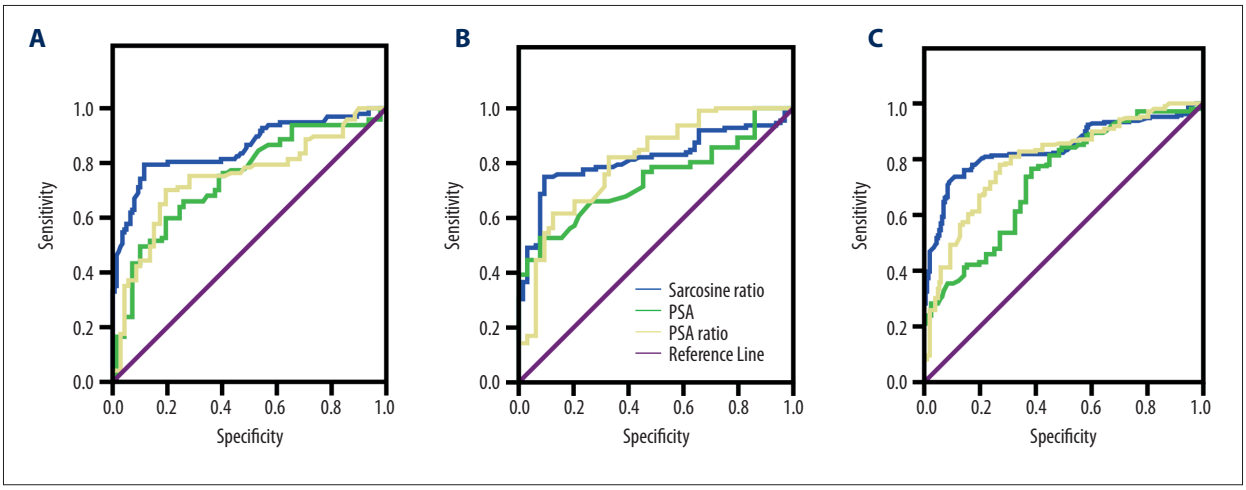

Figure 1. Receiver-operating characteristic (ROC) curves of the urinary sarcosine/creatinine ratio, prostate-specific antigen (PSA), and the free/total (F/T) PSA ratio in the diagnosis of prostate cancer. (**A**) Prostate-specific antigen (PSA) <10 ng/ml. (**B**) PSA ≥10 ng/ml. (**C**) PSA, any concentration.

hyperplasia (BPH), are presented in Table 1. There was no significant difference in age between the two group of patients. However, the urinary sarcosine/creatinine ratio, serum level of prostate-specific antigen (PSA), and the free/total (F/T) PSA ratio were significantly different between the two groups (P<0.05). For further analysis, the patients with prostate cancer were grouped according to tumor grades (Gleason score ≤6, 7, or ≥8) and metastatic tumor status, or stage (metastatic prostate cancer or non-metastatic prostate cancer) based on clinical and pathological data.

Receiver-operator characteristic (ROC) curves, area under the curve (AUC), and the differential diagnosis

The diagnostic performances of the variables studied are summarized in Table 2. In the PSA <10 ng/ml group, the $AUC_{sar/cr}$=0.855 (95% CI, 0.802–0.908) was the highest. The AUC_{PSA} and $AUC_{F/T-PSA}$ were 0.743 and 0.745, respectively. When 0.063 was used as the cutoff value of the urinary sarcosine4creatinine ratio, the sensitivity and specificity for the diagnosis of prostate cancer were 79.4% and 88.5%, respectively (Figure 1A). In the PSA ≥10 ng/ml group, the $AUC_{sar/c}$=0.816 (95% CI, 0.753–0.879) was the highest. The AUC_{PSA} and $AUC_{F/T-PSA}$ were 0.740 and 0.805 respectively. When 0.069 was used as the cut-off value, the sensitivity and specificity of the urinary sarcosine/creatinine ratios were 77.7% and 76.7%, respectively (Figure 1B). In the PSA at any concentration group, the $AUC_{sar/cr}$=0.841 (95% CI, 0.802–0.881) was the highest. The AUC_{PSA} and $AUC_{F/T-PSA}$ were 0.728 and 0.797, respectively. When 0.062 was used as the cut-off value of the urinary sarcosine/creatinine ratio, the sensitivity and specificity were 81.3% and 75.9%, respectively (Figure 1C). The AUC of the urinary sarcosine/creatinine ratio was higher when compared with the serum PSA and the F/T PSA ratio, suggesting that the urinary sarcosine/creatinine ratio might be a good diagnostic metabolomics biomarker of prostate cancer.

