Original Article

The efficacy of dietary Spirulina as an adjunct to chemotherapy to improve immune function and reduce myelosuppression in patients with malignant tumors

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Background: Recent studies have demonstrated functional benefits of Spirulina (*Arthrospira sp.*) in the treatment and prevention of cancer. However, it is unclear if Spirulina can be used to limit the side effects of chemotherapy in patients with malignant tumors.

Methods: In this study, cancer patients receiving four cycles of chemotherapy were randomized into control or treatment groups. The treated group consumed Spirulina for the first two cycles while the control group did not. The extent of myelosuppression and immune function were assessed after each cycle of chemotherapy, and patients were monitored for myelosuppression-related adverse events throughout the study period.

Results: In total, 100 patients were recruited and randomized into control (n=40) or treatment (n=60) groups. The white blood cell (WBC) and neutrophil (NEU) levels were similar in both groups at baseline while they were higher in the treated group relative to controls after Cycle1 (P=0.028 for WBC; P=0.006 for NEU) and Cycle2 (P=0.023 for WBC; P=0.013 for NEU). Hemoglobin (HGB) and platelet counts (PLT) were not statistically different between the groups at baseline or after treatment. Patients in the treatment group had a significantly lower rate of severe myelosuppression (P=0.034) and less modification of the chemotherapy regimen was necessary (P=0.012). After four cycles of chemotherapy, the IgM level and number of $CD8^+$ T cells increased in the treatment group, but decreased in the control group (P=0.004 for IgM; P=0.022 for $CD8^+$ T cells).

Conclusions: Spirulina reduces myelosuppression and improves immune function after chemotherapy in patients with malignant tumors.

Keywords: Spirulina; myelosuppression; immune; malignant tumor; chemotherapy

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Introduction

Malignant tumors are a leading cause of death and constitute an enormous social burden worldwide (1). In general, surgical resection is currently the first choice for treatment in early-stage cancer, while chemotherapy is indispensable for advanced cancer. Due to the expanded availability of chemotherapy and the emergence of new anti-cancer drugs over the past decades, cancer patient survival rates have dramatically increased (2). However, conventional chemotherapies are often non-specific and target not only cancer cells, but also certain normal cells. As a result of this toxicity, patients may experience side-effects including granulocytopenia, febrile neutropenia, thromboembolic events, and neurosensory toxicity, necessitating skipped chemotherapy sessions, alternative chemotherapy regimens, or discontinuation of chemotherapy (3,4).

Currently, there is much focus on the use of natural products as nutritional support to improve the physical condition of patients undergoing chemotherapy. Spirulina is a genus of filamentous cyanobacteria that belongs to the Oscillatoriaceae family. *Spirulina platensis* and *Spirulina maxima* are the most widely used species and have been extensively studied in the medicine and food industry (5). Spirulina is a rich source of proteins, essential fatty acids, phenolic phytochemicals, phycobiliprotein C-phycocyanin, vitamin and minerals such as iron, copper and zinc. Beyond its rich nutritional content, it also demonstrates anti-inflammatory, oxidative stress inhibiting, and immune enhancing properties (6,7). In fact, a variety of studies have concluded that dietary Spirulina is helpful in the treatment and prevention of diabetes, diabetic nephropathy, hypercholesterolemia, and cancer (8,9).

The immunomodulatory effects are regarded as one of the most valuable properties of Spirulina. Pugh reported that oral administration of Immulina, a commercial extract from Spirulina, can reduce the severity of influenza A (H1N1) viral infection in mice model by activating innate immune cells (10). Other research has demonstrated that Spirulina can enhance innate immunity in mice and inhibit tumor growth by modulating the balance between interleukin (IL)-17/IL-23 and interferon (IFN)-γ (11). An investigation in elderly Korean participants found that Spirulina supplementation may influence the expression of inflammatory markers like IL-2 and tumor necrosis factor (TNF)-α through monocyte chemotactic protein-1 (MCP-1), suggesting that Spirulina is useful for improving immune function (12). Spirulina has also been widely applied to patients with human immunodeficiency virus (HIV). Randomized, single-blind studies showed that Spirulina could improve the nutritional status of malnourished HIV patients, leading to a significant increase in $CD4^+$ cells and corresponding decrease in viral load (13,14). Moreover, Spirulina was reported to promote proliferation of human neural stem cells *in vivo* and hematopoietic stem cells *in vitro* through its immunomodulatory effects (15,16). Selmi *et al.* found that Spirulina supplementation could help to increase corpuscular hemoglobin and ameliorate anemia and immunosenescence in older patients (17). A related study concluded that Spirulina in combination with conventional iron-folic acid supplementation can bring about striking improvements in patients with nutritional anemia (18). In addition, some *in vivo* investigations have also reported the protective effects of dietary Spirulina on the hepatic inflammation caused by aging or toxicants (19,20). These studies revealed the anti-inflammatory, antioxidant and antihepatotoxic effects of Spirulina.

