REVIEW PAPER

HIV/HTLV-1 co-infection: a systematic review of current evidence

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Abstract

Human T-cell leukemia/lymphoma virus type 1 (HTLV-1) infection is associated with myelopathy/tropical spastic paraparesis (HAM/TSP) and adult T cell leukemia/lymphoma (ATLL), which is a malignancy of mature T lymphocytes. HTLV-2 pathogenesis for humans remains undefined. As they share the same transmission routes, co-infection with human immunodeficiency virus (HIV) and HTLV-1 are often reported among the world, mainly among patients living in highly endemic areas like South America and sub-Saharan Africa. Nevertheless, many clinicians are not aware of the potential risks of co-infection with HTLV-1 when treating an HIV patient. Since both viruses infect CD4+ T lymphocytes, scientists have investigated interactions at the cellular and molecular levels, clinical associations, and related complications. Studies have shown that co-infection with HTLV-1 resulted in an increased CD4+ T lymphocyte count, which might be mistaken for immune compatibility, and lead to a delay in the establishment of antiretroviral therapy (ART) in HIV-positive patients. Some authors have observed that co-infection with HTLV-1/HIV-1 can lead to an acceleration of AIDS progression and lessening survival times. Even so, conflicting results and controversies have been reported. These conflicts highlight the requirement of further studies to provide valuable information within this area. In this systematic review, we summarize the current evidence on the co-infection with HTLV-1 among HIV-positive patients, its associated complications, and the impact on progression of AIDS.

HIV AIDS Rev 2021; 20, 3: 158-165
DOI: https://doi.org/10.5114/hivar.2021.108835

Key words: HIV, AIDS, HTLV, human T cell lymphotropic virus, co-infection.

Introduction

Human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2), a family of retroviruses, are the causative agents of acquired immunodeficiency syndrome (AIDS). HIV-1 is the more common cause worldwide, while HIV-2 is less pathogenic, but mostly prevalent in West Africa [1-4]. Human T cell leukemia/lymphoma viruses (HTLV) comprise of two types: type 1 (HTLV-1) and type 2 (HTLV-2), retroviral infections [1]. Research suggests that HTLV-1/2 causes proliferation of infected T cells [2].

HTLV-1 infection is associated with myelopathy/tropical spastic paraparesis (HAM/TSP) and adult T cell leukemia/

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Article history:
Received: 10.11.2020
Received in revised form: 21.11.2020
Accepted: 22.11.2020
Available online: 30.08.2021

International Journal of HIV-Related Problems
HIV & AIDS Review

lymphoma (ATLL) [1], which is a malignancy of mature T lymphocytes [2]. HTLV-2 pathogenesis for humans remains undefined [5]. HTLV-1 and HTLV-2 are common co-pathogens related to HIV infection [6]. Interactions between both HTLV-1 and HTLV-2 are reported among people living with HIV (PLWH), affecting clinical progressions of the disease. Moreover, HIV can alter clinical manifestations associated with HTLV-1 infection [7, 8].

The routes of transmission of HTLV and HIV are the same, including parenteral, vertical, and sexual. Also, both of these viruses have a tropism for T cells [1]. HIV can be transmitted more efficiently than HTLV [2]. However, infected individuals with diseases associated with HTLV-1 are asymptomatic and response poorly to therapy; therefore, their prognoses are mostly deadly [9]. CD4+ T lymphocytes are the target of HIV and HTLV-1 through various cell-surface receptors [10].

HTLV-1 co-infection among PLWH accelerates CD4+ T lymphocyte proliferation, and prompts higher expression of markers activation and a serious lack of naive cells, which could lead to a rapid development of AIDS [8]. According to some studies, HIV/HTLV co-infection may change the course of AIDS, including clinical and laboratory patterns. Nevertheless, the effects of co-infection on clinical findings of AIDS patients are poorly understood [1, 5]. In a study, double HTLV-1/HIV-1 infection caused a faster progression of AIDS and shorter survival times [7]. However, it is suggested that co-infection with HIV-1/HTLV-2 decreases HIV-1 replication [11], leading to a delay of AIDS progression and death [7].

HTLV-1 co-infection among PLWH is identified mainly among individuals with high-risk behaviors and living in highly endemic areas [12]. Based on regional studies, the prevalence of HTLV-1 and HIV-1 is reported at different rates worldwide [2]. This systematic review focuses on the HTLV-1 co-infection among HIV-positive patients in recently published data.

