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Review Article

A value analysis of TPA, TPS, and CA242 single and combined tests in diagnosing renal carcinoma

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Abstract: Objective: This study set out to analyze the value of TPA (tissue polypeptide antigen), TPS (tissue polypeptide specific antigen), and CA242 single and combined tests in diagnosing renal carcinoma (RC). Methods: A total of 126 RC patients and 102 healthy subjects were selected as a research group (RG) and a control group (CG) respectively. The TPS, TPA and CA242 expression levels were determined, and the diagnostic value of the three for RC as well as the diagnostic effects of TPS combined with CA242 and TPA combined with CA242 were analyzed. The relationships among TPS, TPA, CA242, and the pathological features of RC were observed, and the effects of the three on the prognosis of RC patients were analyzed. Results: The TPS, TPA, and CA242 expression levels in the RG were higher than those in the CG ($P < 0.05$). TPA, TPS, and CA242 alone have a good diagnostic value for RC, but TPS combined with CA242 and TPA combined with CA242 each have a better diagnostic efficacy than a single test. TPS, TPA, and CA242 are relevant to the clinical stage, lymph metastasis, invasion depth, distant metastasis, differentiation degree, and tumor diameter ($P < 0.05$). TPA, TPA, and CA242 are closely linked to patient prognosis. Conclusion: TPS, TPA, and CA242 are highly expressed in RC patients. The combined quantifications of TPS and CA242 as well as TPA and CA242 have a good diagnostic effect for RC's occurrence and are relevant to its prognosis. It may be an excellent potential indicator for RC's future diagnosis and treatment.

Keywords: TPA, TPS, CA242, renal carcinoma (RC), combination

Introduction

Renal carcinoma (RC) is a common malignant tumor in the urinary system [1]. It is a malignant tumor originating from the renal parenchymal urothelial system, also known as renal cell carcinoma [2]. Its morbidity is second only to bladder cancer [3]. RC accounts for 80%-90% of renal malignancies and 2%-3% of adult malignancies [4, 5]. Its mortality ranks first among cancers in the genitourinary system [6]. Its main clinical symptoms are hematuria, lumbago, and lumps. [7]. According to relevant research, RC's occurrence is tied to smoking, obesity, hypertension, heredity, and other factors [8]. In recent years, its morbidity has gradually increased, and the efficacy of radiotherapy and chemotherapy is insignificant [9]. Currently, the main treatment for RC is surgery, with laparoscopic surgery as the first choice [10]. However, its recurrence rate is high and its prognosis is poor, which not only causes renal function damage, but also causes malignant metastasis, seriously endangering patients' lives [11]. Therefore, finding reliable markers is still the focus and challenge of clinical prevention and treatment.

Tissue polypeptide specific antigen (TPS) is a soluble fragment of tissue antigen recognized by cytokeratin 8, 18, and 19 antibodies. A serum tumor marker with a high sensitivity, TPS has been used as a serological indicator for monitoring various tumors after surgery [12]. Tissue polypeptide antigen (TPA) is a non-specific tumor marker and belongs to the cytoskeletal proteins. Studies have shown that the TPA level correlates with the degree of cell division and implantation [13]. Boyle et al. [14] pointed out that TPA and TPS are used for the auxiliary diagnosis and post-treatment monitoring of tumors such as lung cancer and primary liver cancer. CA242 is a commonly used tumor marker clinically that can exist in

the bodily fluid, blood, and cells of patients and is a vital diagnostic index for various cancers, such as gastric cancer [15]. Hence, we suspect TPA, TPS, and CA242 may also have a certain diagnostic significance for RC. In order to verify our conjecture, this experiment will explore the value of the three in diagnosing RC, providing new ideas and directions for its clinical diagnosis and treatment in the future.

Materials and methods

General information

A prospective analysis was conducted on RC patients and healthy subjects admitted to Tianjin City Nankai Hospital from July 2016 to July 2018. Among them, 126 RC patients assigned to the research group (RG), and 102 healthy subjects were assigned to the control group (CG). This experiment was approved by the Ethics Committee of Tianjin City Nankai Hospital. All the above research subjects signed informed consent forms.

