Joinpoint regression analysis with time-on-study as time-scale. Application to three Italian population-based cohort studies

Federico Rea [(1)], Eleonora Pagan [(1)], Matteo Monzio Compagnoni [(1)], Anna Cantarutti [(1)], Pietro Pugni [(1)], Vincenzo Bagnardi [(1)], Giovanni Corrao [(1)]

(1) Unit of Biostatistics, Epidemiology and Public Health, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy

CORRESPONDING AUTHOR: Eleonora Pagan, Dipartimento di Statistica e Metodi Quantitativi, Sezione di Biostatistica, Epidemiologia e Sanità Pubblica, Università degli Studi di Milano-Bicocca, Via Bicocca degli Arcimboldi, 8, Edificio U7, 20126 Milano, Italy. Tel.: +39.02.64485859, Fax: +39.02.64485899; E-mail: e.pagan@campus.unimib.it

ABSTRACT

Background: Joinpoint regression analysis is usually applied to study varying trends over time in order to identify the time point(s) in which the trend significantly changes. We illustrate three epidemiological investigations in which this methodology was applied with time-on-study as time-scale.

Methods: Data were retrieved from the healthcare utilization databases of Lombardy Region (Italy). We investigated the trend of the: (1) mortality rate among centenarians hospitalized for hip fracture (2004-2011); (2) proportion of persistent patients after the initial prescription of antihypertensive drugs during the first year of treatment according to gender (2005); (3) prescription rate of statins in the year before and after the hospital admission among patients hospitalized for a transient ischemic attack (2008-2009).

Results: The following results were obtained: (1) a joinpoint was identified in the fourth month, showing an increased risk of death during the three months after hip fracture hospitalization; (2) the proportion of patients still under antihypertensive treatment falls until the fifth month, remaining stable afterwards; there was evidence that the prevalence of patients who discontinued the treatment was significantly higher among women than men; (3) during the year after the transient ischemic attack episode, monthly rate of available statins was double than the previous year with a significant decrease in the first four months.

Conclusions: The joinpoint regression analysis can be a useful tool in epidemiologic framework when a temporal trend is the objective of the investigation since it allows to make inference by means of a quantitative method rather than a qualitative evaluation.

Key words: Joinpoint regression analysis, Hip Fracture, Antihypertensive drugs, Statins, Pharmacoepidemiology

INTRODUCTION

Joinpoint regression analysis, firstly proposed by Kim et al. [1], is a well-known approach used to study varying trends over time. This model i) identifies the time point(s) in which the trend significantly changes, that is the joinpoint(s), and ii) estimates the regression function with joinpoint(s) previously identified.

Joinpoint regression analysis may be used when the temporal trend of a given quantity, like incidence, prevalence and mortality (e.g., referred to cancer data), is of interest [2-4]. However, although it is easy to implement, such technique has nearly always been applied using calendar year as time-scale [5-8]. Only few studies have considered a different time-scale, including deciles of thyroid stimulating hormone value [9], number of telephone calls [10], age [11,12] and time-on-study [13-17]. The latter characterizes the epidemiological studies in which the starting date of the follow-up period can be easily identified (e.g., when the disease is detected or a drug treatment begins). Joinpoint regression analysis can be therefore applied in several investigations in the framework of public health, for example to answer questions as "Is there an increase in the incidence rate of a specific disease after an environmental or pharmacological exposure?".

The objective of our study is to show the usefulness and the advantages of applying this methodology with time-on-study as time-scale in different epidemiological settings. Data from three already published cohort studies were re-analysed in order to evaluate the trend of: 1) the mortality rate among centenarians in the year after a hospital discharge for hip fracture [18], 2) the proportion of persistent patients in the year after the initial prescription of antihypertensive drugs [19], and 3) the prescription rate of statins one year before and one year after a hospital admission for transient ischemic attack (TIA) [20].

This article is organized as follow. After an introduction to the joinpoint regression model and a brief description of data, we illustrate the applications of the joinpoint regression model to our data and finally the results' discussion.

