"CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST

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Research on the clinical, biological, and histological parameters of advanced or metastatic renal cancer and their prognostic implications

PHD THESIS ABSTRACT

PhD supervisor:

POF. UNIV. DR. Cornelia Nitipir

PhD student:

Paroșanu Andreea Ioana

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PHD THESIS SUMMARY

"Research on the clinical, biological, and histological parameters of advanced or metastatic renal cancer and their prognostic implications"

The doctoral thesis is divided into two parts. The first part includes two chapters that present the current state of knowledge on the topic by synthesising the most significant data from the literature. The second part, the personal contributions section, consists of the results obtained from the three studies carried out during the doctoral research.

GENERAL PART

Chapter 1. Prognostic factors in renal carcinoma

This chapter describes the prognostic role of clinical, biological, histological and molecular factors in renal carcinoma. Multiple variables can predict both the oncological disease's evolution and the treatment response. Age, tumour stage, and presence of comorbidities may affect prognosis, but performance status is one of the essential variables in cancer care [1]. In addition, biological parameters easily measured from patients' blood can be used to characterize inflammatory and health status economically and conveniently. The main biological factors with a negative prognostic impact include anaemia, increased lactate dehydrogenase values, calcium, the number of neutrophils or platelets, and inflammatory markers.

However, the most important prognostic factor remains TNM staging. Tumour staging facilitates the exchange of information between clinicians and researchers within the same department or between different institutions, providing a tool for comparing clinical cases across regions, periods, and treatment modalities. From a histopathological point of view, increased tumour grade, the presence of sarcomatoid or rhabdoid features, microvascular invasion and tumour necrosis have a negative prognostic value [2-4].

Ensuring timely medical intervention for cancer patients is a top priority. Thus, the timing of therapy, defined as the time from diagnosis to initiation of treatment, surgical or systemic, has adverse effects on survival. In subsection 1.6. I highlighted the prognostic role of treatment in renal carcinoma. Currently, surgery continues to play an essential role in the management of

patients with metastatic renal cell carcinoma. Thus, nephrectomy can be performed as part of a combined approach to decrease tumour burden before systemic therapy and palliative nephrectomy can control severe local and systemic symptoms secondary to the primary tumour. In selected patients with metastatic renal cell carcinoma, surgical resection of metastatic foci is a therapeutic option that can prolong long-term disease-free survival. Currently, lymph node dissection is optional but recommended for patients with resectable adenopathy on preoperative imaging or palpable or visible adenopathy at the time of surgery. Furthermore, the extent of lymph node dissection remains controversial. Few urologists in the United States (6.6%) remove more than five lymph nodes during radical nephrectomy [5-7].

Chapter 2. Prognostic models in renal carcinoma

As mentioned before, renal cell carcinoma is highly heterogeneous. Although the prognosis of patients with recurrent or metastatic renal carcinomas is unfavourable, data from the literature mention specific clinicopathological correlations associated with a longer survival interval. Different variables have been associated with prognostic models because a prognostic factor cannot be precise when used alone.

Multiple nomograms have been developed that use preoperative variables to predict tumour recurrence after nephrectomy in patients with renal carcinoma. However, some authors argue that preoperative clinical algorithms do not perform as well as those that incorporate pathological information. Thus, the postoperative pathological prognostic models were much more accurate [8].

PERSONAL CONTRIBUTIONS

Chapter 3. Working hypothesis and general objectives

This PhD thesis aimed to assess potential prognostic factors and enhance current risk models in metastatic renal cell carcinoma.

The objectives of the doctoral thesis derived from the stated goals were:

1. evaluation of the prognostic and predictive role of clinical, biological and histological factors in patients with advanced or metastatic renal carcinoma

2. prognostic peculiarities of sarcomatoid differentiation

3. evaluation of overall survival according to the type of surgery

4. correlation of prognostic factors with the type of first-line treatment

5. defining the clinical benefit of a line of treatment and the prognostic impact on overall survival

6. research of prognostic models and especially of the neutrophil-lymphocyte ratio in subsequent therapeutic lines

7. therapeutic particularities depend on the metastases' anatomical location, both in the first line of treatment and in the subsequent lines.

