


Impact of COVID-19 vaccination on the use of PD-1 inhibitor in treating patients with cancer: a real-world study

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ABSTRACT

Anti-COVID-19 vaccination may have functional implications for immune checkpoint inhibitor treatment in patients with cancer. This study was undertaken to determine whether the safety or efficacy of anti-PD-1 therapy is reduced in patients with cancer during COVID-19 vaccination. A large multicenter observational study was conducted in 83 Chinese hospitals between January 28, 2021 and September 30, 2021. A total of 3552 patients were screened and 2048 eligible patients with cancer receiving PD-1 inhibitor treatment were recruited. All enrolled patients had received camrelizumab treatment alone or in conjunction with other cancer therapies. Among these, 1518 (74.1%) patients received the BBIBP-CorV vaccine and were defined as the vaccinated subgroup. The remaining 530 (25.9%) patients did not receive anti-COVID-19 vaccination and were defined as the non-vaccinated subgroup. For all participants, Response Evaluation Criteria in Solid Tumor and Common Terminology Criteria for Adverse Events criteria were used to evaluate the efficacy and safety of camrelizumab treatment, respectively. Propensity score match analysis with the optimal pair matching was used to compare these criteria between the vaccinated and non-vaccinated subgroups. A total of 2048 eligible patients with cancer were included (median age 59 years, 27.6% female). Most patients (98.8%) had metastatic cancer of the lung, liver or intestinal tract. Aside from the PD-1 inhibitor treatment, 55.9% of patients received additional cancer therapies. 1518 (74.1%) patients received the BBIBP-CorV vaccine with only mild side effects reported. The remaining patients did not receive COVID-19 vaccination and had a statistically greater percentage of comorbidities. After matching for age, gender, cancer stage/types, comorbidity and performance status, 1060 patients (530 pairs) were selected for propensity score match analysis. This analysis showed no significant differences in overall response rate (25.3% vs 28.9%, $p=0.213$) and disease control rate (64.6% vs 67.0%, $p=0.437$) between vaccinated and non-vaccinated subgroups. Immune-related adverse events (irAEs) were reported in both subgroups after camrelizumab treatment. Among vaccinated patients who experienced irAEs, the median interval between the first dose of camrelizumab treatment and the first vaccine shot was ≤ 16 days. Compared with the non-vaccinated subgroup, irAEs in vaccinated patients were more frequently reported as mild (grade 1 or 2 irAEs;

33.8% vs 19.8%, $p<0.001$) and these patients were less likely to discontinue the PD-1 inhibitor treatment (4.2% vs 20.4%, $p<0.001$). Severe irAEs (grade 3 irAE or higher) related to camrelizumab treatment were reported, however no significant differences in the frequency of such events were observed between the vaccinated and non-vaccinated subgroups. The COVID-19 vaccine, BBIBP-CorV, did not increase severe anti-PD-1-related adverse events nor did it reduce the clinical efficacy of camrelizumab in patients with cancer. Thus, we conclude that patients with cancer need not suspend anti-PD-1 treatment during COVID-19 vaccination.

BACKGROUND

PD-1 inhibitors have been widely used for treatment of multiple types of cancer.¹ With the ongoing coronavirus pandemic, the effect of anti-COVID-19 vaccination on PD-1 safety and efficacy has become a critical question for oncologists and patients with cancer alike.² To avoid potential treatment complications, some physicians have opted to suspend PD-1 inhibitor treatments for recently vaccinated patients with cancer. However, little data exist to support such a decision. Recent studies have found that anti-COVID-19 vaccines such as BNT162b2 (Pfizer BioNTech, New York, New York, USA) and mRNA-1273 (Moderna, Cambridge, Massachusetts, USA) are well tolerated in patients with cancer,^{3–5} and side-effect profiles from these vaccines were similar between healthy volunteers and patients with cancer.⁶ One recent meta-analysis summarizing multiple COVID-19 vaccine trials studies concluded that patients with cancer have a significantly lower likelihood of attaining acceptable immune response to COVID-19 immunization when compared with the general population given compromised cancerous immune system.⁷ However, whether anti-COVID-19 vaccines have any functional impact on the efficacy of immune checkpoint inhibitor (ICI) treatment was unknown. Thus, we

conducted a large multicenter study to explore the effects of COVID-19 vaccination on PD-1 inhibitor treatment in patients with cancer.