Inclusion and exclusion criteria

Inclusion criteria: Patients showing the clinical manifestations of RC and those confirmed as having RC after a biopsy by the pathology department of our hospital (the patients received follow-up treatment in our hospital after their diagnoses); patients who were 18-70 years old; patients with complete case data; patients who agreed to cooperate and participate in the research work of our hospital; patients who did not receive adjuvant therapy before their admission.

Exclusion criteria: Patients with other tumors, cardiac, or cerebral blood diseases, chronic diseases, mental diseases, or autoimmune diseases; patients with organ failure; patients with hepatic or renal insufficiency; patients with drug allergies; patients with a physical disability requiring them to lie in bed for a long time and unable to take care of themselves; patients transferred from one hospital to another during treatment; patients who died during treatment.

Measurement methods

The TPS, TPA, and CA242 levels were determined using the ELLSA method. The kit was provided by CanAg, Sweden. We set up a blank well, a standard sample well, and a sample well to be tested. And we supplemented the S0 standard with a concentration of 0 into the blank well, and we supplemented the standard with different concentrations into the standard well to be 50 μL. After that, we first added 10 μL of the sample to be tested to the sample well, and then we added the sample diluent 40 μL. We added nothing into the blank well. In addition to the blank wells, 100 μL of HRP labeled detection antibody was supplemented to each of the standard wells and the sample wells. The reaction wells were sealed with a sealing plate membrane and incubated for 65 min in a water bath at 37°C. The liquid was discarded, and the absorbent paper was patted dry. Each well was filled with washing liquid, allowed to stand for 2 min, and then the washing liquid was thrown off, and the absorbent paper was patted dry. This was repeated 6 times. Substrates A and B were supplemented to each well, 50 μL each, and incubated for 10 min at 37°C in the dark. The OD value of each well was measured at 450 nm wavelength within 15 min after adding 50 μL of the stop solution.

Outcome measures

Main outcome measures: The expression levels of TPS, TPA, and CA242 as well as the diagnostic value of TPS, TPA, and CA242 in renal cell carcinoma were determined using an ROC curve analysis; the diagnostic efficacy of TPS combined with CA242 and TPA combined with CA242 on renal cell carcinoma was calculated using a binary logistic formula and an ROC curve.

Secondary outcome measures: The relationship between TPS, TPA, and CA242 the pathological characteristics of renal cell carcinoma, and the influence of TPS, TPA, and CA242 on the prognosis of renal cell carcinoma patients were confirmed: The patients were followed up for 3 years at our hospital, and their prognoses and survival were recorded.

Statistical methods

In our research, the collected data were statistically analyzed using SPSS 20.0 (IBM, Armonk, New York, USA) medical statistical

Table 1. Comparison of the general data in the two groups [n (%)]

	Research group (RG) (n=126)	Control group (CG) (n=102)	t/x^2	P
Age (years)	52.3±8.2	53.1±7.6	0.757	0.450
BMI (KG/cm^2)	24.62±2.84	24.78±3.38	0.388	0.698
Gender			0.216	0.642
Male	74 (58.73)	63 (61.76)		
Female	52 (41.27)	39 (38.24)		
Smoking			0.631	0.427
Yes	65 (51.59)	58 (56.86)		
No	61 (48.41)	44 (43.14)		
Alcoholism			0.105	0.746
Yes	48 (38.10)	41 (40.20)		
No	78 (61.90)	61 (59.80)		
Exercise habits			0.027	0.871
Yes	53 (42.06)	44 (43.14)		
No	73 (57.94)	58 (56.86)		
Place of residence			0.497	0.481
Cities and towns	86 (68.25)	74 (72.55)		
Countryside	40 (31.75)	28 (27.45)		
Nationality			0.417	0.518
Han	110 (87.30)	86 (84.31)		
Ethnic minorities	16 (12.70)	16 (15.69)		
Family medical history			0.096	0.756
Yes	42 (33.33)	36 (35.29)		
No	84 (66.67)	66 (64.71)		