8. the prognostic and predictive role of metastases depending on the affected organs

Chapter 4. General research methodology

In this chapter, the fulfilment of the objectives is presented through the three doctoral studies: the first study, presented in Chapter 5, responds to objectives 1-5; the second study, presented in Chapter 6, responds to objective 6; and the third study, represented by Chapter 7, responds to objectives 7 and 8.

The criteria for the inclusion of patients in the evaluated group, which were based on [specific criteria], the source and collection of data, as well as the variables of interest and the statistical tests that I used in the data analysis of the doctoral thesis were presented.

Chapter 5. Dynamics of prognostic factors in patients with advanced or metastatic renal cell carcinoma treated with first-line therapy

This chapter presents the first study's results, which are structured in the introduction, methods, results, discussion and conclusions.

Introduction:

Prognostic factors in renal cell carcinoma include anatomical (TNM classification, tumour size), histological (Fuhrman grade, histological subtype), clinical (symptoms and performance status) and molecular characteristics. These factors cannot accurately assess prognosis when used individually. Thus, multiple prognostic models of survival in patients with metastatic renal cell carcinoma have been proposed. Currently, two prognostic models are routinely used in clinical practice: IMDC and MSKCC [9].

Apart from the already established risk stratification scores, other parameters have been evaluated for prognostic value. For example, administering a therapeutic line for at least three months correlates with increased survival in metastatic renal cell carcinoma [10].

Another marker studied with interest in multiple solid neoplasms is the neutrophil-lymphocyte ratio. An elevated NLR reflects the presence of both neutrophilia and lymphopenia and may suggest decreased cell-mediated immunity in cancer patients. Therefore, NLR is a robust prognostic biomarker in certain tumours, including digestive or genitourinary cancers [11]. Therefore, I can consider this ratio, which is easy to calculate and widely measured in daily clinical practice.

Methods:

This observational retrospective cohort study included 74 adult patients with renal cell carcinoma from the Oncology Clinic of the Elias University Emergency Hospital. Patients were followed up between January 2020 and October 1, 2022, with a mean follow-up time of 15.3 months (range: 9.3–20.6 months).

Inclusion criteria included a renal carcinoma diagnosis, clear cell histology, stage IV, no previous systemic therapy, and age over 18. Subjects with other tumour histology or previously treated systemically were excluded. In the first line of treatment, patients received Sunitinib, Pazopanib, or Nivolumab plus Ipilimumab.

All patients' pretherapeutic demographic, clinical, and laboratory data were retrospectively collected. The histopathological results of renal tumours were also analyzed.

Results:

At the initiation of systemic therapy, most patients (93%) presented with distant metastases, 4% of subjects had locally advanced and unresectable stage IV renal tumours, and 2.7% presented with locoregionally recurrent tumours.

Regarding the type of surgery, the most common surgical procedure was simple nephrectomy (55.4%), followed by radical nephrectomy with regional lymph dissection (24.3%). Only 9.5% of patients underwent partial nephrectomy and 10.8% renal tumour biopsy.

From a biological point of view, 55.4% of the patients included in the study presented anaemic syndrome (HB<12 mg.dl), 21.6% hypercalcemia, 32.4% thrombocytosis,14.9 % neutrophilia, and 16.2% increased values of lactate dehydrogenase.All these data formed the basis of the IMDC and MSKCC prognostic models.

Additionally, I calculated the neutrophil/lymphocyte ratio for each patient. With the help of the ROC curve, I chose an NLR value of 3 as the cut-off value.

According to univariate logistic regression analysis, Karnofsky performance status, time from diagnosis to initiation of therapy, lactate dehydrogenase value, NLR value and MSKCC IMDC patterns were significantly associated with survival. Among the determinants, Karnofsky's performance status and IMDC and MSCKK models were associated with the most significant statistical significance ($p<0.001$). Also, time from diagnosis to initiation of therapy has proven prognostic value. Thus, patients with a period from diagnosis to initiation of therapy longer than 12 months (13 months, range: 7.25-25 months) showed a higher average survival than patients who initiated therapy less than 12 months after diagnosis (7.50 months, range 4-14.50 months), $p=0.009$.

Because of the biologically aggressive behaviour, patients with renal cell carcinoma and sarcomatoid differentiation (9.5% of patients) presented an unfavourable overall survival ($p=0.004$), but increased Fuhrman tumour grade (3-4) did not negatively influence these results.