METHODS

A total of 3552 consenting adult patients with cancer were screened from 83 Chinese hospitals and medical centers beginning on January 28, 2021. Eligible participants met the following inclusion criteria: (1) their malignancy had been histopathologically confirmed; (2) they had received at least one dose of camrelizumab⁸ (one of the most commonly used PD-1 inhibitors in China) after the COVID-19 vaccination program was launched in China in January 2021. Clinical information, demographic data, and medical history were collected at enrollment, and patient treatment, adverse events and outcomes were followed through September 30, 2021. Efficacy and safety of PD-1 treatment were evaluated according to Response Evaluation Criteria in Solid Tumor V.1.1⁹ and National Cancer Institute Common Terminology Criteria for Adverse Events V.5.0,¹⁰ respectively. Patient functionality/performance status was evaluated using Eastern Cooperative Oncology Group (ECOG) criteria. Categorical variables were described as n (%) and characteristics between subgroups were compared using Fisher's exact test. Continuous variables were shown as median with IQR, and the Mann-Whitney U test was conducted to compare the variables between subgroups. Propensity score match analysis was applied with the optimal pair matching algorithm.

RESULTS

A total of 2048 patients with cancer were included (median age 59 years, IQR 54–66, range 18–92; 27.5% female; **table 1**). Fifteen different types of cancer were present in this cohort: 722 (35.3%) lung, 469 (22.9%) liver, 218 (10.6%) intestinal tract, and 639 (31.2%) other tissues (**table 1**). The majority of patients had metastatic disease (n=2048, 98.8%). Aside from PD-1 inhibitor treatment, 1145 (55.9%) patients received additional therapy, including chemotherapy (908; 44.3%), targeted therapy (211; 10.3%), and radiotherapy (26; 1.3%). Patients received first-line (1146; 56.0%), second-line (804; 39.3%), third-line treatment (74; 3.6%), as well as adjuvant therapy (24; 1.2%). At enrollment, most patients (1428; 69.7%) had ECOG scores of 0–1 and therefore were considered to be in a good state of health. However, 462 (22.6%) patients had comorbidities which included hypertension (208; 10.2%), diabetes (63; 3.1%), and other conditions (191; 9.3%). Thirteen (0.6%) patients had a history of COVID-19 infection from which they had subsequently recovered. Most patients, 1518 (74.1%), received BBIBP-CorV vaccine¹¹ (an inactivated SARS-CoV-2 virus), with 1134 patients (74.7%) receiving two shots, 288 (19.0%) receiving one shot, and 96 (6.3%) receiving three shots. This subgroup was defined as the

vaccinated subgroup. Among them, 483 (31.8%) patients experienced only mild side effects related to COVID-19 vaccination, including muscle pain (307; 20.2%), fever (168; 11.1%), and pneumonia (8; 0.5%). In this cohort, no severe side effect of COVID-19 vaccination was reported. Median interval between the first dose of camrelizumab treatment and the first shot of vaccination was 42.3 days (IQR 6.1–81.5). The remaining patients (530; 25.9%) did not receive COVID-19 vaccination and were defined as the non-vaccinated subgroup. The main reasons given for lack of vaccination included medical advice (288; 58.3%), self-willingness (144; 29.3%), and inferior health condition (16; 3.3%), as reflected in the statistically greater percentage of comorbidities in this subgroup.