Material and methods

This study was a systematic review conducted in 2020 to explore the current evidence on HIV/HTLV-1 co-infection. A systematic search was carried out in Cochrane database systematic reviews, Google Scholar, PubMed, Scopus, Embase, and Web of Science. A literature search was conducted using the following keywords: "HIV", "AIDS", "HTLV", and "human T cell lymphotropic virus".

English written, peer-reviewed original papers, abstracts, reports, and letters to editor published from May 2010 to May 2020 were considered. Non-English articles, ongoing projects, review articles, which included ongoing studies, and papers addressing non-human studies, or discussing HIV infection in general, without reference to co-infection with HTLV-1, were all excluded. Registration of systematic review protocol was removed due to expected limited availability of data and need of the topic.

The title and abstract of each article were evaluated, and the most relevant articles were chosen based on previously mentioned inclusion and exclusion criteria. To ensure the quality of selected articles, a checklist (Table 1) with 15 items was developed based on relevant studies [13-15]. The quality of articles was evaluated by two independent researchers and rated on a three-point scale, with "low quality" (0-5), "medium quality" (6-10), and "high quality" (11-15) papers. Full texts of selected articles were then thoroughly read in order to extract essential findings.

Table 1. Quality assessment checklist

No.	Question
1	Does the study address any research question(s) or objective(s)?
2	Does the study provide any theoretical framework for evaluation method?
3	Does the theoretical framework of the study include any health promotion theory?
4	Does the study provide a time frame for data collection?
5	Does the study identify the country where it was conducted?
6	Does the study mention if the reviewed current co-infections were downloaded for evaluation?
7	Does the study discuss selection criteria for the current co-infections to be included or excluded in a review?
8	Does the study provide a clear description of evaluation method?
9	Are there at least two independent data extractors, with a consensus procedure in case of disagreement?
10	Does the study provide a list of the review of current co-infections?
11	Does the study discuss findings form the evaluation?
12	Does the study consider the reviewed HIV/HTLV-1 co-infection to promote or enable behavioral change?
13	Does the study discuss any limitations?
14	Does the study provide any future recommendations in general?
15	Does the study state any conflict of interest?

Results

Using the applied search strategies, 915 sources were identified and retrieved.

General specifications

After initial evaluation of the retrieved articles, 194 duplicates were removed, and titles and abstracts of the remaining 615 articles were reviewed. Applying the selection criteria, 584 articles were excluded, and only 31 papers that fulfilled inclusion criteria were used in the final analysis (Figure 1). These 31 studies were published from 2011 to 2020. The mean quality score of the selected articles was 13 (range, 11-15), indicating high quality of these articles. All the articles provided original data, except for review articles and meta-analyses, which prevented omitting information on HIV and HTLV-1 co-infection.

The studies examined associations between HIV and HTLV-1 as well as its impact on conditions, such as mortality, AIDS progression, and a variety of infectious disorders, including tuberculosis, strongyloidiasis, and pneumonia. The summary of the studies' findings are illustrated in Table 2.

Discussion

Previous studies had proven that this issue is of utmost importance, especially in key populations that are at higher risks of developing HIV/HTLV-1 co-infections. The rate of co-infection with HTLV-1 among PLWH was found to be 5.4% in French Guiana [36]. Co-infection rates were reported at 3.9% and 1.2% in Mozambique and Indonesia, respectively [25, 44]. Additionally, a Brazilian group of scientists found equal rates of HTLV-1 and HTLV-2 co-infections among PLWH [30].

Various studies found that people with substance use disorder, having concurrent HBV and HCV infections, men who have sex with other men (MSM) and bisexuals, individuals of black or Pardo origins as well as those with previous minor surgery and blood transfusions, tend to have higher rates of HIV/HTLV-1 co-infection [12, 21, 30, 33, 36]. In terms of gender, two studies observed females as those having higher rates of a co-infection [30, 36], while the opposite was observed in another research [33]. Younger patients were found to have higher co-infection rates [12], while another research found that individuals above 40 years of age presented higher chances of co-infection [36].

