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Review Paper

Seroprevalence of Bovine Herpesvirus Type 1 Among the Cattle Population in Iran: A Systematic Review and Meta-Analysis

Masoud Hassani[1*], **Farhid Hemmatzadeh**[2]

1. Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran.
2. School of Animal and Veterinary Sciences, The University of Adelaide, Adelaide, Australia.

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ABSTRACT

Bovine herpesvirus type 1 (BHV-1) is the causative agent of several clinical manifestations, including infectious bovine rhinotracheitis, infectious pustular vulvovaginitis/balanoposthitis, conjunctivitis, encephalitis, abortion, infertility, mastitis, enteritis, dermatitis, and the systemic form of the infection in newborn calves. Although many investigations regarding the prevalence of BHV-1 infection in cattle in Iran have been conducted, until now there has been a lack of comprehensive information on the BHV-1 status in Iran. We aimed to present the seroprevalence of BHV-1 in the cattle population in Iran based on a systematic review and meta-analysis study and also to give useful outputs in formulating the infection-control strategies. The meta-analysis study was conducted using national and international databases to find articles which evaluated BHV-1 seroprevalence by antibody-capture enzyme linked immono sorbert assay (ELISA) in cattle in Iran by searching terms including Bovine herpesvirus type 1, cow, cattle, bovine, Iran, epidemiology, and prevalence alone or in combination in both English and Farsi languages. After reviewing 124 published documents, a total of 25 studies from 20 documents were eligible to be included in this meta-analysis study. The analysis was performed using the Comprehensive Meta-Analysis software, VERSION 3. The total seroprevalence of BHV-1 in apparently healthy cattle at the animal and herd levels based on the ELISA test was 40.2% (95% CI, 32.3%, 48.6%) and 75.5% (95% CI, 63.9%, 84.2%), respectively. A well-defined control strategy for preventing and controlling BHV-1 infection in Iran should be based on further studies on BHV-1 epidemiology, control of animal and semen importation, the use of marker vaccines, and planned biosecurity measures to control the epidemiological risk of infection due to the presence of BHV-1 latent carriers.

*** Corresponding Author:**
Masoud Hassani
Address: *Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran.*
Tel: *+98 (918) 3186977*
E-mail: *Masoud.Hassani@ut.ac.ir*

1. Context

Bovine herpesvirus type 1 (BHV-1) is an enveloped DNA virus, a member of the genus *Varicellovirus* in the subfamily Alphaherpesvirinae, which belongs to the Herpesviridae family in the order Herpesvirales. Based on genomic analyses and viral peptide patterns, four different serotypes of BHV-1 have been characterized, of which the respiratory subtype BHV-1.1 is associated with respiratory disease, subtypes BHV-1.2a and BHV-1.2b are related to genital disease, and BHV-1.3 is related to neurological disorders and has been reclassified as three genotypes, BHV-5a, BHV-5b, and BHV-5non-a/non-b [1-3].

The virus is the cause of multiple clinical signs in cattle populations worldwide; however, other *Artiodactyla* may be infected with BHV-1 and show clinical signs [4].

The disease associated with BHV-1 is an OIE-listed B disease and may show several clinical manifestations, including inflammatory reactions in both respiratory (Infectious Bovine Rhinotracheitis) and genital tracts (infectious pustular vulvovaginitis/balanoposthitis), conjunctivitis, encephalitis, abortion, infertility, mastitis, enteritis, and dermatitis. Also, the systemic form of the infection affecting visceral organs may develop in newborn calves [5-7]. When the disease occurs in unvaccinated dairy cattle, the incidence of the morbidity and case-fatality rates is 8% and 3%, respectively, but morbidity and mortality are higher in feedlot cattle [8].

The infection is mainly transmitted via nasal exudate and coughed-up droplets, ocular and genital secretions, fresh or frozen semen, as well as contaminated equipment and fetal fluids and tissues [9, 10].

The BHV-1 virus is able to establish lifelong latency after a primary infection with a field isolate or vaccination with a weakened strain, and stressful conditions such as transportation, parturition, and glucocorticoid therapy may lead to reactivation and shedding of the virus, complicating control and eradication strategies [11, 12].

