Section: Immunohematology and Blood Transfusion

Original Research Article

EXPERIENCE WITH MINIPOOL NUCLEIC ACID AMPLIFICATION TECHNOLOGY IN BLOOD DONOR SCREENING FOR HBV, HCV, & HIV AT A TERTIARY CARE MEDICAL INSTITUTE OF ROHILKHAND REGION

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Received : 12/08/2024
Received in revised form : 04/10/2024
Accepted : 18/10/2024

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DOI: 10.70034/ijmedph.2024.4.37

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2024; 14 (4); 190-196

ABSTRACT

Background: NAAT is a molecular Amplification technology that targets amplifies and detect genetic material (RNA/DNA) of a pathogen highly sensitive and specific for viral nucleic acid. NAAT reduces the window period of HIV, HBV, and HCV by early detection of viral genome. Testing is molecular technique for screening blood donors to reduce the risk of transfusion transmitted infections, providing an additional layer of blood safety. **Aims & Objectives:** To evaluate the overall NAAT yield of HBV, HCV and HIV in blood donors; and further, to observe the distribution patterns of NAAT reactive cases, with respect to donor age, gender, occupation, residence (urban/rural), first time and repeat, voluntary, family and replacement donors.

Materials and Methods: This retrospective analysis was conducted in the Department of Immunohematology and Blood Transfusion, over a three-year period from January 2019 to December 2022, at tertiary care medical institute of rohilkhand region. Serological screening was performed on 29,524 Whole blood donors. Those found non - reactive were subjected to NAAT testing which comprised 28,318 numbers of donors. All blood units were tested after meeting inclusion and exclusion criteria for donor selection and deferral. Preliminary serological screening was performed by Electro-chemiluminescence technology while molecular testing was performed on mini-pool NAAT testing platform. NAAT yield was calculated for Hepatitis B, C and HIV.

Results: Out of 28,318 sero-negative samples subjected to nucleic acid testing, 45 samples were found reactive with an overall NAAT yield of (1:629), HBV reported the highest NAAT yield (1:885) followed by HCV (1:2360) and HIV (1:28,318). In males overall NAAT yield was 1:614. Overall NAAT yield was highest in urban blood donors than rural blood donors (1:608 vs 1:767). NAAT yield was highest among replacement donors than voluntary donors(1:548vs1:716). NAAT yield was highest in older age group (56-65 yrs) and lowest in younger age group 18-25 yrs (1:150 vs 1:890).

Conclusion: NAAT is more sensitive and specific in detection; it detects both window period and occult infection. NAAT-PCR can be used as an adjunct to Elisa test. Considering the high prevalence of viral infection, the no. of transfusions and high proportion of component separation, in INDIA implementation of NAAT will be an important step towards providing safe blood.

Keywords: Nucleic acid testing, Minipool, Chemiluminescence, Blood center.

INTRODUCTION

Nucleic acid amplification technology for detection of microbial genome finds its presence in diagnostic medicine since 1985, with the invention of polymerase chain reaction by Kary B Mullis.[1] Technological improvements and advancements with the introduction of heat resistant Thermophilus acquaticus (Taq) DNA polymerase by Saiki in 1986, revolutionized the applications of the technology using more affordable and easier to perform procedure on automated platforms.[2,3]

Immunoassay, the traditional method for screening of blood donations, is the mainstay of detecting antibody to viral antigens. The interval between donor exposure to viruses and appearance of detectable antibodies against them is known as window period. It is during this period that the risk of transmission of infection through donated blood can be missed. NAAT testing shortens this window period offering much higher sensitivity and specificity for detecting viral infections.[4]

The continuing risks of transfusion associated hepatitis and HlV, by hepatitis B,C and HIV virus, respectively, despite mandatory screening of blood donors using automated serological screening platforms, led to the introduction of viral nucleic acid amplification technology for routine blood donor screening in mid to late 1990s.[5,6]Currently, approximately 33 countries have implemented NAAT for HIV and 27 for Hepatitis B for blood donor screening.[7]

