Prevalence of myopia and high myopia, and the association with education: Shanghai Child and Adolescent Large-scale Eye Study (SCALE): a cross-sectional study

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ABSTRACT

Objectives To report on: (a) overall myopia and high myopia prevalence, and (b) the impact of education on the spherical equivalent refractive error in children across Shanghai.

Design Cross-sectional study.

Setting Across all 17 districts of Shanghai.

Participants 910,245 children aged 4–14 years from a school-based survey conducted between 2012 and 2013.

Main outcome measures Data of children with non-cycloplegic autorefraction, visual acuity assessment and questionnaire were analysed (67%, n=606,476). Prevalence of myopia (≤−1.0 D) and high myopia (≤−5.0 D) was determined. We used a regression discontinuity design to determine the impact of school entry cut-off date (1 September) by comparing refractive errors at each age, for children born pre-September to post-1 September, and performed a multivariate analysis to explore risk factors associated with myopia. Data analysis was performed in 2017–2018.

Results Prevalence rates of myopia and high myopia were 32.9% (95% CI: 32.8% to 33.1%) and 4.2% (95% CI: 4.1% to 4.2%), respectively. From 6 years of age onwards, children born pre-September were more myopic compared with those born post-1 September (a) and by comparing refractive errors at each age, for children born pre-September to post-1 September, and performed a multivariate analysis to explore risk factors associated with myopia. Data analysis was performed in 2017–2018.

Conclusions Our findings suggest that myopia is associated with education, that is primarily focused on near-based activities. Efforts to reduce the burden should be directed to public awareness, reform of education and health systems.

INTRODUCTION

The intractable and escalating rise in the prevalence of myopia is fuelling a public health crisis worldwide. In many East and South East Asian countries, including certain parts of China, the prevalence is nearly 80% among children aged 17–18 years. Although the prevalence differs geographically, myopia is prevalent and rising in other parts of the world, including North America, Australia, Europe and Middle East.1–4 For 2015 alone, the global burden related to myopia was estimated at US$244 billion.5 Most alarmingly, the recent decades have seen a trend with myopia presenting at younger ages than before; and consequently, there is a higher overall risk of the individual eye reaching high myopia.1,4 In younger individuals, high myopia increases the risk of retinal breaks and retinal detachment, whereas in older individuals, there is an increased risk for a myriad of complications such as glaucoma, cataract and myopic maculopathy. Indeed, myopic maculopathy is already one of the leading causes of low vision and blindness among working adults in China and South East Asian region.6,7

It is well known that environmental factors such as time outdoors, socioeconomic status, and urban location are significant risk factors for myopia and high myopia. Although a number of studies reported an association between education and myopia,8–11 there is lack of direct evidence that schooling results...
in a more myopic refractive error in younger school-aged children, as well as the impact of early education, including education in kindergarten and primary school, which would be more important for myopia prevention in children. There is a need to better understand the influence of education as they aid in developing interventions to better address the growing burden of myopia.

The Shanghai Child and Adolescent Large-scale Eye Study is a large-scale, prospective, school-based survey undertaken across all 17 districts of Shanghai that provides the prevalence estimates for 606,476 children aged 4–14 years. In this article, we present the overall prevalence of myopia, report the prevalence across the districts and determine the effect of schooling on refractive error.

**MATERIALS AND METHODS**

**Study overview**

Detailed methods of the study were previously reported. Briefly, at the first visit undertaken in 2012–2013, it was aimed to screen all children aged 4–14 years, from kindergarten to junior high, from all the 17 districts and counties of Shanghai, China. All schools and kindergartens, including the school for blind and vision-impaired children were involved in the study. Written consent was obtained from at least one parent/carer. Parents were informed of the study prior to any examination. Details of the process were explained in the methodology article published previously, where related supporting information has also been provided.

**Data collection**

For each participant, both unaided and presenting (ie, with a corrective device if worn) visual acuity (VA) was measured and parents/carers were required to fill in a simple questionnaire in consultation with the child. The questionnaire was designed to elicit known risk factors and behavioural patterns of the child and details of the questionnaire were presented previously. Distance VA was measured using a standard logarithmic VA E chart (National Standard of People’s Republic of China, GB 11533-1989) mounted on an illuminated cabinet with a luminance of 80–320 cd/m². Refraction was conducted using either the Topcon KR-8900 (Tokyo, Japan), Nidek AR-350A (Nagoya, Japan) or HUVITZ HRK-7000A (Gemjeong-dong, South Korea) autorefractors. Measurements taken with these autorefractors were found comparable. The procedure adopted for quality control was previously presented.