In Iran, BHV-1 was for the first time reported between 1964 and 1968 based on clinical observations and serology [13]. In 1973-1975 BHV-1 was isolated from nasal secretions of imported cows with acute respiratory disease [14]. Since then, BHV-1 infection has been reported from several provinces and union territories of the country. As reports are available from different provinces at different time periods, unified data on the status of BHV-1 infection in Iran are missing. To address this critical knowledge gap, a systematic review and meta-analysis was conducted to determine the seroprevalence of BHV-1 infection in the cattle population of Iran and also to give useful outputs in formulating infection-control strategies.

2. Data Acquisition

2.1. Database search

For gathering information, articles regarding seroprevalence of bovine herpesvirus type 1 in apparently healthy cattle in Iran based on antibody-capture enzyme linked immono sorbert assay (ELISA) tests in both English and Farsi languages were searched in nine databases. These included: Five English databases (PubMed, Google Scholar, ScienceDirect, Web of Science, and Scopus) and four Persian databases (Magiran, Irandoc, and the Scientifc Information Database [SID]) for the articles published prior to November 2023. We also checked dissertations and all abstract books of scientific conferences in Iran from 2000 to 2023. In order to avoid missing any articles, the citations of the included articles were reviewed to seek out other relevant studies. The searched terms were: “Bovine herpesvirus type 1”, “cow”, “cattle”, “bovine”, “Iran”, “epidemiology”, and “prevalence” alone or combined with “OR” and/or “AND”.

2.2. Data collection

Figure 1 shows the items used for the meta-analysis study (preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews [PRISMA]) process. After screening the titles and abstracts of articles identified by the initial search, those that describe the seroprevalence of BHV-1 by antibody-capture ELISA in apparently healthy cattle (cattle of all ages, irrespective of their breed) in Iran were considered for the study. Studies with other purposes, such as those with other animal species as target populations, those evaluating the molecular characteristics of the isolated virus, and studies detecting the virus or antibody in milk, semen, or aborted fetuses, were excluded. In the next step, for quality assessment of eligible studies, the strengthening the reporting of observational studies in epidemiology (STROBE) checklist was used. For each study, the following data were extracted: First author’s name, publication date, location of study, sample size, number of positive, study type, herd type, age of samples, and BHV-1 vaccination. Then the studies were grouped based on the animal level, i.e. individual and herd (Table 1).

2.3. Statistical analysis

We estimated the pooled seroprevalence of Bovine herpesvirus type 1 in cattle using either the fixed-effects or random-effects model with a 95% confidence interval (CI) and a significant level of 5%, and the results are displayed using a forest plot accumulation chart. Heterogeneity among the included studies was assessed using Cochran's heterogeneity statistic (Q-test) and I^2 statistic. Egger's regression test was used to evaluate possible publication bias. The analysis was done using Comprehensive Meta-Analysis software, version 3.

3. Results

As presented in Figure 1, initially, a total of 124 documents were collected. In secondary screening, based on title and abstract, 41 duplications were removed and 83 remained for full-text review. Of those, 34 documents were excluded based on title and abstract, and 29 documents were excluded based on the selection criteria. Finally, a total of 25 studies from 20 documents were eligible to be included in this meta-analysis study (Table 1). Based on our analysis, evidence of publication bias was not observed (P=0.295) (Figure 2).

The provinces where seroprevalence of BHV-1 among cattle in Iran was studied, are shown in Figure 3. The total seroprevalence of BHV-1 in apparently healthy cattle at the animal level, based on an antibody-capture ELISA test, was reported in 25 studies. Our study included a total of 10,151 cattle, and the overall prevalence of BHV-1, based on the random-effects model (I^2=98.2, Q test P=0.00), was 40.2% (95% CI, 32.3%, 48.6%) (Figure 4). Also, the total prevalence of BHV-1 infection at the herd level was reported in 12 studies and 288 herds, and the overall prevalence, based on the random-effects model (I^2=61.56, Q test P=0.00), was 75.5% (95% CI, 63.9%, 84.2%) (Figure 5).