The relationship between the urinary sarcosine/creatinine ratio and the Gleason score in prostate cancer

When the patients with prostate cancer were divided into three groups according to the Gleason scores (Gleason score ≤6, 7, or ≥8), statistical analysis showed a significant difference between the urinary sarcosine/creatinine ratio between the groups (P<0.05) (Table 3). As shown in Figure 2A, in the prostate cancer group not distinguished by the histopathological tumor

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Table 3. The sarconine/creatinine ratio of PCa with the pathological types and the Gleason sorces.

		Specimens from surgical removal		Specimens from prostate biopsy		No distinguishing specimens	
		n	Sarcosine/creatinine ratio	n	Sarcosine/creatinine ratio	n	Sarcosine/creatinine ratio
Gleason sorces Median (range)	≤6	22	0.050 (0.018–0.105)	15	0.049 (0.014–0.094)	37	0.050 (0.017–0.102)
	7	34	0.088 (0.031–0.570)	57	0.099 (0.035–0.667)	91	0.096 (0.037–0.573)
	≥8	25	0.130 (0.069–0.919)	56	0.128 (0.072–0.700)	81	0.129 (0.073–0.693)
P-value*		–	0.000	–	0.000	–	0.000

* Kruskal-Wallis test

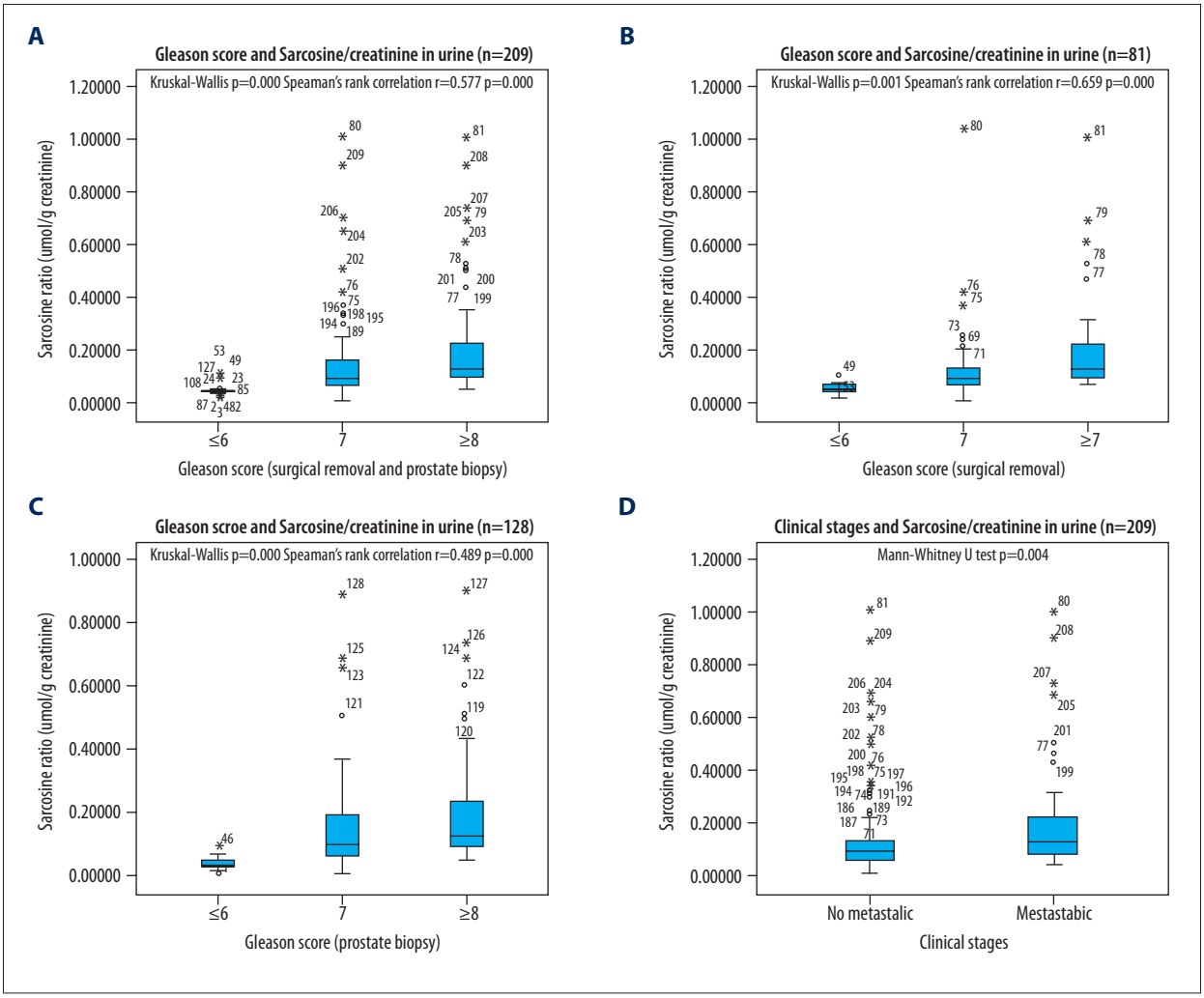

Figure 2. The urinary sarcosine/creatinine ratios and the Gleason scores and the stages of prostate cancer. (**A–C**) The urinary sarcosine/creatinine ratio and Gleason scores. (**D**) The urinary sarcosine/creatinine ratio according to clinical stages (non-metastatic and metastatic prostate cancer).

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Table 4. The test value of metastatic and non-metastatic PCa.

	Metastatic PCa	Non-metastatic PCa	P-value*
n	50	159	
Sarcosine/creatinine ratio Median (range)	0.133 (0.052–0.814)	0.097 (0.020–0.513)	0.004
PSA (ng ml^{-1}) Median (range)	23.83 (1.78–253.08)	10.78 (2.12–214.48)	0.177
F/T PSA ratio Median (range)	0.126 (0.043–0.326)	0.126 (0.052–0.328)	0.891

* Mann-Whitney U-test.

type (on surgical resection and prostate biopsy), there was a positive correlation between the urinary sarcosine/creatinine ratio and Gleason score (r=0.577). In the specimens from the surgical resection group, the urinary sarcosine/creatinine ratio was also positively correlated with the Gleason score (r=0.659) (Figure 2B). Also, the urinary sarcosine/creatinine ratio in specimens obtained from prostate biopsy was positively correlated with the Gleason score (r=0.489) (Figure 2C). There was a significant difference in the urinary sarcosine/creatinine ratio between patients with non-metastatic tumor and those with metastatic cancer (P<0.05) (Table 4; Figure 2D).