The advantage of NAAT over the traditional method for screening TTI is reduction of window period from 22 to 11 days for HIV,59 to 25 -30 days for Hepatitis B and 70 to 12 days for Hepatitis C.[8] With the introduction of NAAT in 2008 in India, NAAT yield has been widely studied at various blood centres from across the country using diverse automated or semiautomated NAAT platforms.[9-11] Preliminary serological screening of blood donors also varies from place to place and from blood centre to blood centre in terms of assays and technology. A review on Nucleic acid amplification testing in blood centre reports a NAAT yield of 1:476 to 1:4403.[12]

Differences in the prevalence of HBV, HCV, and HIV infection in various geographical regions, technology used, and the initial TTI screening methods have greatly affected the interpretation of data on NAAT yield.[13] Electro-chemiluminescence (ECL) as the initial blood donor screening platform for transfusion transmissible infections has been adopted at few centres and only few studies on NAAT yield with ECL as the preliminary screening method have been undertaken.

The present study was undertaken to evaluate the yield of nucleic acid amplification testing (NAAT) for HBV, HCV, and HIV in blood donors who were non-reactive for HBV, anti-HCV, and anti-HIV 1 and 2 by Electro-chemiluminescence. This was followed by minipool NAAT of six donor samples in a blood donor population from the Rohilkhand region of North India, with an aim to observe the distribution of these infections with respect to various donor variables.

MATERIALS AND METHODS

This retrospective cross-sectional observational study was conducted in the Department of Immuno-hematology and Blood Transfusion at a tertiary care medical institute of Rohilkhand region. Blood donor screening and testing records from the period January 2019 to December 2022 were retrieved from the electronic data base after obtaining clearance from the institutional ethics committee.

Total 29,524 blood donors were screened for TTI by Electo-chemiluminiscence and out of which 28,318 sero-negative samples were subjected to NAAT testing. Donor information regarding donors' age, gender, place of residence (Urban/Rural), donor category (Voluntary, replacement and family); results of transfusion transmissible infection screening for HBV(HBsAg), HCV(anti-HCV), HIV (anti-HIV 1 &2), HBV DNA, HIV and HCV RNA were retrieved from the electronic data base.

Donor selection process of the above blood donors included inclusion and exclusion criteria, followed by testing and processing as per the National statutory requirements.[14,15]

Preliminary serological screening for viral markers was performed on fully automated chemiluminescence platform using Electrochemiluminescence technology (Cobas e411, Roche Diagnostics). The assay included testing of HbsAg by Elecsys HbsAgII, Anti HCV by Elecsys Anti-HCV II and Anti- HIV by Elecsys HIV combi PT along with controls (Pre controls).

NAAT was performed on a fully automated platform, Cobas Taqscreen MPX v 2.0 using 201 Roche molecular system with strict adherence to the manufacturer's instruction for the assay. A pool of six samples was prepared by Hamilton Microlab Starlet IVD pipettor sample pooler followed by nucleic acid extraction and amplification in the Ampliprep, and detection of the amplified DNA in the Cobas TaqMan analyzer. A reactive pool created was subjected to a process known as resolution wherein all six samples in the reactive pool were subjected to NAAT testing as individual samples.

NAAT yield was calculated by the formula: Number of cases reactive by NAAT / total number of donor sample non-reactive by Chemiluminence and reported as occurrence of a single case.

Data was compiled and tabulated in windows-7 excel spread sheet and descriptive statistics was used for data analysis

RESULTS

Population characteristics

In the current study a total of 29,524 whole blood donors who underwent screening for TTI, males outnumbered females, comprising 98.33%(n=1000), while females comprised only 1.67%(n=17) of the total donor population. Donors from the urban and rural areas comprised 83.25% (n=847) and 16.72% (n=170) of the population respectively. Representation of donor as voluntary, family and replacement donors was 3.24% (n=33), 29.89%(n=304) and 66.86%(n=680), respectively. When stratified under five age categories, maximum number of donors were observed in the age group 26-35 years comprising 48.48%(n=493) and lowest between 56-65 years comprising 0.29% (n=3) of the population.

