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Clinical features in cancer patients with COVID-19 in Santa Fe and Buenos Aires, Argentina

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Abbreviations: COVID-19: Coronavirus Disease 2019; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; PCR: Real-Time Polymerase Chain Reaction; ICU: Intensive Care Unit.

Abstract

During the COVID-19 (SARS-CoV-2) pandemic, cancer patients have represented a high-risk population. We aimed to describe the clinical characteristics of patients with cancer and COVID-19 in the cities of Santa Fe and Buenos Aires, Argentina, and to compare the clinical evolution of cancer and non-cancer patients with severe COVID-19. We conducted a retrospective, hospital-based study involving 79 patients with laboratory-confirmed SARS-CoV-2 infection and pathological diagnosis of a malignant tumor. We then performed a case-control comparison of 16 cancer patients with severe COVID-19 and 32 sex- and age-matched non-cancer patients with severe COVID-19. Among the 79 cancer patients with COVID-19, 56.4% were female and the median age was 65 years. We found that mortality was significantly associated with dyspnea, severe pneumonia, the presentation of one or more complications during the COVID-19 infection, ICU admission, the percentage of of neutrophils and the percentage of lymphocytes. Besides, having dyspnea and severe pneumonia, being admitted to the ICU and receive respiratory assistance significantly increased the probabilities of death. The case-control study showed that having cancer increased 5.4 times the probabilities of dying from severe COVID-19. Considering these results, it should be a priority that cancer patients with COVID-19 infection receive regular screening and preventive therapies.

Keywords: Covid-19; Sars-cov-2; Cancer; Mortality risk.

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic has had worldwide implications and has challenged the health care system of every country in the world. In Argentina, at the beginning of 2021, the Ministry of Health reported a total of 1,714,409 confirmed COVID-19 cases, 1,504,330 of whom had recovered and 44,417 of whom had died [1]. This information indicates that, during the period between the beginning of the pandemic (March 2020) and the beginning of 2021, the mortality rate due to COVID-19 infections in the general population was 2.59%.

Regarding cancer patients, both the research community and international organizations have recognized them as a vulnerable population, with higher susceptibility to infectious diseases due to the malignancy and/or anticancer treatments they receive [2,3]. During 2020, the Global Cancer Observatory of the International Agency for Research on Cancer (IARC) reported 130,878 new cases of cancer in Argentina [4]. Taking into consideration all tumor sites, the age-adjusted incidence rate in 2020 was 212.4 cases per 100,000 habitants, placing Argentina as a country with a medium-high incidence of cancer (range 181.1 to 248.3 per 100,000 habitants) [4].

The COVID-19 evolution in cancer patients is still not fully understood and controversial. Some studies have reported that cancer patients have an increased risk of COVID-19 infection [3,5], as well as poor outcomes and more severe evolution [3,6,7]. Furthermore, numerous authors have found that, after COVID-19 infection, cancer patients have a higher risk of mortality [7-12]. However, controversially, some studies have found no differences in mortality between cancer and non-cancer patients after COVID-19 infection [13,14]. Additionally, Barlesi et al. observed that the cancer population studied did not present higher incidence of COVID-19 infection [13].

Despite the immunocompromised condition of cancer patients, several factors potentially linked to it, such as age, gender, comorbidities, hematological parameters, eosinopenia, increased D-dimer, C Reactive Protein, LDH level, coma, seizures and palliative therapy, can increase their risk of mortality [1,8,12,14-20].

Taking this into account, the aim of the present study was to describe the clinical characteristics and factors associated with mortality in cancer patients with confirmed COVID-19 infection, and to compare the clinical course of severe COVID-19 in cancer and non-cancer patients in two cities of Argentina.

Materials and methods

Study patients

We performed a retrospective multicenter study in five different health medical centers of two cities of Argentina (Santa Fe and Buenos Aires). The participating hospitals were the Hospital Italiano, located in Buenos Aires city, and the Hospital Cullen, Hospital Iturraspe, Sanatorio San Jerónimo and Sanatorio Mayo, located in Santa Fe city. From March 20th to December 20th 2020, we enrolled 79 patients with laboratory confirmed COVID-19 (SARS-CoV-2) infection and diagnosis of a malignant tumor. We also collected data from patients with severe COVID-19 and no cancer and compared them with data from COVID-19 cancer patients. At the time of data collection, none of the patients had received vaccination against COVID-19.