analysis software, and the figures showing our data were drawn with GraphPad Prism 7 (San Diego, GraphPad Software Co., Ltd.). The counting data usage (%) was under chi-square tests and expressed as x^2. The measurement data were expressed as the mean ± standard deviation (Mean ± SD), and all the data conformed to a normal distribution. The comparison between two groups were conducted using independent-samples T tests, and the comparison within a same group were conducted using paired T tests. ROC curve analyses were employed to determine diagnostic values. The survival rate was calculated using the Kaplan-Meier method, and the comparisons were determined using log-rank tests. $P < 0.05$ was regarded as a statistically significant difference.

Results

Comparison of the general data

There was no difference in terms of the age, BMI, gender, smoking, drinking, exercise habits, place of residence, nationality, or family medical history of the patients in the two groups ($P > 0.050$) (**Table 1**).

The TPS, TPA, and CA242 expression levels

Before the treatment, the TPS, TPA, and CA242 expression levels in the two groups were observed. The results indicated that the levels in the RG were higher than those in the CG, and the difference was statistically significant ($P < 0.05$) (**Figure 1**).

The diagnostic value of TPS, TPA, and CA242 in the RC

Based on the ROC curve analysis, we found that when the cut-off value was 51.650, the diagnostic sensitivity and specificity of TPS for RC were 81.37% and 77.78%, respectively; when the cut-off value was 4.534, TPA had a diagnostic sensitivity of 89.22% and a specificity of 77.78%; when the cut-off value was 8.056, the sensitivity and specificity of CA242 to RC were 80.39% and 67.46%, respectively (**Figure 2** and **Table 2**).

The diagnostic efficacy of TPS combined with CA242 and TPA combined with CA242 on RC

A binary logistic regression analysis indicated that the TPS combined with CA242 detection model was Log (P) = -12.934+TPSx0.179+CA242X0.532. When the cut-off value was 0.538, the diagnostic sensitivity and specificity of this model for RC were 83.33% and 84.92%, respectively. The TPA combined with CA242 detection model log was Log (P) = -12.994+TPAx2.028+CA242X0.534. When the cut-off value was 0.479, the diagnostic sensitivity and specificity of the model for RC were 84.31% and 86.51%, respectively (**Figure 3** and **Table 3**).

The relationship between TPS, TPA, and CA242 and the pathological features of RC

TPS, TPA, and CA242 are not tied to patients' age, BMI, or gender ($P > 0.05$) but are relevant

