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### Original Article

## Aberration detection in influenza trends in Iran by using cumulative sum chart and period regression



Yousef Alimohamadi, PhD<sup>a</sup>, Ahmad Mehri, MSc<sup>b</sup>, Majid Janani, MSc<sup>b</sup> and Mojtaba Sepandi, PhD<sup>c,\*</sup>

<sup>a</sup> Antimicrobial Resistance Research Center, Institute of Immunology and Infectious Diseases, Iran University of Medical Sciences, Tehran, Iran

<sup>b</sup> Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

<sup>c</sup> Health Research Center, Lifestyle Institute Baqiyatallah University of Medical Sciences, Tehran, Iran

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### المخلص

**أهداف البحث:** تهدف هذه الدراسة لتحديد الحدود المقلقة لتفشي الإنفلونزا وكشف الانحرافات في اتجاه الإنفلونزا في إيران باستخدام المبلغ التراكمي وانحدار المرحلة.

**طرق البحث:** قمنا باستخدام حالات الإصابة بفيروس الإنفلونزا (النوع أ، وب) المبلغ عنها أسبوعياً في إيران خلال الفترة من يناير ٢٠١٥ إلى نوفمبر ٢٠١٨. تم استخدام نموذج انحدار الفترة، وجدول المجموع التراكمي للكشف الحسابي لمعرفة الحدود المقلقة.

**النتائج:** كان المتوسط  $\pm$  الانحراف المعياري والوسيط (فاصل الثقة ٩٥٪) من البداية المحددة في الأسبوع  $34.85 \pm 15.29$  و  $28.30$  و  $17.67-64.62$ . تبعاً لانحدار الفترة، وكان هناك تسع فترات وبائية للإنفلونزا من ٢٠١٥-٢٠١٩. باستخدام المجموع التراكمي ومراعاة مختلف القيم المناسبة التي تؤدي إلى التقدير المطلوب للحد الأعلى للتحكم، وتم تحديد الأسابيع ٦٧، ٧٣، ٨٤، و ٨٨ كفترات وبائية.

**الاستنتاجات:** وفقاً للدراسة الحالية، أظهرت الإصابة بالإنفلونزا نمطاً دورياً وحدوث الوباء كل عام. يمكن أن يساعد فهم هذا النمط الدوري صانعي السياسات الصحية لإطلاق برامج الوقاية مثل التطعيم في أشهر معينة من العام.

**الكلمات المفتاحية:** الإنفلونزا؛ كشف الانحراف؛ إيران؛ المجموع التراكمي؛ انحدار الفترة

### Abstract

**Objectives:** This study aims to determine the alarm thresholds in influenza outbreaks and aberration detection in the influenza trend in Iran by using cumulative sum control chart (CUSUM) and period regression.

**Methods:** We used the weekly reported influenza-positive (types A and B) cases from Iran between January 2015 and November 2019. The period regression model and CUSUM chart were used as detection algorithms to figure out the alarm thresholds.

**Results:** The mean  $\pm$  SD and the median (95% CI) of the determined threshold per week were  $34.85 \pm 15.29$  and  $28.30$  (17.67–64.62). According to the period regression, there were nine epidemic periods of influenza from 2015 to 2019. By using the CUSUM and considering a different  $h$  ( $h$  is an appropriate value that leads to the desired estimation for upper control limit) for the calculation of the upper control limit, 88, 84, 73 and 67 weeks were determined as the epidemic period.

**Conclusion:** According to the current study, the incidence of influenza showed a cyclic pattern and the epidemic recurred each year. Understanding this cyclical pattern can help health policymakers launch prevention programs such as vaccination during certain months of the year.

**Keywords:** Aberration detection; CUSUM; Influenza; Iran; Period regression

\* Corresponding address: Health Research Center, Lifestyle Institute, Baqiyatallah University of Medical Sciences, Nosrati Alley, South Sheykhbahae Ave, Tehran 143591-13189, Iran.