Although the immune function and antioxidant effects of Spirulina are well supported in patients with viral infections and anemia, limited studies have assessed its immunomodulatory effects in cancer patients receiving chemotherapy. To address this shortcoming, we performed a clinical trial to evaluate the effectiveness of Spirulina as an adjunct to chemotherapy to improve immune function and reduce myelosuppression in patients with malignant tumors.

Methods

Participants

From May 2017 to April 2018, 100 patients with malignant tumors undergoing chemotherapy under the supervision of the Oncology Department of Beijing Chao-Yang Hospital qualified to be included in the study. The research was carried out according to the principles set out in the Declaration of Helsinki 1964. The study protocol was approved by the Human Ethics Committee of Beijing Chao-Yang Hospital (2017-ke-313) and informed consent was obtained from all participants. Sample size and inclusion and exclusion criteria for this study were based on previous investigations with a comparable study design (21).

Inclusion criteria

Patients with an age between 18 and 70; stage II/III/IV malignant tumor; histologically confirmed malignant tumor, with or without grade I/II bone marrow suppression after

receiving chemotherapy; no prior radiotherapy; adequate bone marrow reserve (HGB ≥90 g/L, absolute NEU ≥1.5×10^9/L and PLT ≥100×10^9/L) hepatic function (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤2.5× upper normal limits, total bilirubin ≤1.25× upper normal limits), and renal function (creatinine clearance ≥60 mL/min); an Eastern Cooperative Oncology Group performance score ≤2; generally good health and more than 3 years remaining life expectancy.

Exclusion criteria

Patients demonstrating pregnancy or lactation; evidence of central nervous system metastasis; other serious non-cancer primary diseases (e.g., cardiovascular disease, cerebrovascular system disease, hematopoietic system disease, hepatic and nephric insufficiency, psychiatric disorders, and other severe medical conditions as judged by the investigators); grade III/IV bone marrow suppression after receiving chemotherapy. Additionally, patients undergoing treatment with investigational drugs were excluded.

Treatment protocol

Patients were randomly divided into treatment and control groups according to a random number table. Spirulina was obtained from InM Wushenzhao Ecological Development Co., Ltd. (suppliers' manufacturing lot Number: 020602B01) and the dosage included 3 capsules of 100 mg each administered 3 times daily with meals. Patients in the treated group consumed Spirulina during the first two cycles of routine chemotherapy. The control group did not consume Spirulina capsules or other drugs containing Spirulina during chemotherapy. All patients completed four cycles of personalized chemotherapy regimens.

Data collection

The characteristics of all patients were collected, including: gender, age, primary tumor, tumor metastasis, duration of chemotherapy, and treatment protocol for each cycle.

The primary effectiveness end point of this study was evaluated by detecting bone marrow suppression between the two groups in each cycle, including routine blood tests [white blood cell (WBC), neutrophilic granulocyte (NEU), hemoglobin (HGB) and platelet (PLT)], and myelosuppression-related adverse events (treatment of leukopenia, III–IV grade bone marrow suppression and alteration of chemotherapy). The lowest values of WBC, NEU, HGB and PLT were included in the analysis if there was more than one routine blood test in each cycle. The change in the results of the routine blood test across cycles was calculated using the formula: d_n = baseline – $Cycle_n$.

The secondary end-point was assessed by testing the change of immune function after all four cycles, including the level of immunoglobulins (IgA, IgG, IgM), complements (C3, C4), and $CD4^+$ and $CD8^+$ T lymphocytes. The change in immune function was calculated using the formula: △ = baseline – Cycle 4.