Sero-reactivity in blood donors on preliminary screening of all the 29,524 samples screened serologically by electro-chemiluminescence,1017(0.03%) samples were reactive for HIV, HBV and HCV. The proportion of sero-reactive samples was highest for HCV (n=558,54.87%), followed by HBV (n=391,38.45%) HIV (n=6, 6.69%). [Figure 1]

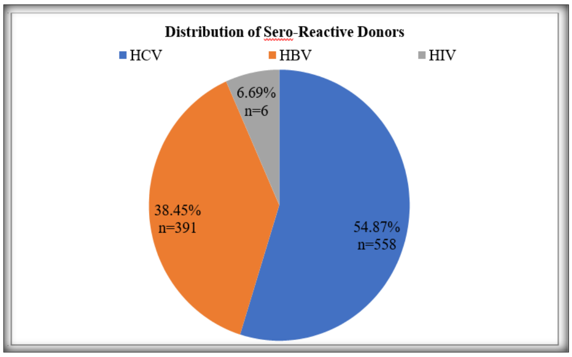

Figure 1: Distribution of Sero-Reactive Donors

Figure 2: The sero-prevalance rate of HCV, HBV and HIV by Electro chemiluminescence was 1.89%,1.32% & 0.23%respectively. [Figure 2]

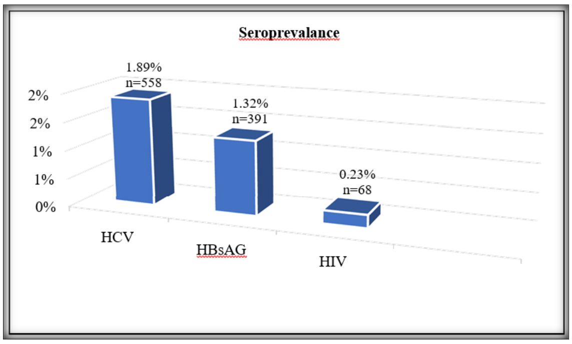

Figure 2: Sero prevalence of HBV, HCV and HIV infection in blood donors

Table :1 Represent NAAT yield of HBV, HCV and HIV infection with respect to donor variables.

NAAT yield with respect to gender.

In males, overall NAAT yield was 1:614. NAAT yield was highest for HBV ie. (1:864) followed by HCV (1:2304) followed by HIV (1:27643). No NAAT reactive cases were detected in females.

NAAT yield with respect to area of residence.

Overall NAAT yield was higher in urban blood donors than rural blood donors (1:608 vs 1:767). NAAT yield of HCV, HBV and HIV for urban and rural blood donors are given.

NAAT yield with respect to donation type.

NAAT yield for various categories blood donors was highest for Replacement donors (1:584), followed by Voluntary blood donors (1:716), and Family blood donors (1:745).

NAAT yield was highest in older age group of 56-65 years and lowest in younger age group 18-25 years (1:150 vs 1:890). NAAT yield of HCV, HBV and HIV for different age groups are as given in table-02. [Table 2]

Figure 3: Represents the prevalence of HBV, HCV and HIV infection among blood donors with and without NAAT.

Prevalence of HBV and HCV infection with serological and molecular testing was slightly more compare to that of only with serological testing for HBV the prevalence was 1.43% with combined serological and molecular testing while it was 1.32% only with serological testing. HCV the prevalence was 1.93% with combined serological and molecular testing while it was 1.83% only with serological testing. With HIV result was almost same.

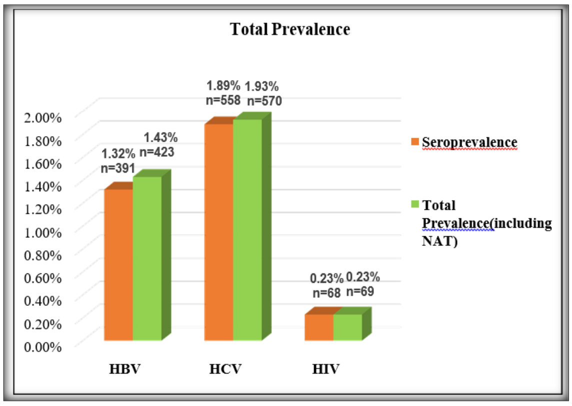

Figure: 3 Prevalence of HBV, HCV and HIV infection among blood donors with and without NAAT

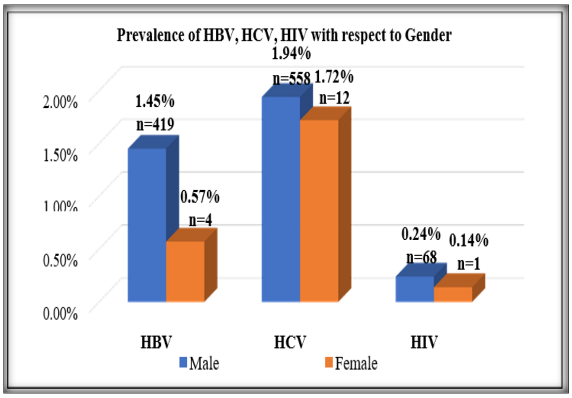

Figure 4: Prevalence of HBV, HCV and HIV infection with combined serological and molecular (NAAT) testing with respect to various donor variables.

