

## Assessment the Incidence of Transitional Cell Carcinoma (TCC) of the Bladder Cancer

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### ABSTRACT

**Background:** Transitional cell carcinoma (TCC) of the bladder is the second most common malignancy of the genitourinary tract and the third most common cause of death among people with genitourinary tumors, besides, tumors of the bladder are an important source of both morbidity and mortality. **Objectives:** The purpose of the study are 1. formulate an idea about the number of patients with bladder cancer (TCCs) in sample of Iraqi population. 2. Study the histopathological features of TCCs of bladder 3. Assessment the prevalence of (TCC) of bladder in both sex (male and female) with smoking as risk factor. **Patients and Methods:** A study was conducted at one institution were identified that teaching-hospital of Baghdad. All patients included in the present study diagnostic with TCC of bladder. The total of subjects participated in the study were 42 patients and 20 subjects as control through six months' period from July 2014 to January 2015. **Results:** The mean of participates age was  $65 \pm 5.7$  years and the youngest was 21 years and the oldest was 75 years. Out of 42 patients, the most common age group was 54-64 years (52.38%) with Male to female ratio was 5.2:1.32 were male 32 and 10 were females. However, the prevalence bladder cancer (TCCs) was higher in male than in female, with more pronounced decreases in younger age ( $\leq 31$  year) 3(7.14), have been found. In addition, age specific rate was observed higher in the older age groups for most patients with cancer. The population attributable risk for ever smoking in our study was 33(78.57) out of 42 patients. Moreover, current study shows there was a correlation between grade and stage of bladder TCC, 24(57.14%) bladder TCCs that classified as grade I, while 2(4.76%) of bladder TCC were classified as grade II. Conversely, of the bladder TCC lesions (11.9%, 14.28%, 57.14 and 4.76) were stage (pTa-T1-T2-T3) respectively. Although this study showed 5(11.9) little-known stage and grade. The area of histopathological changes included were showed hyperplastic changes, involving the entire bladder lining, that ranged from flat hyperplasia to small areas of nodular and papillary hyperplasia. The smallest recognizable nodular and papillary lesions were associated with angiogenesis in the contiguous stroma. In addition, there were chromatin irregularities and nucleoli of variable numbers, shape and size. Nuclear chromatin irregularity and mitoses were easily identified, these cells continued to have the appearance of hyperplastic epithelium. The changes noted by generalized and orderly proliferative reaction and appeared reparative. **Conclusions:** Our study has revealed that the bladder TCC, where appeared the high prevalence and incidence rate of TCC of bladder in sample of Iraqi population were of concern, especially for older age groups.

**Keywords:** Bladder cancer, TCCs, Histopathology, tumors stage and grade, cigarette smoking

### INTRODUCTION

Cancer bladder represents the fourth most common cancer in men and ninth most common cancer in women. It is the second most prevalent cancer in men 60 years of age or older in United States.<sup>[1]</sup> However, tumors arising in the urinary bladder range from small benign papillomas to large invasive cancers. The classification and nomenclature of bladder cancers have undergone revision. Traditionally, bladder approximately 80% of cases of bladder cancer are diagnosed in people over 60 years old. It is the second most prevalent cancer in men 60 years of age or older in the United States.<sup>[2]</sup> Emergence of newer therapeutic approaches has given physicians the scope to

offer patients the option of bladder preservation. Also, looking further down, continuing advancements in cancer research could potentially offer more choices for clinician and carcinomas have been called transitional cell carcinomas, but the term urothelial neoplasms is preferred by the international society of urologic pathology consensus classification. Urothelial (transitional) cell carcinoma range from papillary to flat (papilloma-papillary carcinoma and flat noninvasive carcinoma), noninvasive papillary carcinoma to invasive flat carcinoma<sup>[3]</sup> and extremely well differentiated to highly anaplastic aggressive cancers. patient with longer survival and better quality of life. Bladder cancer is a disease with