**Definitions**

VA in the better eye was used and the prevalence of vision impairment (VI) was calculated based on both uncorrected and presenting VA. Definitions for VI were in accordance with WHO criteria: no VI defined as 6/12 or better, mild VI as worse than 6/12 to 6/18 inclusive, moderate VI as worse than 6/18 to 6/60 inclusive, severe as worse than 6/60 to 3/60 inclusive, and blindness defined as worse than 3/60.

Prevalence of myopia and high myopia was determined using spherical equivalent refractive error (SE) based on non-cycloplegic autorefraction. Myopia and high myopia were defined as SE of ≤−1.0 D and ≤−5.0 D in either eye, respectively. To enable comparisons with previously published data, we also determined the prevalence of high myopia where SE was ≤−6.00 D. Since non-cycloplegic refraction overestimates myopia, we applied an equation to correct for the overestimation, with the equation based on data gathered from a subset of 6017 children of Shanghai of similar ages whose refractive errors were measured using both non-cycloplegia and cycloplegia. The model used non-cycloplegic refractive error, age and uncorrected VA to arrive at the equation:

\[ y = 0.831 + (0.954 \times \text{non cycloplegic SE}) + (0.065 \times \text{age}) + (0.539 \times \text{VA}) \]

\[ R^2 = 0.91, \quad (\text{Eq. 1, where } y = \text{cycloplegic SE}) \]

This adjustment provided an improved and conservative estimate of the myopia prevalence rather than that based on non-cycloplegic refraction alone.

**Statistical analysis**

Prevalence of myopia and high myopia was determined by age, gender and district and was adjusted using equation 1 and further standardised to the age–gender distribution of all eligible children (1.19 million) in Shanghai. The 95% confidence limits were based on Wilson score method. The data for the 145 blind/vision-impaired children were included in the VI assessment but not for analysis related to prevalence of myopia and high myopia. Association of demographic and behavioural factors with myopia and high myopia was explored using univariate and multivariate analysis with factors at \(p<0.05\) included in the multivariate analysis. Model was developed using logistic regression and standard errors adjusted using robust estimation of variance for the clustering effects within each school. Steps included backward elimination followed by forward entry until only significant factors remained and strength of association was described using OR and 95% CI. Area under Receiver Operating Characteristic (ROC) curve was the indicator for model discrimination. Statistical significance was set at 0.01.

The inter-relationship between age, education and refractive error was evaluated using a regression discontinuity (RD) model. RD model is used to estimate the impact of a policy or programme in situations where exposure to a risk factor is based on whether they exceed or fall behind a designated cut-off point. In the present analysis, we considered education as a risk factor. Children born in a given year (same age) were assigned to either pre-September or post-September groups based on the school entry cut-off criteria of 1 September; those born pre-September are admitted to a higher class/grade compared with those born on or post-1 September.
Thus, the aim was to determine if for a given age, children born pre-September had a more myopic refractive error compared with post-September as they were in a higher class at school (greater academic load). Therefore, 1 September was the cut-off point and refractive error was the outcome. The difference in refractive error pre-September and post-September 1 is a measure of the effect of education on refractive error. For each age group, RD was used to model the effect of discontinuity on refractive error (difference of mean RE and 95% CI) at the cut-off point. The RD model used non-parametric local polynomial regression where weights for each data reduce as they move further from the cut-off point and the size of each bin to estimate the discontinuity effect is determined using mean square error.17

Data cleaning and analysis were performed using SAS V.9.3 (SAS Institute) and R V.3.2.0 (Vienna, Austria) in 2017–2018.

Patient and public involvement
Participants and the public were not involved in the design or planning of the study. The study had no patient advisers. Participants were not involved in recruiting other participants or conduct of the study. The study results are not planned to be disseminated to the participants.

RESULTS
Study population
Of the 1196763 eligible children in Shanghai during the study period, a total of 910245 children, with a mean age of 9.0±2.8 years, and a male–female ratio of 53.3:46.7, were enrolled. A total of 2002 schools (average of 452 children per school) participated and the distribution of the population across the ages was previously presented.12 Of the data for the 910245 children, only data from 606476 children (66.6%) were complete with both VA and non-cycloplegic refraction data. The mean age of these children was 9.1±2.8 years and gender distribution was 53.3:46.7 for male versus female and was comparable with the larger sample of 910245 children.