E-mail: msepandi@bmsu.ac.ir (M. Sepandi)

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## Introduction

Influenza is one of the most pernicious contagious diseases and a cause of pandemic throughout the world.<sup>1,2</sup> Several factors can contribute to an influenza epidemic. Two of the main factors are the expansion of urbanization and the increase in population density.<sup>3</sup> The unique property of this disease is its high infectivity; it can potentially infect 9.5% to 19.8% of a population.<sup>4</sup> Owing to its high morbidity and mortality, as well as the high rate of hospitalization, especially in children and older people, influenza can impose a high economic burden on societies.<sup>5</sup> While most of the symptoms of influenza are usually mild and self-limiting, in some cases, they can lead to the need to skip work and school, hospitalization, the need for an intensive care unit and even death.<sup>6–8</sup> According to the world health organization (WHO) reports, influenza can infect up to 20–30% of children, and 5–10% of adults in a population annually.<sup>9</sup> There are three to five million influenza patients who suffer from the disease severely and 250,000 to 500,000 who die from it, worldwide.<sup>10</sup>

Early detection of an outbreak is one of the critical challenges to the disease care system of any country.<sup>11</sup> Although there are various ways to detect outbreaks early, statistical detection algorithms of diseases play a critical role in early detection of the outbreaks.<sup>12</sup> In the past century (1919–2019), there have been various influenza outbreaks that have occurred in Iran; they have all been duly recorded. The year 2019 witnessed a significant wave of influenza outbreaks. According to the WHO report, 11–20% of Iran's population was infected.<sup>13</sup> A systematic review and meta-analysis showed that the prevalence of influenza was 0.18% during 2000–2016 in Iran.<sup>14</sup> The appropriate alarm threshold for detecting influenza outbreaks can control the outbreak in early stages, and can help reduce the mortality, morbidity and burden of this disease.<sup>12</sup> To increase the validity, especially the external validity of results, two distinct methods were used in the current study. The purpose of this study was to determine the alarm thresholds of influenza outbreaks and detect aberrations in the influenza trends in Iran.

## Materials and Methods

In the current study, we used the weekly reported influenza-positive (types A and B) cases found in Iran from January 2015 to November 2019. This data was extracted from the Flu Net web-based tool, WHO ([http://www.who.int/influenza/gisrs\\_laboratory/flunet/en](http://www.who.int/influenza/gisrs_laboratory/flunet/en)).

Every year, a laboratory sample is taken from all the cases of suspected influenza found in the Iranian health care system. After its laboratory and clinical approval, the influenza care system considers it a confirmed case of influenza. The Iranian Ministry of Health's Center for Disease Management reports its cases to the WHO based on its routine reports. After extracting data from WHO reports, the data were evaluated for the study and then analysed.

### Aberration detection

In the current study, the period regression and CUSUM (cumulative sum control chart) were used to detect aberrations in the normal trend.

#### Period regression model

In this model, the expected disease count at time  $t$  is calculated as follows:

$$E(y_t) = \mu + \alpha t + \sum_{i=1}^r \{ \beta_i \sin(\omega_i t) + \gamma_i \cos(\omega_i t) \}$$

Wherein,  $E(y_t)$ , the expected disease count at time  $t$ , is calculated as the mean of observed counts at times  $t - 1$ ,  $t$ ,  $t + 1$  over a certain pre-specified number of years.<sup>15</sup> If the number of positive cases was more than that of the expected cases, it can be considered as an aberration from the normal trend.

#### CUSUM (cumulative sum control chart)

##### Upper control limit

The CUSUM statistic is calculated as follows:

$$\text{CUSUM } t = \text{MAX} (0, \text{CUSUM } t-1 + Y_t - \sigma/2).$$

Wherein,  $Y_t$  is the number of reported influenza cases in days  $t$  ( $t = 1, 2, \dots, n$ ),  $\text{CUSUM } t-1$  is the value of CUSUM in days  $t-1$ , and  $\sigma$  is the standard deviation of observed data during the week in question. The upper control limit of this formula is calculated as follows:

$$\text{Upper Control Limit} = \text{UCL} = \mu + h \times \sigma^{16,17}$$

Wherein,  $\mu$  is the mean of observed data during the week in question,  $h$  is an appropriate value that leads to the desired estimation of an upper control limit that ranges from 1 to 3, and  $\sigma$  is the standard deviation. If the reported cases were more than the UCL, it can be considered as an aberration from the normal trend. The period analysis performed using online software is available at [http://www.u707.jussieu.fr/periodic\\_regression](http://www.u707.jussieu.fr/periodic_regression). Further, the UCL by CUSUM algorithm is determined by using the 2010 version of Excel software.