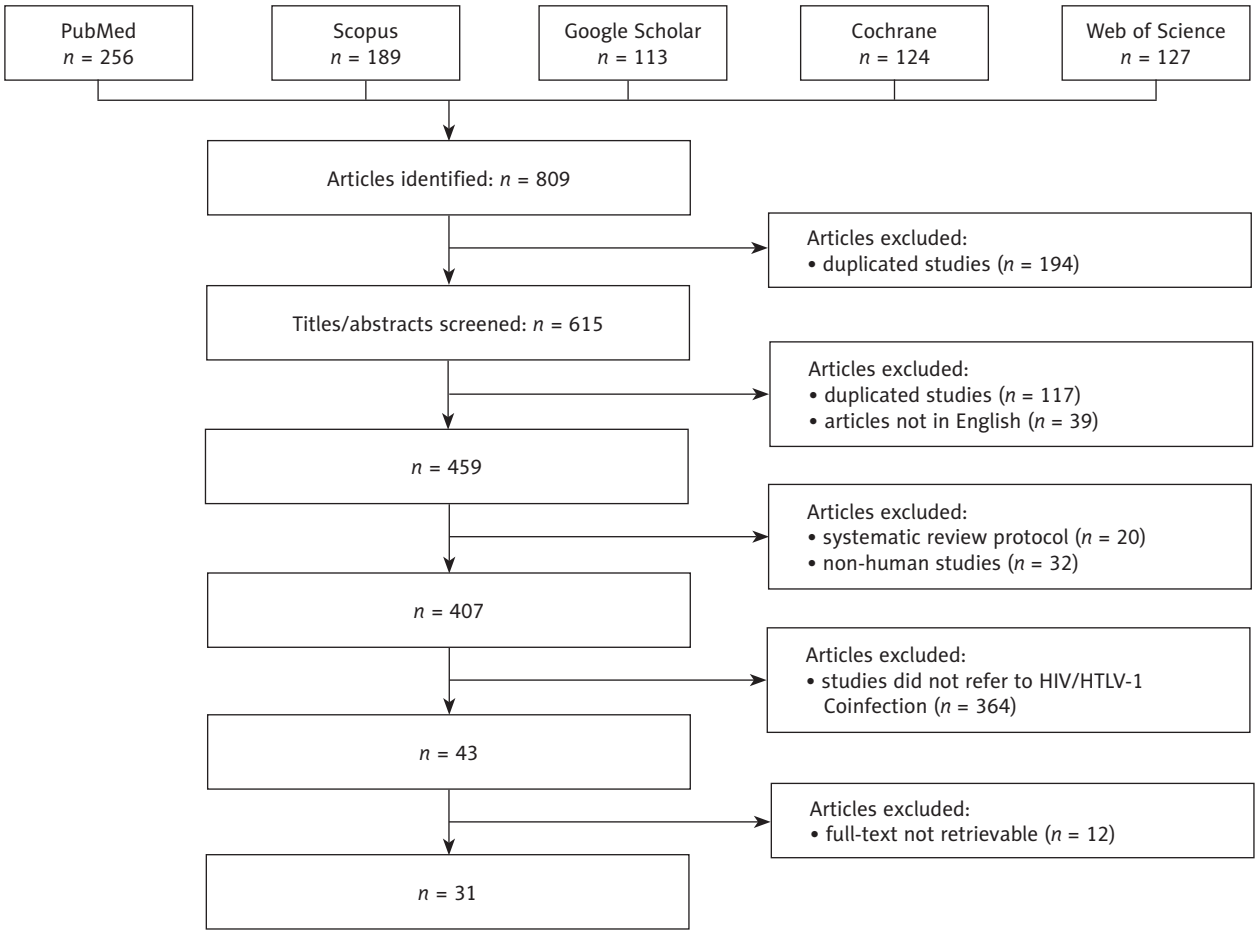

Figure 1. PRISMA flow diagram of selection process of the identified articles

Table 2. Identified evidence on HIV/HTLV-1 co-infection

First author [reference]	Type of study	Country	Population	Results
Geddes [16]	–	Brazil	*In vitro*	HTLV-1[1]/Tax hijacks cellular partners, promoting HIV-1 transcription.
Cucca [17]	Case report	Italy	1 co-infected	Acute myelitis as presenting symptom of HIV-HTLV-1 co-infection.
Ribeiro [18]	Cross-sectional	Brazil	720 (11 co-infected)	CD4+ count was higher in co-infected patients than mono-HIV-infected. Median of first HIV viral load was higher in mono-infected patients.
Laher [19]	Case report	South Africa	1 co-infected	Severe/refractory hypercalcemia in an adult patient with ATLL[2] and HTLV-1/HIV-1 co-infection.
Abrahão [20]	–	Brazil	*In vitro*	Higher production of Th 1 cytokines in HIV/ HTLV co-infected.
De Oliveira [21]	Cross-sectional	Brazil	13 co-infected	Minor surgery (removal of small skin tumors, warts, cysts, or foreign bodies) and blood transfusions were significantly associated with HIV-1 and HTLV-1/2 co-infections (p = 0.004). No association found between co-infection and HIV-1 viral load or CD4+ T lymphocyte levels.
Assone [22]	Cohort	Brazil	273 HTLV-1 cases (29 co-infected)	No significant increase of basal T cell proliferation among HTLV-1 co-infected individuals found.
Rockwood [23]	Case report	England	1 co-infected	Paradoxical resolution of CD4+ T cell lymphocytosis in a co-infected patient, following introduction of Cart[3] and suppression of HIV-1 plasma viremia. A decrease in HTLV-1 proviral load.