Prevalence of myopia and high myopia
The overall adjusted and standardised prevalence of myopia was 32.9% (95% CI: 32.8% to 33.1%).

The adjusted mean SE was −0.57±1.99 D (range: −22.4 to +15.5 D). Table 1 presents the age and gender-wise distribution of adjusted myopia prevalence and shows that prevalence increased with age with nearly 50% of children aged 11 years old having myopia. Slightly greater prevalence was observed in girls (p<0.001).

The adjusted prevalence of high myopia (≤−5.00 D) was 4.2% (95% CI: 4.1% to 4.2%). Prevalence of high myopia was low until age 8 years (<1%) and increased in prevalence thereafter to approximately 10% or more from age 13 years and reached 15.2% in 14 years. When using a higher cut-off criteria of ≤−6.00 D, the adjusted prevalence fell to 2.1% (95% CI: 2.0% to 2.1%). With the higher cut-off threshold, high myopia was observed in less than 1% of the cohort until age 9 years and thereafter, increased steadily reaching a prevalence of 8.1% in age 14 years.

Considering uncorrected VA, of the 606476 children, 92413 (15.3% of entire sample) had VA ≤6/12 which was mostly due to myopia (86243 eyes, 14.2% of entire sample). Similarly, when presenting VA was considered, 39076/606476 (6.4% of entire sample) had VA ≤6/12 of which 34298 or 5.7% of entire sample were myopic (table 2).

Table 1 Adjusted and standardised prevalence of myopia and high myopia by age and gender

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number</th>
<th>Myopia # of kids</th>
<th>% (95% CI)</th>
<th>High myopia (≤−5.00 D) # of kids</th>
<th>% (95% CI)</th>
<th>High myopia (≤−6.00 D) # of kids</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>16895</td>
<td>1246</td>
<td>7.1 (6.7 to 7.5)</td>
<td>122</td>
<td>0.7 (0.5 to 0.8)</td>
<td>65</td>
<td>0.4 (0.3 to 0.5)</td>
</tr>
<tr>
<td>5</td>
<td>50382</td>
<td>2968</td>
<td>5.7 (5.5 to 5.9)</td>
<td>212</td>
<td>0.4 (0.3 to 0.5)</td>
<td>134</td>
<td>0.3 (0.2 to 0.3)</td>
</tr>
<tr>
<td>6</td>
<td>59531</td>
<td>3821</td>
<td>6.1 (5.9 to 6.3)</td>
<td>267</td>
<td>0.4 (0.4 to 0.5)</td>
<td>160</td>
<td>0.3 (0.2 to 0.3)</td>
</tr>
<tr>
<td>7</td>
<td>73581</td>
<td>7135</td>
<td>9.4 (9.2 to 9.6)</td>
<td>396</td>
<td>0.5 (0.5 to 0.6)</td>
<td>237</td>
<td>0.3 (0.3 to 0.4)</td>
</tr>
<tr>
<td>8</td>
<td>74794</td>
<td>12445</td>
<td>16.8 (16.5 to 17.1)</td>
<td>514</td>
<td>0.7 (0.6 to 0.8)</td>
<td>286</td>
<td>0.4 (0.4 to 0.5)</td>
</tr>
<tr>
<td>9</td>
<td>72516</td>
<td>18912</td>
<td>26.0 (25.7 to 26.3)</td>
<td>942</td>
<td>1.3 (1.2 to 1.4)</td>
<td>442</td>
<td>0.6 (0.5 to 0.6)</td>
</tr>
<tr>
<td>10</td>
<td>62199</td>
<td>22822</td>
<td>36.5 (36.1 to 36.9)</td>
<td>1649</td>
<td>2.7 (2.5 to 2.8)</td>
<td>749</td>
<td>1.2 (1.1 to 1.3)</td>
</tr>
<tr>
<td>11</td>
<td>60492</td>
<td>29682</td>
<td>48.5 (48.1 to 48.9)</td>
<td>2679</td>
<td>4.3 (4.2 to 4.5)</td>
<td>1217</td>
<td>2.0 (1.9 to 2.1)</td>
</tr>
<tr>
<td>12</td>
<td>49366</td>
<td>28898</td>
<td>57.3 (56.9 to 57.7)</td>
<td>3626</td>
<td>7.1 (6.9 to 7.3)</td>
<td>1699</td>
<td>3.3 (3.2 to 3.5)</td>
</tr>
<tr>
<td>13</td>
<td>47253</td>
<td>32077</td>
<td>66.4 (66.0 to 66.9)</td>
<td>5478</td>
<td>11.0 (10.7 to 11.3)</td>
<td>2682</td>
<td>5.4 (5.2 to 5.6)</td>
</tr>
<tr>
<td>14</td>
<td>39447</td>
<td>29343</td>
<td>72.3 (71.9 to 72.8)</td>
<td>6419</td>
<td>15.2 (14.9 to 15.6)</td>
<td>3375</td>
<td>8.1 (7.8 to 8.4)</td>
</tr>
<tr>
<td>Total</td>
<td>606476</td>
<td>189349</td>
<td>32.9 (32.8 to 33.0)</td>
<td>22304</td>
<td>4.2 (4.1 to 4.2)</td>
<td>11046</td>
<td>2.1 (2.0 to 2.1)</td>
</tr>
<tr>
<td>Boys</td>
<td>322953</td>
<td>96555</td>
<td>31.5 (31.3 to 31.7)</td>
<td>10831</td>
<td>3.8 (3.8 to 3.9)</td>
<td>5382</td>
<td>1.9 (1.9 to 2.0)</td>
</tr>
<tr>
<td>Girls</td>
<td>283523</td>
<td>92794</td>
<td>34.6 (34.4 to 34.7)</td>
<td>11473</td>
<td>4.6 (4.5 to 4.6)</td>
<td>5664</td>
<td>2.3 (2.2 to 2.3)</td>
</tr>
</tbody>
</table>
Risk factors associated with myopia and high myopia

