

# The use of TAP for the primary diagnosis of renal cell carcinoma

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## Research article

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# Abstract

**Objective** To study the value of TAP expression in peripheral blood for early diagnosis of renal cell carcinoma. **Materials and Methods** TAP expression was analyzed in the peripheral blood of 45 patients with renal cell carcinoma, 32 patients with benign renal lesions and 42 healthy patients. An analysis of the relationship between TAP expression and the clinicopathological features in renal cell carcinoma was performed; the ROC curve was used to evaluate the diagnostic efficacy of TAP detection for renal cell carcinoma diagnosis. **Results** TAP levels were significantly higher in RCC patients than in patients with nonneoplastic diseases. We also found that the rate of positive TAP expression in the peripheral blood of the renal cell carcinoma group showed no significant difference when evaluated by age, sex, histological grade, tumor stage, tumor size or tumor location ( $P > 0.05$ ). The area under the ROC curve was 0.92 (95% CI: 0.82-0.95), and the sensitivity and specificity in the diagnosis of RCC was 73% and 91%, respectively. **Conclusions** The expression of TAP in peripheral blood of patients with renal cell carcinoma was significantly higher than that in nonneoplastic patients, which may provide an effective means of primary diagnosis for renal cell carcinoma

## Background

Globally, renal cell carcinoma ranks sixth among common tumors in men and tenth in women, accounting for 5% and 3% of all tumors in men and women, respectively [1]. However, due to a lack of typical clinical manifestations of renal cell carcinoma, only approximately 30% of patients are diagnosed on the basis of clinical symptoms [2]. Although most kidney cancers manifest small tumors, some patients are already in advanced stages of cancer at the time of diagnosis, and as many as 17% of patients have distant metastases. Therefore, patients with kidney cancer often have a poor prognosis[2]. At present, CT and ultrasound are the main diagnostic methods for renal cell carcinoma. Due to concerns regarding cost, radiation dose and other factors, CT is unlikely to be used in population screening. However, the accuracy of ultrasound detection is limited by the size of tumors; further, its diagnostic sensitivity and specificity are poor. For tumors larger than 3 cm, the detection rate of ultrasound is 85-100%, while the detection rate for tumors larger than 2-3 cm is only 67-82%[3-5]. Therefore, searching for alternative early diagnostic methods is of great significance for the diagnosis and prognosis of renal cell carcinoma.

In recent years, many molecular markers, such as aquaporin 1 (AQP1) and perilipin 2 (PLIN2), have been proposed as potential early diagnostic tools for renal cell carcinoma[6, 7]. However, due to the high cost, time-consuming and highly technical requirements needed to use these markers as diagnostic tools, these markers are not recommended for renal cell carcinoma screening. Tumor abnormal protein (TAP), also known as abnormal glycoprotein, is a newly discovered biomarker produced by tumor cells that can be detected in peripheral blood. The use of TAP as an early diagnostic marker for carcinoma has the following advantages: 1. the role of sugar chains in tumorigenesis and development has been studied for many years; 2. both N-sugar and O-sugar chains are small molecules and easy to detect; and 3. glycosylation is the most common form of posttranslational modification of proteins. Approximately 70%

of proteins in vivo have glycosylation modifications[8]. It has been reported that TAP plays an important role in improving the diagnosis of cancerous tumors, such as bladder, gastric, thyroid, colorectal, and endometrial cancers[9-13]. However, the role of TAP in the diagnosis of renal cell carcinoma remains unclear.

From March 2018 to January 2019, 45 patients with renal cancer admitted to the Fourth Affiliated Hospital of China Medical University and the Cancer Hospital Affiliated to China Medical University participated in a study to explore whether TAP could be used as a tumor marker for early diagnosis of renal cancer.

## Methods

### General information:

From March 2018 to January 2019, 45 patients with renal cancer underwent surgical treatment at the Fourth Affiliated Hospital of China Medical University and the Cancer Hospital Affiliated to China Medical University. All 45 patients were confirmed to have RCC via postoperative pathology. The patients in this study group included 20 males and 25 females between 31 and 83 years of age. During the same period, 32 patients, 14 males and 18 females, with benign renal lesions such as renal cysts, polycystic kidney disease and hydronephrosis were also selected for study. As a control group, 42 healthy patients were also selected for evaluating during this time period. The criteria for inclusion in this study were that patients had no previous history of cancer and had received no preoperative anti-cancer treatment, such as radiotherapy or chemotherapy. Those with immunodeficiency, hepatitis, diabetes, tuberculosis and incomplete clinical data were excluded from the study. This study was approved by the ethics committee of the Fourth Affiliated Hospital of China Medical University, and all subjects provided signed informed consent documents.