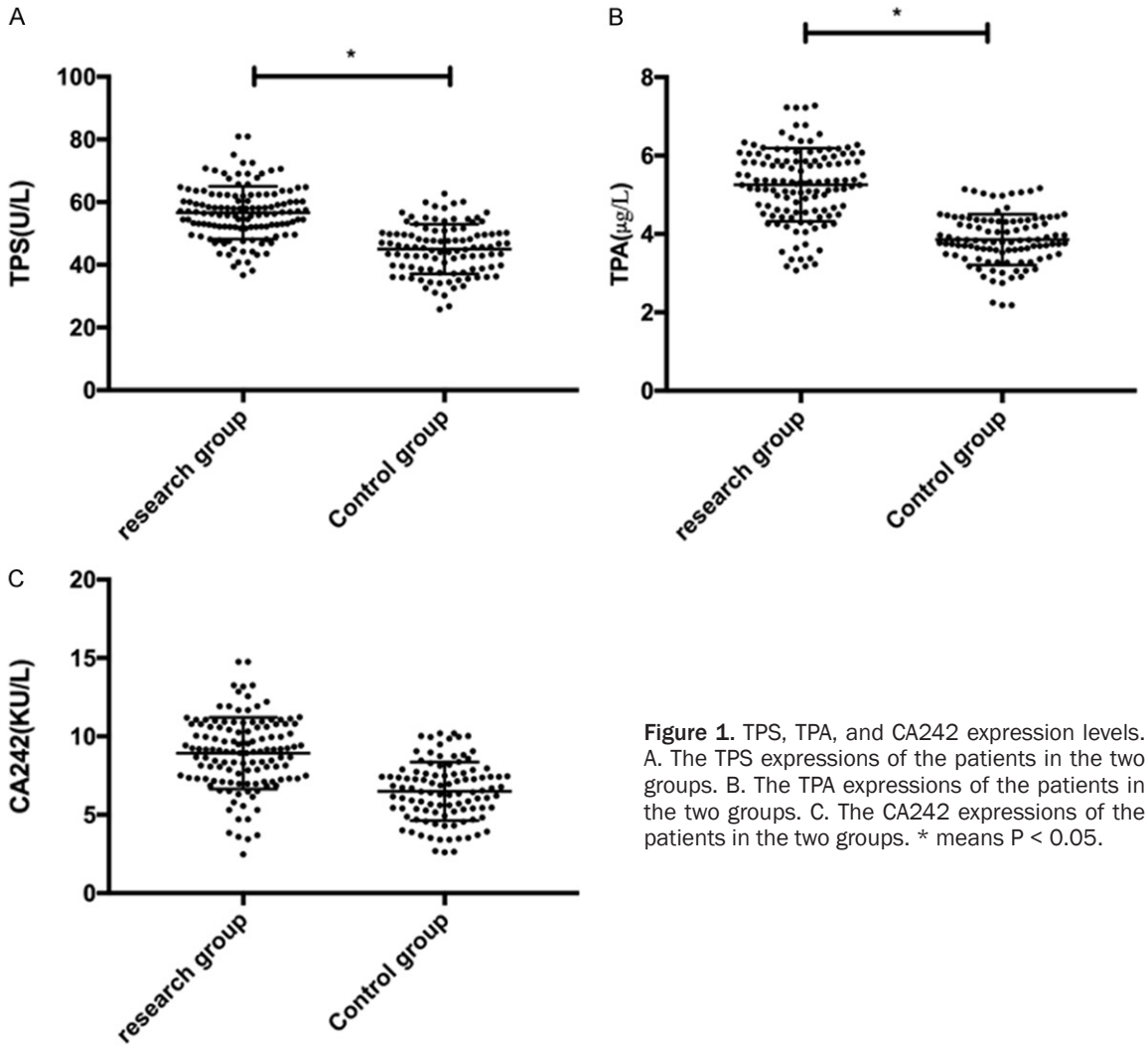

Figure 1. TPS, TPA, and CA242 expression levels. A. The TPS expressions of the patients in the two groups. B. The TPA expressions of the patients in the two groups. C. The CA242 expressions of the patients in the two groups. * means $P < 0.05$.