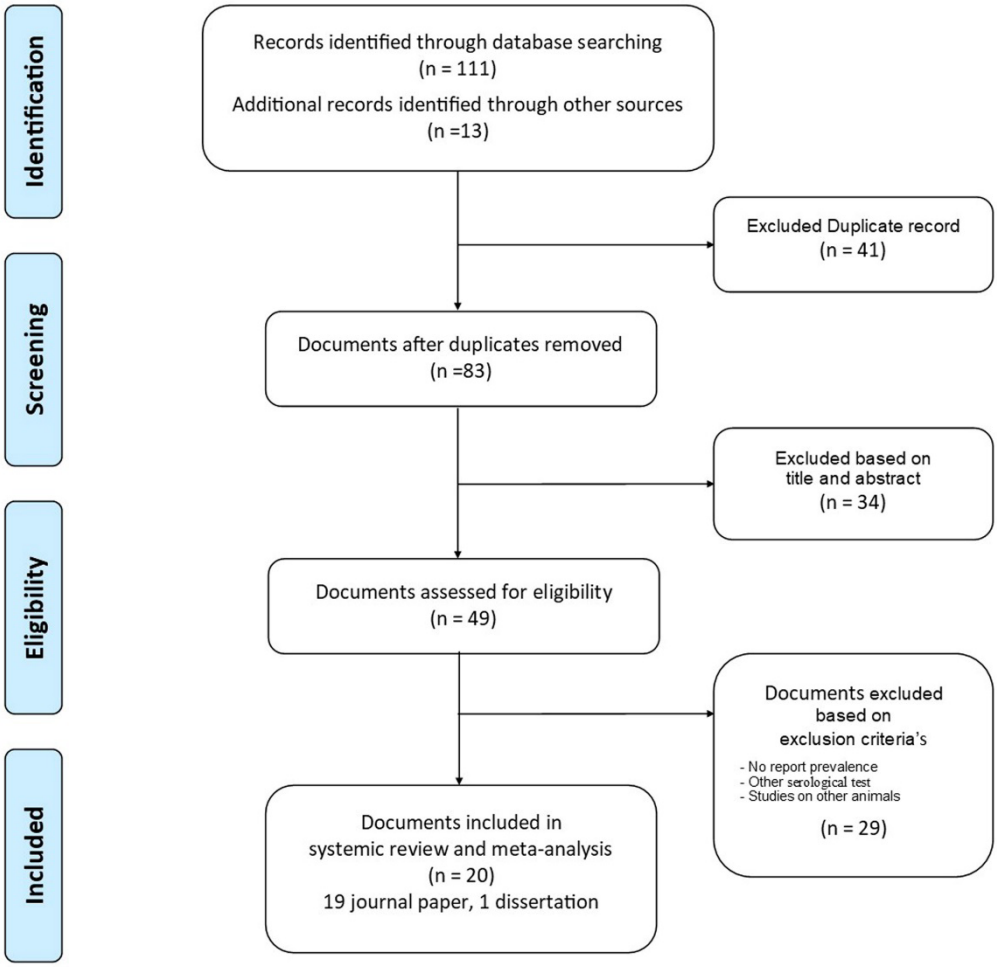

Figure 1. PRISMA (preferred reporting items for systematic reviews and meta-analyses) flow diagram illustrating the selection process of included and excluded records