METHODS

Model fitting remarks

Joinpoint regression model analyses rates, proportions, or any other measure that can be considered (e.g., counts) over time in order to (i) identify the possible time point(s) at which any given trend changes, that is the joinpoint(s), and to (ii) estimate the regression function with joinpoint(s) previously identified. The joinpoint regression model for the observations $(x_1,y_1),\ldots,(x_n,y_n)$, where $x_1<x_2<\ldots<x_n$ represents the time variable and y_i ($i=1,\ldots,n$) is the response variable, can be written as [1]:

$$y_i=\alpha+\beta_1 x_i+\delta_1(x_i-\tau_1)^++\ldots+\delta_k(x_i-\tau_k)^++\varepsilon_i^{(k)}$$

where:

$$(x_i - \tau_k)^+ = \begin{cases} x_i - \tau_k & for\ x_i > \tau_k \\ 0 & otherwise \end{cases}$$

and $\tau_1<\ldots<\tau_k$ are the joinpoints.

The joinpoint regression is different than other similar models, like *piecewise regression*, because it has the constrain of continuity at the change-point(s) and the choice of the number of joinpoint(s) and their locations is estimated within the model. A distinguishing characteristic of this model is that the minimum and the maximum number of joinpoints allowed is arbitrarily set before the analysis while the final number of joinpoint(s) is not fixed *a priori* by the researcher, as in a classical piecewise regression model, but it is established on the basis of a statistical criterion. To determine where to locate the joinpoint(s) on the time-scale in our analyses was adopted the *grid search* method suggested by Lerman [21], which allows the joinpoint(s) to occur exactly at the x_i. A grid is created for all possible positions of the joinpoint (or of the combination of joinpoints), then the model is fitted for each possible position of the joinpoint(s) and the final position of joinpoint(s) is the one that minimizes the sum of squared errors (SSE) of the model [1]. Once the minimum (k_{min}) and the maximum (k_{max}) number of joinpoints is set, the choice of the number of joinpoints statistically significant is made through a scheme of hypothesis tests that compares each time a simpler model, called the null model, and a more complicated model, called the alternative model. The first test performed compares the null model with k_{min} joinpoints to the alternative model with k_{max} joinpoints. If the null hypothesis is rejected the number of joinpoints under the null model is increased by one, while if the null hypothesis cannot be rejected then the number of joinpoints under the alternative model is decreased by one. This procedure continues until the test of the null hypothesis of k joinpoints against the alternative of $k+1$ joinpoints for some $k_{min} \le k < k_{max}$ is completed [1]. For each of the previous hypothesis tests, the statistic used is the ratio between the SSE under the null model and the SSE under the alternative model. Since the distribution of the statistic is not known, an approximate permutation Monte Carlo method is used to calculate each time the p-value under the null hypothesis and the overall asymptotic significance level is maintained through a Bonferroni correction of the overall alpha level [1]. It is important to take into account that even if the final selected model has k joinpoints, the slopes of the $k+1$ temporal segments identified will not be necessarily statistically significant at a pre-specified overall alpha level. The selection of k joinpoints implies only that the model with these joinpoints has a better fit compared to all the other models with $k_{min} \le k < k_{max}$ joinpoints.

In addition, it is possible to compare two joinpoint linear regression functions specifically to determine the identity (coincidence) and the parallelism of the two functions. For the test of coincidence, the null hypothesis investigates if all the parameters of the two regressions (intercepts, slopes and joinpoints) are identical; whereas for the test of parallelism it is studied if the two regression functions are parallel allowing different intercepts. Once

again, the p-value of the test under the null hypothesis is estimated through an approximate Monte Carlo permutation procedure [22]. A full and detailed explanation of the entire methodology is available in the reference articles of Kim et al. [1,22].

Setting

Data were retrieved from the healthcare utilization (HCU) databases of Lombardy, a region of Italy which accounts for about 16% (almost ten million) of its population. The National Health Service covers the entire Italian population and in Lombardy this has been associated since 1997 with an automated system of databases to collect a variety of information. Full details of HCU databases of the Lombardy Region and of the procedure for linking them are reported elsewhere [23-25].

Example 1: Mortality rate in centenarians

The target population included Lombardy residents who experienced a hospital admission for hip fracture after the 100th birthday between January 1st, 2004 and December 31st, 2011. Of these, we selected those who underwent surgery and were discharged alive. Cohort members were followed from the hospital discharge until censoring, i.e., the earliest among the date of outcome onset (death), emigration, or 365 days after the hospitalization discharge.