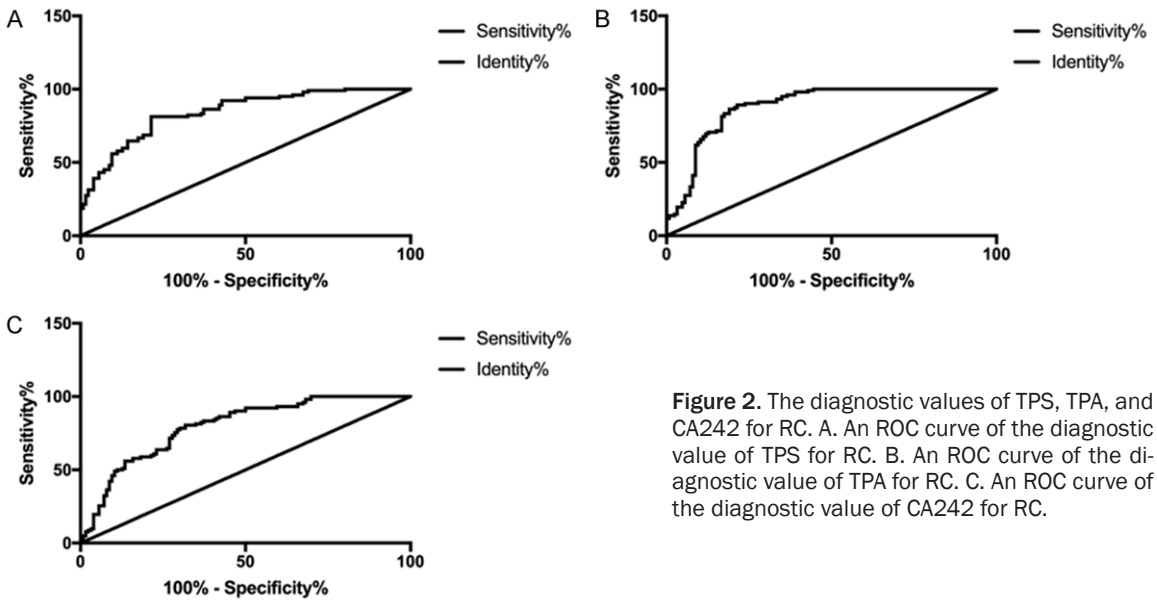

Figure 2. The diagnostic values of TPS, TPA, and CA242 for RC. A. An ROC curve of the diagnostic value of TPS for RC. B. An ROC curve of the diagnostic value of TPA for RC. C. An ROC curve of the diagnostic value of CA242 for RC.

Table 2. The diagnostic efficacy of TPS, TPA, and CA242 on RC

	TPS	TPA	CA242
AUC	0.842	0.885	0.797
Std. error	0.026	0.022	0.029
95% CI	0.792-0.893	0.841-0.929	0.740-0.856
Cut-off	< 51.650	< 4.534	< 8.056
Sensitivity (%)	81.37	89.22	80.39
Specificity (%)	77.78	77.78	67.46
Youden index (%)	59.15	67.00	47.85
P	< 0.001	< 0.001	< 0.001

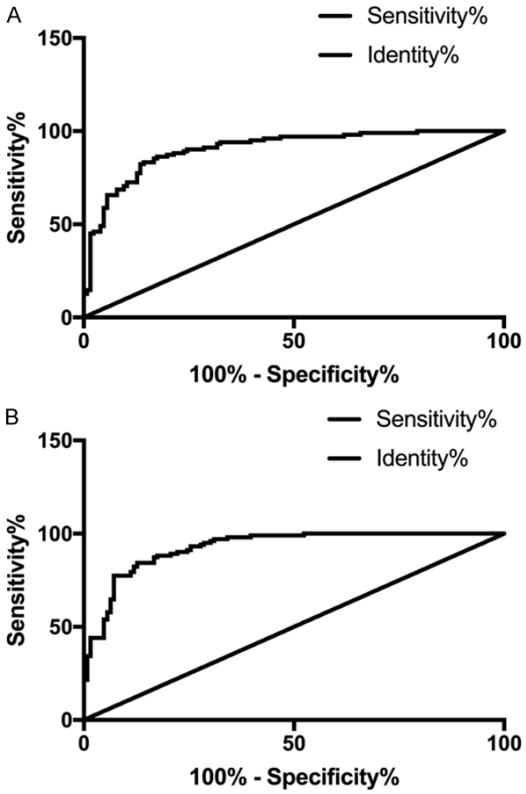

Figure 3. The diagnostic efficacy of TPS combined with CA242 and TPA combined with CA242 on RC. A. The diagnostic efficacy of TPS combined with CA242 on RC. B. The diagnostic efficacy of TPA combined with CA242 on RC.

to the clinical stage, lymphatic metastasis, invasion depth, distant metastasis, differentiation degree, and tumor diameter ($P < 0.05$) (**Table 4**).