### TAP detection method:

The expression of TAP in peripheral blood was assessed in 45 patients with RCC, 32 patients with benign renal lesions and 42 healthy patients. Whole fasting blood was taken during the morning hours and dripped on a slide. A blood smear was then carried out. A coagulant was added after natural drying, and agglutinating particles formed after 1.5-2 hours. The morphology of the agglutinate was observed under a detection image analyzer. TAP detection kits and a TAP detection system were provided by Zhejiang Ruisheng Medical Technology Co. Ltd. Procedures were carried out in strict accordance with the manufacturer instructions.

A sample was considered TAP negative if condensates of abnormal glycoproteins having an area of  $<121 \mu\text{m}^2$  (Figure 1a) were observed.

A sample was considered TAP positive if condensates of abnormal glycoproteins having an area of  $\geq 121 \mu\text{m}^2$  (Figure 1b) were observed in the specimen.

## Statistical processing:

All data was analyzed using SPSS 17.0 and GraphPad Prism 5.0. Student's t-test or chi-square test was applied to determine statistical significance. The diagnostic efficacy of using TAP for renal cell carcinoma detection was analyzed by using a ROC (receiver operating characteristic) curve with a test level of  $\alpha=0.05$

## Results

### Early Diagnostic Value of TAP in Renal Carcinoma

To explore the role of TAP in renal cell carcinoma, we measured the average TAP expression in the peripheral blood of 45 patients with renal cell carcinoma, 32 patients with benign renal disease and 42 healthy patients. The results showed that the expression of TAP in renal cell carcinoma patients was significantly higher than that in patients with benign renal disease or in healthy patients (Figure 2). To further explore the value of TAP as an early diagnostic tool for renal cell carcinoma, we compared the rate of positive TAP expression in the peripheral blood of 45 patients with renal cell carcinoma, 32 patients with benign renal lesions and 42 healthy patients; the positive detection diagnostic criterion was a TAP condensate area  $> 121 \mu\text{m}$ . The results showed that there were 33 cases with positive TAP expression and 12 cases with negative expression in the renal cancer group, 2 cases with positive expression and 30 cases with negative expression in the benign renal disease group, and 5 cases with positive expression and 37 cases with negative expression in the healthy patients group. The rate of positive TAP expression in the peripheral blood of the renal cancer group (73.33%) was higher than that of the benign renal disease group (6.25%) and the healthy patients group (11.90%). This difference was statistically significant (Table 1,  $P<0.001$ ).

### Analysis of the relationship between TAP positive expression and clinicopathological features in renal cell carcinoma

The rate of positive TAP expression in the peripheral blood of the renal cell carcinoma group showed no significant difference when evaluated by age, sex, histological grade, tumor stage, tumor size or tumor location (Table 2,  $P > 0.05$ ).

### Diagnostic efficacy of TAP for RCC

In order to evaluate the diagnostic efficacy of TAP detection for renal cell carcinoma, we established a ROC curve. A TAP condensate area  $> 121 \mu\text{m}^2$  was used as the positive diagnostic criterion. As shown in Figure 3, the area under the curve was 0.92 (95% CI: 0.82-0.95), and the sensitivity and specificity for the diagnosis of RCC using TAP expression was 73% and 91%, respectively.

## Discussion

RCC kills more than 140,000 people per year according to the most recent figures from the World Health Organization, making it the 13th leading cause of cancer related deaths globally [14]. Despite increasing research in the field of renal cancer, 50% of renal cancer still goes undetected during an abdominal CT examination. Due to concerns regarding cost, radiation dose and the limitation of screening accuracy, traditional diagnostic methods, such as CT and ultrasound screening, are deficient in the ability to accurately diagnose renal cell carcinoma. Concerns with accuracy, safety and other factors have also limited the use of renal biopsy. Additionally, the standard treatment for renal masses is pre-resection; consequently, renal biopsy has little impact on the diagnosis and treatment of renal cell carcinoma [2]. In the past decade or so, there have been relatively few studies on renal cancer screening. If renal cell carcinoma can be detected at an early stage, then advanced minimally invasive techniques, such as robotic or laparoscopic partial nephrectomy and tumor ablation, may reduce the incidence of open surgery, reduce hospitalization time and improve the prognosis and quality of life of patients[15-18]. Therefore, it is of great importance to find a reliable early diagnostic method for the treatment and prognosis of renal cancer patients.