a variable natural history, at one end of the spectrum, low grade tumors have a low progression rate and require initial endoscopic treatment with surveillance but rarely present a threat to the patient. At the other extreme, high-grade tumors have a high malignant potential associated with significant progression and cancer death rates.<sup>[4]</sup> Bladder cancer is the fourth most common cancer and ranks eighth as a cause of death from cancer among men in the United States (Jemal et al., 2007), following prostate, lung, and colon cancers. The risk of developing bladder cancer at 75 years of age is 2% to 4% for men and 0.5% to 1% for women, compared with the risk of lung cancer which is 8% for men and 2% for women.<sup>[1]</sup> Carcinoma of the urinary bladder is a common cancer with high incidence and prevalence.<sup>[5]</sup>

However, other agents represented by the cytotoxic/ immunosuppressive agent cyclophosphamide increment the risk of bladder cancer up to nine-fold with a latency period of generally less than 10 years, as well as types of syndromes as pelvic irradiation for prostate, cervical, schistosomiasis and ovarian cancer rise the risk of a secondary bladder cancer.<sup>[6]</sup> Some literature that proposes other risk factors for the development of bladder cancer, such as coffee and alcohol consumption. There is some evidence that increased fluid consumption (including water) may reduce the risk of bladder cancer, however the source of drinking water (arsenic in water) may also be an important risk factor for the development of bladder cancer.<sup>[7]</sup>

To assess the role of oral pentosan polysulphate (PPS) in the reduction of bacille Calmette-Guérin (BCG)-related local side effects in patients with high grade Ta/T1 non-muscle-invasive bladder cancer (NMIBC). Nineweh (3.49%) where it was the tenth most common tumor.<sup>[8]</sup>

Therefore, this study aimed to improve our understanding of such patients with bladder cancer. The present study also aimed to investigate cancers in Baghdad. histopathological features of various lesions of transitional cell carcinoma (TCC) of bladder over a period of six months in Baghdad Teaching Hospital with appraisal prevalence among both sex (male & female) also included.

## MATERIALS AND METHODS

### Patients and Methods

Written consent form was signed by all the participation before start collecting data and samples. The study consisted of 42 subjects with incident and histologically confirmed of bladder cancer. The samples of patients were obtained from teaching Hospital in Baghdad. Patients age ranged from 21 to 75 years while control subjects ages ranged from 32 to 56 years. Questionnaire form was filled for each patient including; name, age, gender, employment.

### Histopathological examination

The material for the current study was comprised of biopsy from Transurethral resection of bladder Tissue (TURBT). Biopsies were fixed in 10% formalin to perform fixation for 24 hours. Paraffin sections were performed by dehydration by graduate ethanol alcohol (50%, 70%, 90% and 100%) and after that clearing by Xylene, then

Table 1: Bladder cancer and healthy profiles

Characteristics	Patients	Percentage
Age(years)		
Mean	63±5.7	_____
Range	21-78	_____
Age(years)		
Mean		
Range		
Age(years)		
Mean		
Range		
gender		
Male	32±3.2	76.19
female	10	23.80
Smoking		
Yes	33±4.5	78.57
No	9±1.2	21.42

Table 2. Age group and gender distribution of patients with bladder cancer(TCCs)

Age group (years)	Gender		Total	Percentage
	Male	Female		
21- 31	3	0	3	7.14
32-42	3	1	4	11.90
43- 53	5	2	6	11.90
54-64	16	5	22	52.38
65-75	5	2	7	16.66

embedding in paraffin to make blocks. Histological paraffin blocks were cut by microtome at 5 micrometers in thickness sections, stained with hematoxylin and eosin and then mounted in DPX follow the standard method by Vacca et al., 1985.<sup>[9]</sup> The histological changes were evaluated by observe of lesions microscopically(40X) in the target organ.