No significant differences of age, gender, cancer stage, or history of COVID-19 infection were observed between the two subgroups. Compared with the non-vaccinated subgroup, vaccinated patients were statistically more likely to be in better health (ECOG <2, 73.8% vs 58.1%, $p < 0.001$, Fisher's exact test; **table 1**), have significantly fewer comorbidities (18.2% vs 34.9%, $p < 0.001$), and were statistically more likely to experience stable disease (45.7% vs 38.1%, $p = 0.003$, Fisher's exact test) following camrelizumab treatment, resulting in a higher disease control rate (DCR, 72.2% vs 67.0%, $p = 0.026$, Fisher's exact test). However, vaccinated patients were statistically less likely to experience partial remission (20.2% vs 24.7%, $p = 0.031$, Fisher's exact test). Further, vaccinated patients were more likely to experience mild immune-related adverse events (irAE ≤ 2) (35.6% vs 19.8%, $p < 0.001$, Fisher's exact test) but less likely to experience severe irAE ≥ 3 (3.0% vs 5.5%, $p = 0.007$). No significant differences were observed in experiencing irAEs following camrelizumab treatment plus additional therapies including chemotherapy, targeted therapy, and radiotherapy between vaccinated and non-vaccinated subgroups. Median intervals between the first dose of camrelizumab treatment and the first shot of vaccination in patients experiencing no, mild, and severe irAEs were 45.1 days (IQR 7.3–88.2), 16.0 days (IQR 4.6–56.5), and 0 days (IQR 0–41.0), respectively. The most frequent irAEs following camrelizumab treatment included reactive cutaneous capillary endothelial proliferation (29.5%), fever (3.0%), pancytopenia (1.4%), anthema (1.1%), and dry mouth (0.9%) (online supplemental table 1). Moreover, vaccinated patients were less likely to discontinue their camrelizumab treatment (7.4% vs 20.4%, $p < 0.001$, Fisher's exact test; **table 1**), with the main reasons/factors being: irAEs of camrelizumab (107; 40.8%) and low efficacy of camrelizumab (46; 17.6%); no patient discontinued anti-PD-1 treatment due to COVID-19 vaccination.

After 1:1 matching for age, gender, cancer stage/type, comorbidity, and ECOG in this cohort, 1060 patients (530 pairs) were selected for further analysis. Comparing the vaccinated and non-vaccinated subgroups, no significant differences in overall response rate (ORR) or DCR with camrelizumab treatment were observed (online supplemental table 2). However, compared with matched

Table 1 Clinical characteristics and treatments

	Overall	Vaccinees	Non-vaccinees	P value
Characteristics				
Number of patients	2048	1518	530	—
Median age, years	59.0 (54.0–66.0)	59.0 (54.0–66.0)	59 (52.0–66.0)	0.821
Gender	—	—	—	0.579
Male	1483 (72.4)	1079 (71.1)	404 (76.2)	—
Female	565 (27.6)	439 (28.9)	126 (23.8)	—
ECOG	—	—	—	<0.001
<2	1428 (69.7)	1120 (73.8)	308 (58.1)	—
≥2	620 (30.3)	398 (26.2)	222 (41.9)	—
History of COVID-19 infection	13 (0.6)	7 (0.5)	4 (0.8)	0.112
Number of vaccination shots	—	2844	—	—
1 shot	—	288 (19.0)	—	—
2 shots	—	1134 (74.7)	—	—
3 shots	—	96 (6.3)	—	—
Adverse effect of vaccination	—	483 (31.8)	—	—
Muscle pain	—	307 (20.2)	—	—
Fever	—	168 (11.1)	—	—
Pneumonia	—	8 (0.5)	—	—
Comorbidities	462 (22.6)	277 (18.2)	185 (34.9)	<0.001
Hypertension	208 (10.2)	119 (7.8)	89 (16.8)	—
Diabetes	63 (3.1)	45 (3.0)	18 (3.4)	—
Heart disease	44 (2.1)	31 (2.0)	13 (2.5)	...
Cerebral infarction	33 (1.6)	22 (1.4)	11 (2.1)	...
Others	114 (5.6)	60 (6.6)	54 (10.2)	...
Cancer types	—	—	—	...
Lung	722 (35.3)	562 (37.0)	160 (30.2)	0.041
Liver	469 (22.9)	337 (22.2)	132 (24.9)	0.208
Intestinal tract	218 (10.6)	189 (12.5)	29 (5.5)	<0.001
Urinary system	84 (4.1)	62 (4.1)	22 (4.2)	1.000
Nasopharyngeal	76 (3.7)	58 (3.8)	18 (3.4)	0.790
Others	479 (23.4)	310 (20.4)	169 (31.9)	<0.001
Cancer stages	—	—	—	0.815
Non-metastasis stage	24 (1.2)	19 (1.3)	5 (0.9)	—
Metastasis stage	2024 (98.8)	1499 (98.7)	525 (99.1)	—
Treatments				
Therapy				
Camrelizumab (Cam)	903 (44.1)	670 (44.1)	233 (44.0)	0.960
Cam+chemotherapy	908 (44.3)	711 (46.8)	197 (37.2)	<0.001
Cam+targeted therapy	211 (10.3)	120 (7.9)	91 (17.2)	<0.001
Cam+radiotherapy	26 (1.3)	17 (1.1)	9 (1.7)	0.366
Immune-related adverse events	719 (35.1)	585 (38.5)	134 (25.3)	—
≤2	645 (31.5)	540 (35.6)	105 (19.8)	<0.001
≥3	74 (3.6)	45 (3.0)	29 (5.5)	0.007
Treatment efficacy				
Complete remission	118 (5.8)	96 (6.3)	22 (4.2)	0.066
Partial remission	438 (21.4)	307 (20.2)	131 (24.7)	0.031
Stable disease	895 (43.7)	693 (45.7)	202 (38.1)	0.003