## Results

### Descriptive statistics

During the study period, about 11,286 influenza-positive cases were reported. While the mean of the

**Table 1: The descriptive statistics of reported influenza-positive cases and the determined threshold found using period regression.**

Indices	Reported cases	Determined thresholds
Mean + SD <sup>a</sup>	44.08 ± 113.24	34.85 ± 15.29
Median	5	28.30
Minimum	0	16.80
Maximum	930	70.60
<sup>b</sup> Q2.5	0	17.67
Q25	0	22.1
Q50	5	28.30
Q75	31.75	48.15
Q97.5	374.4	64.62

<sup>a</sup> Standard deviation.<sup>b</sup> Quartile.**Table 2: Detection of epidemic periods for the influenza-positive cases from January 2015 to November 2019 in Iran using the period regression model.**

Start week	End week	Excess cases <sup>a</sup>	Expected cases	Cases	Excess percentage (%) <sup>b</sup>
5	13	500	321	821	156
41	41	24.7	9.31	34	265
49	57	2363	363	2726	650
61	61	45	30	75	150
100	105	357	198	555	180
156	162	396	261	657	152
164	164	21.5	30.5	52	70
206	216	1852	420	2272	442
251	256	2318	133	2451	1738

<sup>a</sup> The frequency of cases that were more than expected.<sup>b</sup> The percentage of cases that were more than expected.

reported cases was found to be  $44.08 \pm 113.24$ , the median (95% CI) of the reported cases was found to be 5 (0–374.4) (Table 1). Most of the cases were reported from the last month of autumn to the end of winter (about three months), and the lowest number of cases was reported during the summer.

