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HTLV-1 Infection as a Serious Health Issue among Iranian Multi-Transfused Patients: Evidence from a Systematic Review and Meta-Analysis

Dayyani M [1,2], Hedayati-Moghaddam MR [1]*, Amini AR [3]

1. Research Centre for HIV/AIDS, HTLV and Viral Hepatitis, Iranian Academic Centre for Education, Culture and Research (ACECR), Mashhad Branch, Mashhad, Iran.
2. Student Research Committee, Mashhad University of Medical Sciences, Mashhad, Iran.
3. Student Research Committee, Faculty of Health, Mashhad University of Medical Sciences, Mashhad, Iran.

***Corresponding Author:** Hedayati-Moghaddam MR, **Email:** drhedayati@acecr.ac.ir*

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Abstract

Background: A high prevalence of human T-cell lymphotropic virus type 1 (HTLV-1) infection among general population in the northeast of Iran has been reported. Multi-transfused patients are known as 'at-risk' group for the infection. This systematic review and meta-analysis was conducted to estimate the prevalence of HTLV-1 infection among Iranian multi-transfused patients.

Materials and Methods: Electronic databases including PubMed, Scopus, ISI, Google Scholar, ProQuest, ScienceDirect, IMEMR, IranMedex, Magiran, IranDoc, ISNet, RICeST and SID as well as grey literatures in both English and Persian were searched up to December 2013 and the related studies were critically appraised. Data were analyzed with R software version 3.1.2.

Results: A total of 551 non-duplicate and non-overlapping citations were found in primary search, of which 18 documents surveyed HTLV-1 infection prevalence among Iranian multi-transfused patients. Six non-duplicate and non-overlapping studies were added from grey literatures search. Out of these 24 documents, 16 studies conducted among 3922 patients from 14 provinces met the inclusion criteria. The HTLV-1 infection prevalence varied considerably and the highest prevalence (14.4%) was reported among hemodialysis patients from Neyshabour, Northeastern Iran. Overall estimation of HTLV-1 prevalence was 3.2% (95%CI: 2.2-4.8). The HTLV-1 infection prevalence among patients with thalassemia and hemodialysis were 4.1% (95%CI: 3.4-4.9) and 2.9% (95%CI: 0.96-8.3), respectively.

Conclusion: HTLV-1 infection prevalence among patients with frequent transfusions in Iran varies greatly in different parts of the country, but it is endemic in nearly all provinces. Therefore, the infection should be considered as a serious health problem in the whole country.

Keywords: HTLV-1 infections, multi-transfused patients, review, meta-analysis, Iran.

Introduction

Human T lymphotropic virus type 1 (HTLV-1) is a single stranded RNA retrovirus that expresses special proteins with oncogenic potential. For the first time, HTLV-1 was identified in 1980 in a patient with cutaneous T cell lymphoma and was also recognized in adult T cell leukemia (ATL) patients [1]. It is estimated that approximately 15 to 20 million people are infected with the virus worldwide [2]. HTLV-1 infection is endemic in Southwestern Japan, sub-Saharan Africa and the Caribbean region and is also frequently found in several countries in South America [2], some Islands of Oceania [3], and Northeastern Iran [4].

Although there is no symptoms showing the infection in most infected people, association of the virus with exceptionally severe diseases such as ATL and HTLV-1-associated myelopathy/tropical spastic paraparesis have been proven [5]. Moreover, HTLV-1

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is less commonly associated with a wide spectrum of inflammatory conditions and tumors such as HTLV-1 associated uveitis [6], chronic inflammatory arthropathy [7], dermatitis, polymyositis, lymphadenitis, Sjogren's syndrome [2], non-Hodgkin's T cell lymphoma [8], T-prolymorphocytic leukemia, small cell carcinoma, large granular lymphocytic leukemia [9] and B cell chronic lymphocytic leukemia [10].

HTLV-1 seropositivity can occur through the several routes which include mother to child mainly through breastfeeding; sexual intercourse; and parenteral transmission by transfusion of infected blood products or sharing of needles and syringes [11]. Almost 12% of HTLV infections occur by blood transfusion and contrary to HIV-1, whole cell transfusion is needed for transmission of the virus [12,13] with a seroconversion rate of almost 50%. Nevertheless, the risk of transmission decreases noticeably if the blood units are stored for more than one week before transfusion [14].