Continued

**Table 1** Continued

	Overall	Vaccinees	Non-vaccinees	P value
Progression disease	597 (29.2)	422 (27.8)	175 (33.0)	0.026
Overall response rate	556 (27.1)	403 (38.0)	153 (28.9)	0.308
Disease control rate	1451 (70.8)	1096 (72.2)	355 (67.0)	0.026
Treatment pause	221 (10.8)	113 (7.4)	108 (20.4)	<0.001

ECOG, Eastern Cooperative Oncology Group.

unvaccinated patients, a statistically greater percentage of vaccinated patients had mild irAE ≤ 2 (33.8% vs 19.8%, $p < 0.001$) following camrelizumab treatment. The percentage of patients having camrelizumab-related irAE ≥ 3 was not statistically different between matched vaccinated and non-vaccinated subgroups (6.0% vs 5.5%, $p = 0.792$; online supplemental table 2), indicating that the safety of camrelizumab treatment was not altered during COVID-19 vaccination. Finally, matched vaccinated patients were statistically less likely to discontinue the camrelizumab treatment (4.2% vs 20.4%, $p < 0.001$; online supplemental table 2).

DISCUSSION AND CONCLUSION

Patients with cancer can be immunocompromised owing to multiple factors.¹² By design, ICI treatment such as camrelizumab modulates immune responses in these patients and can be associated with irAEs of varying severity. Similarly, active immunization against SARS-CoV-2 generates a robust immune response which could, theoretically, increase the frequency and/or severity of such events and/or reduce the efficacy of PD-1 inhibitors. Such concerns have prompted some physicians and patients to discontinue anti-PD-1 therapy during anti-COVID-19 vaccination. Although studies have shown that anti-COVID-19 vaccination in patients with cancer is safe¹³ and because ICI treatment does not increase the severity of COVID-19 infection,¹⁴ until now, little data existed regarding the implications of anti-COVID-19 vaccination on the safety and efficacy of PD-1 inhibitor treatment.

Our large multicenter study showed that the efficacy of camrelizumab treatment was not reduced in the anti-SARS-CoV-2-vaccinated (BBIPB-CorV) subgroup, compared with the non-vaccinated subgroup, although vaccinated patients were statistically more likely to experience mild irAE following camrelizumab treatment. Interestingly, one recent study suggested that mild irAEs following anti-PD-1 treatment may be associated with improved clinical benefit.¹⁵ Considering our findings that the DCR significantly increased in the vaccinated subgroup (72.2% vs 67.0%, $p = 0.026$), anti-COVID-19 vaccination might increase immune-related responses to checkpoint inhibitor therapy. Moreover, receiving additional anti-cancer therapy did not statistically correlate with the occurrence of irAEs following camrelizumab in these subgroups. Comparing the median intervals between the first dose

of the camrelizumab and the first shot of vaccination in this cohort, it appeared that the optimal window for anti-COVID-19 vaccination for patients receiving anti-PD-1 treatment might be >16 days in order to avoid possible irAEs. As demonstrated in other studies, irAEs from anti-PD-1 treatment were attributable to general dysfunction of T cell function.¹⁶ Administering both anti-COVID-19 vaccines and anti-PD-1 agents in a close temporal proximity (eg, <16 days), may simultaneously enhance co-stimulatory¹⁷ and reduce co-inhibitory regulation¹⁶ between antigen-presenting cell (in context of major histocompatibility complex (MHC)) and T cell receptor. This may result in an additive effect of immune response, associated with increased frequency of serious irAEs in such patients. However, future studies are warranted to clarify this issue and determine an optimal timespan between anti-COVID-19 vaccination and anti-PD-1 treatment.

