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Association of serum vitamin D with active human cytomegalovirus infections in Chinese children with systemic lupus erythematosus, CHINA

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# These authors contributed equally to this work

Running title: Association of vitamin D with cytomegalovirus infections

Keywords: vitamin D; human cytomegalovirus; children; systemic lupus erythematosus;
**Abstract:** Vitamin D (VD) plays an important role in infectious and autoimmune diseases. We investigated the association between serum VD levels and active human cytomegalovirus (HCMV) infections in pediatric systemic lupus erythematosus (SLE) patients. From January 2015 to June 2021, one hundred and twenty children diagnosed with SLE and 100 healthy children were enrolled. Using ELISA, serum 25(OH)D levels were detected. Serum anti-HCMV IgM antibodies were measured by a chemiluminescence immunoassay. Comparisons of 25(OH)D levels between SLE patients and healthy children were performed, as well as subgroups of SLE patients with or without active HCMV infections. Serum 25(OH)D levels of SLE patients were significantly lower than those of healthy children (35.3 ± 12.9 vs 49.3 ± 15.3, \( P < 0.001 \)). VD deficiency ratio was higher in SLE patients (89.2%) than that in healthy children (52.0%). Serum 25(OH)D levels in the positive anti-HCMV IgM group were significantly lower than those of the negative anti-HCMV IgM group (30.6 ± 12.3 vs 38.2 ± 12.5, \( P < 0.001 \)). The severe VD deficiency ratio was significantly higher in HCMV-IgM(+) SLE patients (42.2%) than that in HCMV-IgM(-) SLE patients (13.3%). This study suggested that serum VD level is associated with active HCMV infections in pediatric SLE patients.

**Introduction**

Systemic lupus erythematosus (SLE) is a prototypical complex autoimmune disease, which is featured by a large array of autoantibody productions that results in multiorgan damage, including kidney, skin, and blood vessels (1). While the specific etiologic mechanisms of SLE remain unknown, the interactions between genetic,
metabolic, hormonal, and environmental factors are generally thought to be involved (2). Several studies indicated that SLE patients had significantly lower serum vitamin D (VD) levels and higher ratios of VD insufficiency when compared with healthy controls. VD deficiency might be an important environmental factor in the occurrence and progression of SLE (3). However, other studies drew inconsistent results (4, 5). Moreover, research on the relationship between pediatric SLE and VD is relatively sparse, that remains nevertheless to be investigated.

Pathogen infection is one of the most significant causes of morbidity and mortality in pediatric SLE (6). SLE patients are at increased risk of opportunistic infection due to immune dysfunction and the application of glucocorticoids or immunosuppressants (7). As one of the most frequent pathogens in SLE patients, human cytomegalovirus (HCMV) remains latent in the host for a lifetime after infection and can be reactivated when the immune system is dysfunctional (8). Furthermore, HCMV was thought to be one of the causal etiologies of SLE. HCMV antigens may cross-react with antibodies against nuclear antigens to cause new or recurrent SLE (9, 10). Recently, additional studies have shown that VD can enhance immune clearance against pathogens and promote the secretion of inflammatory cytokines (11). Moreover, epidemiological studies have elucidated the link between VD deficiency and susceptibility to virus infection (12). Nevertheless, few studies have been conducted to define any association between VD levels and active HCMV infections in SLE patients.

Consequently, we inquired about the correlation between pediatric SLE and VD
by comparing the serum 25(OH)D levels in pediatric SLE patients with healthy children, for the 25(OH)D is exactly the main circulating form of vitamin D in vivo. At the same time, we further investigated the association of 25(OH)D with active HCMV infections in pediatric SLE patients by comparing with noninfected SLE patients.