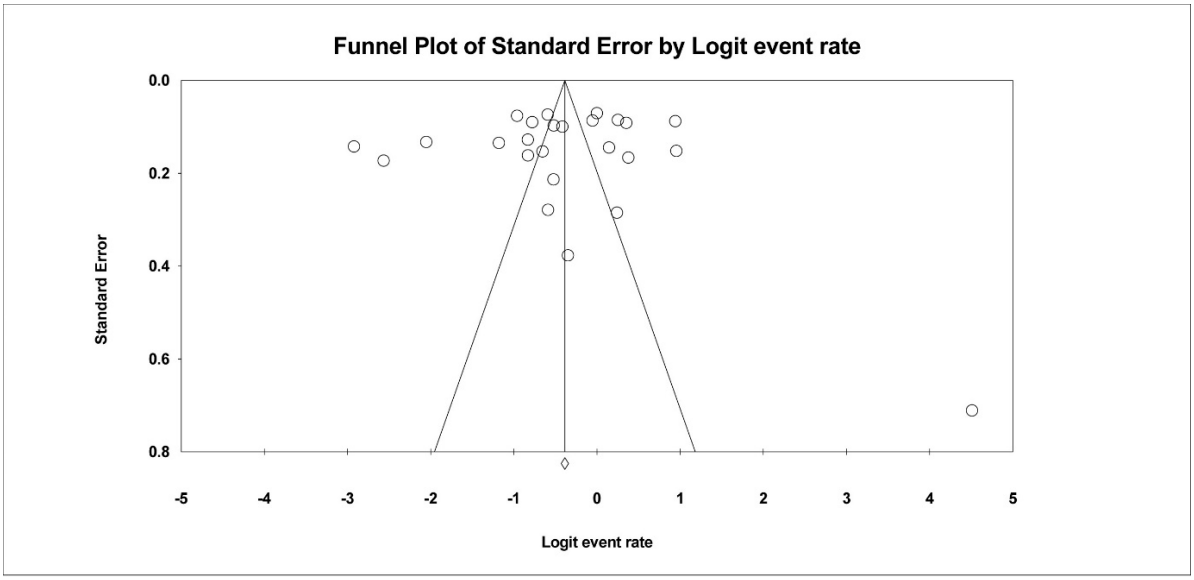

Figure 2. Funnel plot to assess publication bias

Figure 3. Provinces where the seroprevalence of BHV-1 among cattle in Iran was studied

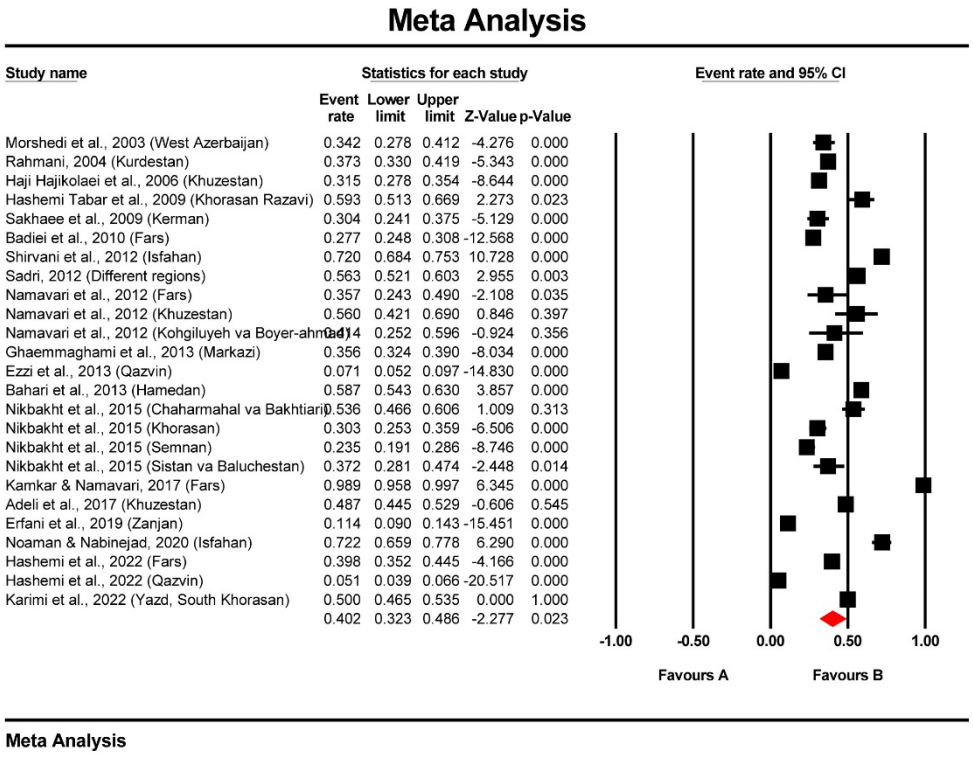

Figure 4. Forest plot for the seroprevalence of BoHV-1 in the cattle population at the animal level in Iran

4. Discussion

According to the report by the Iranian Ministry of Agriculture (2018), there are approximately 8,000,000 cattle of three groups of cattle breeds in Iran, including pure exotic, crossbred native and exotic breeds, and pure native breeds that are kept in industrial, semi-industrial, and traditional husbandry systems. The most important breed is the Holstein, with an estimated annual milk and meat production of approximately 1,059,000 and 830 (×1000 tons), respectively.

