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A Study on the Value of Serum Phosphorus Levels in Predicting the Efficacy of Immunotherapy in Patients with Advanced Renal Cancer

Serum phosphorus and immunotherapy in renal cancer

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Abstract:

Background: Serum biomarkers for predicting immunotherapy outcomes in advanced renal cancer remain an unmet clinical need. This study investigated whether baseline serum phosphorus levels correlate with treatment response and survival in patients receiving immune checkpoint inhibitors (ICIs).

Methods: We retrospectively analyzed 137 patients with advanced renal cancer treated with ICIs. Receiver operating characteristic (ROC) curves were used to determine the optimal phosphorus cut-off (1.085 mmol/L) for predicting the objective response rate (ORR) to immunotherapy. Whilst the Kaplan-Meier method was employed to plot survival curves and perform Log-rank tests to analyse the relationship between serum phosphorus levels and progression-free survival (PFS) and overall survival (OS).

Results: ROC curve analysis showed that the area under the curve (AUC) for predicting response to immunotherapy based on baseline serum phosphorus levels was 0.647 (95% CI: 0.550–0.744, P = 0.0057). Kaplan-Meier analysis showed that PFS(P = 0.005) and OS(P = 0.037) were significantly better in the low-serum phosphorus group than in the high-phosphorus group (P = 0.005). Subgroup Kaplan-Meier analysis showed that, in the IMDC intermediate-risk group, serum phosphorus had some predictive power for prognosis (P = 0.013). Multivariate analysis identified elevated serum phosphorus as an independent poor prognostic factor for PFS (HR=17.537, 95% CI 3.858–79.727, P<0.001) and OS (HR=6.286, 95% CI 1.45–27.254, P=0.014). The clinical benefit rate was higher in the low-phosphorus group (79.4% vs 56.2%).

Conclusion: High baseline serum phosphorus predicts adverse prognosis in ICI-treated renal cell carcinoma (RCC) . It may act as a promising predictive biomarker pending further validation.

Keywords: serum phosphorus; renal cancer; immunotherapy; response prediction; biomarker; prognosis.

Introduction

Renal cancer is one of the most common cancers worldwide, ranking 14th in global incidence among malignant tumours. It accounts for approximately 5 percent of newly diagnosed cancer cases in men and 3 percent in women[1], and is the sixth and tenth most common cancer in men and women, respectively[2]. According to China's 2022 cancer registry data, the incidence of renal cancer ranks 16th among malignant tumours in the country, with a mortality rate of 2.4 per 100,000[3]. Approximately one-third of cases are diagnosed as metastatic, and a further 20-50% will progress to metastatic cancer despite surgical resection[4].In recent years, immunotherapy, particularly immune checkpoint inhibitors, has radically transformed the treatment landscape for advanced renal cancer, significantly prolonging patient survival[5].

Tumour cells can evade surveillance and attack by the immune system through various mechanisms; this process is known as tumour immune escape. One important mechanism involves the utilisation of immune checkpoint pathways. Immune checkpoints are immune regulatory molecules that, under normal circumstances, prevent excessive activation of the immune response and maintain self-tolerance.

Tumour cells often overexpress immune checkpoint ligands, such as PD-L1, which bind to PD-1 (programmed death ligand 1) on the surface of T cells, thereby inhibiting the anti-tumour activity of T cells[6]. Immune checkpoint inhibitors (ICIs) block these pathways to reactivate endogenous anti-tumour immunity. High PD-L1 expression predicts poor prognosis in renal cancer[7]. PD-1 pathway inhibitors are effective for metastatic CCR[8], and combination regimens of such agents are now first-line therapy for this population[9]. However, not all patients benefit from immunotherapy, with an objective response rate of only 20–40 per cent. Furthermore, some patients may develop primary resistance or experience severe immune-related adverse reactions[10-11]. This has prompted the search for new, more precise, simpler, and cost-effective biomarkers to assess the prognosis of renal cancer. Whilst several potential biomarkers are currently under evaluation, effective markers capable of reliably identifying patients likely to benefit from immunotherapy and guiding treatment strategies have yet to be fully validated. Integrating biomarkers into predictive models and ensuring their safe application remain key challenges in the coming years[12-14].

Previous studies have suggested that serum phosphorus levels may be elevated in cancer patients[15-19], and that phosphorus can regulate the activity of cancer cells. Studies have found that phosphorus promotes the transformation of precancerous tissue into cancer by increasing cellular uptake of phosphorus and facilitating its biosynthesis into nuclear RNA (ribosomal RNA), thereby accelerating the proliferation of cancer cells[20]. However, there are currently few studies on the association between serum phosphorus levels and renal cancer. The aim of this study is to evaluate the independent

predictive value of serum phosphorus levels for the efficacy of immunotherapy and prognosis in patients with advanced renal cancer.

Materials and Methods

2.1 Study Population

Clinical data were retrospectively collected from patients with renal cancer who received immunotherapy at Zhejiang Cancer Hospital between 22 May 2022 and 26 May 2026. Patients were included if they met the following criteria. First, they had received at least one cycle of monotherapy or combination therapy with immune checkpoint inhibitors. Second, they had complete clinical data, laboratory parameters, treatment regimens, response assessments, and follow-up data. The exclusion criteria were as follows. First, they had concurrent malignancies of other types. Second, they had severe hepatic or renal impairment, parathyroid dysfunction, or other diseases affecting phosphorus metabolism. Third, they had used medications affecting serum phosphorus levels within the past month. Fourth, they had previously received anti-tumour immunotherapy. Fifth, they had incomplete clinical and pathological data.

2.2 Data Collection

The following patient data were collected via the hospital's electronic health record system: (1) General clinical data: age, sex, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status score, TNM staging, histological type, number of metastatic sites, etc.;(2) Laboratory parameters: baseline

serum phosphorus, serum calcium, alkaline phosphatase (ALP), lactate dehydrogenase, albumin, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), etc.;(3) Treatment regimens: type of immunotherapy agent (PD-1/PD-L1 inhibitors), monotherapy or combination therapy; (4) Efficacy and follow-up data: best response (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD]) assessed according to RECIST 1.1 criteria; objective response rate (ORR = CR + PR) and disease control rate (DCR = CR + PR + SD) calculated;Progression-free survival (PFS) is defined as the time from the start of treatment to disease progression or death from any cause; overall survival (OS) is defined as the time from the start of treatment to death from any cause or the last follow-up.