Discussion

Cell metabolism of malignant cells differs from that of normal cells, which is why metabolomics analysis of serum and urine can provide markers of cancer, including prostate cancer [9]. Rapidly proliferating cancer cells require higher concentrations of nutrients, which derive energy from ATP, and thus higher concentrations of the corresponding metabolites are generated [9]. Sarcosine plays an important role in ATP metabolism, and high concentrations of sarcosine are produced by cancer cells [10]. Because the pathogenesis of prostate cancer is associated with the methylation and replication of DNA [11], the metabolism of methyl groups in prostate cancer will be elevated. Because sarcosine is important in maintaining methyl balance, the sarcosine concentrations in body fluids during prostate cancer, even at an early-stage are likely to be elevated.

There have been several recently published basic research studies and clinical studies to evaluate the role of sarcosine in the diagnosis of prostate cancer [12,13]. However, currently, studies have shown no significant differences in sarcosine levels between the prostate cancer samples and control samples. Struys et al. [14] compared sarcosine concentrations, measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS), between three groups of men, one group were prostate cancer patients, the second group were men who had increased levels of prostate-specific antigen (PSA) without a confirmed diagnosis of prostate cancer, and the third group were men who had serum samples evaluated for vitamin B12 status. The results obtained by Struys and colleagues demonstrate that the concentrations of sarcosine in serum did not discriminate between the three groups of men [14]. Jentzmik et al. [15] showed that the urinary sarcosine/creatinine ratio was 13% lower in men with prostate cancer when compared with a control group, but receiver-operating characteristic (ROC) analysis showed that the discrimination between patients with prostate cancer and controls was not improved by measurement of sarcosine levels when compared with serum PSA measurement [15]. However, these investigators did not divide the patients into different groups by PSA level and did not perform an independent evaluation [15].