## RESULTS

A total of 42 patients with bladder cancer were recruited over the period of six months. The current study was showed that the youngest was 21 years and the oldest was 75 years. The mean age was found to be 63 years. The study displayed that cancer of the bladder (TCCs) was more in males than in females with 3.2:1 ratio. The number of male diagnosed in TCC during the study period was 32 (76.19) while number of female was 10 (23.80) only (table 1). Regarding to the age the study recoded that 22 (52.38%) of the patients were between 54-65 years; and 3 (7.14%) of the patients were between 21-31 years of age (table 2 & Figure 1). Furthermore, the present study was showed that there was a high association between cigarette smoking and TCCs, and that among nonsmokers 33 (78.57), 9 (21.42) respectively (table 1).

As for, stage and grad of bladder cancer (TCC), our study was appeared that could not be completed in four patients with bladder cancer. Therefore, all 42 patients were included in the analysis of grade and tumor stage. Majority (57.14) of the bladder cancer (TCC) were in the T1 stage

Table 3. Different pT stages of TCCs

Staging	Number	Percentage%	Grading	Number
Tcc, pTa	5	11.90	I	4
			II	1
Tcc, pT1	6	14.28	I	4
			II	2
Tcc, pT2	24	57.14	I	15
			II	9
Tcc, pT3	2	4.76	III	2
Unknown	5	11.90	I	5

Tcc = Transitional cell carcinoma, Ta; Non-invasive papillary carcinoma, T1; Tumour invades subepithelial connective tissue, T2; Tumor invades superficial muscle, T3 Tumor invades per vesical tissue(Microscopically).

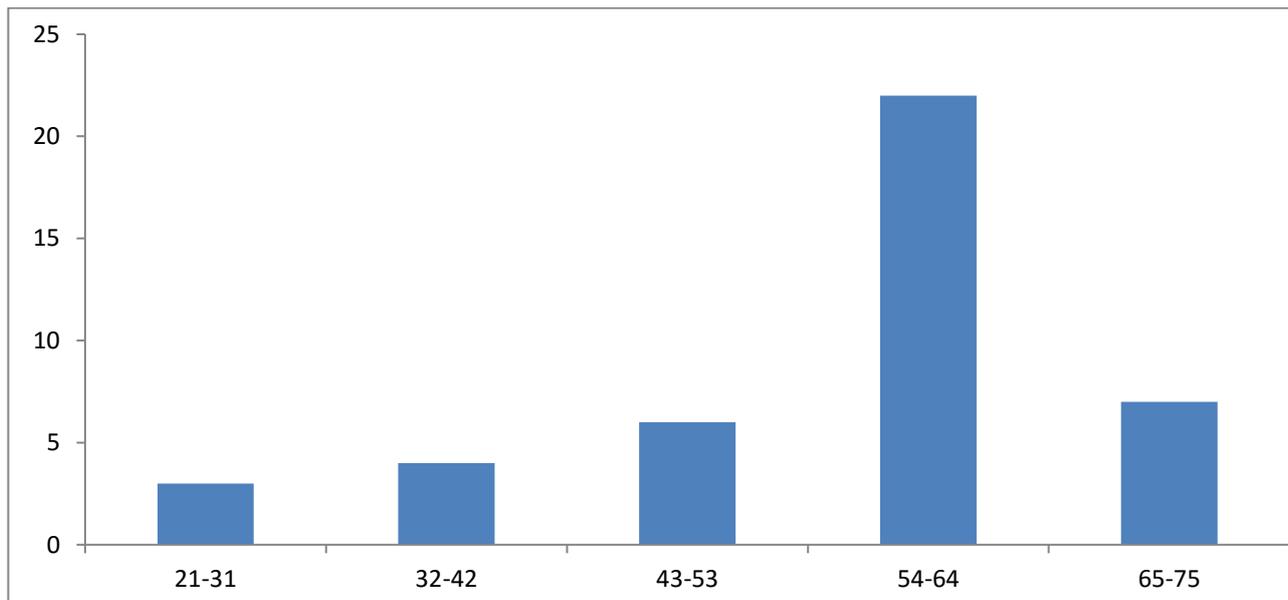


Figure 1: Age Specific Incidence Rate of cancer.