Analyzing survival, I obtained superior results in patients with partial nephrectomy (22.43±23.25 months) compared to the other surgical interventions (21.73±18.24 months for simple nephrectomy and 18.72±15.68 for nephrectomy with lymph dissection).

The lowest survival values were described in patients with tumour biopsy (8.88±5.98 months), a result possibly explained by the association of comorbidities or poor biological data that limited radical surgical treatment. Anaemia and elevated LDH values have shown a negative prognostic role.

In multivariate Cox model analysis to determine their independent effects, of all these factors, only two were independently associated with survival: Karnofsky performance status < 80% and time from diagnosis to initiation of therapy < 12 months.

I assessed the clinical benefit of each therapy administered and reported trends in survival for these patients. Clinical benefit was attributed to a line of treatment if a patient remained on therapy for three months or more. Conversely, lack of clinical benefit was attributed to a line of therapy if a patient discontinued drug treatment before three months (either because of tumour growth or because of adverse drug side effects). I set the value of three months as the cut-off value because this time value was used in previous studies. The results support that patients who

received first-line therapy for at least three months had a significantly superior overall survival (22.25 months versus 7.62 months).

I observed that sarcomatoid differentiation influences the clinical benefit of treatment. The results show that more than half of the patients with renal carcinomas and sarcomatoid differentiation (57.14%) progressed in the first three months of treatment, compared to 13.43% of patients without sarcomatoid differentiation. These results support the likelihood of intrinsic resistance of more aggressive tumours to subsequent lines of therapy.

Chapter 6. Subsequent treatment of renal cell carcinoma in the era of predictive biomarkers

This chapter presents the results of the second study, structured in the introduction, methods, results, discussion and conclusions.

Introduction:

Currently, approximately one-third of renal cell carcinomas are diagnosed at the metastatic stage, with a five-year survival rate of only 17% [12]. Unfortunately, patients diagnosed with unresectable or metastatic advanced stage experience disease progression during first-line treatment, and only 60% of them survive long enough to receive second-line therapy. Despite recent therapeutic advances, there are limited data on prognostic factors or patterns in subsequent therapies [13]. Previous studies support the fact that the duration of the first-line treatment period in renal cell carcinoma may have a prognostic role. Thus, patients with rapid progression on first-line regimens are less likely to benefit from subsequent therapy [14,15]. To deepen these limited data, I performed a retrospective analysis to evaluate the prognostic significance of clinical and biological factors in patients with renal cell carcinoma undergoing second-line therapy.

Methods:

A retrospective observational study was conducted on patients diagnosed with metastatic renal cell carcinoma. The study was performed in the oncology department of the Elias University Emergency Hospital.

The main inclusion criteria were the following: clear cell renal cell carcinoma histology, progression on first-line therapy, clinical and imaging data available before initiation of each line of treatment, written informed consent, and age ≥ 18 years.

Exclusion criteria included short-term follow-up (<6 months), active autoimmune disease, evidence of active infection before initiating systemic therapy, multiple primary cancers, brain metastases, and histologies other than clear cells.

Between January 2020 and October 2022, 74 patients diagnosed with renal cell carcinoma initiated first-line therapy. During the follow-up period, 51.3% (38 patients) required second-line treatment. Nivolumab was the most frequently administered second-line regimen (39.4%), followed by Cabozantinib (26.3%), Pazopanib (18.4%), Axitinib (13.1%) and Temsirolimus (2.6%).

Results:

In this study, 51.3% of patients with metastatic clear cell renal cell carcinomas received second-line therapy. Before starting second-line therapy, the patient's baseline characteristics were assessed, with the majority falling into the intermediate-risk group, according to the IMDC and MSKCC prognostic models. Although these models were initially developed and validated for patients with metastatic renal cell carcinomas who received first-line treatment, they maintain their prognostic role in subsequent therapies. Favorable-risk patients had better overall survival than unfavourable or intermediate-risk patients (HR = 8.907, 2.148–36.935, p = 0.004 for MSKCC; and HR = 1.826, 1.068–3.122, p = 0.028 for IMDC).

