Observational Study of 1-Year Mortality Rates Before and After a Major Earthquake Among Chinese Nonagenarians

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Background. Little is known about mortality among nonagenarians after an earthquake.

Methods. Using secondary data analyses from the 2005 study called the Project of Longevity and Aging in Dujiangyan (n = 870), 1-year mortality rates were compared among a pre-earthquake group and a post-earthquake group of nonagenarians. All participants were from Dujiangyan, 50 km from the epicenter of the May 12, 2008 earthquake, in China. The pre-earthquake group was a subset of the 870 Project of Longevity and Aging in Dujiangyan participants, ages 93–95 years at the beginning of “Time Frame 1” (July 2005 through June 2006; n = 228). The post-earthquake group was a different subset of the 870 Project of Longevity and Aging in Dujiangyan participants, ages 93–95 years and alive at the beginning of Time Frame 2 (July 2008 through June 2009; n = 235). Time Frame 2 excluded a 7-week period following the earthquake in order to account for deaths due to trauma. Pre-earthquake health assessment data from the 2005 Project of Longevity and Aging in Dujiangyan study were used to calculate unadjusted/adjusted hazard ratios (HRs) for mortality.

Results. One-year mortality rates were 8.3% (19/228) and 16.2% (38/235) in the pre-earthquake group and the post-earthquake group, respectively (p = .01). In unadjusted analyses, only “being in the post-earthquake group” was associated with death (HR = 2.04; 95% confidence interval [CI], 1.17–3.53; p = .011). In the multivariable Cox regression model, being in the post-earthquake group continued to be the strongest risk factor associated with mortality (HR = 2.47; 95% CI, 1.39–4.40; p = .002). Other significant risk factors included impaired cognition (HR = 1.97; 95% CI, 1.10–3.53; p = .024), serum albumin (HR = 0.90; 95% CI, 0.82–0.98; p < .015), and serum triglycerides (HR = 1.51; 95% CI, 1.15–1.99; p = .003).

Conclusion. The May 12, 2008 earthquake in Wenchuan, China, was associated with a twofold increase in the 1-year mortality among a group of nonagenarians who lived nearby.

Key Words: Earthquake—Nonagenarians—Mortality.

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Earthquakes are one of the most dramatic examples of a psychological stress affecting physical health. Several reports have linked the stress related to earthquakes to an increase in non-trauma mortality rates (1–6). On May 12, 2008, a 7.8 magnitude earthquake struck the southwest region of China. It is believed that 69,227 people died as a direct result of the earthquake. The epicenter of the earthquake was Wenchuan, which is 50 km away from a city called Dujiangyan. Approximately 3 years prior to the earthquake (July 2005), the Project of Longevity and Aging in Dujiangyan (PLAD) study collected health data on 870 Chinese aged 90 years and older.

The purpose of this paper is to compare mortality rates among nonagenarians who experienced or did not experience the earthquake and to identify risk factors associated with mortality, using pre-earthquake health assessment data from the PLAD. Our hypothesis was that among the very elderly, being exposed to a major stressful event such as an earthquake is a more important risk factor associated with 1-year mortality than conventional risk factors such as sociodemographic characteristics, self-rated health, disability, having three or more chronic illnesses, and cognitive impairment.

Methods

Setting and Participants

Dujiangyan had a population of 621,980 in 2005. It is near Chengdu, the capital of Sichuan province in southwest China. In July 2005, the PLAD study was done in which researchers from Sichuan University in conjunction with...
local officials and hospitals/clinics conducted face to face interviews, physical measurements, and collected blood samples on 870 of 1,401 Chinese elderly aged 90 years and older (62.1% capture rate) (7,8). The measures for the PLAD were based on studies from the United States (9), Canada (10), and China (11). They included sociodemographic characteristics, geriatric assessments, and biomedical measurements.

Ages (dates of birth) are felt to be accurate in the PLAD study for the following reason: (1) The participants were recruited from a government registry and the Bureau of Statistics at the Dujiangyan City government has registered each person; (2) all Chinese have identification cards; the Chinese government began issuing “hukoben” cards (identification cards) in the 1950s (the People’s Republic of China was established in 1949); in the 1950s, this population would have been ages 30 to early 40s and would have been given one of these cards; (3) the Chinese zodiac (“which animal year were you born in?”) is an integral part of the culture and all Chinese know their zodiac animal (this practice can be traced back to at least the 14th century BC); and (4) age was also verified during the interview with family members.