**Materials and methods**

**Participants:** We studied inpatients diagnosed with SLE who attended the Children's Hospital, Zhejiang University School of Medicine from January 2015 to June 2021. Inclusion criteria were as follows: 1) Patients meet SLE diagnostic criteria defined by the American College of Rheumatology criteria (13). 2) Patients and guardians agreed to participate in this study. Exclusion criteria were as follows: infected with hepatitis B virus, hepatitis C virus, HIV, syphilis, Epstein-Barr virus, and other infectious diseases in addition to HCMV infections. The patient's clinical presentation and medication status were obtained from medical records. Systemic lupus erythematosus disease activity index (SLEDAI) was used to assess disease activity. The healthy control group included 100 age- and sex-matched healthy children who underwent physical examination in the physical examination center of our hospital. This study was approved by the Ethics Committee of Children's hospital, Zhejiang university school of medicine.

**Laboratory measurements:** The serum concentration of 25(OH)D was detected by enzyme-linked immunosorbent assay (ELISA) (Idsisys, England). We defined vitamin D deficiency as serum 25(OH)D below 50 nmol/l, vitamin D severely
deficiency as serum 25(OH)D below 25 nmol/l, and vitamin D sufficiency as serum
25(OH)D above 50 nmol/l (14).

Serum anti-HCMV IgM antibodies were analyzed by using a fully automatic
chemiluminescence immunoassay processor (YHLO, China). According to the
manufacturer's instructions, all specimens were treated with a diluent containing
rheumatoid factors and lupus-associated autoantibodies neutralization reagent to avoid
interference by rheumatoid factors and lupus-associated autoantibodies (15). The
results were not affected by jaundice, hemolysis, lipemia, and total serum
protein. There was no cross-reaction with anti-toxoplasma IgM, anti-rubella IgM,
anti-herpes simplex virus (type 1 and 2) IgM, anti-mycoplasma pneumonia IgM,
anti-HCMV IgG, anti-treponema pallidum IgM, anti-Epstein-Barr virus early antigen
IgM, and anti-Epstein-Barr virus capsid antigen IgM. The titer of serum anti-HCMV
IgM indexes at $\geq 22.0$ AU/ml was regarded as positive, indicating an active HCMV
infection.

The serum biochemical index was measured by a standardized colorimetric test
(Beckman AU5800 USA). All assays were performed according to the manufacturer's
instructions.

**Statistical analysis:** Data analyses were performed using SPSS software version
19.0. All data were described as mean $\pm$ standard deviation (SD). Quantitative
variables conforming to normal distribution were compared by T-tests of hypotheses.
Measurement data that did not conform to the normal distribution were compared by
the Kruskal–Wallis test, providing an odds ratio (OR) and 95% confidence interval
Frequencies were described as percentages (%) and they were compared by the chi-square test. \( P \)-value < 0.05 was considered statistically significant.

**Results**

From January 2015 to June 2021, a total of 120 SLE patients met our inclusion criteria. The group consisted of 99 females and 21 males ranging from 8 to 17 years old. The mean age was 12.7 ± 2.2 years old. The controls consisted of 83 females and 17 males. The mean age was 12.3 ± 2.2 years old. Demographic and baseline characteristics of the HCMV IgM positive rate are provided in Table 1. The treatment status of SLE patients was as follows: 112 patients (93.3%) had used glucocorticoids (> 10 mg/day) before laboratory examination; 114 cases (95.6%) were treated with immunosuppressants (mainly including cyclophosphamide, mycophenolate mofetil, methotrexate, and cyclosporine) within 30 days. Forty-five SLE patients (37.5%) exhibited positive anti-HCMV IgM and no positive individuals were found in the control group.

As shown in Table 1, SLE patients exhibited significantly lower serum 25(OH)D levels than controls (35.3 ± 12.9 vs. 49.3 ± 15.3, \( P < 0.001 \)). The cutoff value of serum vitamin D deficiency is recommended by the Institute of Medicine (US) Committee and the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (14,16). In adults, serum 25(OH)D \( \leq 50 \) nmol/L is the criteria for vitamin D deficiency, vitamin D severe deficiency as serum 25(OH)D below 25 nmol/l, which has been widely accepted by the international community (17). However, the cutoff for grading vitamin D status in children is controversial (18). Thus, the 50 nmol/L
serum 25(OH)D concentrations were used as the threshold for vitamin D deficiency and 25 nmol/L serum 25(OH)D concentrations were used as the threshold for vitamin D severe deficiency in our study according to the adult criteria. In our study, the proportion of serum vitamin D deficiency in the SLE group was 89.2%, which was significantly higher than that in the healthy group (52.0%). In addition, the severe vitamin D deficiency rate in the SLE group (24.2%) was also significantly higher than that in the healthy group (5.0%).