2.3 Measurement of serum phosphorus levels

Fasting venous blood samples were collected from all patients prior to the commencement of immunotherapy, and serum phosphorus levels were measured using a fully automated biochemistry analyser (normal reference range: 0.85–1.51 mmol/L). A ROC curve was used to determine the optimal cut-off value for serum phosphorus in predicting response to immunotherapy, and patients were subsequently categorised into low-serum phosphorus and high-serum phosphorus groups accordingly.

2.4 Statistical Analysis

Statistical analysis was performed using SPSS 27.0 and GraphPad Prism 10.0 software. Depending on whether the data followed a normal distribution, t-tests or non-parametric tests were used to compare serum phosphorus levels with clinical characteristics; the Kaplan–Meier method was used to plot survival curves and compare

PFS and OS between groups with different serum phosphorus levels, with the Log-rank test used to assess the significance of survival differences between groups. For OS and PFS, univariate analysis (UVA) and multivariate analysis (MVA) were performed using the Cox proportional hazards model, and the hazard ratio (HR) and its 95% confidence interval were reported. In the MVA analysis, variables controlled for included sex, ethnicity, IMDC stage, histological type, and number of prior treatment lines to assess the association between serum phosphorus levels and OS and PFS. ROC curve analysis was performed to assess the ability of serum phosphorus to predict response to immunotherapy; the area under the curve (AUC) and 95% confidence interval (CI) were calculated to evaluate the sensitivity and specificity of serum phosphorus levels in predicting response to immunotherapy and to determine the optimal cut-off value for serum phosphorus in predicting response to immunotherapy. A p-value of <0.05 was considered statistically significant.

Results

Baseline clinical characteristics

This study enrolled a total of 146 patients with renal cancer receiving immunotherapy. After excluding 9 patients with missing serum phosphorus data, the demographic and clinical characteristics of 137 patients were analysed in this study. Of the 137 patients, 106 were male (77.3 percent), and 31 were female (22.6 percent). All patients received immunotherapy. According to the IMDC criteria, 7.9%, 57.2%, and

33.3% of patients were classified as low-risk, intermediate-risk, and high-risk, respectively. The optimal cut-off value derived from the ROC curve was 1.085 mmol/L. Based on this cut-off, patients were divided into a high-serum phosphorus group (>1.085 mmol/L, n = 64) and a low-serum phosphorus group (<1.085 mmol/L, n = 73), with the high-serum phosphorus group accounting for 46.7% of patients. There were no statistically significant differences between the two groups in terms of age, sex, BMI, and ECOG PS (all $p > 0.05$). The rate of liver metastasis was significantly higher in the high-serum phosphorus group than in the low-serum phosphorus group (14% vs 4.1%, $p = 0.04$). The median OS and PFS for the entire cohort were 359 days and 992 days, respectively.

Table 1. Baseline demographic and clinico-pathological characteristics of patients

Variables of interest	**Total (N=137)**
Age (years), median (range)	62 (18–79)
Gender, n (%)	
Male	106 (77.3)
Female	31 (22.6)
ECOG performance status[a], n (%)	
0	26 (18.9)
1	97 (70.8)

≥2	3 (2.1)
IMDC risk score[b], n (%)	
Favorable	11 (7.9)
Intermediate	79 (57.2)
Poor	46 (33.3)
Pathological type, n (%)	
Renal cell carcinoma	123 (89.1)
Other	12 (8.6)
Number of prior treatment lines, n (%)	
Line 1	63 (45.6)
2nd line	41 (29.7)
3rd line and above	33 (23.9)
Number and specific sites of metastases, n (%)	
No metastases	25 (18.1)
Lung metastases	55 (39.8)
Non-pulmonary metastases	57 (41.3)
Baseline serum phosphorus[c], n (%)	
Low	73(53.2)
High	64(46.7)
Alanine aminotransferase (ALT), median (range)	17 (3–133)

Aspartate transaminase (AST), median (range)	21 (12–145)
Alkaline phosphatase (ALP), median (range)	94 (15–1141)
Gamma-glutamyltransferase (GGT), median (range)	30 (4–560)
Albumin (ALB), median (range)	41.9 (21.3–50.9)
Creatinine (Cr)	82.3 (28.6–192.6)
Urea	5.995 (2.56–16.58)
Cystatin C	1.07 (0.59–2.52)

[a] Eastern Cooperative Oncology Group classification ranging from 1 to 5, with lower scores indicating better functionality.

[b] International Metastatic RCC Database Consortium used to risk-stratify disease within favorable, intermediate, and poor risk classes.

[c] Optimal cut: P> 1.085, with 46.7 % of patients in the high serum phosphorus group.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IMDC, International Metastatic RCC Database Consortium.

Correlation between serum phosphorus levels and the efficacy of immunotherapy

We further compared recent efficacy indicators, including objective response rate (ORR) and disease control rate (DCR), between patients in the high-phosphorus group and the low-phosphorus group. Of the 137 patients, 46.7 percent were in the high-phosphorus group. Compared with the high baseline serum phosphorus group, patients in the low baseline serum phosphorus group had a higher disease control rate (56.2% vs 79.4%, p = 0.004, Figure S2A in the Supporting Information)), suggesting that patients with lower serum phosphorus levels exhibit a better objective response to immunotherapy. Patients with low baseline serum phosphorus levels and those with high baseline serum phosphorus levels had similar objective response rates (30.1% vs 26.5%, Figure S2B in SI), with no statistical significance. The above results indicate that serum phosphorus levels are closely associated with the disease control rate following immunotherapy, and that patients with low serum phosphorus levels are more likely to experience tumour shrinkage from immunotherapy; however, its predictive value for objective response rates remains unclear; this may be related to sample size or the fact that disease control is influenced by various confounding factors (such as tumour indolence and baseline lesion measurability). We further compared the differences in baseline serum phosphorus levels between patients who achieved disease control (non-PD group, i.e. CR + PR + SD) and those who experienced disease progression (PD group) following immunotherapy. The results showed that the mean serum phosphorus level in the non-PD group was 1.05 mmol/L, whilst that in the PD group was 1.14 mmol/L, representing a statistically significant difference (P = 0.0108,