**Design**

This was an observational study using 2009 follow-up mortality data and secondary data analyses of the original PLAD data obtained in 2005. The following epidemiological design was developed in order to take into account the need for a “control group” who did not experience the earthquake (pre-earthquake group), which would have similar characteristics (ie, from the same population, same environment, same age) to a group who experienced the earthquake (post-earthquake group).

The pre-earthquake group was a group of participants (subset of the 870 PLAD participants) who were aged 93–95 years at the beginning of “Time Frame 1” (July 2005 through June 2006; n = 228). The post-earthquake group was a group of participants (a different subset of the 870 PLAD participants) who were aged 93–95 years at the beginning of Time Frame 2 (July 2008 through June 2009; n = 235). Note, the participants in this group were aged 90–92 years at the beginning of Time Frame 1, but the survival analysis for the exposure to the earthquake was done during “Time Frame 2,” thus controlling for the effect of age. Only participants within the post-earthquake group who were alive at the beginning of Time Frame 2 were included in the survival analysis for this group. In order to account for deaths due to trauma related to the earthquake, we intentionally started Time Frame 2 in July 2008, excluding a 7-week period following the earthquake.

**Outcome Measure**

Mortality data were obtained from the local government in July 2009. The time of death data are believed to be accurate for the following reason. Local governments (the Bureau of Civil Affairs) are required to pay each person aged 80 years and older a type of monthly pension. This is closely followed, and the penalty for any family trying to collect payments for a deceased relative is serious. As of July 2009, 39/870 PLAD participants had not been identified as alive or dead, 12 in the pre-earthquake group, 17 in the post-earthquake group, and 10 of these missing participants were in the greater than or equal to 96 years age group. Data on reasons for death were not available.

**Other Measures**

The following variables were chosen for the analyses in the current study based on findings from other studies of mortality risk and aging (12–19): education (none vs some), religion (none vs any type of religion), self-rated health (very good, good, or average vs bad or very bad), activities of daily living (ADL) impairment (not impaired [0 impairments] vs impaired [1 ADL impairment]), chronic medical conditions (≥3 chronic conditions vs <3), cognitive impairment (“not impaired” >18 on Mini-Mental State Examination vs “impaired” [≤18 on Mini-Mental State Examination]) (20), and number of hospitalizations in the past year.

For each ADL (feeding, dressing, grooming, bathing, walking, and toileting) (21), impairment was considered present if the participant reported “difficulty,” “need for help,” or “can’t do task.” Thirteen chronic medical conditions were queried about: hypertension, heart problems, cerebrovascular diseases, diabetes, respiratory problems, gastrointestinal problems, osteoarthritis, hearing problems, vision problems, fall within past 1 year, fracture, fecal and urinary incontinence (having either), and cancer (excluding skin cancer). For cognitive impairment, the number less than 18/30 was chosen because of the low educational level of this population (22). None of the population had higher than a middle school education. Also, because less than 10% of participants did not have a Mini-Mental State Examination performed, a dummy variable was created for missing data on cognitive impairment (“unknown”). Other dichotomous variables from the original PLAD study included gender, currently smokes, drinks alcohol, or drinks tea. Continuous variables included systolic blood pressure, diastolic blood pressure, hemoglobin, fasting serum glucose, serum albumin, and lipid profiles.

As a measure of psychological health, the Philadelphia Geriatric Center Morale Scale was utilized in the PLAD study. However, participants who had cognitive impairment based on the Mini-Mental State Examination cut off score did not do this scale. The amount of missing data made this variable unusable in the analyses.

