Comparison of the clinical manifestations and chest CT findings of pulmonary cryptococcosis in immunocompetent and immunocompromised patients: a systematic review and meta-analysis

Chunlin Xiong2†, Jianguo Lu3†, Ting Chen1* and Rui Xu4

Abstract

Objective: The purpose of our study was to perform a meta-analysis and systematic review to compare differences in clinical manifestations and chest computed tomography (CT) findings between immunocompetent and immunocompromised pulmonary cryptococcosis (PC) patients.

Methods: An extensive search for relevant studies was performed using the PubMed, EMBASE, Cochrane Library, and Web of Sciences databases from inception to September 30, 2021. We included studies that compared the clinical manifestations and chest CT findings between immunocompetent and immunocompromised PC patients. Study bias and quality assessment were performed using the Newcastle–Ottawa Scale (NOS).

Results: Nine studies involving 248 immunocompromised and 276 immunocompetent PC patients were included in our analysis. The NOS score of each eligible study was above 5, indicating moderate bias. The proportion of elderly patients (>60 years old) in the immunosuppressed group was significantly higher than that in the immunocompetent group (OR = 2.90, 95% CI (1.31–6.43), Z = 2.63, p = 0.01). Fever (OR = 7.10, 95% CI (3.84–13.12), Z = 6.25, p < 0.000) and headache (OR = 6.92, 95% CI (2.95–16.26), Z = 4.44, p < 0.000) were more common in immunosuppressed patients. According to thin-section CT findings, lesions were more frequently distributed in the upper lobe (OR = 1.90, 95% CI (1.07–3.37), Z = 2.2, p = 0.028) in immunocompromised individuals. The proportions of patients with cavity sign (OR = 5.11, 95% CI (2.96–8.83), Z = 5.86, p = 0.00), ground-glass attenuation (OR = 5.27, 95% CI (1.60–17.35), Z = 2.73, p = 0.01), and mediastinal lymph node enlargement (OR = 2.41, 95% CI (1.12–5.20), Z = 2.24, p = 0.03) were significantly higher in immunocompromised patients.

Conclusion: No significant differences in nonspecific respiratory symptoms were found between immunocompromised and immunocompetent PC patients. Nevertheless, fever and headache were more common in
immunocompromised patients. Among the CT findings, cavity, ground-glass attenuation, and mediastinal lymph node enlargement were more common in immunocompromised individuals.

Keywords: Meta-analysis, Clinical manifestations, Radiologic findings, Pulmonary cryptococcosis, Immunocompetent, Immunocompromised

Background

Pulmonary cryptococcosis (PC) is an invasive pulmonary mycosis caused by pathogenic Cryptococcus infection. The major pathogenic Cryptococcus species that cause PC are Cryptococcus neoformans and Cryptococcus gattii [1, 2]. The major route of PC infection is inhalation of cryptococcal spores from aerosols. Due to the clinical application of immunosuppressants, checkpoint inhibitors, chemotherapeutics, glucocorticoids and other drugs that suppress the immune system, the incidence of PC has increased rapidly in recent years [3]. PC has a high affinity for the central nervous system in immunocompromised patients, potentially resulting in cryptococcal meningoencephalitis. Globally, approximately 1 million immunocompromised patients develop cryptococcal meningitis each year, with a 60% mortality rate at 3 months after central nervous system infection [4]. In USA, the incident rate is 0.4–1.3/1,000,000. The incident rate of PC rises to 2–7/1,000,000 in patients with HIV and AIDS [5]. The pathogenesis of PC is related to defects in immune function. Thus, immunocompromised hosts are more susceptible to PC. However, PC can also occur in immunocompetent subjects. With the development of new diagnostic techniques, the rate of PC detection in immunocompetent patients has increased in recent years [6, 7].