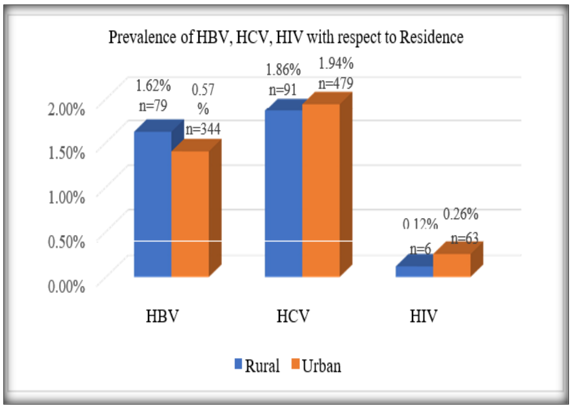

Figure 5: Prevalence of HBV, HCV and HIV infection with combined serological and molecular (NAAT) testing with respect to residence.

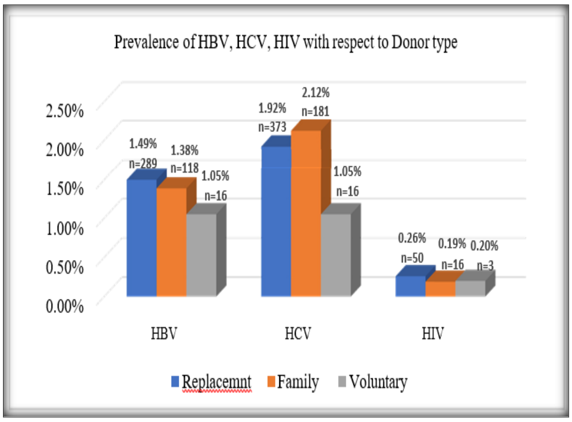

Figure 6: Prevalence of HBV, HCV and HIV infection with combined serological and molecular (NAAT) testing with respect to donor type.

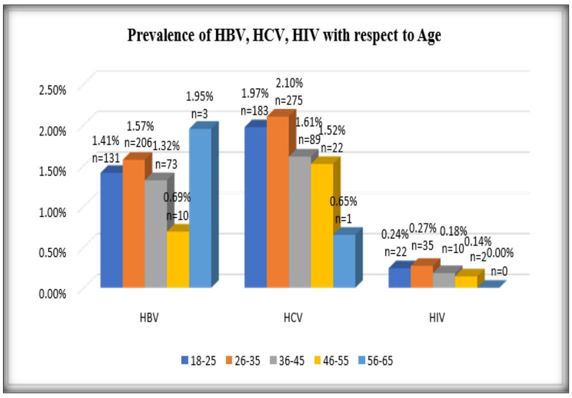

Figure 7: Prevalence of HBV, HCV and HIV infection with combined serological and molecular (NAAT) testing with respect to donor age

Prevalence of HBV, HCV and HIV in male and female donors was 1.45% vs 0.57%, 1.94% vs 1.72%, 0.24% vs0.14% respectively Figure 4. [Figure 4]

Prevalence of HBV, HCV and HIV in rural and urban donors was 1.62% vs 0.57%, 1.86% vs 1.94%, 0.12% vs 0.26% respectively. [Figure 5]

Prevalence of HBV, HCV and HIV infection with respect to donor type is as shown in figure. [Figure 6]

For all three infections prevalence rate was highest for replacement donors.