I determined the mean NLR for patients who initiated second-line therapy, which was 2.85 ± 2.05. In the first doctoral study, ROC analysis identified the optimal NLR cut-off value as 3. I subsequently subclassified patients into two groups: high NLR (>3) and low NLR (<3). The results report a negative prognostic association between an increased NLR value and overall survival. An increase in NLR > 3 was associated with unfavourable outcomes in univariate and multivariate analyses (p = 0.005). Therefore, I hypothesized that associating NLR with well-known risk models might improve prognostic accuracy.

This study also examined whether the duration of treatment in initial or subsequent lines of therapy is associated with survival. The results suggest that patients with a clinical benefit of more than three months had a statistically improved overall survival in first-line (22.25 months versus 7.62 months) and second-line treatment (25.22 months versus 12.33 months).

Histopathological features can predict prognosis and facilitate patient stratification. Thus, I evaluated the pathological characteristics and subsequent outcomes in patients with renal cell carcinoma and sarcomatoid differentiation. Seven patients (9.5%) showed sarcomatoid features.

Only two patients with sarcomatoid differentiation received second-line therapy, which had a modest response rate and low clinical benefit (median survival 14.86 months).

In conclusion, there is limited data in the specialized literature regarding prognostic factors in second-line therapy for metastatic renal cell carcinoma. Therefore, this study contributes new data from clinical practice, highlighting biomarkers' prognostic role and risk models' importance.

7. Study III. The role of metastases as prognostic and predictive factors in treating metastatic renal cell carcinoma.

This chapter presents the results of the third study, which is structured as an introduction, methods, results, discussion, and conclusions.

Introduction:

Risk stratification plays an essential role in advanced or metastatic renal cell carcinoma. The MSKCC and IMDC risk scores are the pillars of this risk stratification, distinguishing three groups with a prognostic role in estimating patient survival. Both scores serve as prognostic biomarkers, incorporating biological and clinical parameters to guide therapeutic decisions [9]. While pivotal trials in renal cell carcinoma have demonstrated efficacy in the general population, there are certain clinical features with important implications for patient prognosis. These characteristics include tumour burden and the specific location of metastases in certain organs.

Different metastatic locations may show variable sensitivity to specific treatment regimens. However, even though most pivotal trials described the distribution of specific metastases in patients with renal cell carcinoma, not all studies reported survival outcomes [16].

In conclusion, due to the need for more consensus regarding the relationship between the location of metastases and the therapeutic response, I performed the present study emphasizing the therapeutic efficacy according to the metastatic locations in specific organs.

Methods:

A retrospective observational study was performed on patients with metastatic renal cell carcinoma treated in the Elias University Emergency Hospital oncology department. The follow-up period of the first two doctoral studies was extended by 12 months between January 2020 and October 2023. The main inclusion criteria were the following: histology of clear cell renal cell carcinoma, the presence of distant metastases, first-line treatment and subsequent therapies,

clinical and imaging data available before initiation of each line of treatment, written informed consent, and age ≥ 18 years. A total of 79 patients with metastatic renal cell carcinomas were analyzed.

Results:

At least one organ was affected by secondary tumour lesions in 51.9% of patients with metastatic cancer. Lung and lymphatic metastases were the most common, followed by bone and liver metastases. There have been rare cases of metastases to the adrenal, peritoneal, and brain glands. Exceptionally, there were two patients with pancreatic and splenic metastases.

The first hypothesis evaluated was whether the number of distant metastatic sites influences specific survival. The results obtained support the fact that patients with metastases in a single organ show significantly improved clinical outcomes in terms of progression-free survival in first-line treatment: PFS of 17.21 months for patients with a metastatic location versus 11.2 months for patients with ≥ 2 metastatic locations, p=0. 032. Regarding subsequent treatment, this benefit, although maintained, did not show statistical significance: PFS of 11.53 months for patients with one metastatic location versus 8.36 months for patients with ≥2 metastatic locations, p=0.169.

The following hypothesis evaluated whether the type of therapy administered influences the survival of patients with more than two metastatic locations. I analyzed progression-free survival according to the first-line therapy, highlighting that TKI treatment (Sunitinib) prolongs first-line PFS in patients with more than two metastatic sites (p=0.018). Thus, the results support the idea that the number of metastatic locations has prognostic and predictive value. Regardless of the type of first-line therapy, the presence of more than two metastatic sites is associated with reduced progression-free survival. In addition, patients with multiple metastatic sites show a sustained clinical response to TKI treatment.