Patients with localized PC often present with nonspecific respiratory or systemic symptoms, such as cough, expectoration, dyspnea, chest pain, and fever. Different from other fungal infections, such as typical Pulmonary Aspergillus Overlap Syndromes (PAOS) caused by invasive aspergillosis [8], some patients may be asymptomatic [9]. Compared with chronic aspergillosis infection with typical air-crescent sign, PC lacks typical CT manifestations [10]. PC characterized by single or multiple nodules is more easily misdiagnosed as peripheral lung cancer or tuberculosis. Some studies focused on the CT manifestations of PC in immunocompromised or immunocompetent patients and identified some thin-section CT features, such as halo signs, solitary or multiple nodules, and so on [11]. However, these radiologic features are nonspecific. Due to nonspecific clinical manifestations and radiologic features, PC patients are often misdiagnosed with bacterial or organizing pneumonia, tuberculosis, or even lung cancer at their initial visit.

Due to the different immune responses elicited by Cryptococcus infection in immunocompromised and immunocompetent patients, immunocompetent and immunosuppressed PC patients exhibit some different clinical manifestations and radiologic findings. Thus, several studies have focused on comparisons of the clinical features and radiologic findings between immunocompetent and immunosuppressed PC patients. Although several reviews have summarized the possible clinical manifestations and imaging features of PC, few meta-analyses have confirmed the different clinical features and radiologic findings between immunocompetent and immunosuppressed patients [12, 13]. In this systematic review and meta-analysis, we aimed to comparing clinical characteristics and radiologic features between immunocompetent and immunosuppressed patients.

Methods

Search strategy and eligibility criteria

Our systematic review was in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14]. An extensive search for relevant studies was performed using the PubMed, EMBASE, Cochrane Library, and Web of Sciences databases from inception to September 30, 2021. The search keywords and the related syntax were (“pulmonary cryptococcosis” OR “lung criptococcosis”) AND “immunocompetent” AND “immunocompromised”. We also checked the references of key articles for any additional eligible articles. Studies were selected if they met the following eligibility criteria: (1) chest CT was used in the diagnosis of PC, and (2) the diagnosis of PC was based on percutaneous biopsy, surgical resection, bronchoalveolar lavage, transbronchial biopsy or culture. We excluded duplicate reports, editorials, correspondences, conference abstracts, commentaries and case reports. The selection of suitable articles was performed by 2 investigators independently. Disparities between investigators were resolved by consensus of all the investigators.

Data extraction and quality assessment

Two independent researchers (C. X and J. L) performed data extraction and evaluated the literature quality. Disagreements were resolved by consensus of all the investigators. We extracted the following variables from each included study: first author, publishing institution,
publication time, number of immunocompromised or immunocompetent patients with PC, patient sex, patient age, clinical symptoms, lesion distributions, and radiologic features. Study bias and quality assessment were performed independently by two authors (T.C and R. X) using the Newcastle–Ottawa Scale (NOS). The NOS consists of 3 sections, selection, comparability, and exposure, with a maximum score of 9 points. Total scores of 0–3 indicate poor quality, scores of 4–6 indicate fair quality, and scores of 7–9 represent high quality [15]. Discrepancies were resolved by discussion with all investigators. The scores of the included studies are shown in Additional file 1: Table S1.

**Statistical analysis**

We used STATA SE version 15.1 software and a random-effects model to calculate pooled prevalence rates (elderly patient ratio, patient sex, clinical symptoms, and CT characteristics) with corresponding 95% confidence intervals (CIs) for clinical data. Pooled odds ratios (ORs) with 95% CIs for the elderly patient ratio, patient sex, clinical symptoms, and CT characteristics in immunocompetent and immunocompromised patients were calculated with STATA SE version 15.1 software. Heterogeneity among the included studies was assessed using Cochran’s Q test and the $I^2$ statistic. When $I^2 < 50\%$, a fixed-effect model was chosen; otherwise, a random-effects model was selected. $p < 0.05$ was considered to be statistically significant. Publication bias was evaluated by Begg’s test and Egger’s test.

**Results**

**Characteristics of the studies and quality assessments**

The study selection process is shown in Fig. 1. In brief, 155 references were collected after searching the databases. Fifty-one references were removed due to duplication. After scanning the titles and abstracts, 95 records were excluded for the reasons listed in Fig. 1. Finally, 9
full texts, including 248 immunocompromised and 276 immunocompetent patients, were assessed for eligibility and included in our meta-analysis [16–24].