Monthly mortality rate was calculated by dividing the total number of deaths by the person-days accumulated from the cohort members during a specific month of follow-up.

Example 2: Persistence with antihypertensive treatment

The target population included Lombardy residents with 40 years or older. Of these, we selected those patients with at least one prescription of an antihypertensive agent dispensed during 2005, and the first dispensation was defined as the index prescription. Patients were excluded whether, within 5 years before the index prescription, they received at least one antihypertensive agent, had at least a hospital admission for cardiovascular disease, or received at least a prescription of a drug used for coronary heart disease or heart failure. The remaining patients were included into the final cohort whose members were followed from the date of the index prescription until censoring, i.e., death, emigration, or 365 days after the index prescription.

We identified all prescriptions of antihypertensive drugs dispensed to the cohort members during the follow-up. The period covered by each prescription was calculated dividing the total amount of the drug prescribed

by the specific defined daily dose. Starting from the index prescription, consecutively refilled prescriptions were considered uninterrupted if the time-span between the end of one prescription and the beginning of the following one was less than 90 days; if the between-prescription time-span was longer, treatment discontinuation was assumed. The proportion of persistent patients in each month (i.e., those who did not experienced discontinuity in that month), was calculated by the ratio between the number of subjects who did not interrupt the antihypertensive treatment and the total number of subjects who were still under investigation. With the aim of identify gender-related differences in the persistence with chronic treatments, calculations were performed according to gender.

Full details of using HCU databases of the Lombardy Region in the field of cardiovascular diseases, including methods to measure discontinuation, have been reported elsewhere [26-28].

Example 3: Pattern of statin use before and after TIA

All Lombardy residents hospitalized at least once with a diagnosis of TIA during the years 2008-2009 were selected, and the first hospital admission recording this diagnosis was defined as the index hospitalization. Patients were excluded whether they: i) already experienced any cerebrovascular hospitalization (including TIA) in the eight years preceding the index date; ii) were admitted for a planned hospital access (i.e. only patients who had access to the hospital from emergency wards were included) ; iii) died during the index hospitalization. The remaining patients constituted the study cohort.

We identified all prescriptions of statins dispensed to the cohort members during the period between one year before and one year after the index hospitalization (observational period). The time-window covered by each prescription was calculated from the number of tablets in the dispensed canister, assuming a treatment schedule of one tablet per day [29]. The ratio between the total number of tablets dispensed every month to the cohort members and the person-days accumulated from the cohort members every month during the observational period, was defined as the monthly rate of available statins.

Data analysis

Initial datasets definition was performed using SAS v.9.4 (SAS Institute, Cary, NC). Joinpoint regression analyses were carried out using the Joinpoint Regression Program version 4.3.1.0 provided by the Surveillance, Epidemiology, and End Results Program (National Cancer Institute; http://surveillance.cancer.gov/joinpoint/). We: i) set up one joinpoint given the relatively short time periods considered, ii) applied the logarithmic transformation of the

outcome variable, iii) assumed the heteroscedasticity of observations using the standard errors as weights and iv) assumed uncorrelated errors. Statistical significance was set at the overall 0.05 level.

RESULTS

Example 1: Mortality rate in centenarians

Trend in mortality rates among centenarians in the year after experiencing hip fracture is shown in Figure 1. During the first three months, the mortality rate is around 4 every 1,000 person-days, whereas it is reduced to about 1.5 during the subsequent 9 months of follow-up. One joinpoint is identified in the fourth month, generating two different linear trends in the mortality rate. The results show that i) the trend is stable within each period identified by the model because the apparent decreases of mortality rates are not significant (p=0.092 in the first four months, and p=0.842 in the following ones) and ii) the risk of death is significantly different between periods because the model with one joinpoint fits better than the model with zero joinpoints (p=0.018).

Example 2: Persistence with antihypertensive treatment

Gender specific trends in the proportion of persistent patients in the year after the beginning antihypertensive prescription are shown in Figure 2. For both genders, the proportion of patients who were still in treatment sharply falls during the first five months (p<0.001), decreasing the value up to about 70%. After the fifth month (the joinpoint), trends remain approximately stable afterwards (p=0.273 for men and p=0.442 for women). Men and women significantly differed for the trend in persistence (test for coincidence p-value <0.001). When parallelism was tested, considering the period from the fifth month to the last one, there was no evidence of gender specific difference in trends (p=0.437).