Nasreddine [24]	Case report	Belgium	1 co-infected	Viral load more than 200 copies/ml while receiving ART. CD4+ T cell count of 21,000/μl. Diagnosed with ATLL (adult T cell leukemia/lymphoma), HTLV-1-positive.
Prasetyo [25]	Cross-sectional	Indonesia	46 HIV cases (8 co-infected)	Co-infection prevalence of 1.2%.
Isache [26]	Case report and review	USA	1 co-infected	Case of tropical spastic paraparesis in an HIV-positive patient who did not report any history of travel or residence in an HTLV endemic area.
Richey [27]	Case report	USA	1 co-infected	Increase in WBC and absolute CD4 counts as well as CD4 : CD8 ratio.
Brites [28]	Nested, retrospective case-control study	Brazil	298 in two groups of co-infected (149) and HIV-infected (149)	Higher initial CD4+ count (417 ± 219 cells) in co-infected than in singly-infected patients, with the same outcome (177 ± 160 cells; p = 0.004). Singly-infected patients had last CD4 : CD8 ratio significantly higher than co-infected. Shorter survival time for co-infected patients with detectable HIV viremia, but not for patients on stable and suppressive ART. Mortality rate of 2.1 person-year was reported (76 deaths, 53 among co-infected patients). Survival time for cases (16.7 ± 0.7 years) was significantly shorter than for controls (18.1 ± 0.4 years; p = 0.001).
Kozlowski [29]	Cross-sectional	Brazil	505 HIV cases (4 co-infected)	Similar CD4+ T counts between HTLV-1/HIV-1 co-infected and HIV-1 mono-infected patients.

Table 2. Cont.