The effects of TPS, TPA, and CA242 on the prognosis of RC patients

A total of 126 patients in the RG were followed up successfully for 3 years, with a follow-up success rate of 100%. According to their TPS, TPA, and CA242 levels after treatment, the patients were divided into the high TPS group (TPS > 56.85, n = 45) and the low TPS group (TPS ≤ 56.85, n = 81), the high TPA group (TPA > 5.25, n = 67), and the low TPA group (TPA ≤ 5.25, n = 59), high CA242 group (CA242 > 8.83, n = 69) and low CA242 group (CA242 ≤ 8.83, n = 57). We found that the prognosis of the low TPS group was better than the prognosis of the high TPS group ($P < 0.01$), the prognosis of the low TPA group was better than the prognosis of the high TPA group ($P = 0.002$), and the prognosis of the low CA242 group was better than the prognosis of the high CA242 group ($P = 0.001$) (**Figure 4**).

Discussion

RC is the most common malignant tumor in the urinary system, and its morbidity is among the highest of all malignancies [16]. In recent years, its morbidity has been on the rise and RC patients are getting younger. The harm to the human body is increasing day by day. At present, the molecular and pathological mechanisms of its occurrence are still not fully understood clinically [17]. Early stage RC patients have no obvious symptoms, and the diagnosis mainly depends on an imaging examination. Some patients have deteriorated by the time they are first diagnosed [18]. Surgical resection is considered to be the only effective cure for RC at present. However, there are still some patients with a local recurrence or a distant metastasis after their operations. The vast majority of patients have a relapse or metastasis and are not sensitive to chemotherapy or radiotherapy [19]. Therefore, there has been a lack of a specific tumor marker as an early diagnostic standard for RC in clinical practice. With the application of TPS, TPA, and CA242 as tumor markers, they have gradually become a major research focus at home and abroad, and we urgently need to find potential markers of RC clinically. By exploring the clinical significance of TPS, TPA, and CA242 to RC, this experiment is of great significance to RC's future diagnosis and treatment.

The experimental results indicate that TPS, TPA, and CA242 are highly expressed in RC patients, suggesting that the three may be

Table 3. The diagnostic efficacy of TPS combined with CA242 and TPA combined with CA242 on RC

	TPS combined with CA242	TPA combined with CA242
AUC	0.906	0.927
Std. error	0.020	0.016
95% CI	0.867-0.945	0.895-0.959
Cut-off	< 0.538	< 0.479
Sensitivity (%)	83.33	84.31
Specificity (%)	84.92	86.51
Youden index (%)	68.25	70.82
P	< 0.001	< 0.001