Glycosylation is the most common posttranslational modification of proteins. Glycosylation reactions are catalyzed by glycosylases and produce a series of polysaccharides. Such sugar chains play an important role in cell growth, adhesion, movement and cell recognition. Interestingly, an increase in the molecular weight of sugar chains produced within the cell is closely related to the occurrence and development of malignant tumors. Alterations in oncogenes can cause malignant transformation of cells, causing changes in the structure of sugars on the surface of cells and leading to abnormal glycosylation in tumor tissues, which then leads to the production of abnormal glycoproteins [19]. These glycoproteins are usually abnormal in quantity as well as quality, having long sugar chains and complex molecular structures [20]. Clinical evidence has shown that changes in glycosylation are closely related to the prognosis and metastasis of tumors; several studies by Moniaux et al. suggest that in the development of pancreatic cancer glycosylation plays an important role in metastasis and tissue invasion[21-23]. The expression of TAP in normal tissues is low; however, TAP expression is higher in tumor cells than in normal tissues. As the number of cancer cells reaches 100,000 and above[24-26], abnormal glycoprotein can be detected in peripheral blood, and its presence indirectly reflects the degree of malignancy of the carcinoma. Since its discovery by Soviet scholars, TAP has been widely used in cancer screening, early diagnosis and evaluation of therapeutic effects on certain tumors[13]. Sun et al. found that in patients with malignant tumors of the digestive tract, negative TAP expression in the peripheral blood indicated the complete elimination of tumors. However, short term positive expression of TAP (for approximately a month), indicated that tumors remained in the digestive tract or had metastasized; furthermore, in patients with colitis in combination with colon polyps, the incidence of malignant tumors found in the digestive tract for patients with positive TAP expression was significantly higher than for patients with negative TAP expression[8]. It can take between 1-3 years for the number of cancer cells in a patient to grow from 100,000 to  $10^9$ [24-26], meaning that the detection of TAP in peripheral blood can indicate the presence of cancer 1-3 years earlier than conventional means. Therefore, in the early stages of some cancers, a peripheral blood TAP test can indirectly indicate the existence of tumors at a stage when the

relevant physical examinations are unable to identify lesions. This evidence indirectly confirms the value of TAP in the early diagnosis of renal cell carcinoma and provides some reference for the differentiation between benign and malignant renal diseases.

Generally, TAP detection in peripheral blood can indicate the presence of malignant tumors earlier than conventional means. Research on abnormal glycoprotein in malignant tumors is relatively well established, and glycoproteins are known to play an important role in the progression of tumors. More importantly, abnormal glycoproteins are easy to detect, and the tests are clinically practical.

The results of this study showed that the expression of TAP in the peripheral blood of the renal cell carcinoma group was significantly different from that of the other two groups. Specifically, the rate of positive TAP expression was significantly higher in the RCC group (73.33%) than in the benign renal lesions group (6.25%) or the healthy patients group (11.90%). Additionally, based on an ROC curve analysis, the AUC of TAP in the diagnosis of renal cell carcinoma was 0.96. This indicates that the detection of TAP in peripheral blood can be used as an effective auxiliary diagnostic method for renal cell carcinoma with high sensitivity and specificity. TAP detection in peripheral blood may also be helpful in the clinical diagnosis of some kidney diseases that cannot be obviously identified as benign or malignant. However, it is necessary to verify the clinical significance of TAP for RCC with further studies and more participants.

## Conclusions

In summary, renal cell carcinoma lacks typical clinical manifestations. At present, there are no sensitive early tumor markers for renal cell carcinoma that are presently applied for detection and diagnosis. As a new tumor diagnostic marker, TAP detection in peripheral blood is highly sensitivity and specific for the diagnosis of renal cell carcinoma, laying a solid foundation for the early diagnosis of renal cell carcinoma.

## Abbreviations

RCC: renal cell carcinoma

TAP: Tumor abnormal protein

## Declarations

### Acknowledgements

Not applicable.

### Funding

Not applicable.

## **Ethics approval and consent to participate**

This study was approved by the ethics committee of the Fourth Affiliated Hospital of China Medical University, and all subjects provided signed informed consent documents.

## **Consent for publication**

Not applicable.

## **Authors' contributions**

L-J Jiang and F-M Dong wrote the manuscript and interpretation. Y-L Liu and H-C Qu participated in data collection and analysis. All authors read and approved the final manuscript.

