

Article

A comparative study on the effects of music intervention on anxiety, depression, and immune function indicators in cancer patients

Gaohua Yue

Saint Petersburg State Conservatory, Saint Petersburg 190000, Russia; yuegh9191@163.com

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Abstract: Background: Based on the bidirectional regulation of modulation of psychological emotion and physiological immune function through the neural auditory pathway, music intervention has shown important value in the integrated treatment of cancer. This study adopted a randomized controlled trial method; 180 cancer patients were randomly assigned to the experimental group (individualized music therapy) and the control group (routine care) respectively, and the subjects were assessed before and after an 8-week intervention. The main outcome was the change in anxiety and depression score (HADS) and immune function (CD4⁺/CD8⁺) and IL-6. **Methods:** The results showed that the intervention group HADS-A score decreased by 40.2%, and the CD4⁺/CD8 plus ratio increased by 33.3%, and the content of IL-6 decreased by 38.8%. In addition, the emotional improvement was significantly positively correlated with the change in immune function ($r = -0.42$). **Results:** The results showed that music intervention can simultaneously improve the psychological state and immune function of cancer patients, which may be realized through the modulation of psychoneuroimmunological.

Keywords: music intervention; cancer patients; anxiety and depression; immune function

1. Introduction

Psychological distress such as anxiety and depression is widely present in cancer patients and greatly impair their quality of life [1,2]. These negative emotions may further inhibit immune function through neuroendocrine effects and further impact disease prognosis [3]. As a non-pharmacological intervention, music intervention may modulate the activity of the limbic system through auditory stimuli, which might alleviate emotional disturbances and immune dysfunction [4,5]. Although a large number of studies have been conducted, there are still many deficiencies in the literature, especially with regard to sample size and the range of evaluative markers in studies on the synergistic effects of music therapy on the psychological well-being of cancer patients and their immune functions [6]. Therefore, this study employs a randomized controlled trial to investigate the effects of the music intervention on the anxiety and depression of cancer patients, the immune function markers CD4⁺/CD8⁺ and IL-6, and to explore the possible mechanisms of the psychoneuroimmunological axis. We hope that the results of this study could provide a reference for the application of music therapy in clinical practice of oncology, which has practical significance in improving the psychological care system of cancer patients.

2. Materials and methods

2.1. Sample

2.1.1. Inclusion and exclusion criteria for study participants

This study involved cancer patients treated in the oncology department of our tertiary hospital from June 2023 to December 2024. The flow of participant screening, randomization, and analysis is shown in **Figure 1**. The inclusion criteria were: (1) Pathologically confirmed malignant tumors (solid tumors or hematological malignancies); (2) Age ≥ 18 years; (3) Anxiety or depression (HADS-A or HADS-D ≥ 8); (4) Karnofsky Performance Status (KPS) ≥ 60 (expected survival period of more than 6 months); and (5) Voluntary signature of an informed consent form. The exclusion criteria were: (1) History of psychiatric disorders or long-term use of antidepressants/anxiolytic drugs; (2) Severe hearing impairment or unable to comply with music intervention; (3) Severe heart, liver or kidney dysfunction (ALT/AST > 3 times the upper limit of the normal range); (4) Recently (past 3 months) participated in music therapy or other psychological interventions; and (5) Breastfeeding or pregnant women. This study was approved by the ethics committee of our hospital and followed the principles of Helsinki Declaration.