Informed consent was obtained from all participants or their legal proxies. The Sichuan University Research Ethics Committee approved the PLAD study, and the Saint Louis University IRB approved the secondary data analyses.
PRE- AND POST-EARTHQUAKE MORTALITY RATES

Table 1. Baseline Characteristic and Comparison of the Pre-earthquake Group and Post-earthquake Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pre-earthquake Group (n = 228)</th>
<th>Post-earthquake Group (n = 235)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female), %</td>
<td>63.4</td>
<td>69.4</td>
<td>.177</td>
</tr>
<tr>
<td>Education (some), %</td>
<td>26.4</td>
<td>28.4</td>
<td>.628</td>
</tr>
<tr>
<td>Religion (any), %</td>
<td>21.2</td>
<td>24.1</td>
<td>.459</td>
</tr>
<tr>
<td>Self-rated health is “bad” or “very bad”, %</td>
<td>19.3</td>
<td>13.2</td>
<td>.082</td>
</tr>
<tr>
<td>ADL impairment (&gt;1 ADL deficit), %</td>
<td>32.2</td>
<td>25.6</td>
<td>.123</td>
</tr>
<tr>
<td>&gt;3 Chronic medical conditions, %</td>
<td>48.2</td>
<td>46.8</td>
<td>.757</td>
</tr>
<tr>
<td>Cognition, %</td>
<td></td>
<td></td>
<td>.023</td>
</tr>
<tr>
<td>Not impaired</td>
<td>36.4</td>
<td>48.9</td>
<td></td>
</tr>
<tr>
<td>Impaired</td>
<td>51.8</td>
<td>40.9</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>11.8</td>
<td>10.2</td>
<td></td>
</tr>
<tr>
<td>Number of hospitalizations in past year, M (SD)</td>
<td>1.2 (2.3)</td>
<td>1.1 (1.9)</td>
<td>.538</td>
</tr>
<tr>
<td>Currently smokes, %</td>
<td>48.5</td>
<td>43.2</td>
<td>.254</td>
</tr>
<tr>
<td>Currently drinks alcohol, %</td>
<td>29.6</td>
<td>26.9</td>
<td>.517</td>
</tr>
<tr>
<td>Currently drinks tea, %</td>
<td>43.2</td>
<td>45.9</td>
<td>.553</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg), M (SD)</td>
<td>139 (23)</td>
<td>140 (22)</td>
<td>.634</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg), M (SD)</td>
<td>73 (12)</td>
<td>72 (12)</td>
<td>.640</td>
</tr>
<tr>
<td>Hemoglobin (g/dL), M (SD)</td>
<td>11.4 (1.7)</td>
<td>11.4 (1.4)</td>
<td>.914</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL), M (SD)</td>
<td>79.3 (23.4)</td>
<td>81.1 (27.0)</td>
<td>.807</td>
</tr>
<tr>
<td>Albumin (g/dL), M (SD)</td>
<td>4.3 (0.32)</td>
<td>4.3 (0.28)</td>
<td>.214</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL), M (SD)</td>
<td>158.3 (30.1)</td>
<td>162.2 (32.8)</td>
<td>.821</td>
</tr>
<tr>
<td>LDL (mg/dL), M (SD)</td>
<td>88.8 (20.9)</td>
<td>84.9 (25.1)</td>
<td>.609</td>
</tr>
<tr>
<td>HDL (mg/dL), M (SD)</td>
<td>59.4 (13.1)</td>
<td>59.8 (12.7)</td>
<td>.728</td>
</tr>
<tr>
<td>Triglycerides (mg/dL), M (SD)</td>
<td>113.6 (74.3)</td>
<td>107.4 (54.0)</td>
<td>.322</td>
</tr>
</tbody>
</table>

Note: The following are the Systeme International (SI) units and conversion factors (multiply) for laboratory values in table. Glucose (mmol/L): 0.0555; albumin (g/L): 10; total cholesterol, LDL, HDL (mmol/L): 0.0259; triglycerides (mmol/L): 0.0113. Odds ratios are based on SI units. ADL = activities of daily living; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Data Analyses

Descriptive statistics for baseline characteristics of the pre-earthquake and post-earthquake groups were compared using chi-square test for dichotomous variables and t tests for continuous variables. A Kaplan–Meier survival curve was done for each group.