The survival of patients with renal carcinoma according to the organs affected by the metastatic disease was also analyzed. Results showed that survival without progression of the disease in the first line of treatment was statistically significantly reduced in patients with lung metastases (p<0.013), liver metastases (p= 0.011), cerebral (p=0.03) and splenic (0.016).

I have noticed that specific clinical outcomes can be determined by the different locations to which cancer has spread. For example, TKI therapy has shown increased efficacy in treating

bone metastases. Thus, Sunitinib increased the PFS of patients with bone metastases in first-line treatment compared to IO-IO or IO-TK combinations. Regarding the second line of treatment, another TKI, Cabozantinib, demonstrated efficacy on bone metastases (PFS= 21.06 months), followed by Nivolumab (PFS= 20.52 months) In patients with renal cell carcinoma and visceral metastases, double blockade IO-IO has been shown to be an effective therapeutic option, especially in secondary lung lesions. Thus, Nivolumab and Ipilimumab therapy doubled first-line PFS in patients with lung metastases compared to TKIs or IO-TKI combinations. Nivolumab plus Ipilimumab combination therapy also maintained its first-line efficacy in patients with lymphatic metastases. Median progression-free survival was 45.54 months in patients treated with IO-IO, 23.99 months in Pazopanib treatment, and 10.09 months and nine months in IO-TKI treatment, respectively.

Metastatic progression is a major therapeutic challenge and presents a significant obstacle in establishing a rational therapeutic approach due to unpredictable tumour heterogeneity both between patients and within each tumour. Patient selection for first-line treatment in renal cell carcinoma is also a challenging task, as no specific biomarker has been identified to help identify the ideal patient for a particular therapy. Therefore, additional studies are needed to validate the accumulated knowledge about renal tumour biology and the organ-specificity of the metastatic potential to develop new effective diagnostic and prognostic strategies.

8. Conclusions

The management of renal cell carcinoma has undergone a significant change in the past two decades with the approval of targeted therapies and immunotherapy. These drugs have improved clinical outcomes in patients with renal cancer. However, there is a significant number of patients who do not achieve the desired objective responses.

Although the biology and pathology of renal cancer have been carefully studied, to date, we have not been able to identify molecular targets to effectively treat all patients. As we become familiar with new-generation drugs, it is essential to understand that the response to these therapies is not universal in every patient and may instead expose some patients to unnecessary toxic effects and a financial burden on society.

As we move into the era of “precision medicine,” validated biomarkers are being used to guide therapeutic choices and facilitate the identification of pathways of treatment resistance. Thus, the present doctoral studies propose a real challenge: evaluating possible prognostic or predictive factors in renal carcinoma and comparing the data obtained with the progress recorded in this field.

Definitive biomarkers in clear cell carcinoma remain elusive. At present, the IMDC and MSKCC models are frequently employed to categorize risk groups and forecast disease behaviour. These models were developed and validated during the era of angiogenic therapies. However, the treatment landscape for renal cell carcinoma has since evolved. Immune checkpoint inhibitor-based therapies have emerged as the new first-line standard of care, demonstrating clear survival benefits compared to VEGF inhibitors. Regrettably, responses to these therapies are inconsistent and unpredictable. The reasons for this variability are not well understood. Importantly, it has been observed that pretreatment prognostic criteria, such as IMDC and MSKCC scores, do not seem to perform effectively in predicting responses to these new therapies, highlighting a significant gap in our current understanding and management of the disease.

Recent studies suggest that inflammatory markers such as the neutrophil-to-lymphocyte ratio could reflect the inflammatory microenvironment more accurately. An elevated pretherapeutic NLR has been described as an adverse prognostic factor in renal carcinomas. However, a clinically helpful cut-off for this ratio's predictive and prognostic value has yet to be well defined. While assessment of disease response in metastatic renal cell carcinoma currently relies heavily on imaging, the incorporation of inexpensive and readily available biomarkers could enable more robust decision-making and assessment of prognosis early in treatment.