## **Availability of data and materials**

All data generated or analysed during this study are included in this published article

## **Conflict of interest**

All authors have no conflict of interest

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## Tables

groups	n	the detection of TAP			P-values
		Negative	Positive	Percentage%	
RCC	45	12	33	73.33	P=0.001
Benign renal lesions	32	30	2	6.25	
Control group	42	37	5	11.9	

Table 1 A comparison of TAP expression in RCC and nonneoplastic diseases

groups	n	the detection of TAP			P-values
		Negative	Positive	Percentage%	
<b>Sex</b>					
Male	29	7	22	75.86	P=0.728
Female	16	5	11	68.75	
<b>Age</b>					
≤60	24	8	16	66.67	P=0.28
≥60	21	4	17	80.95	
<b>Tumor size</b>					
≥5 cm	13	1	12	92.31	P=0.134
≤5 cm	32	11	21	65.63	
<b>Histological grade</b>					
I-II	24	8	16	66.67	P=0.28
III-IV	21	4	17	80.95	
<b>Tumor stage</b>					
T1	28	10	18	64.29	P=0.096
T2-T4	17	2	15	88.24	
<b>Tumor location</b>					
Left	21	6	15	71.43	P=0.787
Right	24	6	18	75.00	

Table 2 A comparison of TAP expression in the RCC group and clinicopathological factors

# Figures

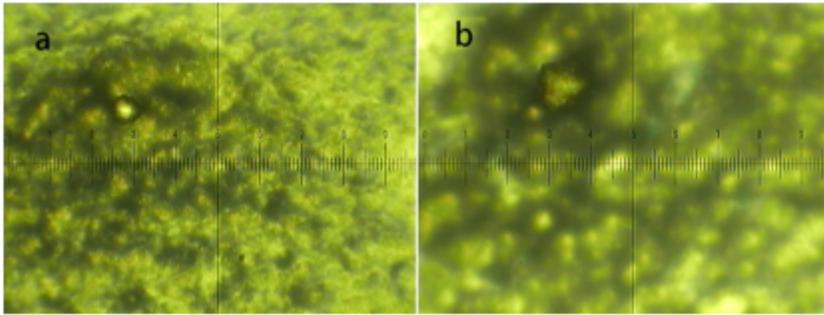


Figure 1

1a. TAP negative expression. Figure 1b. TAP positive expression.

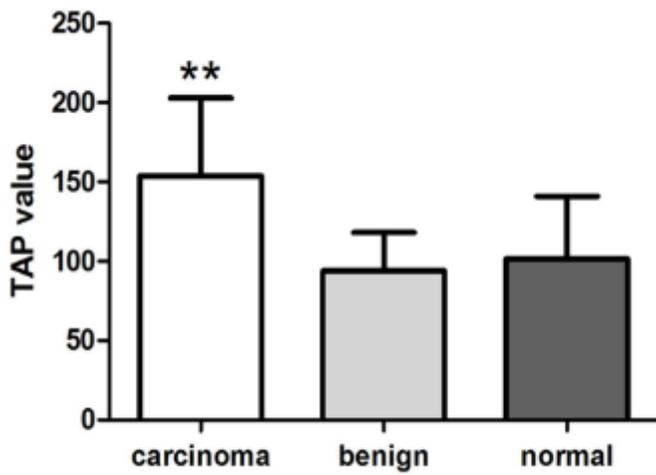
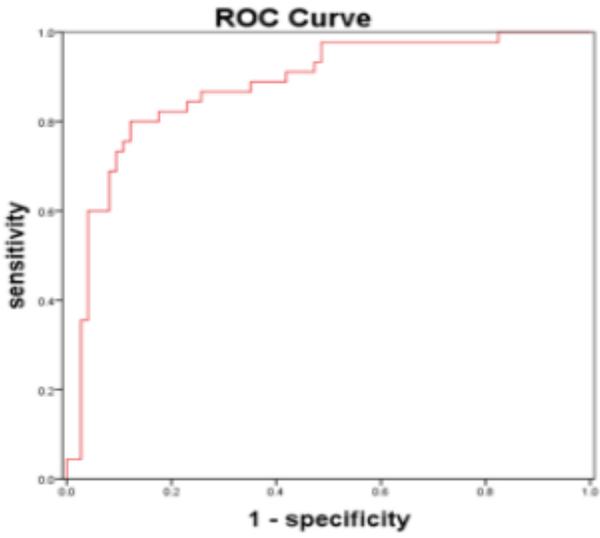


Figure 2

TAP levels between each group. The TAP value in the renal cell carcinoma group (carcinoma) was significantly higher than that in the benign renal lesion group (benign) and the healthy patients group (normal).



**Figure 3**

The receiver operating characteristic curves. The value of TAP in differential diagnosis of renal cell carcinoma and nonneoplastic diseases.