Risk for mortality was modeled using Cox regression survival analyses to calculate hazard ratios (HRs) (with 95% confidence intervals [CI]) in two steps to reduce the number of variables and avoid overfitting models since the number of events (deaths) was small (23). These analyses examined all participants (pre-earthquake group and post-earthquake group) together. In the first step, Cox regression analyses were done for each demographic, physical measurement, and laboratory value to obtain unadjusted HRs. For the second step, a Cox regression analysis was done using all variables from the first step with associations of p ≤ .10. In addition, the following variables were added to the second step because they have been found to be associated with mortality in other studies of older populations: gender, chronic illnesses, ADL impairment, and cognitive impairment. For the Cox regression analysis, the assumption of proportionality was tested and met. All analyses were performed using SPSS, version 15.0 (SPSS, Inc., Chicago, IL).

RESULTS

As seen in Table 1, there were no differences in baseline characteristics of the pre-earthquake group and the post-earthquake group except for cognitive impairment. The 1-year mortality rate in the pre-earthquake group was 8.3% (19/228) and that of the post-earthquake group was 16.2% (38/235; p < .001). The month-by-month mortality over 12 months is depicted in the Kaplan–Meier survival curve (Mantel–Cox log rank chi-squared = 6.8, p = .009; Figure 1).

In the unadjusted Cox regression analyses, only “being in the post-earthquake group” reached statistical significance (Table 2). Two variables reached the p value <.10: albumin (HR 0.93; 95% CI, 0.86–1.01; p = .084) and triglycerides (TG; HR 1.27; 95% CI; 0.99–1.64; p = .063). These two variables were used in the adjusted Cox regression analysis.

The adjusted Cox regression analysis examining risk factors for mortality are seen in Table 3. As noted in the methods, gender, chronic illnesses, ADL impairment, and cognitive impairment were entered into this analysis in order to control for variables that have been found in other studies to be associated with risk of mortality, in addition to albumin and TG. Being in the post-earthquake group continued to be the strongest risk factor associated with mortality (HR 2.47; 95% CI, 1.39–4.40; p = .002). Other risk factors with statistically significant associations were impaired cognition (HR 1.97; 95% CI, 1.10–3.53; p = .024), serum albumin (HR 0.90; 95% CI, 0.82–0.98; p = .015), and serum TG (HR 1.51; 95% CI, 1.15–1.99; p = .003). Female gender approached significance (HR 0.56; 95% CI, 0.31–1.02; p = .059).

When the unadjusted Cox regression analyses were performed on each group separately, there was a trend toward significance in the pre-earthquake group for three variables,
which trend was not present for the post-earthquake group. HRs for the pre-earthquake group for ADL impairment, three or more chronic illnesses, and cognitive impairment were 2.32 (95% CI, 0.942–5.708; \( p = .067 \)), 1.91 (95% CI, 0.750–4.839; \( p = .175 \)), and 2.33 (95% CI, 0.760–7.144; \( p = .139 \)), respectively. HRs for the post-earthquake group for ADL impairment, three or more chronic illnesses, and cognitive impairment were 0.62 (95% CI, 0.273–1.409; \( p = .254 \)), 1.14 (95% CI, 0.602–2.147; \( p = .693 \)), and 1.42 (95% CI, 0.744–2.712; \( p = .287 \)), respectively. None of the sociodemographic characteristics or behavioral risk factors (gender, educational level, religion, currently smokes, currently drinks alcohol, currently drinks tea, or self-rated health) were significantly associated with mortality or showed a trend toward significance except for currently drinks alcohol in the post-earthquake group (HR 1.96; 95% CI, 1.020–3.747; \( p = .043 \)). For biomedical and laboratory parameters, two variables were associated with mortality in the pre-earthquake group (albumin: HR 0.89; 95% CI, 0.793–0.999; \( p = .048 \), and TG: HR 1.54; 95% CI, 1.199–1.967; \( p = .001 \)), and none were associated with mortality or trended toward significance in the post-earthquake group.

**DISCUSSION**

The results of this study suggest that the 1-year mortality rate for a group of Chinese nonagenarians following an earthquake is increased compared with a group of age-matched Chinese nonagenarians during a 1-year time frame before an earthquake. The findings in this study highlight what has been found in 9 of 10 published studies about earthquakes: There is an unexplained increase in mortality following an earthquake (1–6,24–27) (Table 4). Of note, for the current study is the exceptional magnitude of the Wenchuan earthquake.