According to whether anti-HCMV IgM was positive or not, SLE patients were divided into two groups, and demographic characteristics were similar in patients with and without HCMV infection (Table 2). There was no significant difference in age, sex, BMI, the percentage of patients taking glucocorticoids and immunosuppressants, and seasonal distribution between the two groups. The positive anti-HCMV IgM group had lower serum albumin and higher erythrocyte sedimentation rate (ESR) than the negative anti-HCMV IgM group, but the differences were not statistically significant. Although both C3 and C4 in the positive anti-HCMV IgM group were lower than those in the negative anti-HCMV IgM group, only C4 showed significant differences between the two groups. The SLEDAI was significantly higher in the positive anti-HCMV IgM group than that in the negative anti-HCMV IgM group (7.9 ± 5.0 vs 4.7 ± 4.3, P < 0.001). The mean value of 24-hour urinary protein in both infected and non-infected groups was increased, and it was significantly higher in the positive anti-HCMV IgM group than that in the negative anti-HCMV IgM group (1392.0 ± 1532.9 vs 441.7 ± 826.9, P < 0.001).
As shown in Table 2, compared with the negative anti-HCMV IgM group, the serum 25(OH)D concentrations in the HCMV infected group were significantly lower than those in the negative anti-HCMV IgM group (30.6 ± 12.3 vs 38.2 ± 12.5, \( P < 0.001 \)). The proportion of serum 25(OH)D concentration below 50 nmol/l in the positive anti-HCMV IgM group and the negative anti-HCMV IgM group was 91.1% and 89.3%, respectively, with no significant difference. However, the proportion of serum 25(OH)D concentration below 25 nmol/l which means severe deficiency in the positive anti-HCMV IgM group was 42.2%, which was significantly higher than that in the negative anti-HCMV IgM group (13.3%, \( P < 0.001 \)). In the negative anti-HCMV IgM group, the serum concentrations of 25(OH)D were mainly 25-50 nmol/l, accounting for 76%. The difference in the distribution of 25(OH)D status between the two groups was statistically significant.

**Discussion**

Vitamin D plays an important role in various systemic autoimmune disorders. Accumulating studies have indicated that SLE patients widely present with varying degrees of vitamin D deficiency. Low serum vitamin D levels in SLE patients are prevalent in different areas of the world, and vitamin D deficient rates by nation were not uniform such as Thailand (29.6%), Saudi Arabia (9.1%), Brazil (50%), Spain (15%), and France (15.9%) (19-23). Our study showed that the deficiency rate of Chinese pediatric SLE patients was up to 89.2%, which was significantly higher than that reported in other countries. Additionally, the vitamin D deficiency rate in the healthy control group in our study was also up to 52.0%, which was similar to an
earlier study on Chinese children (24). The present study showed that the serum vitamin D levels of pediatric SLE patients were significantly lower than those of healthy children, and the incidence of vitamin D deficiency was significantly higher in Chinese pediatric SLE patients. Several studies also indicated that the incidence of vitamin D deficiency is significantly higher in SLE patients than that in healthy subjects. Interestingly, other studies showed the opposite results (4, 5). On one hand, these differences may be related to ethnic differences. On the other hand, the difference may be due to wide variations in food habits, sun exposure, and any other environmental differences between different areas. The exact mechanisms for vitamin D deficiency in SLE have not been fully elucidated. The relationship between vitamin D deficiency and SLE disease activity might be bi-directional, because vitamin D deficiency may also contribute to the activation of SLE (19).