Statistical analysis

Double data entry and consistency checking were performed using EpiData 3.1. Data analyses were performed using SPSS 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables such as age and blood test results are presented as mean ± standard deviation (SD). Gender and myelosuppression-related adverse events are presented as categorical variables. Significance was assessed using Chi-square test for binary categorical variables and the student's *t*-test for continuous variables. P<0.05 was considered to be statistically significant.

Results

Characteristics of the study participants

A total of 100 patients that underwent four cycles of routine chemotherapy were included in the study, including 40 participants in the control group and 60 in the treatment group (*Table 1*). The mean age was 58.4±9.2 yrs in control group compared to 55.3±11.4 yrs in treated group. The gender proportion, types of tumor, metastasis rate, and chemotherapeutic drugs were not significantly different between two groups.

Change of routine blood test after treatment

As shown in *Table 2*, WBC and NEU levels were similar in the two groups at baseline and in the final two cycles (P>0.05), but were increased in the treatment group compared to the control group in the Cycle1 (P=0.028 for WBC; P=0.006 for NEU) and Cycle2 (P=0.023 for WBC; P=0.013 for NEU) (*Figures 1*,*2*). HGB and PLT levels revealed no statistical differences between the two groups at baseline or following any cycle.

Changes in routine blood test results during cycles were calculated by comparison with baseline (*Table 3*). WBC and NEU levels in the control group significantly decreased in Cycle 1 (P=0.002 for WBC; P=0.006 for NEU) and Cycle2 (P=0.005 for WBC; P=0.010 for NEU) compared to the treatment group which experienced a relatively moderate decrease (*Figures 3*,*4*). HGB and PLT levels were not significantly different compared with baseline in each group and in each cycle.

Table 1 Characteristics of participants

Characteristic	Control group	Treated group
Number of patients	40	60
Age (yrs, mean ± SD)	58.4±9.2	55.3±11.4
Gender (%)		
Male	17 (42.5)	28 (46.7)
Female	23 (57.5)	32 (53.3)
Types of tumor (%)		
Colorectal cancer	12 (30.0)	18 (30.0)
Lung cancer	7 (17.5)	15 (25.0)
Breast cancer	4 (10.0)	8 (13.3)
Pancreatic cancer	4 (10.0)	4 (6.7)
Gastric cancer	3 (7.5)	3 (5.0)
Esophageal cancer	2 (5.0)	2 (3.3)
Bladder cancer	1 (2.5)	2 (3.3)
Gallbladder carcinoma	1 (2.5)	1 (1.7)
Other type of tumor	6 (15.0)	7 (11.7)
Metastasis of tumor (%)	23 (57.5)	32 (53.3)

SD, standard deviation.

Table 2 Results of routine blood tests (mean ± SD)

Blood test	Control group	Treated group	P value
WBC ($\times10^9$)			
Baseline	5.92±1.73	5.78±1.69	0.698
Cyc1	3.90±1.56	4.58±1.47	0.028
Cyc2	3.80±1.41	4.47±1.43	0.023
Cyc3	4.06±1.75	4.18±1.28	0.727
Cyc4	4.39±1.80	4.21±1.60	0.599
NEU ($\times10^9$)			
Baseline	3.93±1.68	3.75±1.33	0.550
Cyc1	2.09±0.93	2.70±1.14	0.006
Cyc2	2.06±0.92	2.55±0.97	0.013
Cyc3	2.20±1.25	2.35±0.91	0.495
Cyc4	2.57±1.44	2.41±1.30	0.568
HGB (g/L)			
Baseline	117±16	119±17	0.689
Cyc1	111±15	116±16	0.098
Cyc2	109±16	113±15	0.177
Cyc3	109±16	113±15	0.222
Cyc4	110±15	115±16	0.120
PLT ($\times10^9$)			
Baseline	227±71	233±80	0.714
Cyc1	171±47	178±73	0.529
Cyc2	165±42	181±78	0.171
Cyc3	164±58	180±75	0.227
Cyc4	172±62	185±77	0.382

SD, standard deviation; WBC, white blood cell; NEU, neutrophilic granulocyte; HGB, hemoglobin; PLT, platelet.