Data collection

Medical records from the mentioned hospitals were used to extract data on the following variables: sex, age, symptoms (fever, cough, sputum, chest congestion, chills, dyspnea, fatigue, nausea/vomiting, and diarrhea), time between the onset of the symptoms and hospitalization, disease severity, comorbidities (hypertension, diabetes, chronic obstructive pulmonary disease, coronary heart disease, hepatitis B virus infection, and chronic renal disease), vital signs (temperature, cardiac rate, respiratory rate, and oxygen saturation), laboratory and radiological findings, mean hospital stay, type of respiratory assistance received (none, non-invasive, invasive), admission to the Intensive Care Unit (ICU), treatments received for COVID-19, complications, type of cancer, cancer treatments received (surgery, chemotherapy, radiotherapy, immunotherapy, directed therapy), cancer treatments received in the past four weeks, cancer stage (early, advanced), years since cancer diagnosis and ECOG scale.

Statistical analysis

All statistical analyses were performed using the R software [21] with a statistical significance level of $P<0.05$. Categorical variables are presented as frequencies (%) and numerical variables as median (IQR). We compared COVID-19 mortality in cancer patients considering sex, age, symptoms, disease severity, comorbidities, vital signs, laboratory findings, radiological findings, type of respiratory assistance, admission to the ICU, COVID-19 treatments, complications, type of cancer, cancer treatments received and cancer treatment received in the past four weeks, using either Pearson's chi-square test, Fisher's exact test or Mann-Whitney test.

We performed a case-control analysis to compare cancer patients with severe COVID-19 and non-cancer patients with severe COVID-19. Each cancer patient with severe COVID-19 was matched by sex and age with two patients with severe COVID-19 from the Pneumology Department ward of the Hospital Cullen (Santa Fe, Argentina). Cases and controls were compared in terms of laboratory findings, radiological findings, type of respiratory assistance and mortality, using either Pearson's chi-square test, Fisher's exact test or Mann-Whitney test.

Variables with P-values <0.10 in the association tests were analyzed using univariable logistic regression. We did not fit multivariable logistic regression models due to the small sample size (n=79) and high percentage of missing data among explanatory variables (>20%).

Results

Among the 79 cancer patients with COVID-19, 56.4% were women and the median age was 65 years (IQR: 55-73, range: 29-92). Data on sex were missing for one patient (1.3%), whereas data on age were missing for five patients (6.3%). We found no significant associations between mortality and sex (P=0.406) or age (P=0.210).

Data on comorbidities were available for 53 out of the 79 cancer patients (67.1%), 47.2% of whom had hypertension, 18.9% of whom had diabetes, and 34% of whom had other

Table 1: Comorbidities, symptoms and disease severity of cancer patients with laboratory confirmed COVID-19.

	Cancer patients (n=79)	Survivor (n=65)	Non-survivor (n=14)	P-value
Comorbidities (n=53)				
Hypertension	25 (47.2%)	19 (48.7%)	6 (42.9%)	0.948
Diabetes	10 (18.9%)	9 (23.1%)	1 (7.14%)	0.258
Other/s [a]	18 (34.0%)	12 (30.8%)	6 (42.9%)	0.515
Symptoms (n=51)				
Fever	29 (56.9%)	24 (60.0%)	5 (45.5%)	0.498
Cough	28 (54.9%)	23 (57.5%)	5 (45.5%)	0.514
Dyspnea	17 (33.3%)	9 (22.5%)	8 (72.7%)	**0.003***
Fatigue	19 (37.3%)	14 (35.0%)	5 (45.5%)	0.726
Other/s [b]	13 (25.5%)	9 (22.5%)	4 (36.4%)	0.439
Days of hospitalization (n=39)	8.00 [0.50;14.0]	8.00 [0.00;13.5]	9.00 [4.00;16.5]	0.390
Severe Pneumonia	17 (21.5%)	9 (13.8%)	8 (57.1%)	**0.001***
Complications (n=36) [c]	14 (38.9%)	6 (21.4%)	8 (100%)	**<0.001***
Admission to ICU (n=44)	14 (31.8%)	7 (21.2%)	7 (63.6%)	**0.021***