From 1964-70 to date, BHV-1 antibody has been detected in cattle, sheep, goats, buffalo, camel, pig, and horse, and was isolated from cattle in Iran [13, 35]. So far, a number of studies have been carried out on cattle

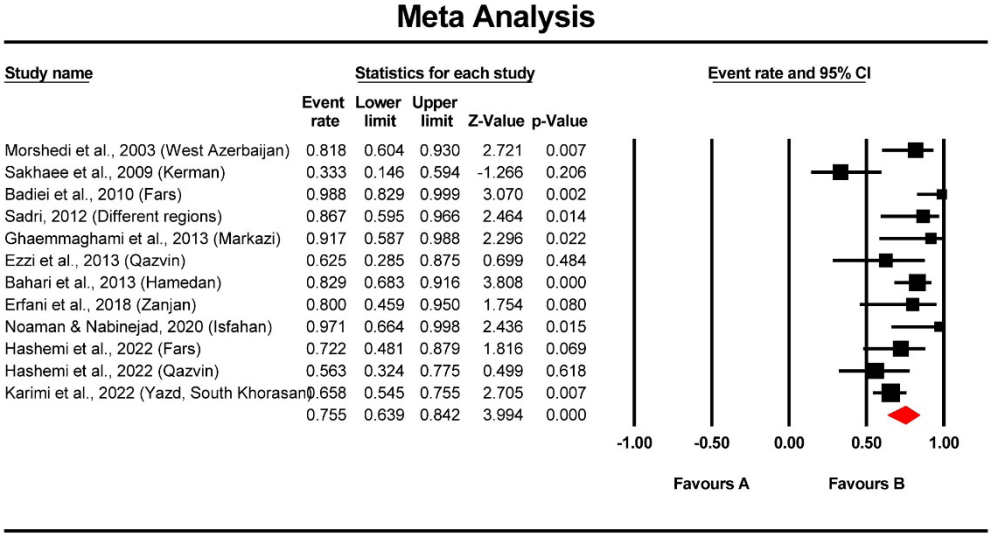

Figure 5. Forest plot for the seroprevalence of BoHV-1 in the cattle population at the herd level in Iran

in various parts of Iran (Table 1). To our knowledge, this is the first meta-analysis of the prevalence of BHV-1 infection in apparently healthy cattle based on the ELISA test in Iran.

There are differences between the reports of the seroprevalence rate from various countries and areas. Probably, this result might be associated with weather conditions, geographical situation, sample size, sampling season, diagnostic methods, diversity of breeds, age and sex, and

Table 1. Documents included in the meta-analysis of the seroprevalence of BHV-1 in the cattle population of Iran

Study Area	Herds (p/s)	Animals (p/s)	Herd Type (Sampling Age [m]), BoHV-1 Vaccination	Study Design	Ref.
West Azerbaijan	18/22	65/190	NA	Retrospective	[15]
Kurdistan	-	169/454	NA	Cross-sectional	[16]
Khuzestan	-	180/572	NA	Cross-sectional	[17]
Khorasan Razavi	-	89/150	Dairy (>24)	Cross-sectional	[18]
Kerman	5/15	55/181	Dairy (12-36), No	Cross-sectional	[19]
Fars	39/39	237/856	Dairy (>12), No	Cross-sectional	[20]
Isfahan	-	462/642	Dairy (>0), No	Cross-sectional	[21]
Fars	-	20/56	NA	Cross-sectional	[22]
Khuzestan	-	28/50	NA	Cross-sectional	[22]
Kohgilooye va Boyer Ahmad	-	12/29	NA	Cross-sectional	[22]
Different regions[a]	13/15	314/558	Dairy, beef (12-48), No	Cross-sectional	[23]
Markazi	11/12	286/803	Dairy (>12), No	Cross-sectional	[24]
Qazvin	5/8	36/504	Dairy (12-48), No	Cross-sectional	[25]
Hamedan	34/41	289/492	Dairy (>6), No	Cross-sectional	[26]
Chaharmahal va Bakhtiari	-	103/192	Dairy	Cross-sectional	[27]
Khorasan	-	88/290	Dairy	Cross-sectional	[27]
Semnan	-	72/306	Dairy	Cross-sectional	[27]
Sistan and Baluchestan	-	35/94	Dairy	Cross-sectional	[27]
Fars	-	182/184	NA	Cross-sectional	[28]
Khuzestan	-	260/534	(>0), No	Cross-sectional	[29]
Zanjan	8/10	64/562	(>0), No	Cross-sectional	[30]
Isfahan	16/16	156/216	Dairy (>12), No	Cross-sectional	[31]
Fars	13/18	167/420	Dairy (>0), No	Cross-sectional	[32]
Qazvin	9/16	52/1017	Dairy (>12), No	Cross-sectional	[33]
Yazd, South Khorasan	50/76	400/800	Dairy (>12), No	Cross-sectional	[34]