Patients with thalassemia, hemophilia and those undergoing hemodialysis are more at risk of HTLV-1 infection due to their need for frequent transfusions [15-17]. A study by Barton et al. [18], showed a higher seroprevalence of anti-HTLV-1 among Jamaican hemodialysis patients (9.5%) compared to an age- and gender-matched control group.

HTLV-1 infection is nearly endemic in some cities of Razavi Khorasan province, Northeast of Iran [4,19,20]. Furthermore, some studies have demonstrated a noticeable prevalence of the infection in multi-transfused patients around the country. Recently, Bidkhori et al. [21], reported a prevalence of HTLV- I infection as high as 14.6% among hemodialysis patients in Neyshabour, Northeastern Iran.

To our knowledge, there is no overall estimation of HTLV-1 infection prevalence among high risk groups in Iran. This systematic review and meta-analysis was conducted to estimate of the prevalence of this infection among Iranian patients with frequent transfusions.

Materials and Methods

Study Question

Desired outcome was the presence of HTLV-1 antibody in blood samples of the Iranian thalassemic, hemophilic and hemodialysis patients which was confirmed by western blot or PCR, until December 2013.

Search Strategy

The following phrase was used anywhere in the text for searching English electronic databases and websites: "HTLV AND Iran AND (multitransfused OR polytransfused OR frequent transfusion OR thalassaemia OR thalassemia OR thalassaemic OR thalassemic OR haemophilia OR haemophilic OR hemophilia OR hemophilic OR haemodialysis OR hemodialysis)". "HTLV" and Persian corresponding substitutes for "multitransfused", "thalassemia", "hemophilia" and "hemodialysis" in all fields, were also used for searching national databases.

Electronic Databases

Six electronic bibliographic databases and publishers of the health and biological sciences including PubMed, Scopus, Web of Knowledge (ISI), Google Scholar, Proquest and Sciencedirect were searched. Moreover, six Iranian literature databases were investigated. These included: Iranian Research Institute for Information Science and Technology (IranDoc), Iranian Database of Medical Sciences Papers (IranMedex), Iranian Database of Publication (Magiran), National Management System for Science and Technology Information (ISNet), the Regional Information Centre for Science & Technology (RICeST), and Scientific Information Database (SID).

Gray Literature Search

All Iranian Medical Universities' websites, official websites of Center for Disease Control of the Iranian Ministry of Health and the Iranian Blood Transfusion Organization, available abstract books as well as some Iranian databases such as IranDoc, RICeST, ISNet, IranMedex and SID were searched to obtain relevant research projects, dissertations, scientific reports of congresses and organization reports.

Critical Appraisal and Selection of Studies

To assess the eligibility of studies, all titles and abstracts were screened and possibly pertinent citations were reviewed completely. The inclusion criteria were all cross-sectional surveys with any sample size that reported prevalence of HTLV-1 infection in thalassemic, hemophilic and hemodialysis patients using valid measurement methods and confirmatory tests such as western blot and/ or PCR, in both English and Persian languages.

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Data Extraction

The selected and included documents were reviewed and the findings were extracted to a table. The extracted data comprised first author, year of the conduction of the study, name of province/ city, disease of the study group, sample size, kits and methods used for HTLV antibody detection, confirmatory tests, mean and standard deviation of subjects' age, percentage of male subjects and total HTLV-1 point prevalence.

Statistical Analysis

The total and sex-related point prevalence of HTLV-1 infection was recalculated according to the number of the infected cases and total observations reported in each study and if the number of cases was not stated, the reported prevalence was assumed as a desired amount. Binomial 95% confidence interval for point prevalence was computed using Epi Info software version 6.04d (CDC, Atlanta, GA) .

Meta-analysis was performed using R software version 3.1.2 (Free Software Foundation Inc., Boston, MA), by random or fixed effect model based on the results of heterogeneity test (Cochrane Q) with significance set at 0.05.