Figure S3 in SI). Furthermore, serum phosphorus levels in the non-PD group showed a trend towards being lower than those in the PD group, suggesting that patients with lower serum phosphorus levels may be more likely to achieve disease control following immunotherapy. To investigate whether the predictive role of serum phosphorus levels on the prognosis of immunotherapy is influenced by baseline risk stratification, we categorised patients into intermediate-risk and high-risk groups according to the IMDC risk model and conducted subgroup survival analyses for each group. Among patients in the intermediate-risk group, the survival curves for the high-phosphorus group and the low-phosphorus group were significantly separated. The median progression-free survival (PFS) was 309 days in the high-phosphorus group and 416 days in the low-serum-phosphorus group of the intermediate-risk group; the former was markedly shorter than the latter, with a statistically significant difference ($p = 0.0129$, Figure 1A). Meanwhile, overall survival (OS) analysis for the intermediate-risk group also revealed a significant survival benefit in the low-serum-phosphorus group($p = 0.019$, Figure 1C), indicating that serum phosphorus level was closely associated with long-term survival outcomes in this group of patients.

Among patients in the high-risk group, the survival curves of the high-serum-phosphorus group and the low-serum-phosphorus group tended to overlap, and the difference was markedly narrowed. No statistically significant differences were observed in progression-free survival ($p = 0.1408$, Figure 1B) and overall survival ($p = 0.317$, Figure 1D) between the high-serum-phosphorus subgroup and the low-serum-phosphorus subgroup within the high-risk group. This indicates that the prognostic

predictive power of serum phosphorus for immunotherapy outcomes is substantially attenuated in high-risk patients. The above findings suggest that the prognostic value of serum phosphorus is dependent on the IMDC risk stratification. Serum phosphorus can serve as an effective prognostic biomarker for immunotherapy in intermediate-risk patients, and its reduction is significantly associated with favorable PFS and OS; in contrast, the predictive performance of serum phosphorus is lost in the high-risk group, which is presumed to be related to the stronger tumor invasiveness and the relatively reduced prognostic weight of metabolism-related signals among high-risk patients.

Table 2. Correlation analysis between serum phosphorus levels and clinical and pathological characteristics

Correlated Variables	**Subgroup**	**Lower baseline serum phosphorus levels (n = 73)[c]**	**Higher baseline serum phosphorus levels (n = 64)**	**p-value[d]**
Disease control[a]	Y	58 (79.4)	36 (56.2)	**0.004**
	N	15 (20.5)	28 (43.7)	
Objective response[b]	Y	22 (30.1)	17 (26.5)	0.644
	N	51 (69.8)	47 (73.4)	
Best answer	CR	1 (1.3)	1 (1.5)	**0.025**
	PD	15 (20.5)	28 (43.7)	

	PR	21 (28.7)	16 (25)	
	SD	36 (49.3)	19 (29.6)	
Median baseline serum phosphorus	Median (min-max)	0.97 (0.5–1.08)	6 (4.7–11.5)	
Median age (years)	Median (min-max)	63 (29–79)	60.5 (18–78)	0.669
Baseline BMI, kg/m²	<25	47 (64.3)	37 (57.8)	0.431
	≥25	20 (27.3)	22 (34.3)	
Gender	M	60 (82.1)	46 (71.8)	0.15
	F	13 (17.8)	18 (28.1)	
Histology	Renal cell carcinoma	66 (90.4)	57 (89)	0.756
	Other	7 (9.5)	5 (7.8)	
ECOG performance status	0–1	66 (90.3)	57 (89)	
	≥2	1 (1.3)	2 (3.1)	
Number of distant metastases	0	11 (15)	14 (21.8)	0.337
	1	36 (49.3)	24 (37.5)	
	≥2	26 (35.6)	26 (40.6)	

Liver metastases present	Yes	3 (4.1)	9 (14)	**0.04**
	No	70 (95.8)	55 (85.9)	
Number of prior treatment lines	1st line	37 (50.6)	26 (40.6)	0.442
	Line 2	21 (28.7)	20 (31.2)	
	Tier 3 and above	15 (20.5)	18 (28.1)	
IMDC risk class	Favorable (0 points)	7 (9.5)	4 (6.2)	0.881
	Intermediate （1–2 points）	41 (56.1)	38 (59.3)	
	Poor (3–6 points)	25 (34.2)	21 (32.8)	

Bolded P-values indicate statistical significance.

[a] Disease control is defined as complete response (CR), partial response (PR), or stable disease (SD).

[b] Objective response is defined as complete response (CR) or partial response (PR).

[c] An optimal cut-off of 1.085 was used to divide baseline serum phosphorus into low and high subclasses.

[d] The P-value is calculated by ANOVA for numerical covariates and chi-square test or Fisher’s exact test for categorical covariates, where appropriate.

Abbreviations: CR, complete response; PD, progressive Disease; PR, partial response; SD, stable disease; BMI, body mass index; M, male; F, female.