Age was the most significant predictive factor for both myopia and high myopia. Compared with a child aged 4–6 years, at 9 years, the OR of having myopia increased by 5 times and to 50 times at 14 years of age (OR=50.9, 95% CI: 46.6 to 55.7; p<0.0001) (online supplemental table 1). Similarly, for high myopia, compared with a child aged 4–6 years, at 9 years of age, the OR for high myopia was 3 times greater and was 44 times greater at 14 years of age (OR=44.1, 38.6 to 50.3; p<0.0001) (online supplemental table 2).

Of the other risk factors, girls had a 20% greater risk of being myopic and highly myopic (for both myopia and high myopia: OR=1.2, 1.1 to 1.2, p<0.0001). Moreover, having either one or both parents myopic increased the odds of myopia in children by 1.6 and 2.2 times compared with children with parents without myopia. A similar trend but slightly higher odds was observed for high myopia, where children with one or both parents with myopia having a higher risk by 1.7 and 2.6 times.

Behavioural factors such as holding a book too close while reading increased the odds for myopia by 20%–50% and watching television at close distances increased the odds by 10%–40%. Interestingly, having a rest after continuous use of eye was protective against myopia (OR:0.80–0.96) and time playing and in entertainment was also mildly protective (OR:0.92). The increase or decrease in odds was similar for both myopia and high myopia suggesting that the behavioural factors experienced and found influencing prevalence were the same.

Additionally, children born post-1 September in a calendar year had an 18%–23% lower risk of being myopic compared with those born pre-September.

Estimating the effect of school start date on SE refractive error

Figure 1 shows the effect of school start date in September on SE refractive error. Considering the case of children aged 6 years old, it is seen that those that born pre-September (corresponding to the vertical grid line) were in first grade of primary school and had a more myopic SE, whereas those born post-September were in upper kindergarten and had a less myopic refractive error. Overall, as children progressed through the school years (or grades), refractive error became more myopic and importantly, the myopic shift in refractive error at the September cut-off point became more pronounced with older children having a significant discontinuity or a much greater difference in refractive error at the 1 September cut-off date.

Figure 2 presents the observed data for each age group and the polynomial line based on the local polynomial regression used in the regression discontinuity model. The graphs illustrate a significant discontinuity at 1 September where the intercept of the polynomial shows a lower refractive error post-1 September. Figure 3 summarises the difference in refractive error for those born pre-September compared with post-1 September.