NA: Not available.

p/s: Number of positive samples/total sample

[a]Provinces of Yazd, Khorasan, Fars, Markazi, East Azerbaijan, and Qom.

husbandry systems. It is reported that colder and higher altitude areas can act as a risk factor for cattle herds experiencing BHV-1 infections [36]. It is well known that all breeds of cattle at any age are susceptible to BHV-1 infections; however, the disease is prevalent in older animals, probably because of their greater exposure to natural sources of infection and the loss of maternal immunity [8].

In light of our outcomes, the seroprevalence of BHV-1 among cows and herds was 40.2% (95% CI, 32.3%, 48.6%) and 75.5% (95% CI, 63.9%, 84.2%), respectively, in Iran. The pooled prevalence of BHV-1 was higher than that reported in a previous study carried out on 9968 sera collected from the whole country using the serum neutralization test, in which the rate of infection was estimated at 30.6% [37]. This shows that the situation of BHV-1 infection in Iran has become more serious in recent years.

There are many serologic reports on the cattle population from around the world. Based on a review of the epidemiology and control of BHV-1 infection in Europe [6], the serologic prevalence has been reported in cows as low as 12% in Scotland to as high as 77.5% in the Southern Italian Apennines, and in herds as low as 22% in Estonia to as high as 100% in Central Italy. The pooled estimate of seroprevalence of BHV-1 at the animal and herd level in Iran, in comparison with other countries, shows that Iran could be considered among the moderately infected countries.

BHV-1 infection can cause major economic consequences in cattle breeding herds, including abortion, infertility, loss of production, and deaths. The costs of treatment, prevention, and control measures should also be taken into account [38]. The most prevalent reason for culling cows in Iran is frequent abortion and reproductive failure [39]. Occurrence of highly prevalent abortion in the cattle population of Iran (11.1-18.6%) has multifactorial etiologies [40]. However, some researchers [41-44] believe that BoHV-1 can act as an abortion pathogen in cattle, as BoHV-1 DNA was isolated in 6.8-100% of aborted fetuses in different regions of Iran.

The control and eventual eradication of BoHV-1 is based on the detection and removal of infected animals, with or without the use of marker vaccines, but this approach is inefficient for the eradication of infection in countries with large herds or high seroprevalence of BHV-1. Alternatively, repeated vaccination of infected herds can be undertaken to increase protection, reduce the effects of disease, and reduce the risk of re-excretion by latently infected animals [26, 45].

5. Conclusion

In conclusion, the endemicity of BHV-1 infection in the cattle population of Iran, with the high prevalence in herds and animals found in this study, suggests the necessity of an intensive control program for reducing BHV-1 infection rates. Based on the present findings, there are no national IBR/IPV control programs in Iran. A well-defined control strategy for preventing and controlling BHV-1 infection in Iran should be based on further studies on BHV-1 epidemiology, control of animal and semen importation, the use of marker vaccines, and planned biosecurity measures to control the epidemiological risk of infection due to the presence of BHV-1 latent carriers.

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Compliance with ethical guidelines

This article is a review study with no human or animal sample.

Data availability

The data that support the findings of this study are available upon request from the corresponding author.

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interest.

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