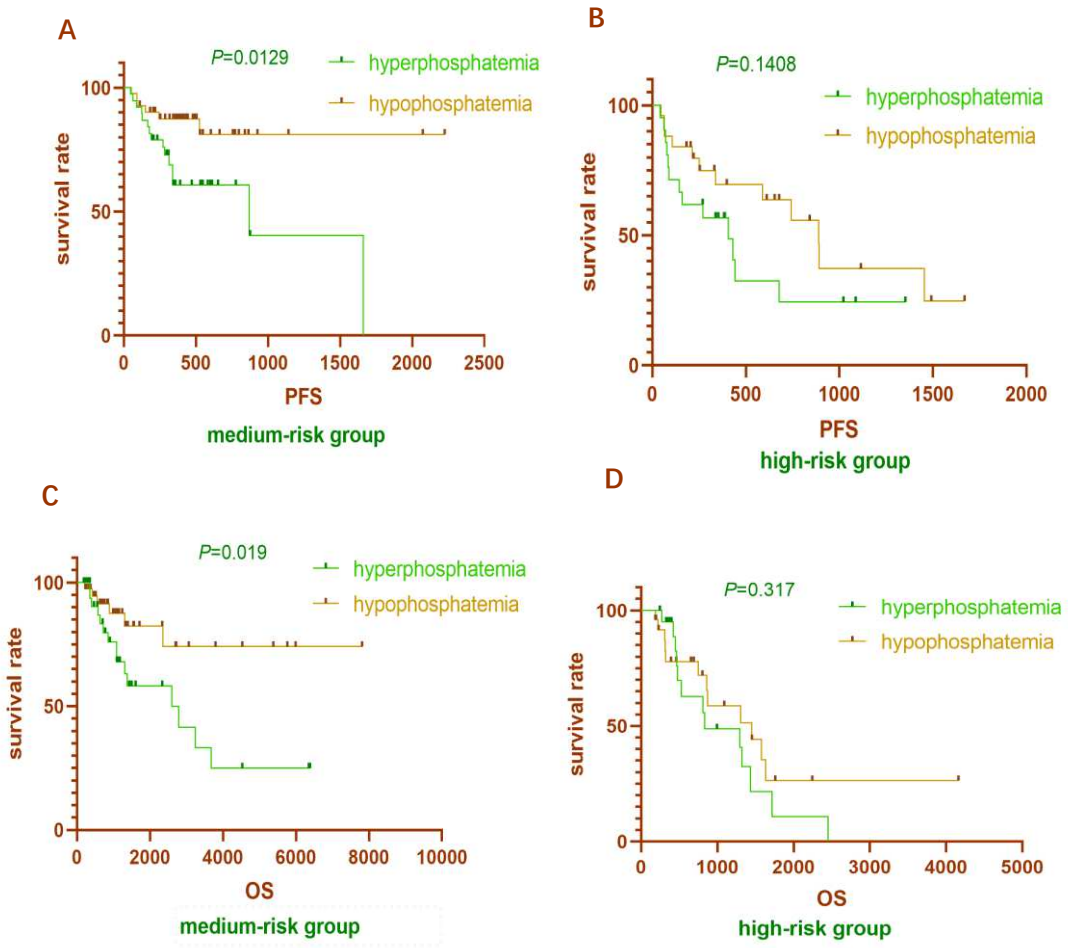


Figure 1. Kaplan-Meier curves illustrating the relationship between serum phosphorus levels and PFS and OS across the IMDC risk groups. PFS (A, B) and OS (C, D) following immunotherapy were compared between patients with high and low serum phosphorus levels, stratified by IMDC risk (intermediate-risk vs. high-risk). In the intermediate-risk group, patients with low serum phosphorus levels demonstrated significantly better PFS (p = 0.0129) and OS (p = 0.019) than those with high serum phosphorus levels; in the high-risk group, there were no statistically significant

differences in PFS (p = 0.1408) or OS (p = 0.317) between the two groups.

Assessment of the predictive value of serum phosphorus levels for response to immunotherapy

We further evaluated the predictive ability of baseline serum phosphorus levels for objective response (CR+PR) to immunotherapy using receiver operating characteristic (ROC) curves.ROC curve analysis showed that baseline serum phosphorus levels had an AUC of 0.647 for predicting response to immunotherapy, with a P = 0.0057 and a 95% CI of 0.551–0.744, suggesting that serum phosphorus has a certain discriminatory ability regarding the efficacy of immunotherapy. The P-value was well below 0.05, indicating statistical significance (Figure 2).

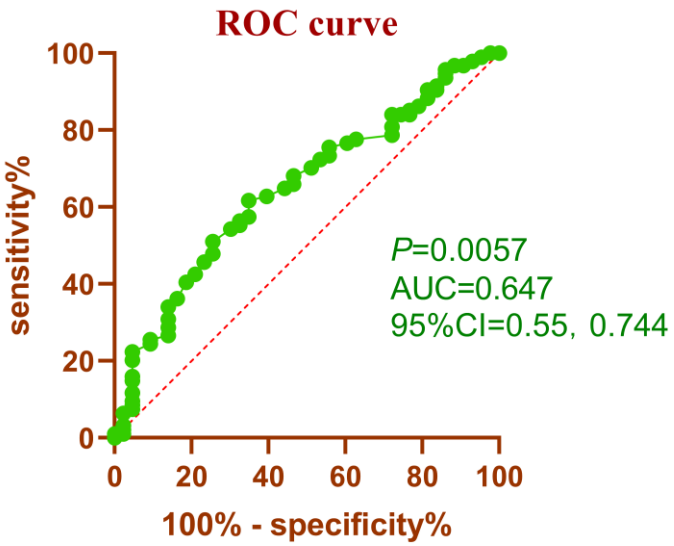


Figure 2. ROC curve for the prediction of objective response to immunotherapy based on baseline serum phosphorus levels. The receiver operating characteristic (ROC) curve assesses the predictive performance of baseline serum phosphorus levels for achieving an objective response (CR+PR) following immunotherapy. The x-axis represents 1-specificity (false positive rate), the y-axis represents sensitivity (true

positive rate), and the area under the curve (AUC) is 0.647.

Relationship between serum phosphorus levels and survival prognosis

We further compared progression-free survival (PFS) and overall survival (OS) between patients in the high-phosphorus group and the low-phosphorus group over a longer follow-up period using Kaplan-Meier survival curves. Kaplan-Meier survival analysis showed that the median PFS for patients in the high-phosphorus group was 312 days, whilst that for the low-phosphorus group was 433 days; patients in the low-phosphorus group had superior PFS compared with those in the high-phosphorus group, and the difference between the two groups was statistically significant (Figure 3A, Log-rank p=0.005, HR=0.443, 95% CI: 0.246–0.797). Concerning OS, the median OS in the high serum phosphorus group was 881 days, whilst that in the low serum phosphorus group was 1,011 days; patients in the low serum phosphorus group had a better OS than those in the high serum phosphorus group, and the difference between the two groups was statistically significant (Figure 3B, Log-rank p = 0.037, HR = 0.538, 95% CI: 0.301–0.961). These results suggest that lower baseline serum phosphorus levels are significantly associated with longer PFS and OS following immunotherapy in patients with renal cancer.