involved in the occurrence and development of RC. However, previous studies have confirmed that TPS increases in cervical cancer, TPA increases in lung cancer, and CA242 is highly expressed in gastric cancer [20-22]. These findings also support the results of this experiment. TPS is a soluble fragment of tissue antigen recognized by cytokeratin 8, 18, and 19 antibodies. It is synthesized between the S1G2 phases of cell division and released out of the cells immediately after meiosis. Therefore, its concentration increases during cell division. TPS is a vital M3 antigenic determinant in TPA and is relevant to epithelial cytoskeleton protein 18. It can reflect cell division and proliferation better than TPA, and it can also better reflect tumor biological behavior [23]. Wang et al. [24] confirmed that TPS has a certain diagnostic value in metastatic breast cancer. Therefore, we suspect that it can also play a diagnostic role in RC. It is expressed in various benign and malignant tumors and is a commonly used tumor marker [25]. Ho et al. [26] proposed that TPA is involved in the occurrence and development of nasopharyngeal carcinoma, while van der Sluis et al. [27] said that TPA has a certain predictive value in RC after radical surgery for colorectal carcinoma. We speculate that it may also play a predictive role in RC. CA242 is a mucin-type carbohydrate antigen and it is mainly distributed in bile duct, pancreas, and colon cancer tissues, but its level is very low in normal human serum. Previous studies have shown that the CA242 expression level in the cancer tissues and serum of intrahepatic cholangiocarcinoma patients is dramatically higher than that of normal people [28], and Lei et al. [29] pointed out that CA242 has a higher diagnostic value in pancreatic cancer. We suspected that it may also be able to evaluate the existence and growth of RC cells. In order to verify our conjecture, we analyzed the diagnostic values of TPS, TPA, and CA242 for RC and found that the three all had a good diagnostic value. When measuring TPS and CA242 as well as TPA and CA242 jointly, we found that they had a better predictive effect for RC's occurrence, which also suggested that the combined diagnosis could be used as a future screening index clinically, thus improving its early diagnosis rate. Compared with traditional imaging methods, TPS and CA242 as well as TPA and CA242 have the advantages of being easy to measure and of having intuitive diagnostic results, so it is not necessary to rely on clinicians' previous judgment experience to analyze any images. Moreover, the peripheral blood samples are stored for a long time, a practice that enables clinical reexamination at any time. It has a higher specificity compared with the single test method, and it can help clinicians to make an early judgment on tumor types and implement relevant intervention measures. Based on their relationship with RC's clinicopathological features, we found that TPS, TPA and CA242 are related to the clinical stage, lymphatic metastasis, invasion depth, distant metastasis, differentiation degree, and tumor diameter of RC. However, due to the effective experimental conditions, we have not been able to analyze the diagnostic value of the three in terms of the different pathological features in more detail, so this will be a focus of our future research for further analysis and discussion. The results of this experiment also confirmed that TPS, TPA and CA242 are tied to RC tumor progression. Finally, through the follow-up process, we found that TPS, TPA, and CA242 are related to patient prognosis, and their expression have a good predictive value for their prognosis and death, suggesting that the clinical monitoring of their TPS, TPA, and CA242 levels can help clinicians to judge recovery and prognosis in the future.

The purpose of this experiment was to explore the clinical significance of TPS, TPA, and CA242 for RC. However, due to the limited experimental conditions, there are still some deficiencies. For instance, first of all, the short

Table 4. The relationship between TPS, TPA, and CA242 and the pathological features of RC

	n	TPS	t	P	TPA	t	P	CA242	t	P
Age (years)			0.752	0.453		0.523	0.602		0.677	0.480
< 52.3	52	55.67±8.15			5.13±0.84			8.32±2.11		
≥ 52.3	74	56.78±8.16			5.21±0.85			8.58±2.13		
BMI (KG/cm^2)			0.551	0.583		0.066	0.947		0.674	0.502
< 24.62	49	55.46±8.14			5.12±0.83			8.43±2.10		
≥ 24.62	77	56.28±8.15			5.13±0.82			8.69±2.12		
Gender			0.543	0.588		0.066	0.948		0.436	0.664
Male	80	55.56±8.16			5.15±0.82			8.55±2.10		
Female	46	56.38±8.17			5.16±0.83			8.72±2.12		
Clinical stage			4.286	< 0.001		2.043	0.043		2.941	0.004
I-II	70	50.23±8.09			5.02±0.81			7.45±2.12		
III-IV	56	56.46±8.13			5.32±0.83			8.57±2.13		
Lymphatic metastasis			3.479	0.001		1.979	0.050		2.427	0.017
Yes	43	56.57±8.13			5.33±0.80			8.74±2.14		
No	83	51.26±8.12			5.03±0.81			7.77±2.12		
Invasion depth			2.282	0.024		2.958	0.004		2.284	0.024
T1-T3	87	53.55±8.12			4.89±0.81			7.66±2.11		
T4	39	57.12±8.11			5.35±0.80			8.59±2.12		
Distant metastasis			2.052	0.042		2.085	0.039		2.227	0.028
Yes	34	57.46±8.08			5.34±0.82			8.95±2.14		
No	92	54.13±8.09			5.00±0.81			8.00±2.12		
Differentiation degree			2.348	0.021		2.191	0.030		2.032	0.044
Moderate and high	82	54.22±8.11			5.02±0.82			8.05±2.10		
Poor	44	57.78±8.12			5.36±0.85			8.85±2.12		
Tumor diameter (cm)			2.072	0.040		2.359	0.020		2.019	0.046
< 5	86	54.25±8.09			5.06±0.81			8.17±2.08		
≥ 5	40	57.46±8.10			5.43±0.84			8.98±2.13		