The results of this study also suggest that a major event such as an earthquake may be a more important risk factor for mortality than conventional risk factors such as disability, comorbidities, and cognitive impairment among the very old (14,15,19). After adjusting for other potential risk factors of mortality, being in the post-earthquake group remained the strongest predictor of death.

A plausible explanation for our findings comes from studies examining the pathophysiology of “earthquake-related stress,” which suggest a role for biochemical changes. One study of 42 older patients living near the epicenter of the Kobe earthquake had pre-/post-earthquake data. Hematocrit, fibrinogen, Von Willebrand factor, and D-dimer all showed a significant increase in levels after the earthquake, but lipid profiles did not change (28). In another study, cortisol, growth hormone, and prolactin levels were assessed in 34 earthquake survivors with Post-Traumatic Stress Disorder (PTSD) (according to DSM-IV), 30 earthquake survivors with subclinical PTSD, and 34 normal controls. Only earthquake survivors diagnosed with PTSD had significantly higher serum growth hormone levels. However, earthquake
Table 2. Unadjusted Cox Regression Analyses for Mortality Risk for All Participants (pre-earthquake group plus post-earthquake group; n = 463)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted Hazard Ratios (95% confidence interval)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Being in the post-earthquake group</td>
<td>2.04 (1.17–3.53)</td>
<td>.011</td>
</tr>
<tr>
<td>Gender (female), %</td>
<td>0.84 (0.49–1.44)</td>
<td>.532</td>
</tr>
<tr>
<td>Education (some), %</td>
<td>0.94 (0.52–1.70)</td>
<td>.845</td>
</tr>
<tr>
<td>Religion (any), %</td>
<td>1.12 (0.61–2.04)</td>
<td>.721</td>
</tr>
<tr>
<td>Self-rated health is “bad” or “very bad”</td>
<td>1.13 (0.57–2.24)</td>
<td>.731</td>
</tr>
<tr>
<td>ADL impairment (&gt;1 ADL deficit)</td>
<td>1.04 (0.59–1.83)</td>
<td>.905</td>
</tr>
<tr>
<td>&gt;3 Chronic illnesses</td>
<td>1.33 (0.79–2.24)</td>
<td>.282</td>
</tr>
</tbody>
</table>

Cognition
- Not impaired: Reference category
- Impaired: 1.47 (0.85–2.53)
- Unknown: 0.54 (0.16–1.82)
- Number of hospitalizations in past year: 0.97 (0.85–1.11)
- Currently smokes: 0.94 (0.56–1.58)
- Currently drinks alcohol: 1.31 (0.76–2.27)
- Currently drinks tea: 1.21 (0.72–2.03)
- Systolic blood pressure: 0.99 (0.98–1.01)
- Diastolic blood pressure: 0.99 (0.96–1.01)
- Hemoglobin: 0.99 (0.98–1.01)
- Fasting glucose: 0.93 (0.76–1.15)
- Albumin: 0.93 (0.86–1.01)
- Total cholesterol: 0.84 (0.61–1.16)
- LDL: 0.87 (0.56–1.36)
- HDL: 0.60 (0.27–1.34)
- Triglycerides: 1.27 (0.99–1.64)

Notes: Odds ratios are based on SI units. ADL = activities of daily living; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Table 3. Adjusted Cox Regression Analysis of Mortality Risk*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Hazard Ratios (95% confidence interval)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Being in the post-earthquake group</td>
<td>2.47 (1.39–4.40)</td>
<td>.002</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>0.56 (0.31–1.02)</td>
<td>.059</td>
</tr>
<tr>
<td>ADL impairment (&gt;1 ADL deficit)</td>
<td>1.12 (0.62–2.01)</td>
<td>.704</td>
</tr>
<tr>
<td>&gt;3 Chronic illnesses</td>
<td>1.26 (0.73–2.16)</td>
<td>.404</td>
</tr>
</tbody>
</table>

Cognition
- Impaired: 1.97 (1.10–3.53)
- Unknown: 0.52 (0.15–1.82)
- Albumin: 0.90 (0.82–0.98)
- Triglycerides: 1.51 (1.15–1.99)