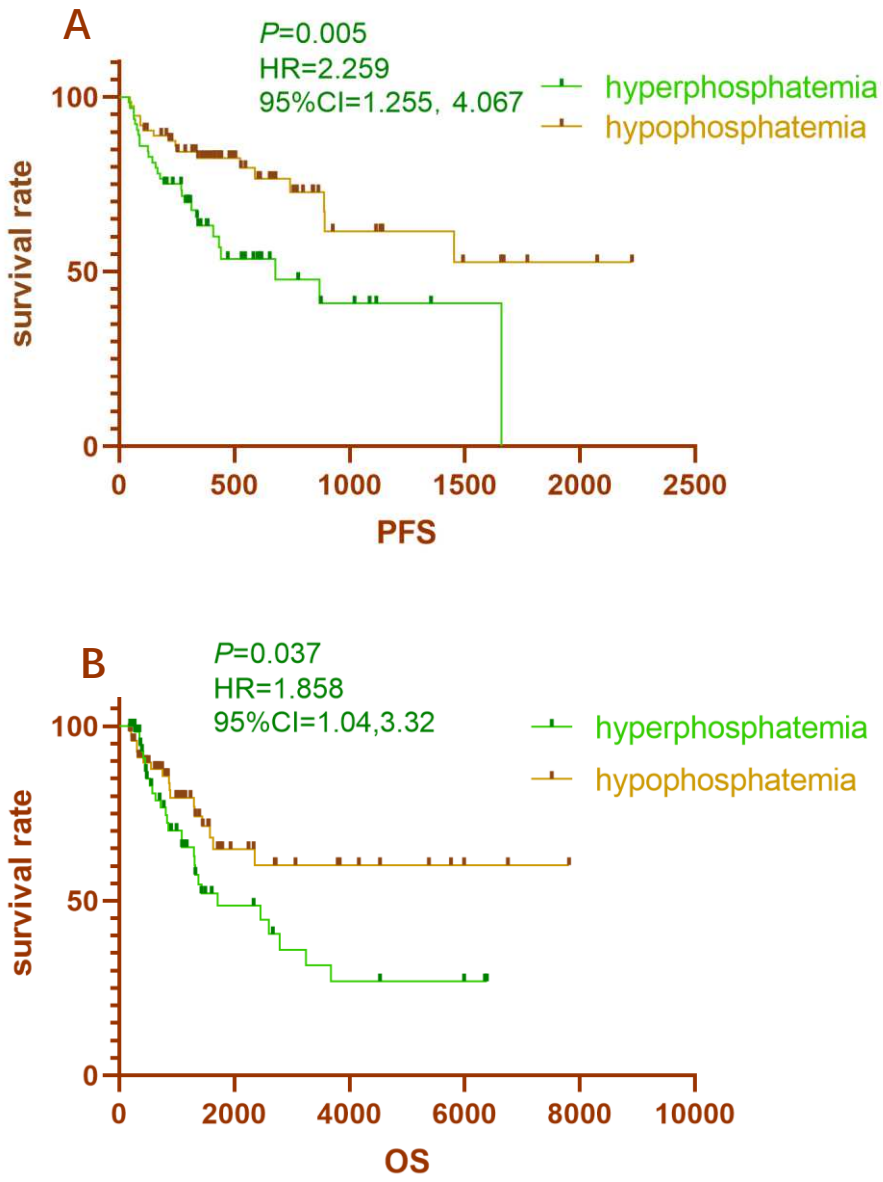


Figure 3. Survival curves (Kaplan–Meier curves) for patients in the high serum phosphorus group and the low serum phosphorus group following immunotherapy. The Kaplan–Meier survival curves compare progression-free survival (PFS) and overall survival (OS) in patients in the high serum phosphorus group and the low serum phosphorus group following immunotherapy.

296 **Univariate and multivariate Cox regression analyses**

297 Univariate Cox regression analysis revealed that serum phosphorus levels (HR =
298 11.775, 95% CI 2.334–59.392, p = 0.003), IMDC high-risk status (HR = 0.542, 95%
299 CI 0.296–0.99, p = 0.046), the number of distant metastases, pathological classification
300 (HR = 3.04, 95% CI 1.402–6.591, p = 0.005), treatment modality and number of
301 treatment lines were significantly associated with PFS. Serum phosphorus levels (HR
302 = 17.537, 95% CI 3.858–79.727,p < 0.001), IMDC risk (HR = 0.344, 95% CI 0.185–
303 0.638, p < 0.001), age (HR = 0.96, 95% CI 0.934–0.986,p = 0.003), pathology (HR =
304 5.088, 95% CI 2.275–11.381,p < 0.001), treatment modality, number of treatment lines
305 (HR = 0.274, 95% CI 0.12–0.622, p = 0.002), and albumin (HR = 0.947, 95% CI 0.907–
306 0.99, p = 0.016) were significantly associated with OS. Multivariate analysis revealed
307 that serum phosphorus levels were an independent risk factor for PFS (HR = 17.537,
308 95% CI: 3.858–79.727, p < 0.001), whilst high-risk status according to the IMDC
309 classification was an independent protective factor for PFS (HR = 0.365, 95% CI:
310 0.176–0.756, p = 0.007). Furthermore, serum phosphorus levels (HR = 6.286, 95% CI:
311 1.45–27.254,p = 0.014) and histology (HR = 5.076, 95% CI 1.862–13.840, p = 0.002)
312 were independent risk factors for OS, whilst age (HR = 0.964, 95% CI 0.927–1.003, p
313 = 0.07) and the number of treatment lines were independent protective factors for OS.
314
315 **Table 3.** Univariate and multivariate Cox regression analyses of the association
316 between serum phosphorus and progression-free survival (PFS) and overall survival
317 (OS)