Results

Search Result

Among a total number of 662 citations found in the electronic search, 551 were non-duplicate and non-overlapping, of which 18 relevant studies had surveyed seroprevalence of HTLV-1 in Iranian multi-transfused patients (Figure 1). Three studies [22-24] were excluded due to lack of reliable confirmatory tests in their diagnostic protocols and 15 studies were included in the analysis [25-39].

In gray literature search, 25 surveys including 11 theses, 8 research reports, and 6 published conference abstracts were found. Six non-duplicate and non-overlapping studies were chosen, of which one eligible document [21] was included in the analysis. Among five remaining surveys; two were excluded due to lack of reliable confirmatory tests, one was excluded because of some methodological errors, and two were not accessible in abstract/ full text.

Studies

The total number of patients participating in these 16 studies was 3922; ranging from 80 to 868 in each study. Selected surveys have been implemented from 1994 to 2013 on patients

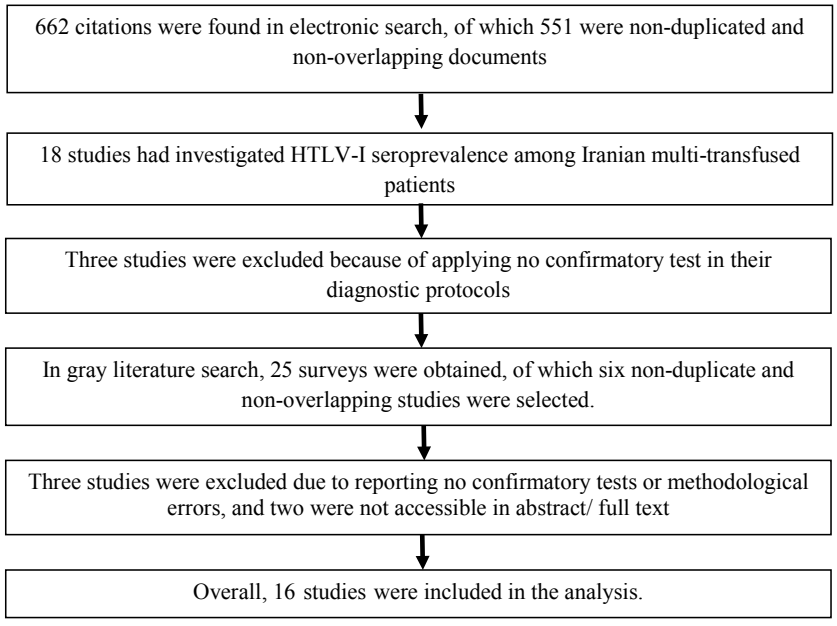

Figure 1: Flowchart of searches for selection of surveys on HTLV-1 infection prevalence among Iranian multi-transfused patients.

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Table 1: Selected studies included in the analysis.