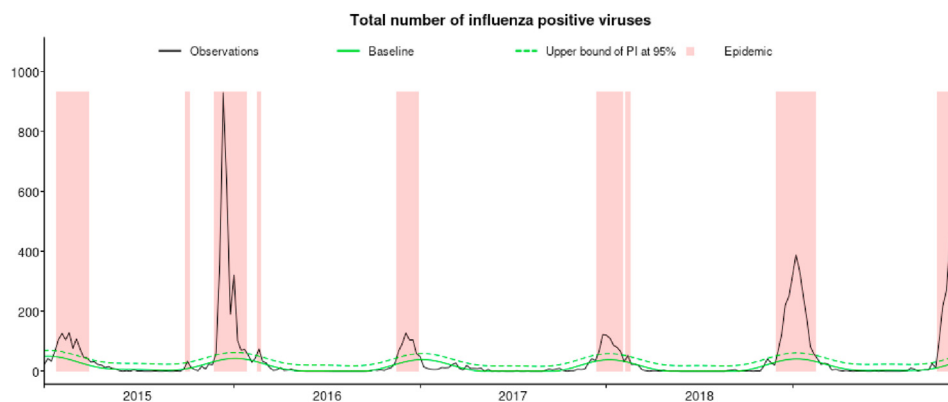
#### Determined thresholds

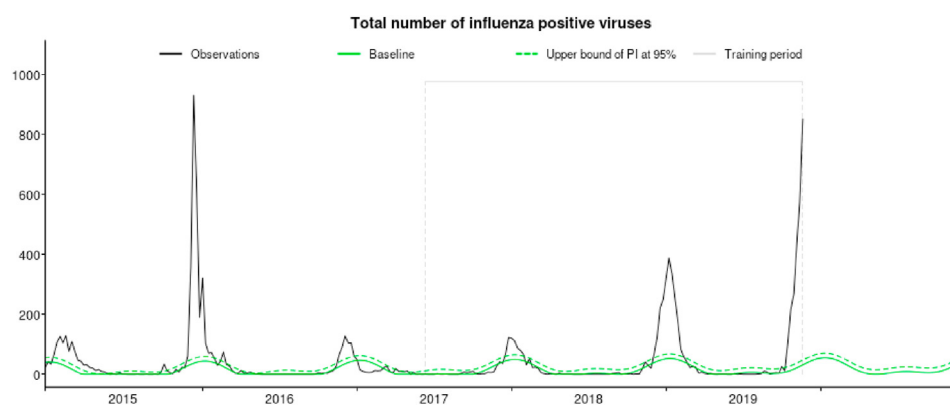
##### Period regression

The mean  $\pm$  SD and the median (95% CI) of the determined threshold per week were  $34.85 \pm 15.29$  and 28.30 (17.67–64.62) (Table 1). When considering the median of the estimated threshold as an alarm threshold level, if the number of influenza-positive reported cases were more than 29 cases per week, it must be considered as an alarm for influenza epidemics. As per this method, there were nine epidemic periods of influenza from 2015 to 2019 in Iran. These periods are shown in Table 2 and Figure 1. Also, this method found the median of the predicted baseline and the predicted threshold for the coming year to be 7.25 (0–53.26) and 22.95 (11.12–68.91, respectively (Figure 2).

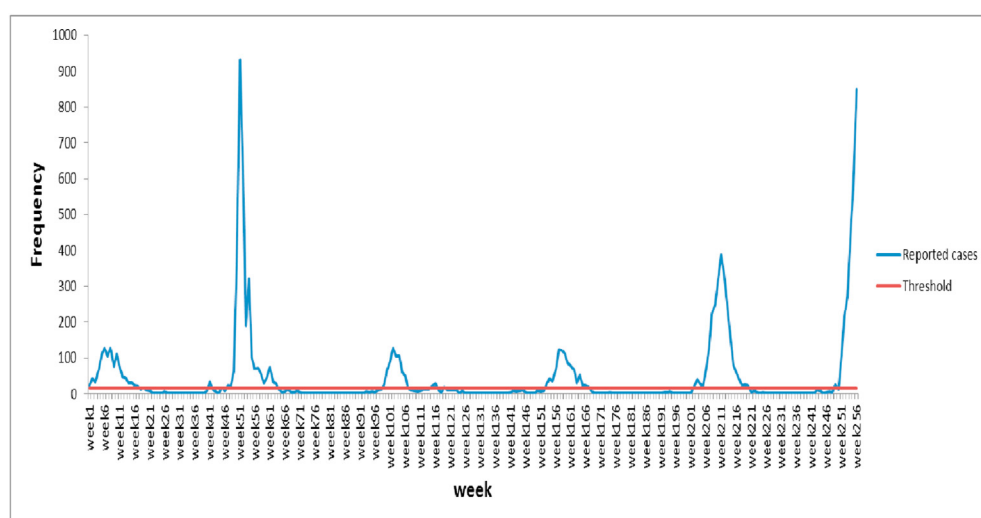
##### CUSUM algorithm

By using this algorithm and considering  $h$ : 1.5,  $h$ : 2,  $h$ : 2.5 and  $h$ : 3, the determined alarm thresholds were found to be 16.45, 20.42, 24.38 and 28.34 cases per week, respectively. For example, the consideration  $h$ : 2 as an alarm threshold level means that the number of reported cases per week was more than 21; it should be considered an alarm for influenza epidemics. By considering these thresholds, 88, 84, 73 and 67 weeks were determined as the durations for the outbreak of the epidemic (Figure 3 to 6).

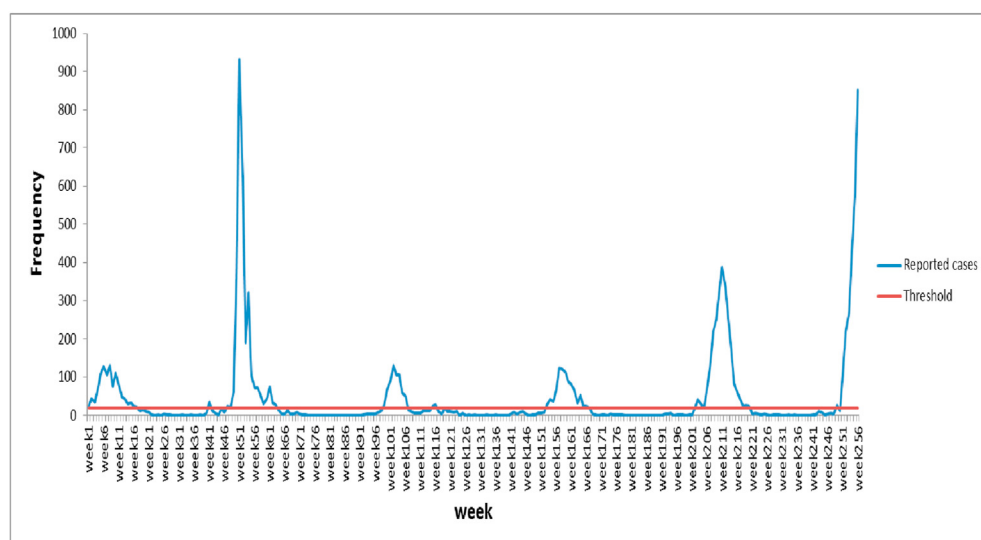
**Figure 1: Detection of epidemic periods for the influenza-positive cases from January 2015 to November 2019 in Iran using the period regression model.**