Demographic characteristics of the patients with PC in the immunocompetent and immunocompromised groups

The demographic characteristics of the patients included in the relevant studies are listed in Table 1. The causes for immunosuppressed status in the included studies were broadly classified into AIDS, organ transplantation, diabetes mellitus, immunosuppressive drugs or corticosteroids used for basic illness, hematological malignancies, solid tumor, and connective tissue disorders. Of the patients recorded in the selected articles, 33.0% (95% CI: 16.7–49.4, \( I^2 = 50.5\% \)) of immunocompromised patients were elderly patients (\( \geq 60 \) years old), while only 13.2% (95% CI: 6.1–20.3, \( I^2 = 0.0\% \)) of immunocompetent patients were elderly patients (\( \geq 60 \) years old). The proportion of elderly patients in the immunosuppressed group was significantly higher than that in the immunocompetent group (OR = 2.90, 95% CI (1.31–6.43), \( Z = 2.63, p = 0.01 \)). Among these patients, 62.8% (95% CI: 56.2–69.3, \( I^2 = 0.0\% \)) were immunosuppressed, and 59.2% (95% CI: 53.1–65.3, \( I^2 = 0.0\% \)) were male. There were no significant differences between the two immune status groups with respect to sex (OR = 1.13, 95% CI (0.75–1.70), \( Z = 0.59, p = 0.56 \)) (Fig. 2).

Clinical features of the patients with PC in the immunocompetent and immunocompromised groups

The general clinical features of PC in the immunocompetent and immunocompromised groups are listed in Table 2. Among all the PC patients, 40.8% immunocompetent and 30.2% immunocompromised patients were asymptomatic. However, no statistic differences were found. Regarding clinical manifestations in immunocompromised patients, cough was reported in 43.6% (95% CI: 20.0–67.3, \( I^2 = 77.5\% \)), expectoration was reported in 35.5% (95% CI: 20.6–50.5, \( I^2 = 0.0\% \)), chest pain was reported in 12.6% (95% CI: 7.9–17.3, \( I^2 = 0.0\% \)), fever was reported in 26.5% (95% CI: 14.9–38.0, \( I^2 = 70.3\% \)), dyspnea was reported in 10.6% (95% CI: 4.5–18.8, \( I^2 = 80.3\% \)).

Table 1  Demographic characteristics of the immunocompetent and immunocompromised patients with PC

| Study            | Immunocompromised patients | Immunocompetent patients |
|------------------|----------------------------|--------------------------|
|                  | Total patients | Age > = 60 | Male | Total patients | Age > = 60 | Male |
| Yan Hu, et al    | 10            | NA         | 5    | 29             | NA         | 16   |
| Dengfa Yang, et al | 9            | 2          | 4    | 13             | 3          | 6    |
| Junyan Qu, et al | 94            | 27         | 64   | 42             | 5          | 23   |
| Xin Sui, et al   | 24            | NA         | 13   | 18             | NA         | 11   |
| Kaixiong Liu, et al | 35           | NA         | 22   | 53             | NA         | 33   |
| Lixuan Xie, et al | 43            | NA         | NA   | 29             | NA         | NA   |
| Jinquan Yu, et al | 5            | 1          | 3    | 19             | 2          | 12   |
| Kyong Doo Song, et al | 11         | 7          | 6    | 12             | 2          | 7    |
| Jingqi Min, et al | 17            | NA         | 11   | 61             | NA         | 38   |