Therefore, the specificity of the urinary sarcosine/creatinine ratio in the diagnosis of patients with low PSA levels requires further investigation. This analysis was not included in the present study and can be considered as a study limitation. However, previous studies had confirmed sarcosine as a potential biomarker for early detection of prostate cancer, and have shown that differences in sarcosine levels were significantly different when patients with prostate cancer were compared with healthy control individuals [16]. Narwal et al. [17] found that sarcosine levels in patients with prostate cancer patients were significantly increased compared with healthy individuals. Heger et al. [18] suggested that measurement of urinary sarcosine might be a non-invasive, rapid, screening method for the diagnosis of prostate cancer. Therefore, the findings of the present study are supported by some previously published studies and showed that the urinary sarcosine/creatinine ratio was significantly different between the group of patients with prostate cancer and the group of patients with benign prostate hyperplasia (BPH). In the present study, the area under the curve (AUC) of the urinary sarcosine/creatinine ratio was found to be significantly increased when compared with the AUC of serum PSA in the patients with PSA less than 10 ng/ml. This finding suggests that in patients with prostate cancer who have low serum PSA levels, the urinary sarcosine/creatinine ratio could be a more reliable biomarker for the detection of prostate cancer.

Sreekumar et al. [4] used RNA interference techniques to inhibit the expression of the enzymes, glycine N-methyltransferase

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(GNMT), dimethylglycine dehydrogenase (DMGDH), and sarcosine dehydrogenase (SARDH) by prostate cells, which affect the intracellular levels of sarcosine and contribute to the invasive properties of certain cancers. Khan et al. [19] validated sarcosine as an important tumor-related metabolite in preclinical models, both *in vivo* and *in vitro*. Also, these investigators confirmed that the overexpression of the *GNMT* gene in cells also elevated the levels of sarcosine, but had no effects on cell proliferation [19]. Elevated intracellular levels of sarcosine have been shown to be positively correlated with the invasive properties of prostate cancer and decreased intracellular sarcosine levels have been shown to be correlated with reduced tumor cell invasion [19]. Also, testosterone and members of the erythroblast transformation-specific (ETS) transcription factor family genes (*ERG*, and *ETV1*) have been shown to be key factors in the development of prostate cancer [4]. Sreekumar et al. [4] treated the androgen-responsive VCaP prostate cancer cell line (*ERG*-positive) and the LNCaP prostate cancer cell line (*ETV1*-positive) for 48 hours and found that sarcosine metabolic pathways were affected by androgens and the expression levels of the *ERG* and *ETV1* genes. These findings might indicate that the sarcosine level is associated with more aggressive forms of prostate cancer.

The histological Gleason score is the main histopathological approach to evaluate the grade and degree of aggression of prostate cancer [20]. The findings of the present study showed a positive correlation between the Gleason score and the urinary sarcosine/creatinine ratio. The urinary sarcosine/creatinine ratio in patients with prostate cancer and a Gleason score ≥8 was significantly increased compared patients with a Gleason score ≤6. These findings are supported by those of Lucarelli et al. [21] who found that increased sarcosine levels were significantly associated with low-grade and intermediate-grade tumors in men with a serum PSA <4 ng/mL. However, at this time, it would be important to combine measurements of sarcosine with other tumor markers, including serum levels of PSA.

In the present study, the role of the urinary sarcosine/creatinine ratio and its association with the clinical stage of prostate cancer was evaluated. There was a significant difference in the urinary sarcosine/creatinine ratio between patients with metastatic and non-metastatic prostate cancer, which suggests that the urinary sarcosine/creatinine ratio in patients might be used as a potential indicator of metastatic prostate cancer. The role of the measurement of the urinary sarcosine/creatinine ratio as a metabolomic diagnostic and prognostic biomarker for prostate cancer requires support from large-scale, multicenter, controlled clinical studies.

Conclusions

The findings from this study showed that the urinary sarcosine/creatinine ratio might be used as a diagnostic indicator of prostate cancer. When the prostate-specific antigen (PSA) concentration was less than 10 ng/ml, its diagnostic value of the urinary sarcosine/creatinine ratio was better than for the measurement of serum PSA and the free/total (F/T) PSA ratio. In this study, the urinary sarcosine/creatinine ratio was significantly correlated with the Gleason score of prostate cancer, and with the presence of metastatic prostate cancer, or tumor stage, which is a clinical indicator of prognosis.

Competing interests

None.

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