**Figure 2:** Calculation of the predicted baseline and future threshold of the influenza-positive cases in Iran using the period regression model.



**Figure 3:** Determining the alarm threshold level of the influenza-positive cases in Iran by using CUSUM with  $h = 1.5$ .



**Figure 4:** Determining the alarm threshold level of the influenza-positive cases in Iran using CUSUM with  $h = 2$ .

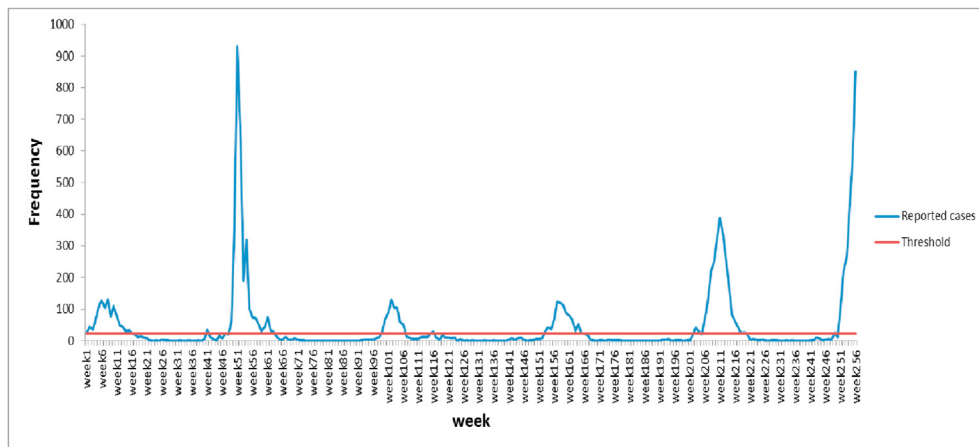


Figure 5: Determining the alarm threshold level of the influenza-positive cases in Iran using CUSUM with  $h = 2.5$ .

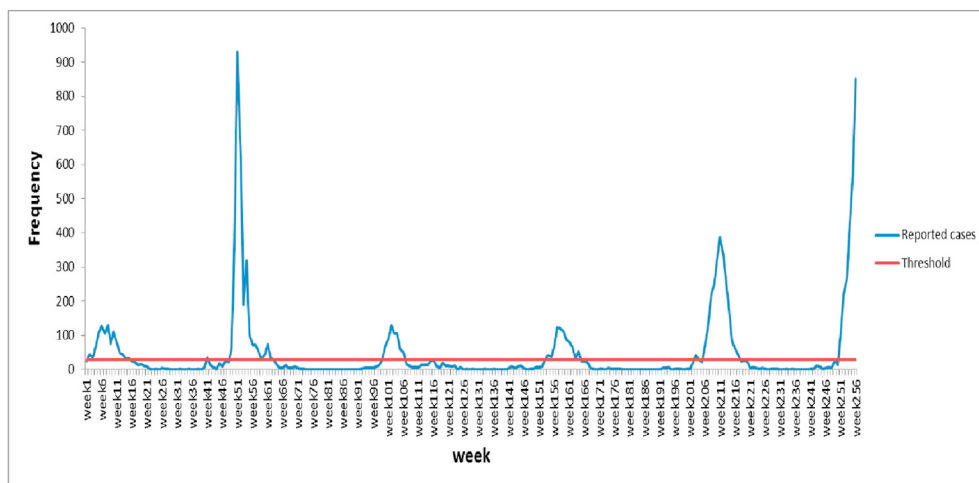


Figure 6: Determining the alarm threshold level of the influenza-positive cases in Iran using CUSUM with  $h = 3$ .