First author	Year of study	Province	Population	Age (year)	Male Gender (%)	Sample size	Prevalence (%)	Method of detection	Kit
Karimi, A	2005	Charmahal-va-Baktiari	Thalassemia	1-45	62	250	6.8	ELISA, WB	Organon
			Hemodialysis	18-90	58	107	6.54		Gen labs
						Total: 357	Total: 6.72		
Sotoodeh, M	1994	Fars	Thalassemia	6-24	----	160	2.5	ELISA, WB	----
Abedi, F	2008	Hormozgan	Thalassemia	9-79	53.3	163	3.06	ELISA, WB,	Gen labs
			Hemophilia			40	0	PCR	Gen labs
			Hemodialysis			7	0		
						Total: 210	Total: 2.38		
Moradi, A	2005	Golestan	Thalassemia	14.1±6.5	51.4	181	4.42	ELISA, WB	DiaPro Gen labs
Pourkarim, MR	2005	Bushehr	Thalassemia	----	----	455	3.08	ELISA, WB	Organon
			Hemophilia	----	----	86	0		Gen labs
			Hemodialysis	----	----	101	0		
						Total: 642	Total: 2.18		
Ghaffari, J	2009	Mazandaran	Thalassemia	21.5±6.6	47.6	288	1.39	ELISA, PCR	DiaPro Qiagen
Ghaffari, J	2011	Mazandaran	Hemodialysis	59.1±14.7	50	160	0.63	ELISA, WB	DiaPro Gen labs
Ghadiri, K	2010	Kermanshah	Thalassemia	16.8±6.6	55.1	116	3.45	ELISA, WB	Organon Gen labs
Rostamzadeh Khameneh, Z	2005-2006	West Azarbayjan	Hemodialysis	<40, >70	50.5	95	1.05	ELISA, WB	DiaPro Gen labs
Anaraki-Mohammadi,GR	2003	Tehran	Thalassemia	18.1±1	57.7	175	6.29	ELISA, WB	Gen labs Gen labs
Moradi, A	2002	Sistan and Balouchestan	Thalassemia	8.8±4.5	57.9	190	1.58	ELISA, WB	Biorad ----
Rezvan, H	1996	Tehran	Thalassemia	----	----	632	4.59	ELISA, WB	Organon
			Hemophilia			236	2.97		DB blot
						Total: 868	Total: 4.15		
Ziaee, M	2007	South khorasan	Hemophilia	21.3±12.1	96.3	80	1.25	ELISA, RIBA	Genlabs
Bidkhori, HR	2012	Razavi Khorasan	Hemodialysis	53.4±17.8	54.9	139	14.39	ELISA, WB	DiaPro
Ardalan, N	2010	Kordestan	Thalassemia	13.3±?	57	46	2.17	ELISA, WB	DiaPro
			Hemodialysis	45.1±?	54	65	0		Gen labs
						Total: 111	Total: 0.9		
Mortezaee, Z	2007	Isfahan	Thalassemia	1-49	58.7	150	3.33	ELISA, WB	DiaPro Gen labs

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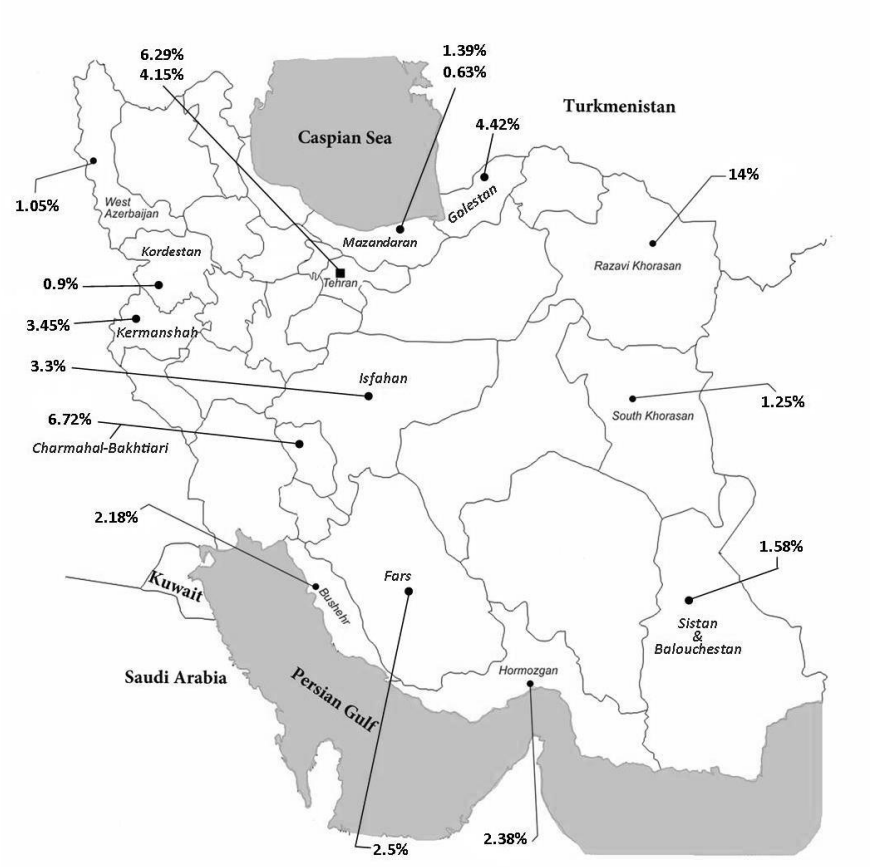

Figure 2: Geographical distribution of HTLV-1 infection among multi-transfused patients in different provinces of Iran.