As a herpesvirus, HCMV is usually latent in the immunocompetent host but could be reactivated when immune function becomes abnormal. Previous studies indicated that the positive rate of anti-HCMV IgM which is a marker of active HCMV infections ranges from 5% to 45% in SLE patients (25). In our study, the positive rate of anti-HCMV IgM in pediatric SLE patients is 37.5%, which is consistent with previous studies. To explore whether the vitamin D deficiency relates to the active HCMV infections in SLE, vitamin D serum levels and deficiency rates were compared between anti-HCMV IgM positive and negative groups. Previous studies indicated that the serum anti-HCMV IgM might appear false positive for autoantibodies (26). In our assay, specimens were treated with a diluent containing
rheumatoid factors and lupus-associated autoantibodies neutralization reagent to avoid interference by rheumatoid factors and lupus-associated autoantibodies (15). Thus, serum anti-HCMV IgM was used to be the indices of active HCMV infections in the present study.

The present study showed the correlation between serum vitamin D levels and the occurrence of active HCMV infection in SLE patients. The proportion of severe vitamin D deficiency was higher in SLE patients with active HCMV infections, and the vitamin D levels of patients with active HCMV infections were significantly lower than those of SLE patients without active HCMV infections. The results obtained might be attributed to the potential anti-infection effects exerted by vitamin D. Vitamin D activates and regulates various cellular pathways to exert its biological effects by binding to vitamin D receptors which are widely found in various immune cells (27). Vitamin D enhances both innate and adaptive immunity, mainly through regulating B/T cell proliferation and inducting functions of antimicrobial peptides which can direct antimicrobial activity against microorganisms including bacteria, viruses, and fungi (28-30). Current evidence suggests a correlation between vitamin D deficiency and an increased risk of infection in the general population (31, 32). Additionally, another study showed that low levels of vitamin D are associated with late HCMV infection in kidney transplant recipients (29). The relationship between vitamin D levels and HCMV infection in SLE patients is rarely reported. Previous studies on vitamin D levels in SLE patients with virus infections indicated that vitamin D could reduce rotavirus replication both in vivo and in vitro (33). Other
studies indicated that women with SLE had a higher prevalence of vitamin D deficiency and cervical HPV infection, but no association was found between vitamin D deficiency and cervical HPV (34). To the best of our knowledge, the present study is the first to demonstrate that there is an association between vitamin D levels and active HCMV infections in pediatric SLE patients.

When comparing clinical manifestations, the SLE disease activity index (SLEDAI) used to measure SLE activity was significantly higher in pediatric SLE patients with active HCMV infections than that in non-HCMV active infections subjects. However, another study drew the opposite conclusion that SLEDAI decreased in adult SLE patients with HCMV infection (35). The reason might be related to the different infection responses to HCMV between adults with SLE and children with SLE. Accordingly, it was concluded that active HCMV infections may aggravate lupus activity in pediatric SLE patients. As far as we know, this is the first reported study on pediatric SLE patients with active HCMV infections. Moreover, the present study indicates that the 24-hour urine protein of active HCMV infections was significantly higher than that of non-HCMV active infections in pediatric SLE patients in our study. Similarly, other studies have shown that the 24-hour urine protein of SLE patients with bacteremia was also higher than that of non-bacteremia SLE patients (36). The result may be attributed to kidney damage worsened by infection.

The present study was characterized by several limitations. Although our study demonstrates an association between lower vitamin levels and the risk of active
HCMV infections, we could not determine a clear cause-and-effect relationship between them. It is still unknown what exactly contributes to the present results, which occurs either due to the increased vitamin D depletion by the host for HCMV infection, or increased susceptibility to HCMV infection in SLE patients caused by vitamin D deficiency. Further studies on specific mechanisms need to be carried out. In addition, it is also possible that IgM-positive patients include those resulting from infection with different genotypes of HCMV. The small sample size of our study was certainly lack of representativeness. Therefore, further large multiple-center prospective research should be launched to obtain definitive results in the future.

In summary, this study has found that vitamin D deficiency is quite prevalent in Chinese pediatric SLE patients, which is significantly lower than that in healthy children. Active HCMV infections may exacerbate SLE activity in pediatric SLE patients. Severe vitamin D deficiency was found to be associated with active HCMV infections in pediatric SLE patients. To detect vitamin D deficiency earlier and reduce the associated adverse consequences, more attention should be paid to serum vitamin D levels in pediatric SLE patients, especially in ones with active HCMV infections.