## Discussion

The influenza epidemic is one of the primary public health challenges in countries all over the world. In Iran, just as with other countries, influenza cases occur each year. Due to the nature of this infectious disease, an epidemic outbreak of this infection is inevitable. Determining the level of alarm threshold is crucial for the timely detection of the epidemic for each country. Different methods have been used to determine this threshold to facilitate the detection of outbreaks, which have been used in different studies based on the outbreak data for a variety of diseases, such as influenza. This study analysed the outbreaks of influenza in Iran from 2015 to 2019 by using the CUSUM and period regression methods, and showed the thresholds required to detect the outbreak of influenza.

Our findings demonstrated that the influenza outbreak occurred at least every winter between 2015 and 2019 in Iran. The outbreaks were found to be more noticeable in January 2016 and November 2019. In correspondence with our results, the WHO statistical analysis showed that Iran was one

of the countries with the highest number of influenza cases in January 2016 and November 2019 in the world.<sup>18</sup> Further, a study held in the north of Iran also found the occurrence of an influenza outbreak in January 2016, which was consistent with the findings of our study.<sup>19</sup>

This study showed that influenza outbreaks in Iran occur more often in the winter and autumn seasons, which fits with the findings of other published literature. Hosseini et al.<sup>20</sup> showed that the seasonal activity of influenza and the outbreaks of this infection occur during the autumn. Further, Durand et al.<sup>21</sup> showed that most of the flu cases occurred from January to March in 2004–2013. It seems like the pattern of influenza outbreaks in Iran has a seasonal trend, with most of the cases reported during the cold months.

In the current study, the CUSUM algorithm was used to detect the aberrations in the trend of influenza outbreaks in Iran. The application of this method has been used in health data by different studies.<sup>22–24</sup> Our study focuses on the potential use of CUSUM for early detection of any aberration in the trend of influenza-positive cases.



Published studies have demonstrated a healthy performance of the respective algorithm.<sup>25–27</sup> Another study showed that the performance of Bayesian outbreak detection algorithm in the detection of influenza outbreaks was better than the modified CUSUM algorithm<sup>28</sup>. However, owing to its simplicity and comprehensibility, the CUSUM algorithm can be very beneficial for early warnings of aberrations in the usual trend.

Period regression was also used in this study to identify influenza outbreaks. The performance of this method in detecting influenza outbreaks has also been investigated by previous studies.<sup>29–32</sup> As shown in this study, nine outbreaks of influenza were detected between 2015 and 2019 using this method. The performance of each model in the detection of outbreaks depends on different factors such as the type of infectious diseases, study location, gold standard and the accuracy of the records in the health care system.<sup>33</sup> Thus, it is better to use a different model for the detection of outbreaks.

Knowing about the future threshold can be very beneficial for early warning, and subsequently for an early diagnosis of outbreaks. The defined level of alarm threshold set by the studied methods can be used in the future for early detection of outbreaks and decreasing the morbidity and mortality of influenza cases. The limitations of this study are that some of the cases of influenza may not have been recorded in the health care system; if they had been recorded, we could have analysed the influenza outbreaks more accurately. Although the issue of underreporting is found across the health care systems of all countries, with the improvement of public health coverage in Iran, there will be better recording of influenza cases over time.

## Conclusion

The current study found the incidence of influenza to show a cyclical pattern. It also found the epidemic to have occurred every year. Considering this cyclical pattern, the next epidemic wave of influenza is predictable, and thus, it is fair to state that its occurrence is inevitable. The findings of this study can be of great help to the health policymakers in adopting the right prevention programs, such as vaccination, at the right time to deal with a high-risk population.

## Recommendations

By considering the change in sensitivity of the surveillance system and change in the pattern of influenza cases, we recommend further studies to periodically determine the level of alarm threshold by using different approaches and different methods.

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## Conflict of interest

The authors have no conflict of interest to declare.

## Ethical approval

There are no Ethical or Financial issues, Conflicts of interests, or animal experiments related to this research.

## Authors contributions

YA conceived and designed the study, conducted research, provided research materials and wrote the initial and final draft of the article. AM wrote the initial and final draft of article and conducted the data analysis. MJ wrote the initial and final draft of the article and conducted the data analysis. MS conceived and designed the study, conducted research and wrote the initial and final draft of the article. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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