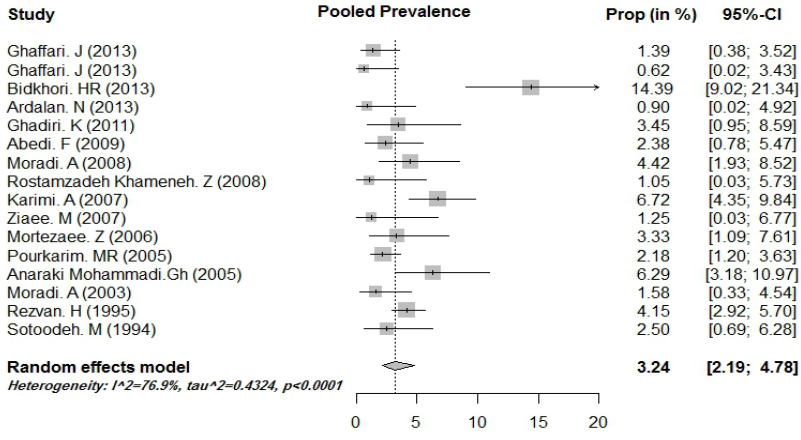

Figure 3: Forest plot of surveys on prevalence of HTLV-I infection among Iranian multi-transfused patients.

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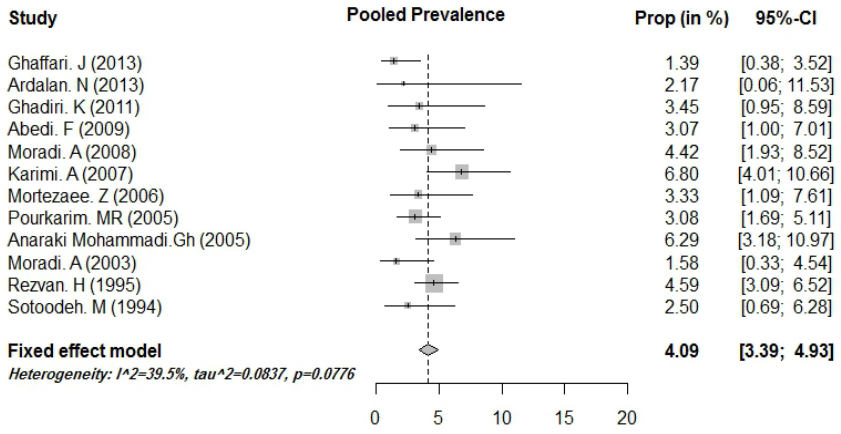

Figure 4: Forest plot of surveys on prevalence of HTLV-I infection among patients with thalassemia.

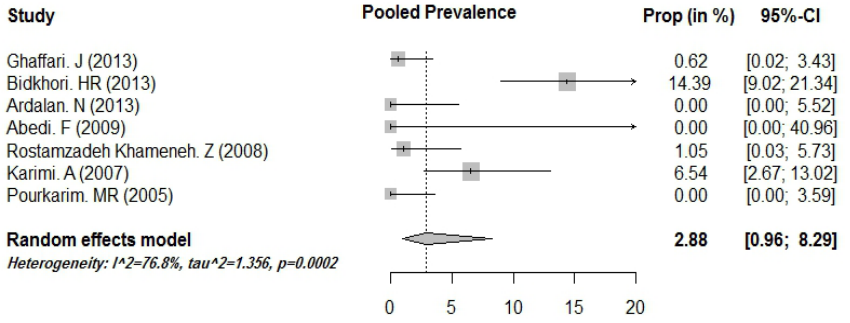

Figure 5: Forest plot of surveys on prevalence of HTLV-I infection among patients undergoing hemodialysis.

with thalassemia, hemophilia and hemodialysis (Table1.) Age of the participants was mentioned just in twelve studies and based on the studies that determined sex distribution, in average 56.3% of patients were male.

Fifteen studies had used different ELISA kits such as Diapro (seven studies), Organon (four studies), Genlab (three studies) and Bio-rad (one study) for primary screening. Three types of immunoblot kits including Genlab, DB Blot and INNO-LIA were applied by 14 studies and polymerase chain reaction (PCR) technique were used by two surveys as confirmatory tests.