Prevalence of HBV, HCV and HIV infection with respect to donor age is as shown in figure 7. [Figure 8]

Table 1: NAAT yield of HBV, HCV and HIV infection blood donors

Donor variable		HBV	HCV	HIV	Total NAAT Yield
Gender	Male (n = 27643)	1:864	1:2304	1:27643	1:614
	Female (n = 675)	Nil	Nil	Nil	Nil

Table: 2 Represents NAAT yield of HBV, HCV and HIV with respect to age

Donor variable		HBV	HCV	HIV	Total NAAT Yield
Residence	Rural (n= 4601)	1:920	1:4601	Nil	1:767
	Urban (n=23717)	1:878	1:2156	1:23717	1:608
Donor type	Replacement (n=18695)	1:779	1:2671	1:18695	1:584
	Family (n=8192)	1:1170	1:2048	Nil	1:745
	Voluntary (n=1431)	1:1431	1:1431	Nil	1:716

Table: 2 NAAT yield of HBV, HCV and HIV with respect to age

Age of donors	HBV	HCV	HIV	Total
18-25	1:1271	1:2967	Nil	1:890
26-35	1:896	1:1568	1:12542	1:545
36-45	1:532	1:5322	Nil	1:484
46-55	Nil	Nil	Nil	Nil
56-65	1:150	Nil	Nil	1:150

DISCUSSION

Advancements in technology have enabled the development of more precise methods for detecting infectious disease markers, such as virus-specific antibodies, antigens, and nucleic acids, to improve the safety of blood transfusions. However, early detection of infections remains a challenge due to the "window period," false negatives from limitations in screening tests, genetic variations in viral strains, and potential laboratory errors.[16,17]

Blood-borne infections continue to pose a significant threat to safe blood transfusions in developing countries. This is due to a lower number of voluntary donations, inconsistent screening policies, the use of less sensitive viral screening tests, and the high prevalence of viral diseases such as hepatitis B, hepatitis C, and HIV.[8]

In this study, we have presented the NAAT yields of HBV, HCV, and HIV from a tertiary care hospital blood center in North India over a duration period of 5 years, emphasizing on a significant benefit, to generate incremental yield over serology alone. The most common infection, that we found in the sero-nonreactive sample, through NAAT was HBV infection, since each blood unit is split up into three different units, to be used, by using NAAT we were able to prevent, the potential transmission of these viral infections, there by demonstrating the significance of NAAT as an essential screening test for blood center in India to enhance blood safety.

The risk of TTI has declined dramatically, in developed countries, as a result of remarkable improvement in blood donation strategies and simultaneous testing of blood donor with NAAT technology. In current study; males out-numbered females comprising 98.33% and 1.67% respectively of total donor population; similar to study done by Sumbul et al,[18] in year 2020, who found majority of the donors males 96.6% as compared to 3.3% females and also similar to study done by Anju Uppal et al[19] in year 2021 where males contributed to 97.2% of total population.

In present study replacement donations were 66.86% and voluntary donations were 3.24%; similar to study done by Sumbul et al [18] in the year 2020; who found majority of replacement donations (92.7%) as compared to voluntary donations (7.2%) and also similar to study done by Anju Uppal et al,[19] in year 2021 where majority of replacement donations was (90%).

Maximum no of donations was found in third decade of life in concordance with the study done by Sumbul et al,[18] in the year 2020 where maximum no of donors was in 3rd decade contributing to (59.5%).

Based on the sero- prevalence study among blood donors, by dual testing strategy using chemiluminescence and NAAT testing, our study reveals serious concerns regarding HCV, HBV and HIV infections among blood donors, chemiluminescence is an antibody test similar to EIA, has sensitivity and specificity similar to 4th generation EIA.

The sero-prevalence of HCV and HBV and HIV was (1.89%;1.32%; and 0.83% respectively) similar to study done by Sangeeta Pathak et al,[16] in the year 2021 where sero-prevalence of HCV,HBV and HIV was (0.74%,0.68%and 0.24%) respectively and by Sukanya et al,[20] where also sero-reactivity was highest for HCV (43.6%).

According to large study conducted by Makroo et al NAAT could interdict3272 infectious donations a year among our approximately 5 million annual donations,[21] NAAT yield for various studies ranged from 1:476to 1:440 in different studies.75-80% of NAAT yield are related to hepatitis .HIV and HCV accounts for 10-20%.Across the globe,Hepatitis B is the most common cause of NAAT yield.