Acknowledgments This work was partially supported by grants from the Analysis and Testing Foundation of Zhejiang Province (grant number LGC19H200006) and the National Natural Science Foundation of China (grant number 81971422).

Conflict of interest None to declare.

References


17. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health


33. Zhao Y, Ran Z, Jiang Q, et al. Vitamin D alleviates rotavirus infection through a


Table 1. Comparison of baseline sociodemographic between pediatric SLE patients and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>SLE patients</th>
<th>Controls</th>
<th>P-value</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>120</td>
<td>100</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Male (N, %)</td>
<td>21 (17.5%)</td>
<td>17 (17.0%)</td>
<td>&gt; 0.05</td>
<td>1.0 (0.5, 2.1)</td>
</tr>
<tr>
<td>Age, mean ± SD (years)</td>
<td>12.7 ± 2.2</td>
<td>12.3 ± 2.2</td>
<td>&gt; 0.05</td>
<td>-</td>
</tr>
<tr>
<td>Season ( N, %)</td>
<td></td>
<td></td>
<td>&gt; 0.05</td>
<td>-</td>
</tr>
<tr>
<td>winter</td>
<td>32 (26.6%)</td>
<td>26 (26.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>spring</td>
<td>20 (16.7%)</td>
<td>18 (18.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>summer</td>
<td>47 (39.2%)</td>
<td>41 (41.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>fall</td>
<td>21 (17.5%)</td>
<td>15 (15.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HCMV IgM positive (N, %)</td>
<td>45 (37.5%)</td>
<td>0 (0%)</td>
<td>&lt; 0.001</td>
<td>-</td>
</tr>
<tr>
<td>Anti-HCMV IgG positive (N, %)</td>
<td>120 (100.0%)</td>
<td>100 (100.0%)</td>
<td>&gt; 0.05</td>
<td>-</td>
</tr>
<tr>
<td>Serum 25(OH)D (nmol/L)</td>
<td>35.3 ± 12.9</td>
<td>49.3 ± 15.3</td>
<td>&lt; 0.001</td>
<td>-</td>
</tr>
<tr>
<td>Vitamin D deficiency (N, %)</td>
<td>107 (89.2%)</td>
<td>52 (52.0%)</td>
<td>&lt; 0.001</td>
<td>7.6 (3.8, 15.2)</td>
</tr>
<tr>
<td>Severe vitamin D deficiency (N, %)</td>
<td>29 (24.2%)</td>
<td>5 (5.0%)</td>
<td>&lt; 0.001</td>
<td>6.1 (2.2, 16.3)</td>
</tr>
</tbody>
</table>