The first two doctoral studies aimed to evaluate the predictive and prognostic value of potential haematological and histological biomarkers. I analyzed the independent prognostic values of the Fuhrman grade, sarcomatoid differentiation, type of surgery, and the variables present in the prognostic models IMDC, MSKCC, and the NLR value. These data were analyzed therapeutically before administering the first line of treatment and later in the subsequent lines.

In the first study, I included 74 patients with metastatic renal cell carcinoma in the fi studio. I found that several factors were associated with unfavourable survival rates. These factors included poor performance status, indicated by a Karnofsky score of less than 80%, a time from diagnosis to beginning treatment of fewer than 12 months, elevated levels of LDH, and anaemia. All of these factors were statistically significant. Also, pre-therapeutic levels of neutrophil-to-leukocyte ratio ≥3 were identified as indicators of adverse prognosis, without considerable differences between patients treated with TKIs or ICIs. I consecutively evaluated the clinical benefit of each therapy administered and reported the survival trends of these patients. Clinical benefit was attributed to a line of treatment if a patient remained on therapy for three months or more. Conversely, lack of clinical benefit was attributed to a line of therapy if a patient discontinued drug treatment before three months (either because of tumour growth or because of adverse drug side effects). We set the value of three months as the cut-off value because this time value was used in previous studies. The results support that patients who received first-line therapy for at least three months had a significantly superior overall survival (22.25 months versus 7.62 months).

Despite therapeutic advances, however, only a minority of patients with metastatic renal cell carcinoma receive subsequent therapies. Also, there is little data on potential prognostic factors in these patients. Therefore, deepening the criteria for stratification of patients eligible for subsequent therapy formed the basis of the second study. In the second study, 51.3% of the patients investigated in the first study received second-line therapy. The obtained results also support the prognostic value of the two MSKCC and IMDC models in the subsequent lines. Thus, favourable-risk patients had superior overall survival to unfavourable or intermediate-risk patients.

Regarding the neutrophil-to-lymphocyte ratio, an elevated pre-therapeutic value (> 3) may predict both relapse and disease progression for patients with renal cell carcinoma. Regarding the histopathological features, we observed that they can predict the prognosis and facilitate the stratification of patients. In total, seven patients (9.5%) showed sarcomatoid features. Only two patients received second-line therapy with a modest response rate and low clinical benefit. The study results also suggest that patients with a clinical benefit of more than three months had statistically improved overall survival in both first-line (22.25 months versus 7.62 months) and second-line line (25.22 months versus 12.33 months). Before this study, I did

not identify consistent data regarding prognostic factors in second-line therapy for clear renal cell carcinoma. Therefore, the obtained results contributed new valuable perspectives in the specialized literature, supporting the prognostic role of biomarkers and underlining the importance of risk models in metastatic renal cell carcinoma.

In the third study, I evaluated some of the most common sites of metastasis in clear cell renal cell carcinoma and how the location of the metastatic disease affects prognosis and treatment options. As previously mentioned, unlike other types of cancer, renal cell carcinoma does not have approved biomarkers to guide therapeutic choice. Therefore, the specific therapeutic decision according to the metastatic location remains challenging. Currently, the applicability of risk stratification according to the IMDC or MSKCC stratification models has decreased, and factors such as tumour burden and the number and location of metastases play an essential role in guiding therapy. In this study, I observed that different metastatic locations can present particular clinical outcomes. For example, TKI therapies such as Sunitinib and Cabozantinib have effectively treated bone metastases.

In contrast, double IO-IO blockade is an effective therapeutic option in patients with visceral lung injury. Also, the combination of Nivolumab and Ipilimumab proved to be much more effective in treating lymphatic metastases. In addition, the prognosis of the patients depended to a large extent on the location of the metastases, with the pulmonary system and liver being the most frequently affected organs. Patients with liver, lung and splenic metastases presented the worst clinical results. Brain metastases have also shown both a poor prognosis and selective responses to oncological treatments, as the blood-brain barrier can limit the delivery of therapies in brain tumours. Current guidelines do not consider the location of secondary findings, but it is essential to understand that specific metastatic locations have prognostic value and affect how we treat these patients.

The available literature on prognostic factors in renal carcinomas must be more comprehensive. The results obtained from recent research complement and add depth to the existing knowledge. This research also provides a starting point for new hypotheses and further investigations.

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