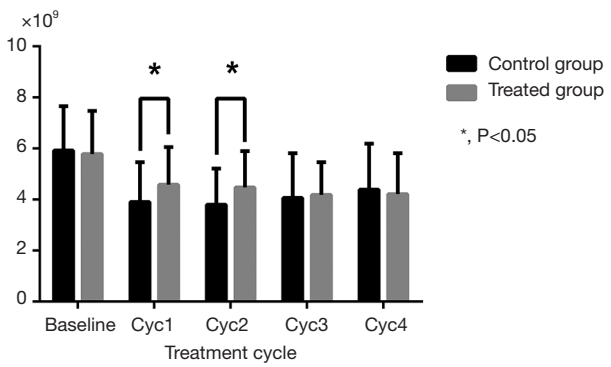

Figure 1 WBC counts at baseline and during each cycle. WBC, white blood cell.

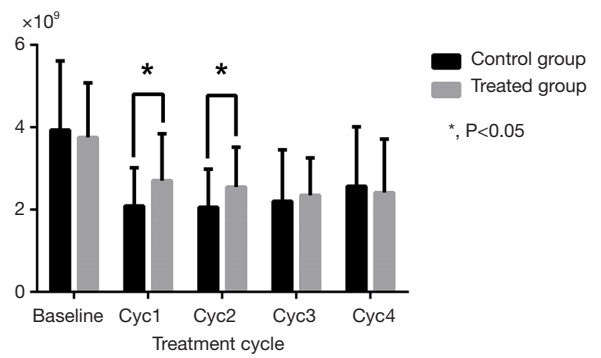

Figure 2 NEU counts at baseline and during each cycle. NEU, neutrophil.

Table 3 Changes in routine blood test analytes between cycles (mean ± SD)

Blood test	Control group	Treated group	P value
WBC ($\times10^9$)			
d1	2.02±1.35	1.20±0.97	0.002
d2	2.12±1.56	1.31±1.26	0.005
d3	1.86±1.84	1.61±1.41	0.447
d4	1.53±1.85	1.58±1.38	0.887
NEU ($\times10^9$)			
d1	1.84±1.53	1.05±1.02	0.006
d2	1.87±1.39	1.20±1.16	0.010
d3	1.73±1.47	1.40±1.32	0.247
d4	1.36±1.69	1.34±1.22	0.939
HGB (g/L)			
d1	6.65±8.72	2.77±11.23	0.068
d2	8.58±10.07	5.70±12.25	0.203
d3	8.80±11.17	6.25±10.78	0.256
d4	7.50±12.19	3.78±9.82	0.096
PLT ($\times10^9$)			
d1	56.40±59.91	54.63±72.23	0.898
d2	62.30±69.89	51.37±59.40	0.403
d3	63.43±70.19	52.90±73.99	0.479
d4	54.50±72.18	47.50±73.07	0.638

dn = baseline – Cyclen. SD, standard deviation; WBC, white blood cell; NEU, neutrophilic granulocyte; HGB, hemoglobin; PLT, platelet.

Table 4 Incidences of adverse events.

Event	Control group	Treated group	P value
Leukogenic treatment (%)	22 (55.0)	25 (41.7)	0.191
Severe myelosuppression (%)	17 (42.5)	20 (33.3)	0.034
Altered treatment (%)	22 (55.0)	18 (30.0)	0.012

Change of myelosuppression after treatment

Compared to the control group, patients in the treatment group experienced fewer instances of severe myelosuppression (P=0.034) and required less alterations to their prescribed chemotherapy regimens (P=0.012) (*Table 4*). However, both groups had a similar leukogenic treatment rate (P=0.191).

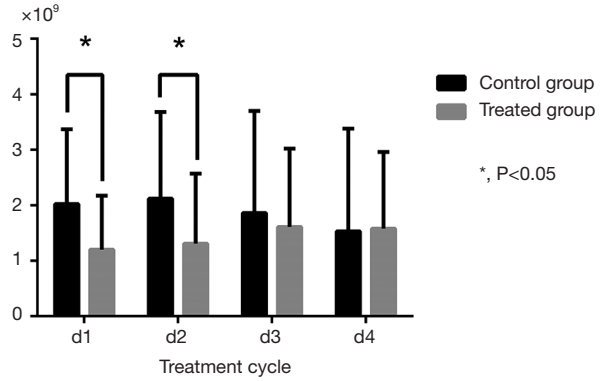

Figure 3 Changes in WBC counts between cycles (dn = baseline – Cyclen). WBC, white blood cell.