Fig. 2  Forest plots depicting the comparisons of demographic characteristics in immunocompetent and immunocompromised PC patients
| Study | Immunocompromised patients | Immunocompetent patients |
|-------|---------------------------|--------------------------|
|       | Asymptomatic | Cough | Expectoration | Fever | Chest pain | Dyspnea | Headache | Altered mental status | Asymptomatic | Cough | Expectoration | Fever | Chest pain | Dyspnea | Headache | Altered mental status |
| Yan Hu, et al | 5 | 2 | 2 | 1 | 2 | 0 | NA | NA | 22 | 4 | 4 | 0 | 2 | 0 | NA | NA |
| Dengfa Yang, et al | 0 | 9 | 5 | 5 | 3 | 0 | NA | NA | 0 | 11 | 7 | 2 | 3 | 0 | NA | NA |
| Junyan Qu, et al | 3 | 37 | NA | 17 | 10 | 12 | 36 | 9 | 15 | 16 | NA | 3 | 5 | 4 | 3 | 1 |
| Xin Sui, et al | 2 | 8 | 8 | 14 | 3 | 1 | 10 | 6 | 5 | 9 | 9 | 2 | 2 | 2 | 2 | 2 |
| Kaixiong Liu, et al | 13 | 13 | 7 | 10 | 4 | 6 | 7 | 7 | 14 | 32 | 19 | 5 | 9 | 6 | 2 | 2 |
| Lixuan Xie, et al | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Jinquan Yu, et al | 0 | 2 | 1 | 2 | 0 | 0 | NA | NA | 8 | 6 | 5 | 3 | 0 | 0 | NA | NA |
| Kyoung Doo Song, et al | 8 | 2 | 1 | 1 | 0 | 0 | NA | NA | 5 | 4 | 1 | 1 | 4 | 0 | NA | NA |
| Jingqi Min, et al | 2 | 15 | 10 | 3 | 4 | NA | NA | NA | 17 | 44 | 34 | 8 | 14 | NA | NA | NA |
The clinical manifestations in patients with PC are generally nonspecific, and patients can even be asymptomatic. Among the immunocompromised patients, asymptomatic infection occurred in up to 30.2%. Immunocompetent patients appeared to have a higher rate of asymptomatic infection (up to 40.8%). However, there was no significant difference in the proportion of asymptomatic cases between immunocompetent and immunocompromised groups. Some investigations have reported asymptomatic PC in more than 50% of patients [13, 25]. The reason for this difference might be differences in patient screening processes based on comorbidities or immune status. PC usually elicits several nonspecific respiratory symptoms, such as cough, expectoration, chest pain, and dyspnea. The incidence of these nonspecific respiratory symptoms was not significantly different between the immunocompetent and immunosuppressed PC patients. Nonspecific respiratory symptoms are likely to cause delays in PC diagnosis and subsequent proper treatments.

Based on the detailed data extracted from 9 studies including 248 immunocompromised and 276 immunocompetent PC patients, our systematic review and meta-analysis provide a comprehensive description of clinical manifestations and CT findings in immunocompromised and immunocompetent PC patients.

**Discussion**

The clinical manifestations in patients with PC are generally nonspecific, and patients can even be asymptomatic. Among the immunocompromised patients, asymptomatic infection occurred in up to 30.2%. Immunocompetent patients appeared to have a higher rate of asymptomatic infection (up to 40.8%). However, there was no significant difference in the proportion of asymptomatic cases between immunocompetent and immunocompromised groups. Some investigations have reported asymptomatic PC in more than 50% of patients [13, 25]. The reason for this difference might be differences in patient screening processes based on comorbidities or immune status. PC usually elicits several nonspecific respiratory symptoms, such as cough, expectoration, chest pain, and dyspnea. The incidence of these nonspecific respiratory symptoms was not significantly different between the immunocompetent and immunosuppressed PC patients. Nonspecific respiratory symptoms are likely to cause delays in PC diagnosis and subsequent proper treatments. Systemic syndromes with an overall low incidence, such as fever and headache, seemed to occur more frequently in immunosuppressed patients. The reason for more frequent systemic symptoms in immunocompromised patients might be due to the deficiency in immune surveillance in immunocompromised patients, resulting in failure to elicit a cryptococcus immune response. This immune surveillance deficiency results in more pulmonary exudative and necrotizing pathological changes, as well as the intrapulmonary or even systemic spread of Cryptococcus [26, 27]. In immunocompetent patients, cryptococcal infection tends to be localized due to phagocytosis by macrophages and granulomatosis formation. Therefore, immunocompetent patients tend to have mild pulmonary dissemination and fewer systemic symptoms.