(Table 3). Conversely, the percentage of pT3 high grade tumor among BCC was recorded in 2(4.76) only. Although this study showed little-known stage and grade 5(11.9). Regarding of the Histopathological findings, bladder sections of patients was showed as figure 2(A,B,C,D,E,F); hyperplastic changes, involving the entire bladder lining, that ranged from flat hyperplasia to small areas of nodular and papillary hyperplasia. The smallest recognizable nodular and papillary lesions were associated with angiogenesis in the contiguous stroma. In areas of flat hyperplasia, cells had increased in size, had dense cytoplasm, altered nuclear polarity, and a single enlarged round nucleolus. In addition, there were chromatin irregularities and nucleoli of variable numbers, shape and size. Nuclear chromatin irregularity and mitoses were easily identified, these cells continued to have the appearance of hyperplastic epithelium. The changes noted by generalized and orderly proliferative reaction and appeared reparative. Papillary lesions with minimal cellular abnormalities predominated. The more marked cellular features of malignancy included a greater degree of chromatin irregularity and nuclear variability. Surface necrosis was a feature in lesions at all-time points. Extreme nuclear abnormality in thickened urothelium with the

architecture of flat hyperplasia was interpreted as dysplasia and carcinoma in situ. Moreover, early nodular hyperplasia associated with sub-urothelial lymphocytic infiltration, mildly hyperplastic urothelium showing focal areas of atypical cells in which there is a disorientated and differential growth pattern. The surrounding urothelium is moderately hyperplastic.

**DISCUSSION**

Bladder cancer is the third most common malignancy in Iraq for both sexes, and bladder cancer remains a major health problem around the world. This type accounts for more than 90% of bladder cancer. Prevention of apoptosis is one of the important mechanisms of the tumor. and the rate of apoptosis in malignant tumors is an important factor for the growth of these tumors. [10]

The results of Iraqi Cancer Registry (ICR) reported that bladder cancer is the third most common malignant tumor (7.01%) in both males and females. It is the second most common tumor in men (11.13%) and the ninth in women (2.97%), the highest incidence of bladder cancer was reported in Thi-Qar (12.24%) and Al-Muthana (11.52%). The demographic characteristics of the patients in present study were analogous to number of previous studies which described the median age of bladder cancer presentation