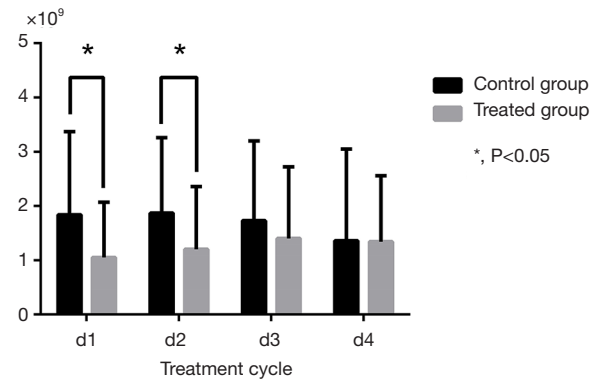

Figure 4 Changes in NEU counts between cycles (dn = baseline – Cyclen). NEU, neutrophil.

Change of immunologic function after treatment

After four cycles of routine chemotherapy, the IgM level and number of $CD8^+$ T cells increased in the treatment group, but decreased in the control group (P=0.004 for IgM; P=0.022 for $CD8^+$ T cells) (*Table 5*). There were no significant differences in the levels of IgA, IgG, C3, C4 or the number of $CD4^+$ T cells between the two groups.

Discussion

The results of the current study support the hypothesis that Spirulina reduces myelosuppression and improves immune function after chemotherapy in patients with malignant tumors. Spirulina supplementation supported

Table 5 Changes in immunologic function (mean ± SD)

Immune index	Control group	Treated group	P value
ΔIgA	8.39±39.94	1.91±62.20	0.527
ΔIgG	30.60±187.07	10.18±253.90	0.664
ΔIgM	6.06±13.11	–5.56±25.86	0.004
ΔC3	1.81±17.34	2.83±14.26	0.750
ΔC4	1.55±5.82	0.56±4.43	0.339
ΔCD4$^+$ T cells	31.20±175.40	–20.12±143.20	0.112
ΔCD8$^+$ T cells	17.40±97.53	–30.37±102.69	0.022

△ = baseline – Cycle 4. SD, standard deviation.

the maintenance of WBC, NEU, IgM, and CD8$^+$ T cell population levels. Chemotherapy combined with Spirulina supplementation decreased the instances of severe myelosuppression and the need to alter treatment regimens. These results are in line with previous studies demonstrating the benefit of Spirulina supplementation in chemotherapy patients. A previous study conducted by Chen *et al.* first determined the effects of MB-6 (mainly composed of Spirulina) in combination with chemotherapy leucovorin/5-fluorouracil, in colorectal cancer (21). Patients receiving MB-6 had a significantly lower rate of disease progression compared to patients in the placebo group. Selmi *et al.* reported Spirulina was able to increase corpuscular hemoglobin steadily in senior citizens and could efficiently ameliorate anemia (17). However, our findings found no changes in HGB or PLT counts in patients receiving chemotherapy.

Most investigations into Spirulina have focused on its anti-inflammatory, antioxidant and immunomodulatory effects. However, only a few studies have attempted to investigate the mechanisms underlying these effects and our current understanding remains limited. Spirulina contains several active compounds, particularly phycocyanin and β-carotene, both of which show promising antioxidant, anti-inflammatory, and immunomodulatory activity (22). Phycocyanin is able to inhibit expression of genes regulating central factors involved in tumorigenesis, such as ornithine decarboxylase, IL-6 and pSTAT3 (23). Several studies have also attempted to elucidate the signaling pathways involved in the biological effects of Spirulina. One study found that Spirulina regulated the ERK1/2, JNK and p38 signaling pathways, resulting in anti-inflammatory and antioxidant effects (24). Others hypothesized that Spirulina might activate the JAK/STAT signaling pathways downstream of the MAPK pathway (25). However, due to the complex chemical components of Spirulina, its molecular mechanisms remain unclear and further studies are needed.