		PFS				OS			
		UVA		MVA[a]		UVA		MVA	
		HR	P-value	HR	P-value[b]	HR	P-value	HR	P-value
Phosphorus	Low phosphorus	11.775(2.334-59.392)	**0.003**	17.537(3.858-79.727)	**<0.001**	12.987(2.621-64.335)	**0.002**	6.286(1.45-27.254)	**0.014**
	High phosphorus								
IMDC risk stratification	Low risk: 0 points		0.138		**0.025**		**0.003**		0.166
	Moderate risk: 1–2 points	0(0-3.576E+281)	0.968		0.971		0.975		0.974

	High risk: 3–6 points	0.542(0.296-0.99)	**0.046**	0.365(0.176-0.756)	**0.007**	0.344(0.185-0.639)	**< 0.001**	0.449(0.196-1.028)	0.058
Age		0.977(0.951-1.003)	0.084			0.960(0.934-0.986)	**0.003**	0.964(0.927-1.003)	0.07
Gender	Male	0.899(0.425-1.861)	0.756			1.080(0.516-2.261)	0.838		
	Female								
BMI		0.988(0.908-1.075)	0.94			0.936(0.857-1.023)	0.144		
ECOG		1.549(0.758-3.163)	0.23			1.754(0.874-3.52)	0.114		
Distant metastasis	No metastasis		**0.031**		0.054		0.219		0.901
	1 transfer	0.325(0.113-0.937)	**0.038**	0.224(0.052-0.956)	**0.043**	0.55(0.189-1.599)	0.272	0.728(1.171-3.11)	0.669

	Multiple metastases	0.505(0.264-0.964)	**0.038**	0.471(0.223-0.996)	**0.049**	0.595(0.312-1.136)	0.116	1.009(0.479-2.127)	0.981
Pathology	Cytology	3.040(1.402-6.591)	**0.005**	2.528(1.107-5.774)	**0.028**	5.088(2.275-11.381)	**<0.001**	5.076(1.861-13.840)	**0.002**
	Non-cellular								
Treatment options	Immunotherapy		0.082		0.802		0.05		0.469
	Targeted immunotherapy	0.107(0.015-0.764)	**0.026**	0.69(0.082-5.82)	0.733	0.1(0.014-0.72)	**0.022**	0.642(0.07-5.916)	0.696
	Chemotherapy	0.357(0.085-1.503)	0.16	1.14(0.245-5.301)	0.868	0.192(0.045-0.822)	**0.026**	1.638(0.296-9.07)	0.572

Number of treatment lines	first-line		**<0.001**		**0.003**		**0.008**	**0.002**
	Second-line	0.2(0.088-0.456)	**<0.001**	0.256(0.109-0.601)	**0.002**	0.274(0.120-0.622)	**0.002**	0.29(0.117-0.717)	**0.007**
	≥Third-line	0.495(0.253-0.968)	**0.04**	1.006(0.426-2.375)	0.989	0.606(0.310-1.185)	0.143	0.792(0.34-1.846)	0.589
Number of treatment lines	first-line		**<0.001**				0.008	
	Second-line	0.271(0.098-0.75)	**0.012**			0.383(0.138-1.059)	0.064	

Third-line	0.667(0.271-1.638)	0.376	0.847(0.345-2.08)	0.717	
≥Fourth-line	1.663(0.661-4.185)	**0.28**	1.776(0.705-4.473)	0.223	
Alanine transaminase (ALT)	0.989(0.972-1.006)	0.195	0.992(0.975-1.009)	0.378	
Aspartate aminotransferase (AST)	0.987(0.966-1.009)	0.241	0.993(0.974-1.013)	0.488	
Alkaline phosphatase (ALP)	1.001(0.999-1.003)	0.429	1.002(1-1.005)	0.054	
Gamma-glutamyltransferase (GGT)	1.001(0.998-1.004)	0.574	1.002(0.999-1.005)	0.216	
Albumin (ALB)	0.966(0.924-1.01)	0.126	0.947(0.907-0.99)	0.016	0.967(0.912-1.026) 0.264

Creatinine (Cr)	0.995(0.984-1.006)	0.364	0.99(0.978-1.002)	0.106
Urea (Urea)	1.042(0.918-1.182)	0.524	0.971(0.851-1.107)	0.656
Cystatin C (CysC)	0.822(0.354-1.908)	0.649	0.677(0.285-1.609)	0.377

[a] The MVA was built by controlling for IMDC risk score, Distant metastasis, pathology, treatment options, and number of treatment lines.

[b] Statistical significance at alpha <0.05.

Discussion

This study retrospectively analysed clinical data from 137 immunotherapy-treated renal cancer patients. The low serum phosphorus group exhibited significantly better progression-free survival (PFS) and overall survival (OS) than the high phosphorus group, indicating that higher baseline serum phosphorus correlates with unfavourable survival outcomes after immunotherapy.

Immunotherapy is playing an increasingly important role in the treatment of renal cancer, which has given rise to a need to identify biomarkers for the clinical efficacy of

immunotherapy. Previous studies have shown that phosphorus metabolism plays a significant role in tumour initiation and progression. Serum phosphorus levels in cancer patients are higher than in non-cancer patients[21], and the phosphorus content in tumours is significantly higher than in normal tissues[22]. Normal cells absorb phosphorus via the sodium-dependent phosphorus cotransporter NaPi2b, whilst the expression of NaPi2b is increased in cancer cells of the thyroid, breast, lung and ovary[23-24]. At the same time, elevated intracellular phosphorus levels promote the biosynthesis of ribosomal RNA, leading to increased protein synthesis, which in turn accelerates the proliferation of cancer cells[20]. At the same time, high levels of Pi in the tumour microenvironment increase the expression of pro-angiogenic genes in cancer cells, such as *FOXC2*, *OPN* and *VEGFα*[25]. This suggests that high blood phosphorus levels may enhance the ability of cancer cells to induce angiogenesis. High phosphorus levels promote the secretion by cancer cells of factors that simultaneously stimulate endothelial cell migration and tube formation[26]; these studies all indicate that serum phosphorus promotes tumour progression. Furthermore, high dietary phosphorus intake has been shown to exacerbate inflammatory responses in gingivitis[27], experimental colitis[28] and chronic kidney disease[29], whilst elevated serum phosphorus levels are associated with acute pancreatitis[30] This suggests that elevated serum phosphorus levels may act as an inflammatory inducer, promoting the inflammation–dysplasia–cancer sequence. This is consistent with research findings indicating that elevated levels of inflammation often portend a poorer response to immunotherapy[31-34]. Although PD-L1 remains the most extensively studied biomarker in various solid tumours treated

with immune checkpoint inhibitors (ICIs), the prognostic value of PD-L1 in renal cancer has not yet been fully evaluated[12]. In this study, the AUC for serum phosphorus in predicting the immunotherapy prognosis of renal cancer patients was 0.647; although this represents only moderate predictive power, it still holds significant potential for clinical application given its advantages of ease of testing, low cost, and high reproducibility.