Example 3: Pattern of statin use before and after TIA

Figure 3 shows the trend in monthly rate of available statins (per 1,000 person-days) one year before and one year after the TIA episode. As far as the one-year period before TIA, the rates are around 60 tablets per 1,000 person-days, a slight significant reduction in trend is observed (p=0.012) and no joinpoint was identified. During the year after TIA, rates more than doubled the previous period (being around 150 tablets per 1,000 person-days) and a significant decrease (p=0.031) is observed in the first four months (the joinpoint), whereas the trend remains stable afterwards (p=0.583).

DISCUSSION

This study extends findings of previous observations by our group and shows clearly the usefulness of joinpoint regression analysis in some instances of epidemiological framework.

The application to survival data of centenarians who experienced a hip fracture (example 1) allowed to identify the time point in which the excess of risk, subsequent to this critical event, decreased. Although the trade-off, beyond which finished the at-high-risk condition due to experiencing hip fracture, was noticed for younger targets [30,31], as well as in our previous study [18], the current evidence based on a statistical procedure strengthened our knowledge on this topic.

As far as patients newly treated with antihypertensive agents (example 2), our results confirm the results of previous studies [32,33] that initial antihypertensive therapy is frequently interrupted following just the first year after its starting dispensation. However, our results added to the previous one that the critical time-window concerns the first five months from starting therapy, when a noteworthy and significant decrease in the proportion of persistent patients was observed, while the phenomenon remained almost stable afterwards. In addition, despite the similarity in the patterns, our results offer further evidence that women are less persistent with their antihypertensive drug therapy compared to men [34].

Finally, concerning patients who experienced TIA hospitalization for the first time (example 3), we observed an increase of statins availability after the index hospital admission (about three times higher than before). Because evidence-based guidelines recommend therapy with statins for the secondary prevention of cerebrovascular events [35,36], the result was widely expected. In addition, the trend analysis adds to the previous results that the use of statins: i) had a decreasing trend in the year preceding the onset of TIA; ii) was greatly reduced just few months after the discharge. From all these findings taken together, jointly with the well-established effectiveness of statins for primary and secondary prevention of cardiovascular morbidity and mortality [37], we can speculate that improving adherence with the lipid-lowering treatment could have prevented a portion of TIA which rose up in our setting, as well as could avoid the onset of stroke among patients who already experienced TIA [38].

Use of joinpoint regression analysis has several elements of strength. First, the method aims of identifying time point(s) where the trend significantly changes, so generating quantitative inferences, rather than qualitative, and then often arbitrary. Second, since the joinpoint software is user-friendly and free of charge, the method can be implemented easily and quickly. Third, since temporal trends of several measures can be inquired (e.g., proportions, rates, counts), joinpoint regression analysis is suitable for several fields of the epidemiologic