Statistically significant (P<0.05); [a] Coronary disease, chronic renal disease, chronic obstructive pulmonary disease; [b] Sputum, chills, chest congestion, nausea and vomiting, diarrhea; [c] ADRS, secondary infection, septic shock, abnormal renal or hepatic function, coagulopathy, arrhythmia.

comorbidities such as chronic obstructive pulmonary disease (9.4%), coronary disease (18.9%), or chronic renal disease (11.3%). None of these comorbidities was significantly associated with mortality (P>0.05, Table 1). Data on the symptoms were available for 51 patients (64.6%), 56.9% of whom reported fever, 54.9% cough, 37.3% fatigue, 33.3% dyspnea, and 25.5% other symptoms (Table 1). Chi-square test detected a significant association between dyspnea and mortality (P=0.03, Table 1). The median days of hospitalization for the 39 patients who had this information was 8 days [IQR: 0.5-14], and this value did not significantly differ between survivor and non-survivor patients (P=0.390, Table 1). Seventeen cancer patients (21.5%) presented severe pneumonia and this was significantly associated with mortality (P=0.001, Table 1). Among the 36 cancer patients that experienced complications (45.6%), 7 (19.4%) presented adverse drug reactions, 7 (19.4%) presented secondary infections, and 9 (25%) presented other complications such as septic shock, abnormal renal or hepatic function, coagulopathy, or arrhythmia (Table 1). In cancer patients, presenting one or more complications in the COVID-19 infection was significantly associated with mortality (P<0.001, Table 1). Information on ICU admission was available for 44 cancer patients (55.7%), and results showed that mortality was significantly associated with being admitted to the ICU (P=0.021, Table 1).

Data on vital signs (cardiac and respiratory frequency, oxygen saturation) at the moment of admission were not considered for the analysis given that they were available for less than 20 patients. About half of the patients (50.6%) presented complete data on laboratory parameters and radiological findings. We detected significant associations between mortality and the percentage of neutrophils (P=0.008), as well as between mortality and the percentage of lymphocytes (P=0.016, Table 2). The most frequent radiological anomaly was bilateral infiltra-

Table 2: Laboratory parameters, radiological findings and treatments received in cancer patients with laboratory confirmed COVID-19.

	Cancer patients (n=40)	Survivor (n=28)	Non-survivor (n=14)	P-value
Laboratory findings				
Leucocytes (mm^3) (n=38)	6448 [3876; 9048]	5550 [3782; 7842]	8566 [5862; 1395]	0.143
Neutrophils (%) (n=36)	80.0 [66.8; 86.0]	75.0 [59.4; 84.9]	86.0 [82.1; 91.0]	**0.008***
Lymphocytes (%) (n=36)	12.3 [6.45; 20.7]	15.0 [9.20; 26.3]	6.60 [4.72; 10.6]	**0.016***
Platelets (mm^3) (n=34)	187900 [152500; 245375]	176800 [151500; 252150]	190000 [163750;2 22600]	0.985
Hemoglobin (g/dl) (n=38)	12.2 [10.9;12.9]	12.3 [10.9;12.9]	11.5 [10.9;12.9]	0.699
Creatinine (mg/dl) (n=32)	0.92 [0.70;1.02]	0.88 [0.70;1.02]	0.98 [0.94;1.04]	0.204
Urea (g/L)) (n=31)	0.38 [0.30;0.58]	0.35 [0.27;0.45]	0.48 [0.38;0.71]	0.076
Radiological findings				
Bilateral infiltration	20 (50.0%)	12 (46.2%)	8 (57.1%)	0.740
Other/s [a]	19 (47.5%)	13 (50.0%)	6 (42.9%)	0.921
Treatments received				
Intravenous antibiotics (n=36)	11 (30.6%)	3 (12.0%)	8 (72.7%)	**0.001***
Intravenous corticosteroids (n=37)	16 (43.2%)	8 (32.0%)	8 (66.7%)	0.101
Oxygen therapy (n=37)	24 (64.9%)	15 (60.0%)	9 (75.0%)	0.476
Respiratory assistance (n=39)	21 (53.8%)	12 (42.9%)	9 (81.8%)	0.066

*Statistically significant (P<0.05); a Ground glass opacity, consolidation, patchy shadowing.