First author [reference]	Type of study	Country	Population	Results
Caterino-de-Araujo [30]	Cross-sectional	Brazil	1,608 HIV cases (25 co-infected)	Risk factors associated with co-infection included females, black/Pardo origin, IDU, and hepatitis B (HBV) and hepatitis C viruses (HCV). Equal distribution of HTLV-1 and HTLV-2 in HIV co-infected patients.
Rahimi [31]	Case-control	Iran	6 HIV/ HTLV-infected	High HIV viral load in co-infected patients. Lower HTLV-1 proviral load in co-infected patients (222.33 ± 82.56) was found, while in HTLV-1-infected patients, it was 373.6 ± 143.3, with $p < 0.05$. Higher CD4+ count in HTLV-1-infected (659.9 ± 110.7) and co-infected patients (431.43 ± 120) was observed than in HIV-infected group (414 ± 97.5); not statistically significant.
Bahia [32]	Cross-sectional	Brazil	39 triply-co-infected with HIV, HCV, and HTLV-1	Median ALT was significantly ($p = 0.05$) higher among HIV/HCV co-infected group (71 IU/ml; IQR, 39-107), whereas in HIV/HCV/HTLV-1 triply-co-infected group, it was 48 IU/ml, with IQR of 33-90.
Moreira [33]	Case-control	Brazil	38 co-infected	Co-infected (HIV/HTLV) group predominantly consisted of males ($p = 0.001$, Yates corrected). Use of illicit drugs, homo-bisexual cases ($p = 0.001$, Yates corrected). HBs Ag was higher in patients with co-infection (OR = 22.03; 95% CI: 2.69-469.7%) as well as in cases with confirmed HCV infection ($p = 0.001$). Concomitant HCV and HBV infections were associated with co-infection. Patients infected with HTLV-1 had a lower chance of detectable HCV viremia (OR = 0.04; 95% CI: 0.002-0.85).
Mazanderani [34]	Case report	South Africa	1 co-infected	HIV/HTLV-1 co-infected patient was found with progressive immune deficiency associated with a raised CD4+ count.
Janssen [35]	Case report	The Netherlands	1 co-infected	HIV patient presented with hemoptysis, weight loss, fulminant diarrhea, subsequent ileus, and elevated CD4+ T cell counts. He was diagnosed with *Strongyloides stercoralis* HTLV-1 infection.
Gouhier [36]	Retrospective comparative study	French Guiana	79 co-infected	Higher age (average, 7 years old; $p < 0.0001$) among co-infected individuals. Higher viral load in patients on treatment and CD4+ counts at the time of diagnosis among co-infected individuals. HTLV-1/HIV co-infection prevalence rate of 5.39%. Higher rates among females, subjects > 40 years of age, and patients of Surinamese origin.
Silva [37]	Cohort	Brazil	47 co-infected	Neurological adverse outcomes were more frequent among co-infected individuals (OR = 8.73). Co-infection was associated with myelopathy (χ^2 U 93, $p < 0.001$), peripheral neuropathy (χ^2 U = 6.5; PU = 0.01), and hepatitis C virus (χ^2 U = 36.5; $p < 0.001$). ART did not protect against neurological diseases and had no impact on HTLV-1 proviral load.
Ramezani [38]	Case-control	Iran	–	Prevalence of co-infection with HTLV-1 in HIV-positive patients was zero.

Table 2. Cont.

First author [reference]	Type of study	Country	Population	Results
Gudo [39]	Cross-sectional	Brazil	32 co-infected	No association between HIV clinical stage and HTLV-1 status by univariate (p = 0.099) was found. Co-infected individuals had higher total leukocyte counts (median, 5.59 vs. 4.63; 10^3 cells/mm^3; p = 0.01; OR = 1.32) and higher total lymphocyte count (median, 2.01 vs. 1.72; 10^3 cells/ mm^3; p = 0.010; OR = 0.28). Higher absolute CD4þ counts (median, 533 vs. 311 cells/ mm^3; p = 0.001; OR = 1.06) and lower relative CD8þ percentage (48.68% vs. 51.31%; p = 0.015; OR = 1.06). Co-infection was more prevalent in patients with higher CD4+ counts.
Pedroso [40]	Case-control	Brazil	63 co-infected	Co-infected patients had shorter mean survival (1,849 days) than controls (2,430 days; p = 0.001), regardless of sex or baseline CD4+ cell count.
Brites [41]	Case-control	Brazil	26 co-infected	Co-infection was associated with intravenous drug use (IVDU). Patients in co-infected group had higher absolute lymphocyte counts (1,921 ± 762 vs. 1,587 ± 951; p = 0.03). In AIDS patients, CD4+ cell counts were significantly higher among those co-infected with HTLV-1/2 (p = 0.36). Utilization of antiretroviral drugs was more frequent among HIV-1 mono-infected patients (64.3%) compared to HTLV-1/2 co-infected cases (42.3%), with p = 0.04 (Yates corrected). Strongyloidiasis was diagnosed more in co-infected patients (OR = 8.55; 95% CI: 1.21-73.62; p = 0.02, Fisher exact test).
Bessong [42]	Cross-sectional	South Africa	41 co-infected (24.1%)	–
de Almeida Rego [43]	Cross-sectional	Brazil	4 co-infected	Similar CD4+ and CD8 T cell counts, viral load, and clinical manifestations.
Manhiça [44]	Cross-sectional	Mozambique	37 co-infected	Prevalence of co-infection of 3.9%.
de Mendoza [12]	Cross-sectional	Spain	369 HTLV-1-infected (3.2% of co-infected)	HIV/HTLV-1 co-infected patients were more frequent among younger people, men having sex with other men, and presented more frequently with AIDS compared to HTLV-1 mono-infected individuals.
Brites [28]	Nested, retrospective case-control study	Brazil	298 in two groups of co-infected (149) and HIV-infected (149)	Higher initial CD4+ count (417 ± 219 cells) in co-infected than in mono-infected patients with the same outcome (177 ± 160 cells; p = 0.004). Mono-infected patients had last CD4:CD8 ratio significantly higher than co-infected patients. Shorter survival time for co-infected patients with detectable HIV viremia, but not for patients on stable, suppressive ART. Mortality rate of 2.1 person-year (76 deaths, 53 among co-infected patients) was found. Survival time for cases (16.7 ± 0.7 years) was significantly shorter than for controls (18.1 ± 0.4 years; p = 0.001).