When patients were matched on age, gender, cancer stage/type, comorbidity, and ECOG in this cohort, and data interrogated by propensity score match analysis, no significant differences in DCR or ORR were observed between the vaccinated and non-vaccinated subgroups. In this matched analysis, the vaccinated subgroup was, again, statistically more likely to experience mild irAEs following camrelizumab therapy. No significant difference in severe anti-PD-1-related adverse events (irAE ≥ 3) was observed between these matched subgroups. In summary, the BBIPB-CorV vaccine did not reduce the safety of camrelizumab in patients with cancer.

This study has its limitations. First, ours is a cohort study, not a prospective randomized clinical trial, which reduces its clinical impact. Second, laboratory findings of this cohort were not collected for detailed immune functional analysis. Third, the PD-1 inhibitor treatment's impact on the efficacy of COVID-19 vaccination was not studied, although no patient with cancer in the vaccinated group was infected with SARS-CoV-2 during this study. Fourth, multiple studies showed that patients with hematological malignancies are less likely to develop an appropriate immune response after COVID-19 immunization.^{18, 19} Our study did not include patients with hematological malignancies, therefore the functional implication of COVID-19 vaccines and anti-PD-1 treatment in these patients remains elusive. Future studies are warranted to investigate these issues. Lastly, additional studies are warranted in patients with cancer with lower functionality

(higher ECOG) scores and/or non-metastatic stage, and with other COVID-19 vaccines (eg, mRNA vaccines).

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Supplement Table 1. Immune-related adverse events (irAE) following camrelizumab treatment

irAE	Overall		Vaccinees		Non-vaccinees	
	2048		1518		530	
Num. Patients	all levels	≥3 level	all levels	≥3 level	all levels	≥3 level
RCCEP	605 (29.5%)	18 (0.9%)	454 (29.9%)	17 (1.1%)	151 (28.5%)	23 (4.3%)
Fever	61 (3.0%)	16 (0.8%)	41 (2.7%)	15 (1.0%)	20 (3.8%)	5 (0.9%)
Leukocytopenia / Neutrocytopenia	28 (1.4%)	0 (0%)	23 (1.5)	0 (0%)	5 (0.9%)	0 (0%)
Anthema	22 (1.1%)	3 (0.1%)	19 (1.3%)	10 (1.9%)	3 (0.6%)	1 (0.2%)
Dry mouth	19 (0.9%)	0 (0%)	0 (0%)	0 (0%)	19 (3.6%)	5 (0.9%)
Pneumonia	16 (0.8%)	4 (0.2%)	14 (0.9%)	3 (0.2%)	2 (0.4%)	1 (0.2%)
Hyper/ hypothyroidism	15 (0.7%)	0 (0%)	13 (0.9%)	0 (0%)	2 (0.4%)	0 (0%)
Diarrhea	15 (0.7%)	0 (0%)	12 (0.8%)	0 (0%)	3 (0.6%)	0 (0%)
Fatigue	25 (1.2%)	1 (0.1%)	19 (1.3%)	7 (1.3%)	6 (1.1%)	2 (0.4%)
Pruritus	14 (0.7%)	0 (0%)	14 (0.9%)	0 (0%)	0 (0%)	0 (0%)
Anorexia	12 (0.6%)	0 (0%)	7 (0.5%)	0 (0%)	5 (0.9%)	0 (0%)
Colitis	7 (0.3%)	0 (0%)	4 (0.3%)	0 (0%)	3 (0.6%)	0 (0%)
Hemorrhage	7 (0.3%)	5 (0.2%)	5 (0.3%)	3 (0.2%)	2 (0.4%)	1 (0.2%)
Vomiting	6 (0.3%)	0 (0%)	2 (0.1%)	0 (0%)	4 (0.8%)	0 (0%)
Liver Dysfunction	6 (0.3%)	1 (0.05%)	2 (0.1%)	1 (0.1%)	4 (0.8%)	0 (0%)
Myocarditis	2 (0.1%)	2 (0.1%)	2 (0.1%)	2 (0.1%)	0 (0%)	0 (0%)
Severe Edema	2 (0.1%)	0 (0%)	1 (0.1%)	0 (0%)	1 (0.2%)	0 (0%)
Kidney Dysfunction	2 (0.1%)	1 (0.05%)	0 (0%)	0 (0%)	2 (0.4%)	1 (0.2%)
Others	15 (0.7%)	2 (0.1%)	6 (0.4%)	2 (0.1%)	9 (1.7%)	2 (0.3%)