In the present study, out of 28,318 sero-negative samples subjected for nucleic acid testing,45 samples were found reactive with an overall NAAT yield of (1:629). HBV reported the highest NAAT yield (1:885), followed by HCV (1:2360) and HIV (1:28318).

As for our centre, the NAAT yield is similar to NAAT yield reported by Sangeeta Pathak et al,[16] 2021 Anju Uppal et al,[19] 2021, reasons in variability in yield is due to several factors like wide variation in the pattern of infections among blood donors, type of kit, type of test employed, sensitivity and specificity of test and accuracy of methods. Our yield may be higher than some studies due to greater sensitivity of test method employed and lower than other studies due to stringent donor screening criteria.

Yield obtained in developed countries is much lower compare to India, A study conducted By USA,[22] found a NAAT yield of 1:2 million for HIV, and 1:270,00 for HCV for 66 million donations, this is due to higher prevalence and incidence of infections in developing nations.

In India, the incidence of HBV is much higher than HCV and HIV, the highest NAAT yield for HBV found in our study is as par as the published data across. In places where the prevalence of HBV is high and there is more chance of window period donations, and occult infections with low viral load is high, this method of assay is very sensitive for detection and identification of HBV DNA.[10]

HBV is a DNA virus which has an average doubling time of around 2.6 days, slower than the doubling time of HCV (0.45) and HIV (0.83).[23] Since HBV has a high prevalence in India, a no infections would be in the window period or resolving phase, when the levels of viral nucleic acid is very low, the chronic occult HBV infection which are not detected by HBsAg testing are a major transfusion risk.

In India due to high prevalence of HBV, proportions of occult infections are generally associated with low levels of circulating HBV DNA. Thus the use of highly sensitive

NAAT in our center led to higher NAAT yield of HBV when compared with HCV though the serology yields were comparable. These results indicate that window period and occult HBV infections that are missed by serology screening could be identified by use of highly sensitive NAAT.

The sero-prevalence of HBV, HCV, and HIV has been observed higher among replacement donors, compared to voluntary donors in India, despite the presence of multiple-steps to reduce TTI, such as repeat donation records, mandatory serological tests, discouragement of cash incentives for blood donation.

Considering the fact replacement donors can outnumber voluntary donors, as observed in our study, its essential to have stringent screening processes to enhance blood safety.

HCV is considered an emerging infection in India, the estimated HCV prevalence at present is 1-1.9%,[24] the majority of the studies in blood donors, reported prevalence from 0.3- 1.85%, the differences can be due to different assays used, and differences in the population and practices between different regions of the country.

Many centres have implemented NAAT but yet to be mandatory regulatory requirement in India, for evidence based implementation, of pooled or ID-NAAT large sample size studies based in India are needed, cost effective adoption of NAAT, by single center testing, in a referral laboratory would help to reduce the disease burden, in society where early diagnosis and management would lead to overall health benefit to both patients and donors.

In India scenario is slowly shifting with blood centers gradually introducing NAAT to provide safe blood. The studies with high NAAT yield suggest, higher prevalence of TTI in India, and thus the need of NAAT in blood centers for screening the donations, providing additional layer of blood safety.

Table 3: NAAT yield observed in various studies

STUDY BY:-	NAAT YEILD	HBV	HCV	HIV
Present	1:629	1:885	1:2360	1:28318.
SangeetaPathak et al (2021)	1:1600	1:1784	1:17246	1:155211.
Anju uppal et al 2021	0.27%	1/464	1/1874	1/86222
Chitta Ranjan et al 2021	0.43%	0.31%	0.01%	0.11%
Sumbul W et al 2020		2.5%	0.5%	0.07%
Sukanya Baruah, Lokesh pal,2019	-----	1:2597	-----	------
Sanghamitra et al2019		1/2535	1/10141	1/2028

CONCLUSION

If highly sensitive serological assays are not used, safety of blood for transfusion may become a big concern, apart from stringent measures in donor screening, screening of blood products by better ID NAAT, would detect potentially infectious blood units in all phases of infection and enhance the safety of the blood and blood components for transfusion.

Considering the high prevalence of viral infection, the no of transfusions and the high proportion, of component separation in the country, need for NAAT testing to prevent TTI is absolute.

Source of funding: No financial support was received for the work within this manuscript.
Conflicts of interest: No conflict of interest.

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