Table 3: History of treatments in cancer patients with COVID-19.

	Cancer patients (n=49)	Survivor (n=38)	Non-survivor (n=11)	P-value
Surgery	22 (44.9%)	20 (52.6%)	2 (18.2%)	0.083
Chemotherapy	35 (71.4%)	25 (65.8%)	10 (90.9%)	0.143
Chemotherapy in the past 4 weeks (n=39)	21 (53.8%)	15 (51.7%)	6 (60.0%)	0.726
Radiotherapy	15 (32.6%)	10 (28.6%)	5 (45.5%)	0.462
Other/s [a]	10 (21.7%)	6 (17.1%)	4 (36.4%)	0.220

Statistically significant (P<0.05); a Directed therapy, immunotherapy.

Table 4: Bivariate analysis of factors associated with death in oncologic patients with COVID-19.

Variable	Odds-ratio [95% CI]	P-value
Dyspnea	9.19 [2.01; 42.01]	**0.004***
Severe pneumonia	8.30 [2.33; 29.58]	**0.001***
Admission to ICU	6.50 [1.47; 28.70]	**0.014***
Neutrophils (%)	1.09 [1.00; 1.19]	**0.050**
Lymphocytes (%)	0.90 [0.80; 1.00]	**0.054**
Respiratory assistance	6.00 [1.09; 33.02]	**0.040***

*Statistically significant (P< 0.05).

Table 5: Comparison between patients with severe COVID-19 with cancer and without cancer.

	Severe COVID-19 N = 48	No cancer N = 32	Cancer N = 16	P-value
Laboratory findings				
Neutrophils (%)	82.6 [74.0;86.4]	80.2 [72.2;85.4]	84.1 [75.5;90.8]	0.147
Platelets (mm^3)	221000 [152000; 310500]	258000 [158000; 321000]	197000 [141000; 222600]	0.098
Hemoglobin (g/dl)	12.6 [11.3;13.2]	12.8 [11.7;13.6]	12.3 [11.1;12.7]	0.193
Urea (g/l) (n=42)	0.41 [0.31; 0.54]	0.35 [0.28; 0.53]	0.44 [0.38; 0.58]	0.085
Radiological findings (n=40)				
Bilateral infiltration	16 (40.0%)	5 (19.2%)	11 (78.6%)	**0.001***
Other/s [a]	31 (77.5%)	21 (80.8%)	10 (71.4%)	0.694
Respiratory assistance (n=39)	37 (94.9%)	24 (96.0%)	13 (92.9%)	1.000
Deceased	13 (27.1%)	5 (15.6%)	8 (50.0%)	**0.018***

* Statistically significant (P<0.05); a Ground glass opacity, consolidation, patchy shadowing.

tion, detected in 20 out of 40 patients (50%, Table 2). Other radiological findings included ground glass opacity, consolidation and patchy shadowing. None of these anomalies was significantly associated with mortality of cancer patients (P>0.05, Table 2). In the patients with complete data on the COVID-19 treatments, received, we found statistically significant associations between mortality and receiving intravenous antibiotics (P=0.001, Table 2).

The most frequent type of cancer among the patients was breast cancer (24.1%), followed by colorectal cancer (11.4%) and lung cancer (10.1%). The majority of the patients (71.4%) had received chemotherapy as treatment for cancer and 53.8% had received chemotherapy in the four weeks prior to the onset of symptoms. The other most frequent treatments received were surgery (44.9%) and radiotherapy (22.6%) (Table 3). We did not found significant associations between mortality and receiving cancer treatments (Table 3).

We fit bivariate logistic regression models for the following explanatory variables: dyspnea, severe pneumonia, admission to the ICU, percentage of neutrophils, percentage of lymphocytes, and receiving respiratory assistance. We did not fit models for the following explanatory variables: complications and receiving intravenous antibiotics, because of the small sample size. We found that having dyspnea, severe pneumonia, being admitted to the ICU and receiving respiratory assistance significantly increased the probabilities of death (P<0.05, Table 4).