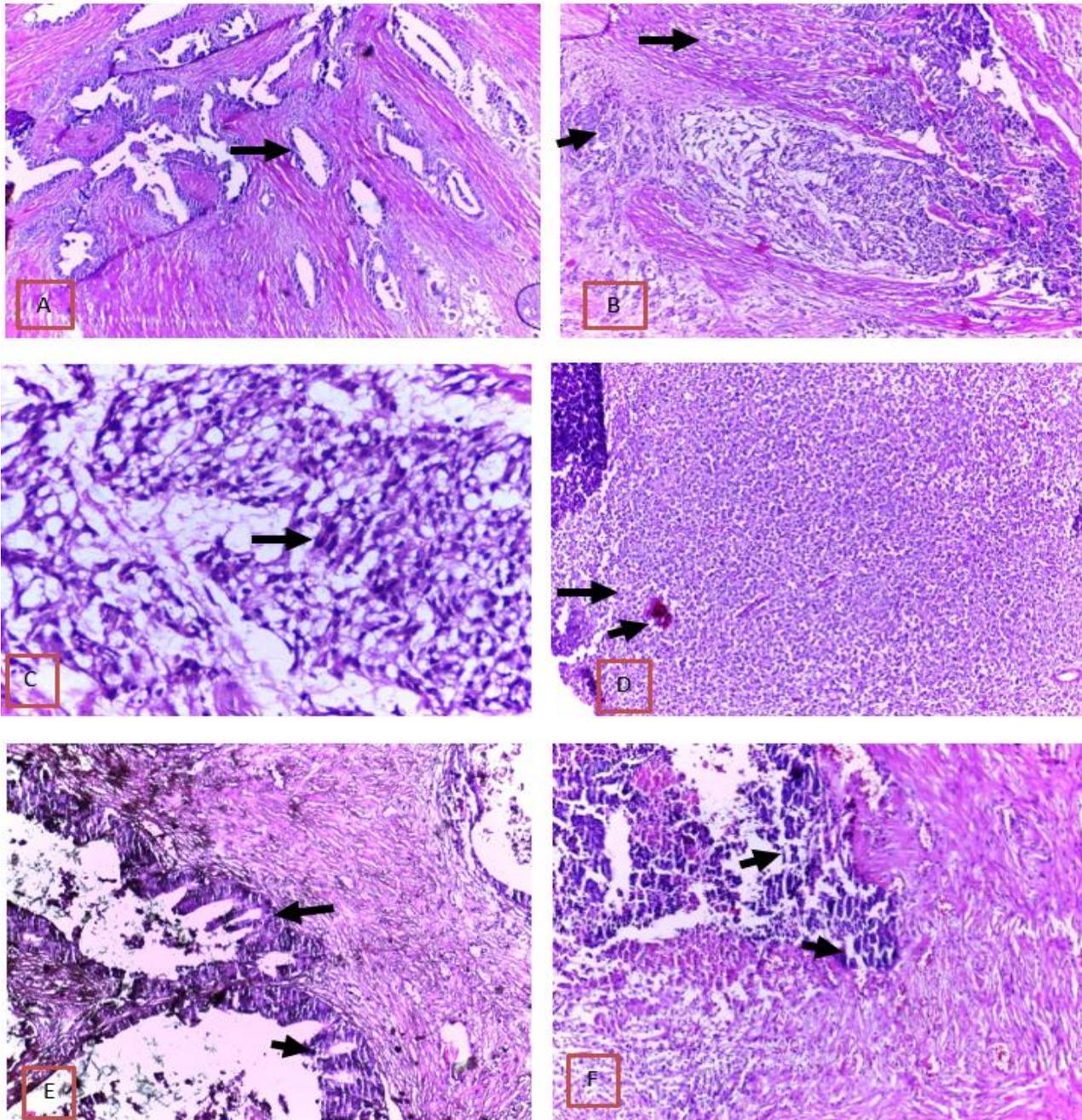


Figure 2: Sections of the bladder tumor Moderately differentiated adenocarcinoma bladder, Part of a tumor with a nodular growth pattern (arrow) (10X) (A) ; Infiltrating urothelial carcinoma with highly pleomorphic cells increased atypical mitosis (arrow) (B); Rounded to polygonal malignant cells with severe nuclear atypia, prominent nucleoli, and abundant, clear cytoplasm seen under (40×)(C); high grade bladder carcinoma with glandular differentiation beside esconspicuous mitosis(long arrow), single cells with irregularly distributed coarsely granular chromatin and prominent nucleoli varying in size and number (short arrow)(10X) (D); Early nodular hyperplasia associated with sub-urothelial lymphocytic infiltration( long arrow) and moderate hyperplastic urothelium showing focal areas of atypical cells in which there is a disorientated and differential growth pattern(short arrow) (40×) (E); Low grade papillary transitional cell carcinoma showing papillae with mild pleomorphic of cells with maintained basal polarity(long arrow) with highly vascularization at this section were associated with angiogenesis (short arrow) (10X) (F). all the sections stained with hematoxylin and eosin stains.

was around 65 years.<sup>[11,12]</sup> The results from this study confirmed that number of men who diagnosed with bladder cancer through the study time was significantly high comparing with women. Additionally, the current results consistent with what has been reported worldwide where

suggested that the bladder cancer is 3-4 time more common in men than women. This excess is not fully explained by the differences in smoking and occupational exposure, which are the two major leading risk factors. Most of the studies identified the age, gender, occupation,

cigarette smoking, diet, drugs and diseases are the risk factors of bladder cancer. Where, Age is a major risk factor for bladder cancer.<sup>[13]</sup> Furthermore, Evidence suggests that occupational exposure to carcinogens consider higher risk of developing bladder cancer than others known factors<sup>[14]</sup> and this in turn would increase the incidence of bladder cancer in men. Men, who are working in the rubber, mining and leather industries, additionally hairdressers, metal workers, printers, painters, textile workers and truck drivers, have been recognized as having a serious risk of bladder cancer than others who are working in other industries.<sup>[15,16]</sup>