According to thin-section CT images, nearly half of the immunocompromised PC patients had bilateral lung involvement. Even though less than one-third of the immunocompetent PC patients expressed bilateral lung involvement, the difference between the immunocompetent and immunocompromised patients was non-significant ($p = 0.052$). However, several retrospective studies revealed that immunocompromised PC patients are more likely to show bilateral lung lesions on chest CT than immunocompetent patients [18, 20]. Our meta-analysis failed to reveal a positive association, possibly...
Fig. 3 Forest plots depicting the comparisons of clinical features in immunocompetent and immunocompromised PC patients.
### Table 3  Lesion distributions in PC patients, according to thin-section chest CT

| Lesion distributions        | Immunocompromised patients | Immunocompetent patients |
|----------------------------|----------------------------|--------------------------|
|                            | tN | Rate (%) | 95% CI       | I² (%) | tN | Rate (%) | 95% CI       | I² (%) |
| Bilateral lung distribution| 178| 50.0      | 36.2–64.7     | 60.4   | 157| 30.4      | 18.6–42.1     | 57.1   |
| Peripheral distribution    | 78 | 62.5      | 37.9–87.1     | 79.3   | 113| 73.5      | 50.1–97.0     | 90.3   |
| Upper lung involvement     | 129| 53.8      | 34.5–73.2     | 67.1   | 115| 40.8      | 28.2–53.4     | 48.6   |
| Middle lung involvement    | 129| 20.0      | 0.00–42.8     | 87.6   | 115| 17.1      | 4.8–29.4      | 59.9   |
| Lower lung involvement     | 129| 71.8      | 55.5–88.0     | 57.7   | 115| 78.6      | 70.6–86.5     | 11.6   |

*I*: total number of included cases; *I²*, heterogeneity test value

**Fig. 4**  Forest plots depicting the comparisons of lesion distributions on thin-section CT in immunocompetent and immunocompromised PC patients
because only 6 studies directly extracted data on uni-
lateral or bilateral lung involvement, and the relatively
small amount of data may cause bias. More than half of
the total patient population showed a peripheral distri-
bution of lesions. Our analysis indicated that PC tended
to involve the lower lobes in both immunocompetent or
immunocompromised patients, which is consistent with
several retrospective studies [28]. Although upper lung
involvement was not predominant in PC, it was relatively
more common in immunocompromised patients.

The radiological features of PC, such as air bronchog-
gram signs, halo signs, cavity, pleural effusion, ground-
glass attenuation, consolidations, enlarged mediastinal
lymph nodes, nodules and masses mimic other pulmo-
nary infectious diseases and even malignant tumors
[29]. This imaging finding similarity could be one of
the reasons for the delay in PC diagnosis. Among these
imaging findings detected by chest CT, cavitation,
enlarged mediastinal lymph nodes, and ground-glass
attenuation were more common in immunocompromised
patients. Pleural effusion was rare in PC patients,
especially in immunocompetent patients, with an inci-
dence of only approximately 5%. Single or multiple
nodules were the most commonly observed chest CT
findings in both immunocompromised and immu-
nocompetent PC patients according to our analysis
and several other reports [20, 30, 31]. Similar to other
pulmonary infectious diseases that induce the for-
mation of granulomatous nodules during the disease
process, the presence and architecture of granulomas,
which present as “nodules” in chest CT imaging, are
likely related to cryptococcus infection and intact host
immune status. Consistent with other studies, our anal-
ysis concluded cavities sign within nodules, masses or
other lesions occurred significantly more frequently in
immunocompromised than in immunocompetent PC
patients [21]. The difference may be caused by the ina-
bility to mount an effective immune response to local-
ize cryptococcal infection in immunocompromised
patients. The proliferating microorganisms destroy the
adjacent lung tissue and promote the formation of cavi-
ties [26, 32]. Ground-glass attenuation was observed to
be more common in immunocompromised patients.
Several investigations of pulmonary fungal infections
found that pulmonary exudation might be consistent
with pulmonary hemorrhage caused by fungal infec-
tion. These pulmonary exudative lesions contain patho-
genic microorganisms [32–34]. This imaging difference
is also evidence of the inability to localize pulmonary
cryptococcal infection in immunocompromised indi-
viduals. Mediastinal lymph node enlargement, which
was more frequently encountered in immunocom-
promised individuals, is probably due to mediasti-
nodal lymphadenitis caused by the lymphatic spread of
microorganisms in immunocompromised patients.