[1]HTLV-1 – human T cell lymphotropic virus type 1, [2]ATLL – adult T cell leukemia-lymphoma, [3]ART – antiretroviral therapy

Several previous review articles reached a hypothesis that an artificial increase in CD4+ counts was observable in HIV/HTLV-1 co-infection. Moreover, in that studies, higher count did not necessarily define a more robust immune system, and co-infected individuals with higher than 200 cells/µl CD4 counts were more prone to developing opportunistic infections than mono-infected PLWH [5, 45-49]. However, in our selected articles, this issue is under a debate. More studies claim that CD4+ count increases in co-infected individuals [18, 27, 29, 31, 36, 39, 41]. Nevertheless, some research reported similar CD4+ counts in co-infected and mono-infected patients [21, 22, 29, 43]. One study reported an elevated initial CD4+ count in co-infected patients while observing a decreased CD4 : CD8 ratio in the last test [28].

Inconsistent results were also seen in terms of viral load. Concurrently, several studies reported higher HIV viral load in co-infected individuals than in mono-infected patients [31, 36], while others declared no significant difference between these two groups [21, 43]. To make matters even more complicated, a research concluded that co-infected individuals demonstrate lower viral loads than patients infected with HIV only [18].

The inclusive nature of the results is even extended to differences in morbidities and clinical course of the disease. In the settings of clinical manifestations and morbidity, co-infection was associated with an increased risk of neurological complications, particularly myelopathy and peripheral neuropathy. Additionally, antiretroviral therapy (ART) did not alter the observed neurological manifestations [37]. More importantly, lower rates of receiving ART were recorded among either HTLV-1 or HTLV-2 co-infected individuals compared to those with HIV only, with 42.3% and 64.3%, respectively [41]. Nevertheless, this decrease in receiving ART might be due to possible higher levels of CD4+ cells in co-infected people, which might be minimized by using ART in all PLWH. Co-infected individuals were also more prone to strongyloidiasis infection [41]. Moreover, three case reports demonstrated acute myelitis, severe refractory hypercalcemia, and tropical spastic paraparesis in three HIV/HTLV-1 co-infected patients [17, 19, 26].

On the other hand, in an article, HCV viremia was found lower in co-infected group [33]. HTLV-1/Tax protein promoting the transcription of HIV-1 as a result of hijacking the cellular partners was proposed as a mechanism for the differences [16]. Contrarily, two studies reported similar clinical manifestations in co-infected individuals and other mono-infected patients [39, 43]. In yet another paper, a reduced mean survival in co-infected patients compared to HIV-infected only was demonstrated [28]. However, an investigation observed this exclusively for patients with detectable HIV viremia, and reported similar survival rates in stable co-infected individuals receiving a combination of ART, with mortality rate reported at 2.1 person per year [28]. Moreover, other study reported an increased mortality rate to be unrelated to gender and CD4+ count [40].

Conclusions

HIV/HTLV-1 co-infection is a matter of great importance, especially among key populations and endemic HTLV-1 regions. Moreover, extensive debates and disagreements are surrounding this issue. Therefore, careful studies are needed to provide priceless information in this field to fade the controversies and improve the treatment and management of co-infected patients.

Acknowledgments

This systematic review was extracted from research project with grant no. 98-02-55-43568 and ethical code IR.TUMS.VCR.REC.1398.845, supported by Tehran University of Medical Sciences.

Conflict of interest

The authors have no conflict of interest.

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