We next compared the data of 16 cancer patients with severe COVID-19 and 32 matched non-cancer patients with severe COVID-19. Cancer patients with severe COVID-19 presented bilateral infiltration more frequently (P=0.001, Table 5) and had higher mortality (P=0.018, Table 5) than non-cancer patients with severe COVID-19. No data on symptoms, complications and treatments received were available in the clinical records of non-cancer patients with severe COVID-19. Results of the bivariate analysis showed that having cancer increased 5.4 times (95% CI: 1.38; 21.20) the probabilities of dying from severe COVID-19.

Discussion

This study aimed to report information about epidemiological and clinical features in COVID-19 cancer and non-cancer patients. To this end, we performed a retrospective multicenter study in health medical centers of two cities of Argentina (Santa Fe and Buenos Aires) to compare the clinical courses of cancer and non-cancer patients with COVID-19, including a similar number of men and women in the same time period. The results of our analysis showed that having cancer increased 5.4 times (95% CI: 1.38; 21.20) the probabilities of dying from severe COVID-19. Seventeen cancer patients (21.5%), who were observed after presenting a positive SARS-COV-2 test, showed signs of advanced stages and progression to critical stages, ending up in severe pneumonia, which our results identified as a risk factor for mortality. In concordance with our results, Liang et al. found that cancer patients not only had a higher risk of SARS-CoV-2 infection, but also showed a higher risk of severe clinical events [3]. Other authors have found an association between higher mortality in cancer patients and a more severe evolution or poorer outcome during COVID-19 infection [6,7,22]. Another retrospective study reported that the overall fatality among 218 COVID-19 cancer patients in New York City was 2-3-fold greater than that among age-adjusted non-cancer patients [22]. Emerging studies have shown a worse trend among cancer COVID-19 patients than among non-cancer COVID-19 patients [5,9]. However, other studies have shown controversial results. Asghar et al., for example, reported no major differences in mortality between cancer and non-cancer COVID-19 patients [14]. In the same line, Barlesi et al. observed that the cancer population studied did not present higher incidence of COVID-19 infection or higher mortality rate due to COVID-19 [13]. We might consider that there are several challenges in determining whether COVID-19 was the direct cause of a patient's death, or whether death was caused by a terminal event in a patient who has come near the end of his/her cancer care. It is also important to highlight that the mortality rate of COVID-19 may vary between countries due to resource limitations, geography, literacy, population, and political factors. Moreover, Lee et al. showed that patients with cancer with different tumor types have different susceptibility to SARS-COV-2 and different COVID-19 disease phenotypes [15].

Interestingly, in cancer patients, presenting one or more complications during the COVID-19 infection was significantly associated with mortality. This may be due to an altered immune system that produces an unregulated immune response with extensive inflammation and increased levels of cytokines. However, accumulated evidence has shown that cancer development and its treatments can weaken immunity by over-

expressing immunosuppressive cytokines or by suppressing the induction of proinflammatory danger signals, which is opposite to the events that are thought to occur in severe cases of cancer and COVID-19 [23]. In addition, both cancer and COVID-19 exploit distinct inflammatory responses that promote disease progression [24]. Macrophages can express different proteins defining different alternative pathways [25]. The data suggest that distinct macrophage activation states distinguish the two diseases by offering a common target cell. The shift between these inverse activation states plays a distinct role in COVID-19 and cancer, suggesting that the immune-metabolic states of the tumor can modify the cancer patient response to COVID-19 [26].

It must be emphasized that, in most cases, the infection tests were performed only in patients with suspected symptoms of infection. The COVID-19 incubation period is thought to be about two weeks, and most patients become symptomatic 5 days after exposure. Many cancer patients had mild disease and moderate symptoms, similar to post-chemotherapy symptoms, and were not tested, which restricted the sample size. Data from a universal pre-chemotherapy testing program at a hospital in Dubai, United Arab Emirates, revealed that 7 out of 85 asymptomatic cancer patients (8.2%; 95% CI 2.4%–14.1%) were positive to SARS-CoV-2 by PCR screening and subsequently developed clinical illness [27].