With regard to survival prognosis, PFS and OS differed significantly between high and low serum phosphorus groups. Multivariate analysis confirmed serum phosphorus as an independent prognostic factor for PFS and OS, indicating it provides supplementary prognostic information even after adjustment for conventional predictors including IMDC risk, distant metastasis, and treatment modality. This finding aligns with prior work reporting that elevated baseline serum phosphorus correlates with poor prognosis in multiple myeloma[35]. This study has several limitations. First, its single-centre retrospective design carries selection bias and confounders; multicentre prospective validation is needed. Second, serum phosphorus is affected by diet, renal function, and medications. Though patients with severe phosphorus metabolic disorders were excluded, residual unmeasured confounders remain. Third, the limited sample size, especially the small number of non-clear cell carcinoma cases, weakens statistical power for subgroup analyses. Finally, we did not dynamically monitor on-treatment serum phosphorus changes, so the association between phosphorus fluctuations and treatment response cannot be evaluated.

In summary, baseline serum phosphorus is a simple, effective marker to predict

immunotherapy efficacy and prognosis in advanced renal cancer. Lower serum phosphorus correlates with higher clinical benefit rates and prolonged PFS and OS, supporting its use as a routine biochemical marker to assist clinical decision-making. Further research should explore the molecular mechanisms linking serum phosphorus to immunotherapy response and validate its predictive value in large prospective cohorts. Interventions targeting abnormal phosphorus metabolism may also be explored to improve patient outcomes.

Conclusion

This study demonstrates that baseline serum phosphorus levels are an independent risk factor for predicting the efficacy of immunotherapy in patients with advanced renal cancer. It has moderate predictive value for the efficacy of immunotherapy in patients with renal cancer. Higher serum phosphorus levels are associated with poorer PFS and OS. Serum phosphorus may serve as a routine and cost-effective predictive marker, providing valuable guidance for the personalised treatment of patients with renal cancer.

Declarations

Ethics Statement

The present retrospective study was approved by the Medical Ethics Committee of Zhejiang Cancer Hospital (Approval No. IRB-2025-1492 [IIT]). The requirement for

informed consent was waived by the IRB due to the non-interventional nature of the study and the use of de-identified clinical data. All research procedures complied with the 1964 Declaration of Helsinki and its later amendments.

Availability of data and materials

Data sharing is available upon reasonable request by contacting the corresponding author via email.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used DeepSeek in order to improve the language and readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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References

[1] Bray, F, Laversanne, M, Sung, H, Ferlay, J, Siegel, RL, Soerjomataram, I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74:229–63. https://doi.org/10.3322/caac.21834.

[2] Ladurner, M, Lindner, AK, Rehder, P, Tulchiner, G. The influence of sex hormones on renal cell carcinoma. Ther Adv Med Oncol 2024;16:17588359241269664. https://doi.org/10.1177/17588359241269664.

[3] Han, B, Zheng, R, Zeng, H, Wang, S, Sun, K, Chen, R, et al. Cancer incidence and mortality in China, 2022. J Natl Cancer Cent 2024;4:47–53. https://doi.org/10.1016/j.jncc.2024.01.006.

[4] Padala, SA, Barsouk, A, Thandra, KC, Saginala, K, Mohammed, A, Vakiti, A, et al. Epidemiology of renal cell carcinoma. World J Oncol 2020;11:79–87. https://doi.org/10.14740/wjon1279.

[5] De Maeseneer, DJ, Delafontaine, B, Rottey, S. Checkpoint inhibition: new treatment options in urologic cancer. Acta Clin Belg 2017;72:24–

8. https://doi.org/10.1080/17843286.2016.1260890.

[6] Srivastava, N, Avigan, D, Rosenblatt, J. PD-1 blockade in cancer immunotherapy. Drugs Future 2014;39:129–32. https://doi.org/10.1358/dof.2014.39.2.2098279.

[7] Thompson, RH, Kuntz, SM, Leibovich, BC, Dong, H, Lohse, CM, Webster, WS, et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. Cancer Res 2006;66:3381–5. https://doi.org/10.1158/0008-5472.can-05-4303.

[8] Motzer, RJ, Rini, BI, McDermott, DF, Arén Frontera, O, Hammers, HJ, Carducci, MA, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. Lancet Oncol 2019;20:1370–85. https://doi.org/10.1016/s1470-2045(19)30413-9.

[9] Powles, T, Albiges, L, Bex, A, Comperat, E, Grünwald, V, Kanesvaran, R, et al. Renal cell carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2024;35:692–706. https://doi.org/10.1016/j.annonc.2024.05.537.

[10] Motzer, RJ, Escudier, B, McDermott, DF, George, S, Hammers, HJ, Srinivas, S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1803–13. https://doi.org/10.1056/nejmoa1510665.

[11] Ribas, A, Wolchok, JD. Cancer immunotherapy using checkpoint blockade. Science 2018;359:1350–5. https://doi.org/10.1126/science.aar4060.

[12] Rosellini, M, Marchetti, A, Mollica, V, Rizzo, A, Santoni, M, Massari, F.

Prognostic and predictive biomarkers for immunotherapy in advanced renal cell carcinoma. Nat Rev Urol 2023;20:133–57. https://doi.org/10.1038/s41585-022-00676-0.

[13] Jafarzadeh, L, Khakpoor-Koosheh, M, Mirzaei, H, Mirzaei, HR. Biomarkers for predicting the outcome of various cancer immunotherapies. Crit Rev Oncol Hematol 2021;157:103161. https://doi.org/10.1016/j.critrevonc.2020.103161.