Table 2. Vision impairment (VI) with myopia and high myopia (based on visual acuity (VA) in the better eye)

<table>
<thead>
<tr>
<th>VI based on presenting VA</th>
<th>VI based on uncorrected VA</th>
<th>VI based on uncorrected VA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snellen VA (% of entire sample)</td>
<td>Number of children with myopia (% of entire sample)</td>
<td>Number of children with high myopia (% of entire sample)</td>
</tr>
<tr>
<td>6/9 (4.8) or better</td>
<td>486 (80.2)</td>
<td>476 (84.1)</td>
</tr>
<tr>
<td>6/9 to 6/12 (4.7)</td>
<td>27 (4.6)</td>
<td>20 (3.9)</td>
</tr>
<tr>
<td>&lt;6/12 (4.7) but 6/18 (4.5)</td>
<td>41 (6.9)</td>
<td>37 (6.2)</td>
</tr>
<tr>
<td>&lt;6/18 (4.5) but 6/60 (4.0)</td>
<td>49 (8.0)</td>
<td>46 (7.9)</td>
</tr>
<tr>
<td>&lt;6/60 (4.0) but 3/60 (3.7)</td>
<td>48 (8.0)</td>
<td>46 (8.7)</td>
</tr>
<tr>
<td>&lt;3/60 (3.7)</td>
<td>46 (8.0)</td>
<td>46 (8.7)</td>
</tr>
<tr>
<td>Total</td>
<td>606 (100)</td>
<td>599 (100)</td>
</tr>
</tbody>
</table>

Table 2 summarises the difference in refractive error for those born pre-September compared with post-1 September.
Those born before 1 September had a more myopic refractive error by approximately 0.2 D at 6 years of age and this difference increased steadily with age and reached approximately 0.5 D at 13 years of age and nearly 0.7 D at 14 years of age.

Using data gathered from the questionnaire, it was seen that during the kindergarten years, time spent outdoors compared with reading/homework was 82.5 vs 48 min but the trend reversed from grade 1 with time spent on reading and homework increasing substantially with each schooling year (figure 4). Compared with kindergarten, in year 9, time spent on reading was nearly 160 min but time outdoors reduced to 56.8 min.

**DISCUSSION**

Our data for 606,476 children aged 4–14 years from the entire Shanghai region found one in three children affected with myopia. At 8, 10 and 14 years of age, prevalence was significantly high at 16.8%, 36.5% and 72.3% for myopia and 0.7%, 2.7% and 15.2% for high myopia, respectively. Previously published data for myopia prevalence (−1.0 D or worse) and using cycloplegic refraction from Shanghai were reported to be approximately 21.9% and 41.8% at ages 8 and 10 years, respectively. The current data using adjusted non-cycloplegic data and indicating high prevalence in young children are a more conservative estimate compared with the previously reported data.
The results demonstrated a striking effect of schooling/education resulting in a more myopic refractive error. Using the discontinuity regression method, the study demonstrated a significant break point or a discontinuity in refractive error at September of each year, that is, at the time children start a new school year. For each age category considered, children born pre-September were in a higher grade at school and had a more myopic refractive error compared with those born post-1 September. For those born pre-September, the refractive error was fairly similar and consistent irrespective of the birth month until the discontinuity point at September. The discontinuity or break point was observed commencing from age 6 years onwards and reached approximately 0.5 D at 13 years of age and 0.67 D at 14 years. An association between myopia and years of schooling was previously reported. Overall, entering the school a year early or being in one grade/class higher at school equated to approximately 0.67 D more myopic refractive error by the time the child was 14 years of age. The threshold date of 1 September coinciding with the start of a new school year in a higher grade is likely associated with an increased academic workload such as greater amount of homework, greater class room workload or other assignments (for example, labs) and this load commonly increases with higher classes at schools. Indeed, data gathered from the questionnaire show a steady increase in the time spent on homework from approximately 1 hour at first grade to nearly 2.5 hours at grades 8–9. Since the predominant form of high myopia in the cohort appears to be an extension of simple myopia, it therefore follows that if myopia is influenced by environmental factors including increased effort at educational tasks, then the same risk factors apply for high myopia.

Figure 3  Estimated difference in refractive error for those born pre-1 September versus post-1 September for each age as determined using regression discontinuity model. Error bars represent 95% CI.

Figure 4  Average reading and outdoor time by grade.