Accumulating reports suggest that severe COVID-19 and mortality in cancer patients are significantly associated with age, disease severity, multiple comorbidities and habits. In a study on 218 cancer patients with SARS-CoV-2 infection, Mehta et al. demonstrated that older age was significantly associated with increased mortality [22]. In a recent study about excess deaths in Stockholm, Sweden, age and socio-economic status were strong predictors of mortality [28]. However, the median age of those who died was 83 years, which is much higher than the expected median age of death for patients who die from cancer, as life expectancy for cancer patients is lower than that for the general population. In fact, older age has been found to be a risk factor for severe events in many studies [8,12], but this was not observed in our study. This difference might be due to the high percentage of middle-aged individuals evaluated.

As reported in other studies [8,22], the results of our study showed that the commonest comorbidities were hypertension and diabetes. In addition, the majority of the patients (71.4%) had received chemotherapy as treatment for cancer. This is in agreement with the strong known association between different chemotherapeutic treatments and development or worsening of hypertension [22,29]. Likewise, other medications used in cancer patients such as erythropoietin, corticosteroids and non-steroidal anti-inflammatory drugs can also increase blood pressure [30]. In our study, in cancer patients, the comorbidities did not lead to increased risk of dying from COVID-19. The median age of patients was 63 years old, and the main symptoms reported were fever, cough, chest distress, fatigue and headache, which were similar to those of the general population after infection with SARS-COV-2. However, about a third of cancer patients with COVID-19 presented dyspnea, which we found to significantly increase the probabilities of death. These results suggest that patients with respiratory distress may have greater complications, and thus the worst prognosis. This point is very relevant when a cancer patient is infected with COVID-19, because it would allow the health system to take urgent measures for a favorable evolution.

A hematological biomarker which is commonly used to study the evolution of both cancer and COVID-19 is blood cell count. Laboratory results of most cancer patients showed a normal white blood cell count, but in cases with severe or critical COVID-19, we observed neutrophilia and lymphopenia. Similar laboratory findings have been reported in hospitalized patients with COVID-19, neutrophilia [31] and lymphopenia [31,32], and seems to be associated with poor prognosis (Wang et al. 2020; Qu et al. 2020). These basic biomarkers can be helpful for early warning and identification of severe disease in this type of patients. Eosinopenia, another possible biomarker, is commonly associated with poor outcomes [19,20]. However, it should be noted that not all laboratory parameters were available for all patients, and that some parameters were only available for about half of the patients. Thus, a larger sample size would be needed to assess whether these biomarkers are significantly associated with mortality.

Admission to the ICU varied in different studies during the pandemic but this is not relevant because this huge difference could be attributed by unlike in the timeline of the pandemic and higher capacities of critical care beds in diverse hospitals. It has been reported that patients with cancer have an increased risk of severe infections, needing mechanical ventilation or ICU admission, and an increased risk of death when compared with non-cancer patients [3]. In our study, data on ICU admission were available for 44 out of the 79 cancer patients (55.7%), and we found a significant association with mortality. A possible explanation is that cancer patients infected with COVID-19 remained in their homes until they had acute manifestations and by the time they were hospitalized it was too late to apply any effective treatment. Nevertheless, these conclusions should be interpreted with caution, considering that data on days since the onset of symptoms and hospitalization and on days since hospitalization and admission to the ICU were only available for some cancer patients and that no data were available for the non-cancer patients.

The most frequent types of cancer among the patients in our study were breast cancer (24.1%), colorectal cancer (11.4%) and lung cancer (10.1%). In contrast with other studies [32,33], our study showed a low prevalence of patients with lung cancer and COVID-19. This may be explained by an effective shielding of lung cancer patients at the early stage of the pandemic in our country. Furthermore, data from the Global Cancer Observatory showed that, in Argentina, breast cancer and colorectal cancer have higher incidence than lung cancer [4], which may be related to the higher lethality of the latter. In our study, the type of cancer was not specified for more than half of the patients with COVID-19, and, among the patients with information on the cancer type, most had breast cancer. In this context, we were unable to consider the type of cancer as a potential risk factor of severity or mortality of COVID-19.

Conclusion

We may conclude that, although it is of interest to study predictors of COVID-19-related deaths in cancer patients, the current evidence remains insufficient to explain a conclusive association between cancer and COVID-19. However, since cancer patients have more deteriorating conditions and higher risk of mortality than patients without cancer, it should be a priority that cancer patients with COVID-19 infection receive regular screening and preventive therapies.

Declarations

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