In the present study, Spirulina enhanced secretary IgM antibody response while it had limited effects on IgA and IgG. IgM, one of the main components of adaptive immune system, serves as the first line of defense in the body and is responsible for recognizing and eliminating abnormal cells and infectious particles. It exerts a cytotoxic effect on tumor cells through the complement cascade. Since IgM is the first antibody species to appear after immunological challenge, it may play a role in early detection of cancer by the immune system. Therefore, stimulating IgM production could be a promising approach by which to prevent or reduce cancer growth and guide subsequent treatment (26). Khafaga *et al.* reported that a specific species of Spirulina, *Arthrospira platensis*, exerted its effects against methotrexate-induced acute toxicity by stimulating serum immunoglobulins excluding IgM (27). The differences between this study and the current study may be related to the fluctuation of serum immunoglobulins or differences in the source material, and future studies should evaluate immunoglobulin levels in the context of these findings.

Our study also detected an increase in CD8$^+$ T cells in patients consuming Spirulina. Immunotherapies are currently considered the most promising avenue in cancer treatment. CD8$^+$ T cells are key effectors in anti-tumor adaptive immunity due to the fact that most tumor cells express major histocompatibility complex class I (MHC-I) (28). They are able to recognize intracellular alterations through peptides presented by MHC-I and mediate cytotoxicity efficiently. However, many studies have demonstrated that CD8$^+$ T cells infiltrating cancer tissue are generally in dysfunctional states (CD8$^+$ T cell exhaustion) characterized by impaired activity and proliferative ability, increased apoptosis, and reduced production of cytokines, representing a significant barrier to successful cancer elimination (29,30). Therefore, further studies should be conducted to assess whether Spirulina has can ameliorate CD8$^+$ T cell exhaustion. Although we did not observe CD4$^+$ T cell stimulation by Spirulina, they are known to exert an important role in tumor immune-surveillance and regulation of antigen specific immune response. Moreover, CD4$^+$ T cells can improve the function of CD8$^+$ T cells with high affinity for T cell receptors (TCRs) (31), so the interplay between these two populations in relation to tumor growth in patients receiving Spirulina also deserves further attention (32).

Recent studies have also argued that the combined antioxidant and immunomodulatory characteristics of Spirulina may have effects on tumor destruction and hence contribute to cancer prevention. Wang *et al.* reported the anti-proliferative activity of Spirulina on five cancer cell lines (HepG-2, MCF-7, SGC-7901, A549 and HT-29) and low toxicity in normal cells, suggesting that Spirulina may be a promising ingredient in food and pharmaceutical applications (33). Similarly, Liao *et al.* demonstrated that phycocyanin, a natural product extracted and purified from Spirulina, can effectively inhibit pancreatic cancer cell proliferation *in vitro* (34), and this effect is exerted by inducing apoptotic and autophagic cell death. *In vivo* chemopreventive effects of Spirulina have also been assessed in the literature. When Spirulina was fed to a rat breast tumor model, the incidence of breast tumors was stunningly reduced from 87% to 13% (35). However, Barakat *et al.* demonstrated that Spirulina lacked antitumor effects against Ehrlich carcinoma in mice, and even increased their mortality when combined with chemotherapeutic drugs like fluorouracil (36). Overall, the mechanism of Spirulina supplementation in cancer remains unclear and further studies are needed.

Limitations

The current study has several limitations. First, it was designed as a proof of concept investigation and the patient population is relatively small. Second, the control group was not prescribed a suitable placebo and the follow-up period was not long enough to evaluate additional clinical outcomes. Third, the study lacked information about the variation in response of patients with different types of neoplasm and chemotherapy regimens. Finally, the underlying direct mechanisms of Spirulina at the molecular level were not investigated in this study.

Conclusions

Our study showed the patients receiving dietary Spirulina had a lower incidence of myelosuppression and enhanced immune function. These findings suggest that Spirulina can serve as an effective and safe adjunct to chemotherapy in patients with malignant tumors.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.06.13). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Human Ethics Committee of Beijing Chao-Yang Hospital (2017-ke-313) and informed consent was obtained from all participants.

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