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We reported on the prevalence of high myopia using both −5.00 D cut-off and −6.00 D. Much of the previously reported data refer to −6.00 D as the cut-off and using this criteria, the prevalence of high myopia in Shanghai among 14-year-old children at 8.1% is higher than that reported from Singapore (4.7%, 14 years old), Hong Kong (3.8%, 12 years old), North America (2.0%, 10–14 years old), Western Europe (2.5%, 10–14 years old), and parts of China including Shandong (5.8%), Ejina (5.2%), Anyang (2.7%) and Yunnan (1.3%), but is comparable with the figures from Taiwan (7.8%), Zhejiang (10.4%), Tianjin (6.1%) and Guangzhou (7%, 15 years old) (figure 5). These data suggest that the burden of high myopia is set to increase in the future due to the current generation of children with high myopia ageing and at risk of developing VI and complications such as glaucoma, myopic maculopathy, retinal detachment and cataract. Although some of these complications may present in the young, they commonly manifest in adult life and therefore the need for monitoring and management significantly increases with age and therefore, there will be an increased need for highly skilled but scarce resources such as retinal surgeons, specialist ophthalmologists and rehabilitation services in the coming decades to manage complications and the resultant burden.

The study has several strengths and limitations. The large sample size across the various districts and ages presents us with an opportunity to determine disparities in prevalence within a region. Also, for the first time, we described the use of regression discontinuity model to better understand the effect of education on myopia and refractive error. With respect to limitations, prevalence was determined with non-cycloplegic autorefraction that tends to overestimate the myopia prevalence especially in younger children. We took steps to minimise this bias by applying an equation that considered uncorrected VA and age to reduce the risk. However, Sankaridurg et al reported that using −0.75 D as the criteria to categorise myopia, in spite of the corrective factor, there remained a risk of misclassification in about 20% especially with emmetropic and hyperopic eyes. Therefore, we used a higher threshold to diagnose myopia (ie, −1.0 D rather than the usual −0.50 D) to improve the sensitivity. However, it is possible that our prevalence data may still be subject to some errors and require to be used with caution. Our study also used a questionnaire to gather data on risk factors. Such questionnaires are subject to various biases based on recall, and the qualitative nature of some of the questions (for example, sitting too close to television) is differential and could possibly overestimate or underestimate related parameters. More objective measurements using wearables that collect data on light exposure, physical activity, etc would provide more accurate estimates on behaviour. Additionally, the regression discontinuity analysis may have been affected by factors stemming from asymmetry of data gathered pre-September versus post-September. For example, there are data from more months pre-September versus post-September. The analysis used a local polynomial estimator, where data closer to the cut-off point of 1 September are weighted more than points further away and therefore we believe that asymmetry would not affect the estimation substantially. However, there may be other factors such as variation in birth rates that may influence—we had not considered the impact of such factors. Lastly, this was a cross-sectional study, and therefore, the causal effects of the observed associations could not be determined. Data from a follow-up visit conducted later are presently being analysed and expected to provide further insights.

**CONCLUSION**

Our data demonstrated that the burden of myopia and high myopia in Shanghai is substantial and will grow in the future. We observed an association with education,
that is, a myopic shift in refractive error is associated with each increasing school year and is reflective of increased near-work and decreased outdoor time observed with increasing age. There is an urgent need for public awareness and for reform of education systems to reduce or balance academic loads. In addition, health system should implement measures to monitor vision and refractive error progression in children to identify children at risk for management so as to reduce future increase in myopia. Finally, our study anticipated the need for increased services to cope with future rise in burden and could help develop policies and systems to target the condition in an effective manner.

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Contributors XX, HZ, JZ and RC conceived the study. XH, JZ and LL designed and conducted the study. XH provided the data. WL, SL, TN and ML cleaned and analysed the data. XH, PS and SX wrote the first draft of the manuscript. XX, HZ, JZ, YM, RW, JW and SR made critical revisions. All authors reviewed and approved the final draft. XX is the guarantor and responsible for the overall content.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The Institutional Ethics Committee of Shanghai General Hospital, Shanghai Jiaotong University approved the protocol (ID: 2015KY1149) and the study followed the tenets of the Declaration of Helsinki for experimentation on humans.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The raw/processed data required to reproduce these findings cannot be shared at this time as the data also forms part of an ongoing study. But it is available upon reasonable request.

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REFERENCES