FIGURE 1. Mortality rate in centenarians in the year after the hospital discharge for hip fracture.
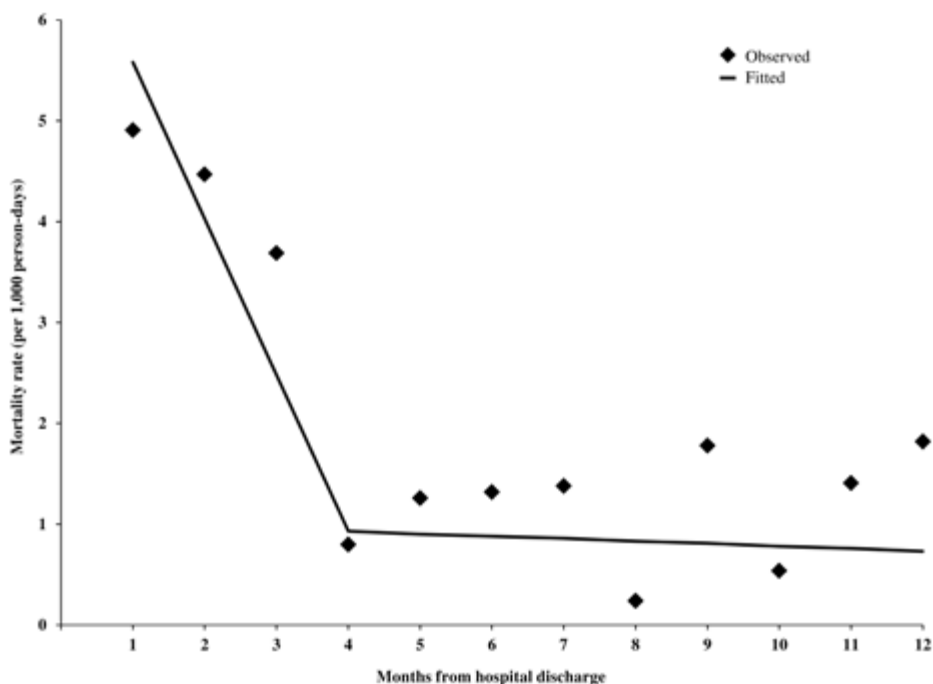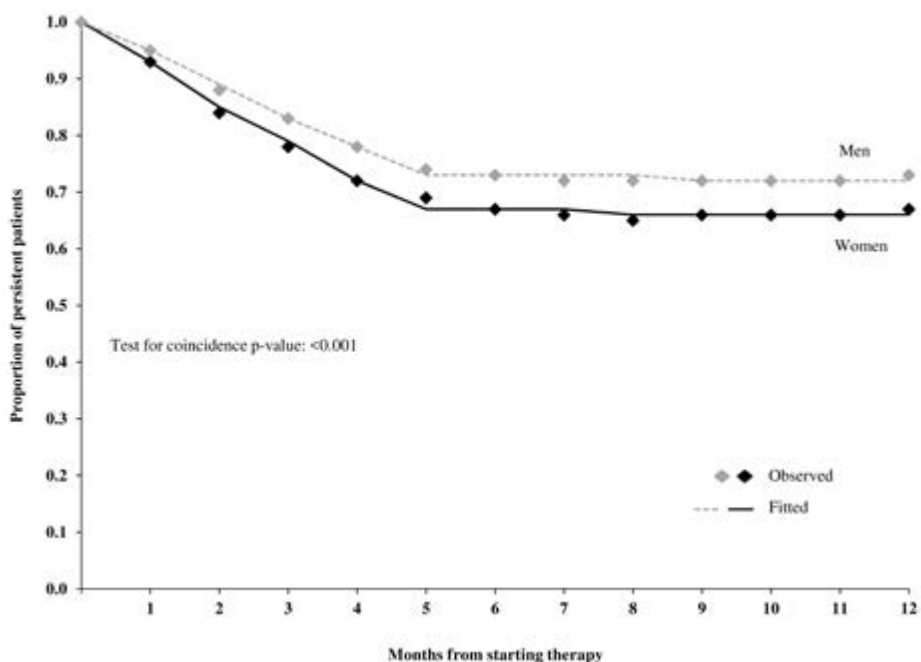

FIGURE 2. Proportion of persistent patients with antihypertensive medications in the year after the beginning of the therapy according to gender.

investigations. Fourth, the joinpoint software allows testing the between-groups trend comparison, i.e., of evaluating null hypothesis of parallelism or coincidence of two segmented-line regression functions. Finally, as above-mentioned, the final number of joinpoint(s) and their position is not fixed by the researcher, as in a classical piecewise regression model, but it is established on the basis of a statistical criterion.

However, the joinpoint regression analysis has some potential limitations. First, as for every statistical model, joinpoint regression relies on some assumptions [1], whose violations and validity must be checked. Since