We acknowledge several limitations of our study. (1)
A limited number of studies had available data related
to the comparison of clinical and imaging features in
immunocompromised and immunocompetent PC
patients. Thus, for our analysis, we extracted only 9
suitable studies. (2) Due to the limited number of stud-
ies and available data, all patients included in our study
were Asian. Ethnic homogeneity might have potential
limitation to the results’ generalizability. (3) In terms
of the “immunocompromised” definition, the majority
of studies defined “immunocompromised” status based
on the presence of comorbidities or concomitant medi-
cations that caused immunosuppression. A few stud-
ies considered a combined evaluation of immune cell
counts and immunoglobulin levels.

Table 4 Typical thin-section CT findings in PC patients

| Typical CT manifestations | Immunocompromised patients | | | Immunocompetent patients | | |
|-------------------------|-----------------------------|---|---|--------------------------|---|---|
|                         | tN  | Rate (%) | 95% CI | I² (%) | tN  | Rate (%) | 95% CI | I² (%) |
| Air bronchogram sign    | 126 | 33.5     | 8.5–58.4 | 92.2   | 161 | 36.9     | 17.3–56.4 | 88.9   |
| Halo sign               | 126 | 38.3     | 24.7–52.0 | 60.4   | 161 | 31.4     | 12.1–50.7 | 91.1   |
| Cavitation              | 220 | 39.8     | 31.3–48.2 | 31.3   | 203 | 10.5     | 6.3–14.7  | 0.0    |
| Pleural effusion        | 220 | 13.0     | 8.1–17.9  | 9.6    | 203 | 5.3      | 0.8–9.8   | 34.2   |
| Ground-glass attenuation| 161 | 23.2     | 13.9–32.5 | 41.8   | 89  | 4.7      | 0.0–11.8  | 40.8   |
| Consolidations          | 212 | 21.3     | 15.7–27.0 | 0.0    | 173 | 19.2     | 13.4–25.0 | 0.0    |
| Enlarged mediastinal lymph nodes | 211 | 12.3     | 7.9–16.7  | 0.0    | 190 | 7.2      | 2.4–11.9  | 17.1   |
| Solitary nodule         | 222 | 26.8     | 11.7–41.9 | 88.1   | 202 | 34.0     | 13.6–54.4 | 91.8   |
| Multiple nodules        | 222 | 53.6     | 38.6–68.7 | 79.9   | 202 | 52.3     | 35.3–69.2 | 85.5   |
| Mass                    | 128 | 18.2     | 9.1–27.3  | 43.3   | 160 | 22.8     | 15.7–29.9 | 0.0    |

*tn*, total number of included cases; I², heterogeneity test value
Fig. 5 Forest plots depicting the comparisons of typical features on thin-section CT in immunocompetent and immunocompromised PC patients.
In conclusion, based on the limited available data, the immunocompromised PC group had a higher proportion of older adults (≥ 60 years) than the immunocompetent PC group. Among the nonspecific respiratory syndromes, we were unable to identify any symptoms that were significantly different between immunocompromised and immunocompetent PC patients. Nevertheless, several systemic symptoms, such as fever and headache, were more common in immunocompromised individuals. According to thin-section CT findings, lesions tended to be peripherally distributed in the lower lobes. However, upper lobe involvement was observed more frequently in immunocompromised patients. Similar as immunocompetent PC individuals, solitary or multiple nodules were the most common appearances in immunocompromised patients. Air bronchogram signs, halo signs, consolidations, and masses are possible radiologic features in immunocompetent and immunocompromised PC patients. Cavitation, ground-glass attenuation, and enlarged mediastinal lymph nodes are common radiologic features in immunocompromised PC patients but not immunocompetent individuals. By comparing the CT manifestations of immunocompetent and immunocompromised PC patients, we concluded the immune status results a significant impact on CT manifestations. For immunocompetent individuals with multiple nodules distributed in the lower lobes according to HRCT, PC should be taken into consideration [35]. Our results might help clinicians identifying the potential cryptococcal pneumonia and recognize the differences in clinical manifestations and CT findings in immunocompetent and immunocompromised PC patients.

Supplementary Information
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Author contributions
TC designed the study and interpreted the data. CX searched the literature. CX and JL performed data extraction and evaluated the literature quality. CX and JL performed statistical analysis and provided figures. RX and TC were responsible for the bias and quality assessment. All authors were responsible for the writing of the paper. All authors read and approved the final manuscript.

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Availability of data and materials
The data analyzed during this study are included in the published articles and its supplementary information.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
All authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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