The present study displayed that smoking increase the risk of bladder cancer and this come along with other studies where it has been reported that cigarette smokers have a 2 to 4 folds increased risk of bladder cancer compared to non-smokers<sup>[17]</sup>, and the risk increases with increasing intensity and/or duration of smoking.<sup>[18]</sup> According to several studies reports, smoking is a major etiological factor linked to increase bladder cancer incidence,<sup>[19]</sup> that would explain the increase number of male getting bladder cancer comparing to the females who do not smoke in Iraq. On the other hands, there are several factors which have been linked with bladder cancer such as dietary that develops bladder cancer as fatty foods consumption.<sup>[8]</sup> There were some limited evidences that adequate consumption of fruit and vegetables have a protective effect against the development of bladder cancer.<sup>[20]</sup>

Regarding histopathology of bladder cancer, the pathological scientist divided the bladder cancer into three types; Transitional cell carcinoma (TCCs) or urothelial carcinoma (UCC), Squamous cell carcinoma (SCC), and adenocarcinoma. TCCs represent about more than 90% of bladder cancer. TCC, in turn, has been divided into three main forms; the majority are papillary TCCs, which appear as exophytic, front like structures. Second, are sessile TCCs, which are less fondler and have a more solid looking lesion with a broad base. A third form is the carcinoma in situ (CIS) which characterized by flat, erythematous lesions that would be multifocal and of a high grade.<sup>[21]</sup>

Transitional cell carcinoma (TCC) of the bladder is the second most common malignancy of the genitourinary tract and the third most common cause of death among people with genitourinary tumors<sup>[22]</sup>. 80% of patients who initially present with bladder TCC have tumors confined to the mucosa or submucosa—so-called superficial “non—muscle-invasive” bladder cancers.<sup>[23]</sup> Superficial bladder tumors represent a heterogeneous group of cancers that include those that are (1) papillary in nature and limited to the mucosa (Ta), (2) high grade and flat and confined to the epithelium (Tis), and (3) invasive into the submucosa, or lamina propria (T1).<sup>[24]</sup>

Grading and tumor staging are the main factors for reappearance and the progression of sickness. Furthermore, knowing the grading and the stage would help the doctors to determine of treatment options for patient.<sup>[3]</sup> The results of this study showed the most common grade is grade I (24 patients 57.14%). Likewise, the cancer lesion was higher at stage T2 (57.14%).

According to WHO grading, the number of TCC- High grade was around 53.57% from all cases observed, followed by low grade TCC with 42.85% and comparing to another study observations, where studied showed 40% cases of high grade and 60% of all cases showed low grade.<sup>[3]</sup> The most common symptoms of bladder cancer are non-specific nature that represent by painless intermittent haematuria and irrelative voiding<sup>[25,26]</sup> which generally lead to late presentation seen in our patient.

Cystoscopes biopsies of 42 patients included in the current study exposed wide spectrum of different path histological lesion. Transitional cell carcinoma (TCC) was the most common bladder neoplasm in this study was diagnosed in most cases and this similar to data which was reported in India and Nepal.<sup>[27,28]</sup> The literature from USA and Europe union this sort of tumor account for 90% of bladder cancer.<sup>[29]</sup> In our study adenocarcinoma and small cells carcinoma kind of tumor were rarely noticed and this come along with previous studies.<sup>[30,31]</sup>

Most incidence bladder cancer was among the older man who smoke. Bladder tumors were the commonest lesions seen in biopsies included in the present studies and urothelial origin was the highest. Transitional cell carcinoma TTC was the greatest common bladder tumor. Furthermost of examined tumors were high grade. Elevated grade transitional cell of carcinomas existing with muscle invasion. Preventive examination should be taken among Iraqi men to get early stage bladder cancer development and it is importance of including smooth muscle in the biopsy specimens which really needs to be emphasized in diagnostic.

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