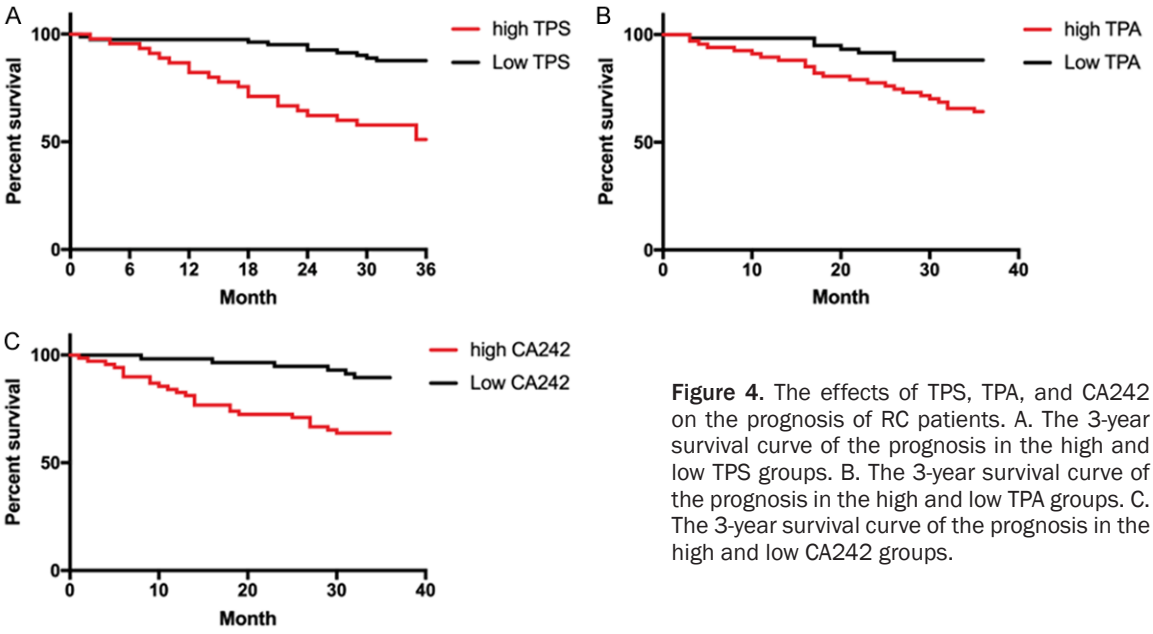

Figure 4. The effects of TPS, TPA, and CA242 on the prognosis of RC patients. A. The 3-year survival curve of the prognosis in the high and low TPS groups. B. The 3-year survival curve of the prognosis in the high and low TPA groups. C. The 3-year survival curve of the prognosis in the high and low CA242 groups.

research period makes it impossible to judge the long-term prognosis of RC patients affected by TPS, TPA, and CA242. Moreover, this experiment lacks the support of in vitro experiments,

and the mechanisms of TPS, TPA, and CA242 that affect RC are still unclear. Finally, we did not use other tumor markers to determine the diagnostic value of RC. We will conduct a more comprehensive and precise analysis in subsequent experiments to obtain the best experimental results.

To sum up, TPS, TPA, and CA242 are highly expressed in RC patients. The combined measurements of TPS and CA242 as well as TPA and CA242 have good diagnostic effects for RC's occurrence and are relevant to its prognosis. The two combined measurements may be excellent potential indicators for RC's future diagnosis and treatment.

Disclosure of conflict of interest

None.

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