[14] Hou, Q, Xu, H. Rational discovery of response biomarkers: candidate prognostic factors and biomarkers for checkpoint inhibitor-based immunotherapy. Adv Exp Med Biol 2020;1248:143–65. https://doi.org/10.1007/978-981-15-3266-5_7.

[15] Kenney, JM, Marinelli, LD, Woodard, HQ. Tracer studies with radioactive phosphorus in malignant neoplastic disease. Radiology 1941;37:683–90. https://doi.org/10.1148/37.6.683.

[16] Marinelli, LD, Goldschmidt, B. The concentration of P32 in some superficial tissues of living patients. Radiology 1942;39:454–63. https://doi.org/10.1148/39.4.454.

[17] Marshak, A. Uptake of radioactive phosphorus by nuclei of liver and tumors. Science 1940;92:460–1. https://doi.org/10.1126/science.92.2394.460.

[18] Papaloucas, AC. Selective uptake of P32 by the cervix in patients with carcinoma before and after treatment, and in normal subjects. Br J Cancer 1958;12:342–5. https://doi.org/10.1038/bjc.1958.41.

[19] Papaloucas, AC. P32 uptake in treated and untreated cervix uteri carcinoma. Nucl Med (Stuttg) 1959;1:62–70. https://doi.org/10.1055/s-0037-1621136.

[20] Ward, DN, Griffin, AC. Phosphorus incorporation into nucleic acids and proteins of liver nuclei of normal and azo dye-fed rats. Cancer Res 1955;15:456–61.

[21] Papaloucas, C, Papaloucas, M, Kouloulias, V, Mystakidou, K. Measurement of blood phosphorus: a quick and inexpensive method for detection of the existence of cancer in the body. Too good to be true, or forgotten knowledge of the past? Med Hypotheses 2014;82:24–5. https://doi.org/10.1016/j.mehy.2013.10.028.

[22] Elser, JJ, Kyle, MM, Smith, MS, Nagy, JD. Biological stoichiometry in human cancer. PLoS One 2007;2:e1028. https://doi.org/10.1371/journal.pone.0001028.

[23] D'Arcangelo, M, Brustugun, O, Xiao, Y, et al. Prevalence and prognostic significance of sodium-dependent phosphate transporter 2B (NAPI2B) protein expression in non-small cell lung cancer (NSCLC). Ann Oncol 2014;25(Suppl 4):iv66–7. https://doi.org/10.1093/annonc/mdu326.28.

[24] Gryshkova, V, Goncharuk, I, Gurtovyy, V, Khozhayenko, Y, Nespryadko, S, Vorobjova, L, et al. The study of phosphate transporter NAPI2B expression in different histological types of epithelial ovarian cancer. Exp Oncol 2009;31:37–42.

[25] Brown, RB, Razzaque, MS. Phosphate toxicity and tumorigenesis. Biochim Biophys Acta Rev Cancer 2018;1869:303–9. https://doi.org/10.1016/j.bbcan.2018.04.007.

[26] Lin, Y, McKinnon, KE, Ha, SW, Beck, GR Jr. Inorganic phosphate induces cancer cell mediated angiogenesis dependent on forkhead box protein C2 (FOXC2) regulated osteopontin expression. Mol Carcinog 2014;53:926–34. https://doi.org/10.1002/mc.22153.

[27] Goodson, JM, Shi, P, Razzaque, MS. Dietary phosphorus enhances inflammatory response: a study of human gingivitis. J Steroid Biochem Mol Biol 2019;188:166–71. https://doi.org/10.1016/j.jsbmb.2019.01.023.

[28] Sugihara, K, Masuda, M, Nakao, M, Abuduli, M, Imi, Y, Oda, N, et al. Dietary phosphate exacerbates intestinal inflammation in experimental colitis. J Clin Biochem Nutr 2017;61:91–9. https://doi.org/10.3164/jcbn.16-117.

[29] Yamada, S, Tokumoto, M, Tatsumoto, N, Taniguchi, M, Noguchi, H, Nakano, T, et al. Phosphate overload directly induces systemic inflammation and malnutrition as well as vascular calcification in uremia. Am J Physiol Renal Physiol 2014;306:F1418–28. https://doi.org/10.1152/ajprenal.00633.2013.

[30] Choi, YH, Jang, DK, Lee, SH, Jang, S, Choi, JH, Kang, J, et al. Utility of serum phosphate as a marker for predicting the severity of post-endoscopic retrograde cholangiopancreatography pancreatitis. United European Gastroenterol J 2018;6:895–901. https://doi.org/10.1177/2050640618764168.

[31] Buder-Bakhaya, K, Hassel, JC. Biomarkers for clinical benefit of immune checkpoint inhibitor treatment: a review from the melanoma perspective and beyond. Front Immunol 2018;9:1474. https://doi.org/10.3389/fimmu.2018.01474.

[32] Voong, KR, Feliciano, J, Becker, D, Levy, B. Beyond PD-L1 testing–emerging biomarkers for immunotherapy in non-small cell lung cancer. Ann Transl Med 2017;5:376. https://doi.org/10.21037/atm.2017.06.48.

[33] Guida, A, Sabbatini, R, Gibellini, L, De Biasi, S, Cossarizza, A, Porta, C. Finding predictive factors for immunotherapy in metastatic renal-cell carcinoma: what are

we looking for? Cancer Treat Rev 2021;94:102157. https://doi.org/10.1016/j.ctrv.2021.102157.

[34] Lalani, AA, Xie, W, Martini, DJ, Steinharter, JA, Norton, CK, Krajewski, KM, et al. Change in neutrophil-to-lymphocyte ratio (NLR) in response to immune checkpoint blockade for metastatic renal cell carcinoma. J Immunother Cancer 2018;6:5. https://doi.org/10.1186/s40425-018-0315-0.

[35] Umeda, M, Okuda, S, Izumi, H, Nagase, D, Fujimoto, Y, Sugasawa, Y, et al. Prognostic significance of the serum phosphorus level and its relationship with other prognostic factors in multiple myeloma. Ann Hematol 2006;85:469–73. https://doi.org/10.1007/s00277-006-0095-3.

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