HTLV-1 infection prevalence

Geographical distribution of HTLV-1 infection in Iran is demonstrated in figure 2. The highest and the lowest prevalence rates have been reported among hemodialysis patients from Neyshabour, Northeastern Iran (14.49%) and Mazandaran province in the north of Iran (0.63%), respectively. Meta-analysis revealed that overall estimation of the HTLV-1 prevalence among patients with frequent transfusions is 3.24% (95%CI: 2.19-4.78 percent) (Figure 3). After excluding the study reporting the highest prevalence 21, analysis showed that overall estimation is 3.03% (95%CI:

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2.2-4.15 percent). The corresponding forest plots for thalassemic and hemodialysis patients were separately outlined (Figures 4, 5). Based on 12 studies among thalassemic patients, the prevalence in this population was 4.09% (95%CI: 3.39-4.93%).

Moreover, a rate of 2.88% (95%CI: 0.96-8.29 percent) was achieved as overall estimation of the prevalence in hemodialysis patients.

Discussion

Northeastern Iran is one of the known endemic areas for HTLV-1 infection [4,19,20]. Thalassemic, hemophilic and hemodialysis patients are considered as high risk groups for the infection because of their need for frequent transfusions. This systematic review revealed that geographical distribution of HTLV-1 infection in Iranian multi-transfused patients is different. The prevalence of the virus among multi-transfused patients in almost all of the provinces is higher than 1%, which is considered as endemic level. Remarkably, in three provinces of Razavi Khorasan, Chaharmahal-Bakhtiari and Tehran, the prevalence rate was higher than 5%. These substantial discrepancies were also observed among blood donors from different provinces of the country in our previous study [40]. Overall estimation of HTLV-1 prevalence rate in the whole multi-transfused patients was 3.2% (95% CI, 2.2-4.8%). This rate is nearly equal to the prevalence of infection in Neyshabour city with a rate of 3.4% (95% CI, 2.4–4.7), the utmost rate among general population in Iran [41]. In addition, there was a small difference in the prevalence between thalassemic and hemodialysis patients that probably can be attributed to the different procedure of transfusion and different types of blood products in these two diseases.

HTLV-1 infection rates are significantly higher among poly-transfused patients in countries with a high prevalence in the general population or blood donors. For instance, Barton et al[18], have reported the prevalence of infection as high as 9.5% among hemodialysis patients in Jamaica where 6.1% of general population and 2% of blood donors have been reported to show seropositivity for the virus. On the other hand, there is no robust evidence on HTLV-1 infection among patients with frequent transfusion in countries with a low frequency of the infection in the general population or volunteers of blood donation. In a multi-center study in Italy [42], prevalence rate of the infection among 14000 blood donors from different cities of the country was 0.03%. More surprisigly, there was no report on the infection from centers of two thalassemia endemic areas and the same results were found among hemophilic and hemodialysis patients of Millan. Correspondingly, none of hemophiliacs in Italy were anti-HTLV-1/2 positive, even though, 63.1% showed reactivity for HIV antibodies [43]. Another study in Germany demonstrated no positive case for either HTLV-1 or HTLV-2 infection among blood donors, hemophilic patients and injection drug users [44]. A study on Lebanese blood donors and multi-transfused patients, reported no seroreactivity for anti-HTLV antibodies [45]. Similar findings have been reported in a large study on blood recipients in London where only one infected blood unit out of 5939 recipients was detected [46]. Similarly, the prevalence among blood donors from London was reported to be 0.005 percent [46]. Furthermore, a survey by Mojaat et al. [47], showed that the prevalence rate of the infection among Tunisian hemodialysis patients is low (0.4%) and there was no positive sample among blood donors and thalassemic patients, however; prevalence of HBV and HCV among hemodialysis patients was 8% and 45.1%, respectively.

Conclusion

HTLV-1 infection prevalence among patients with frequent transfusions in Iran varies greatly in different parts of the country, but it is endemic in nearly all of provinces. Therefore, the infection should be addressed as a serious health problem in the whole country.

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