FIGURE 3. Pattern of statin use during the year before and after a TIA episode.
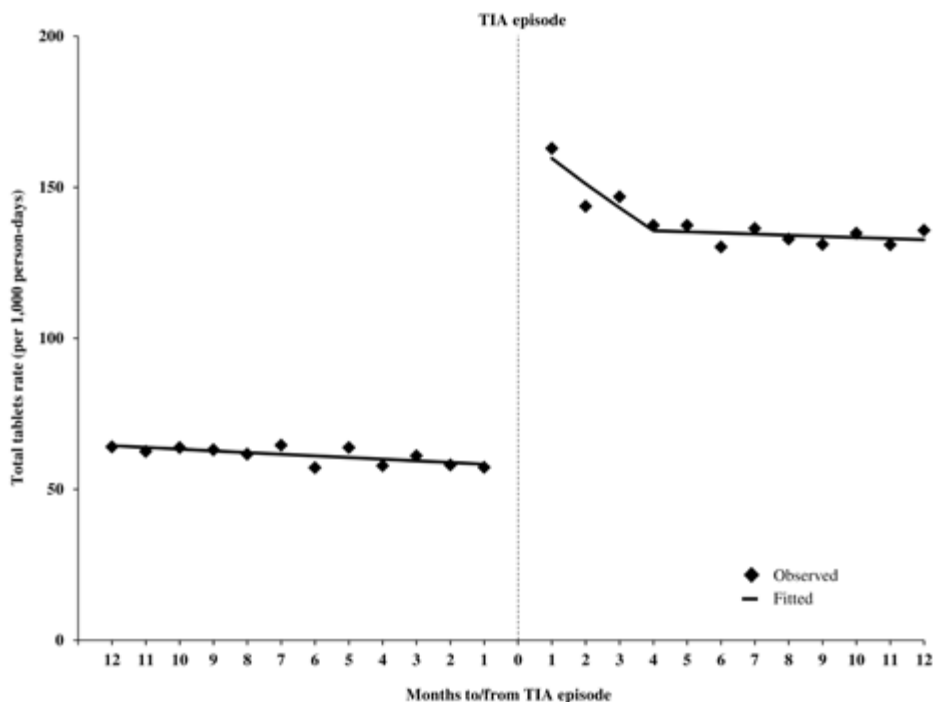
a linear regression is used to fit the data, the following two assumptions were made: i) a straight-line relationship between the outcome variable and the considered time, and ii) the normal distribution with null mean and homoscedasticity for errors. However, if the normality cannot be assumed, an appropriate data transformation, e.g., on a logarithmic scale, may be attempted and easily implemented. Fortunately, the absence of homoscedasticity is not a limit because it may not hold and joinpoint regression model allows to consider different variances for each time value of the outcome variable estimating parameters with the weighted least squares instead of the classical least squares [1].

Second, because joinpoint models analyses aggregated data, it cannot give evidence that may be applied to the individual patient. The example of statins allows us to shed more lights on this limitation. Although we observed an increasing use of statins after the TIA episode, the evidence was based on the rate of drug availability in the whole cohort, rather than on the number of in-treatment patients. In the previous study on this matter, we reported the percentage of patients in treatment before (18%) and after (34%) TIA, showing that cohort members increased the exposure to healthcare services [20]. This suggests that joinpoint regression does not replace conventional analysis, but extends it. Indeed, we evaluated the trend of statins consumption displaying a more pronounced use in the first 4 months. This should alert the physicians because, although some patients begin pharmacological therapy as recommended by guidelines, probably some of those discontinued after few prescriptions undermining

the effectiveness of the treatment. This problem can also be highlighted considering the example of antihypertensives, in which a patient who experienced a discontinuation episode could restart the antihypertensive treatment and we cannot become aware of this. However, since it is unlikely that the same number of patients discontinued and re-started the pharmacological treatment in each month, individuals who interrupted their therapy in the first five months probably did not take any antihypertensive drugs anymore.

CONCLUSIONS

In summary, our applications underscore the usefulness of joinpoint regression analysis in epidemiological framework when the temporal trend is the objective of the investigation. We suggest this tool since it allows the investigators to take advantage of a rigorous statistical procedure instead of carrying out a qualitative evaluation to identify the time point(s) of follow-up at which the trend significantly changes.

Declarations

Ethics approval and consent to participate

According to the rules from the Italian Medicines Agency (available at: http://www.agenziafarmaco. gov.it/sites/default/files/det_20marzo2008.pdf),

retrospective studies using administrative databases do not require Ethics Committee protocol approval.

Conflict of interests

GC received research support from the European Community (EC), the Italian Agency of Drug (AIFA), and the Italian Ministry for University and Research (MIUR). He took part to a variety of projects that were funded by pharmaceutical companies (i.e., Novartis, GSK, Roche, AMGEN and BMS). He also received honoraria as member of Advisory Board from Roche.

Other authors declare that they have no conflict of interest to disclose.

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Authors' contributions

FR and EP conceived the idea for this manuscript. FR, EP and MMC wrote the first draft of the manuscript. All authors participated in the acquisition and analysis of data, statistical interpretation of the data and revision of the manuscript. All authors read and approved the final manuscript.

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