RCCEP: Reactive cutaneous capillary endothelial proliferation

Supplement Table 2. Clinical characteristics and treatments for matched subgroups				
	Overall	Vaccinees	Non-vaccinees	P-value
Characteristics				
Number of patients	1060	530	530	...
Median age, years	59.0 (53.0-65.0)	59.0 (53.0-65.0)	59 (52.0-66.0)	0.855
Gender	0.268
Male	824 (77.7)	420 (79.2)	404 (76.2)	...
Female	236 (21.3)	110 (20.8)	126 (23.8)	...
ECOG	1.000
<2	616 (58.1)	308 (58.1)	308 (58.1)	...
≥2	444 (41.9)	222 (41.9)	222 (41.9)	...
History of COVID-19 infection	6 (0.6)	2 (0.4)	4 (0.8)	0.752
Number of vaccination shots	...	1049
1. Shot	...	29 (5.5)
2. Shots	...	483 (91.1)
3. Shots	...	18 (3.4)
Adverse effect of vaccination	...	128 (24.2)
Muscle pain	...	106 (20.0)
Fever	...	81 (15.3)
Pneumonia	...	2 (0.4)
Comorbidities	370 (34.9)	185 (34.9)	185 (34.9)	1.000
Hypertension	178 (16.8)	89 (16.8)	89 (16.8)	...
Diabetics	36 (3.4)	18 (3.4)	18 (3.4)	...
Heart disease	26 (2.5)	13 (2.5)	13 (2.5)	...
Cerebral infarction	22 (2.1)	11 (2.1)	11 (2.1)	...
Others	108 (10.2)	54 (10.2)	54 (10.2)	...
Cancer Types
Lung	352 (33.2)	192 (36.2)	160 (30.2)	0.043
Liver	246 (23.2)	106 (20.0)	140 (26.4)	0.016
Intestinal Tract	74 (7.0)	45 (8.5)	29 (5.5)	0.070
Urinary system	55 (5.2)	33 (6.2)	22 (4.2)	0.166
Nasopharyngeal	52 (4.9)	29 (5.5)	23 (4.3)	0.477
Others	294 (27.7)	125 (23.6)	169 (31.9)	0.003
Cancer Stages	0.726
Non-metastasis stage	8 (0.8)	3 (0.6)	5 (0.9)	...
Metastasis stage	1052 (99.2)	527 (99.4)	525 (99.1)	...
Treatments				
Therapy				
Camrelizumab (Cam)	477 (45.0)	244 (46.0)	233 (44.0)	0.537
Cam + chemotherapy	436 (41.1)	239 (45.1)	197 (37.2)	0.010
Cam + targeted therapy	131 (12.4)	40 (7.5)	91 (17.2)	<.001
Cam + radiotherapy	16 (1.3)	7 (1.3)	9 (1.7)	0.802
Immune related adverse events	345 (32.5)	211 (39.8)	134 (25.3)	...
≤ 2	284 (26.8)	179 (33.8)	105 (19.8)	<.001
≥ 3	61 (5.8)	32 (6.0)	29 (5.5)	0.792
Treatment efficacy				
Complete remission (CR)	41 (3.9)	19 (3.6)	22 (4.2)	0.751
Partial remission (PR)	246 (23.2)	115 (21.7)	131 (24.7)	0.275
Stable disease (SD)	410 (38.7)	208 (39.2)	202 (38.1)	0.753
Progression disease (PD)	363 (34.2)	188 (35.5)	175 (33.0)	0.437
Overall response rate (ORR)	287 (27.1)	134 (25.3)	153 (28.9)	0.213
Disease control rate (DCR)	697 (65.8)	342 (64.5)	355 (67.0)	0.437

Treatment pause	130 (12.3)	22 (4.2)	108 (20.4)	<.001
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