SLE, systemic lupus erythematosus; HCMV, human cytomegalovirus; 25(OH)D, 25(OH)Vitamin D; OR (95%CI), odds ratios and 95% confidence interval.
<table>
<thead>
<tr>
<th></th>
<th>HCMV-IgM(+)-SLE</th>
<th>HCMV-IgM(-)-SLE</th>
<th>P-value</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>45</td>
<td>75</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Male (N, %)</td>
<td>8 (17.8%)</td>
<td>12 (16.0%)</td>
<td>&gt; 0.05</td>
<td>0.9 (0.3, 2.4)</td>
</tr>
<tr>
<td>Age, mean ± SD (years)</td>
<td>12.3 ± 2.1</td>
<td>13.0 ± 2.3</td>
<td>&gt; 0.05</td>
<td>-</td>
</tr>
<tr>
<td>BMI, mean±SD (kg/m²)</td>
<td>19.1 ± 3.5</td>
<td>20.1 ± 3.2</td>
<td>&gt; 0.05</td>
<td>-</td>
</tr>
<tr>
<td>Glucocorticoids therapy (N, %)</td>
<td>42 (93.3%)</td>
<td>70 (93.3%)</td>
<td>&gt; 0.05</td>
<td>1.0 (0.2, 4.4)</td>
</tr>
<tr>
<td>Immunosuppressants therapy (N, %)</td>
<td>43 (95.6%)</td>
<td>71 (94.7%)</td>
<td>&gt; 0.05</td>
<td>1.2 (0.2, 6.9)</td>
</tr>
<tr>
<td>SLEDAI score</td>
<td>7.9 ± 5.0</td>
<td>4.7 ± 4.3</td>
<td>&lt; 0.001</td>
<td>-</td>
</tr>
<tr>
<td>Season (N, %)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>winter</td>
<td>15 (33.3%)</td>
<td>17 (22.7%)</td>
<td>&gt; 0.05</td>
<td>-</td>
</tr>
<tr>
<td>spring</td>
<td>10 (22.2%)</td>
<td>10 (13.3%)</td>
<td>&gt; 0.05</td>
<td>-</td>
</tr>
<tr>
<td>summer</td>
<td>13 (28.9%)</td>
<td>34 (45.3%)</td>
<td>&gt; 0.05</td>
<td>-</td>
</tr>
<tr>
<td>fall</td>
<td>7 (15.6%)</td>
<td>14 (18.6%)</td>
<td>&gt; 0.05</td>
<td>-</td>
</tr>
<tr>
<td>White blood cells (×10^9/L)</td>
<td>6.8 ± 3.8</td>
<td>5.9 ± 2.7</td>
<td>&gt; 0.05</td>
<td>-</td>
</tr>
<tr>
<td>Lymphocyte (×10^9/L)</td>
<td>1.4 ± 0.8</td>
<td>1.3 ± 0.8</td>
<td>&gt; 0.05</td>
<td>-</td>
</tr>
<tr>
<td>Serum albumin (g/l)</td>
<td>32.6 ± 9.6</td>
<td>39.9 ± 7.5</td>
<td>&gt; 0.05</td>
<td>-</td>
</tr>
<tr>
<td>Hepatic impairment (N, %)</td>
<td>13 (28.9%)</td>
<td>17 (22.7%)</td>
<td>&gt; 0.05</td>
<td>1.4 (0.6, 3.2)</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>42.4 ± 38.1</td>
<td>38.4 ± 34.2</td>
<td>&gt; 0.05</td>
<td>-</td>
</tr>
<tr>
<td>C3 (g/L)</td>
<td>0.7 ± 0.4</td>
<td>0.8 ± 0.4</td>
<td>&gt; 0.05</td>
<td>-</td>
</tr>
<tr>
<td>C4 (g/L)</td>
<td>0.1 ± 0.1</td>
<td>0.2 ± 0.1</td>
<td>&lt; 0.05</td>
<td>-</td>
</tr>
<tr>
<td>Positive anti-dsDNA (N, %)</td>
<td>34 (75.6%)</td>
<td>43 (57.3%)</td>
<td>&gt; 0.05</td>
<td>2.3 (1.0, 5.2)</td>
</tr>
<tr>
<td>24-hour urine protein (mg/24h)</td>
<td>1392.0 ± 1532.9</td>
<td>441.7 ± 826.9</td>
<td>&lt; 0.001</td>
<td>-</td>
</tr>
<tr>
<td>Serum 25(OH)D (nmol/l)</td>
<td>30.6 ± 12.3</td>
<td>38.2 ± 12.5</td>
<td>&lt; 0.001</td>
<td>-</td>
</tr>
<tr>
<td>Vitamin D deficiency (N, %)</td>
<td>41 (91.1%)</td>
<td>66 (89.3%)</td>
<td>&gt; 0.05</td>
<td>1.4 (0.4, 4.8)</td>
</tr>
<tr>
<td>Severe vitamin D deficiency (N, %)</td>
<td>19 (42.2%)</td>
<td>10 (13.3%)</td>
<td>&lt; 0.001</td>
<td>4.7 (1.9, 11.6)</td>
</tr>
</tbody>
</table>

SLE, systemic lupus erythematosus; HCMV, human cytomegalovirus; BMI, Body mass index;
SLEDAI, systemic lupus erythematosus disease activity index; ESR, erythrocyte sedimentation rate; 25(OH)D, 25(OH)Vitamin D; OR (95%CI), odds ratios and 95% confidence interval.