Notes: ADL = activities of daily living.
*Variables entered into the model were “being in the post-earthquake group, gender, ADL impairment, >3 chronic illnesses cognitive impairment, albumin, and triglycerides.

were not associated with mortality, we reviewed the data for outliers. Twelve participants had TG levels greater than 3.4 mmol/L (>300 mg/dL) of which six (50%) died. When the adjusted Cox regression analysis was repeated excluding these 12 participants, serum TG level was no longer associated with mortality (HR = 1.04). The values of the HRs for the other variables in the regression analysis changed less than 0.1 except for “being in the post-earthquake group,” which went from 2.46 to 2.69.

Although the association between female gender and mortality only approached statistical significance, this association is in the expected direction. It is known that general life expectancy of women is longer than men, as well as in certain medical situations, but the biological basis for this is still being sought after (31–33).

One of the strengths of this study was the 1-year time period for analysis of mortality. Previous reports on earthquake stress–related mortality analyzed relatively shorter periods of time (1–6,21–24). The longest was the report on the Kobe earthquake (4 months) (1).

There are several limitations of this study. The study population here was not at the epicenter of the earthquake. It was 50 km. Thus, it is uncertain the degree of stress each participant experienced related to the earthquake. However, over 400,000 of the 621,980 inhabitants of Dujiangyan were displaced from their homes. Also, a study of hospitalized patients on a cardiac telemetry floor in Chengdu, China (80 km away from the epicenter), showed the following. During three time frames (1-month period after the earthquake, 1-month period before the earthquake, and a similar 3-month time period 1 year before the earthquake), the number of hemodynamically unstable ventricular tachyarrhythmias were 67 events/10,000 person-days, 7 events/10,000 person-days, and 14 events/10,000 person-days, respectively (p < .001 for both the 1-month after and 1-month before the earthquake comparison and the 1-month after and 3-month time period 1 year before the earthquake comparison) (34).

Another limitation of the study is that actual reasons for death in our population were unavailable. However, we believe that trauma-related deaths should have occurred within 6 to 7 weeks of the earthquake. This was our reason for analyzing mortality during the chosen time frames. Also, the fact that the survival curves get further apart after 3 months and continue to divide over the full year suggests that early trauma is not the cause of the mortality difference. This does not, however, rule out the possibility of late effects of trauma. We believe that increased mortality should not have been related to infectious causes related to the earthquake. There is evidence of relatively quick medical responses to the disaster (35), and according to one report, the government claimed that “disease outbreaks were avoided, medical services were generally restored rapidly, and a return to the baseline mortality rate was achieved relatively quickly (36).”
Another limitation of this study is that the risk profile of the post-earthquake group could have changed (except for gender and education) between the time they were assessed (2005) and the time that their 1-year mortality was measured (2008–2009). This limits the validity of our findings concerning the comparison of traditional risk factors for mortality and the risk associated with the earthquake exposure.

A related limitation of this study is that traditional risk factors of mortality have been examined in most other studies of older persons over longer periods of time than just 1 year, as was done in this study. However, one study of nonagenarians using 15 months follow-up showed that disability and cognitive impairment were significant risk factors of mortality (14). Another study of persons aged 84 years and older with 2-year increment periods of follow-up showed that disability was associated with mortality (15).

In summary, the May 12, 2008 earthquake in Wenchuan, China, was associated with a twofold increase in the 1-year mortality among a group of nonagenarians who lived nearby. More studies are needed before a conclusion can be made that a major stressful event such as an earthquake may be a more important risk factor for mortality than conventional risk factors among this age group.

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Study concept and design: J.H.F., B.D., J.M.G., and J.E.M.

Literature search: J.H.F., B.D., J.M.G., and J.E.M.

Acquisition of data: B.D., H.W., and Y.Z.


Drafting of the manuscript: J.H.F.

Critical revision of the manuscript for important intellectual content: J.H.F., B.D., H.W., Y.Z., J.M.G., T.K.M., and J.E.M.

Statistical analysis: J.H.F., B.D., T.K.M.

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**References**