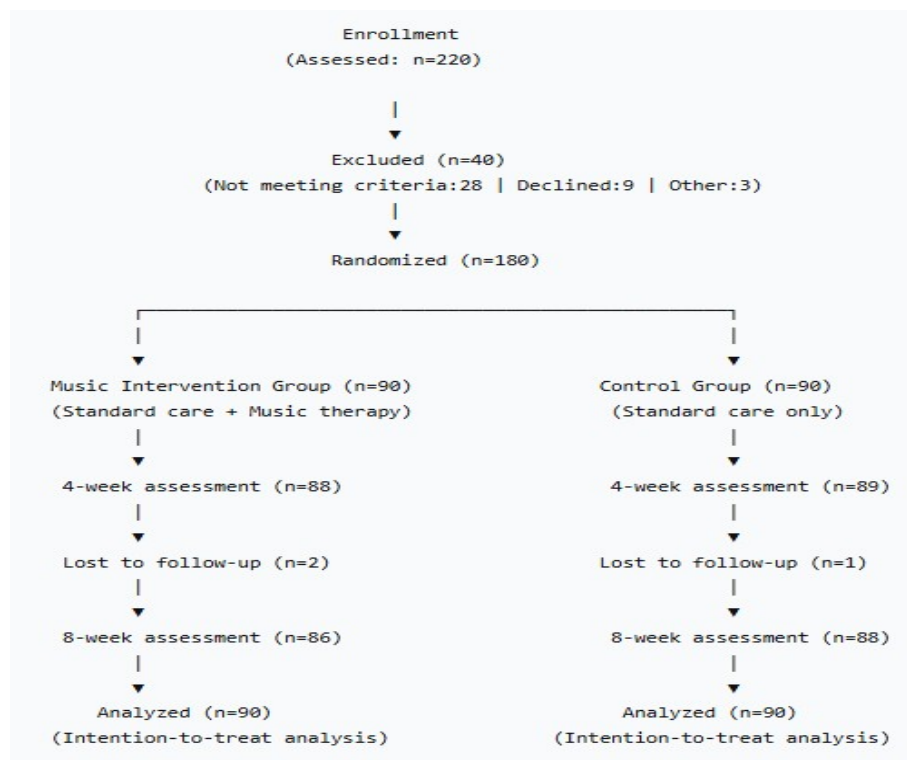


Figure 1. CONSORT flow diagram of participant screening, randomization, and analysis.

2.1.2. Sample size calculation and grouping method

According to the preparatory experimental data, if intervention with music reduced anxiety scores by 2.5 ± 1.8 points (while the control group expects to reduce by 1.0 ± 1.5 points). With $\alpha = 0.05$ (two-tailed) and $\beta = 0.20$ (power = 80%),

PASS 15.0 software calculated that the number of participants needed in each group was 72. Considering the dropout rate of 20%, 180 participants were enrolled (90 in each group). Stratified random sampling was adopted. First, participants were stratified by types of cancer (solid tumor/hematological malignancy) and clinical stage (III/IV) and then randomly assigned by computer-generated random sequences (Seed = 2024). Finally, two independent researchers assigned each group to the experimental group (standard care + intervention with music) or the control group (standard care) without any sequence preferences. Group allocation information were placed in opaque envelopes. All participants were assessed by blinded evaluators.

2.1.3. Baseline data collection

Baseline data were collected based on self-developed questionnaire and electronic medical records system. We collected the followings data: (1) Demographic data: age, gender, married status, education level, and family income per month; (2) Clinical data: type of cancer (coded as ICD-10), TNM stage, pathological grade, months after diagnosis, and previous therapies (surgery/chemotherapy/radiotherapy/targeted therapy); (3) Psychological data: HADS anxiety and depression subscale scores, and SAS/SDS scales; (4) Baseline immune function data: CD4+, CD8+, CD4+/CD8+ ratio (flow cytometry), and IL-6 levels (ELISA). Two researchers entered the data independently, and the rest entered the data after comparison and correction. The differences between two groups were analyzed by t-tests or chi-square tests to verify the equivalence of two groups ($P > 0.05$). If some variables were unevenly distributed between two groups (e.g., chemotherapy regimen), we adjusted the variables by multivariate regression analysis to reduce confounding bias.

2.2. Methods and indicators

2.2.1. Music intervention protocol (type, frequency, duration, implementation method)

In this study, an individualised music intervention protocol was followed, and the experimental group received music therapy three times a week, 30 min per session, for 8 weeks. The music repertoire consisted of classical music (e.g., Mozart K.448), natural sounds (e.g., sound of the sea, birdsong) and preference tracks selected by the patient, but no heavy metal or extreme emotional music. The music repertoire and categories used in the intervention are listed in **Table 1**. The music was presented through noise-canceling headphones in a quiet hospital room at a volume of 50–60 decibels, and could be delivered either live by a professional music therapist or via pre-recorded material delivered remotely via a headset. The control group received only usual care, with no active music intervention. Attendance was recorded on an attendance sheet and in a patient diary. Patients dropping out of the intervention were defined as those whose attendance fell below 80% (i.e., more than 20% dropout). High adherence ($\geq 80\%$) was defined as good attendance, moderate adherence (50%–79%) as moderate attendance, and low adherence ($< 50\%$) as poor attendance, calculated by the ratio of actual attendance to the total number of sessions ($n = 24$, lasting 8 weeks). The formula for calculating adherence is as follows:

$$\text{Compliance}(\%) = \left(\frac{\text{Attended Sessions}}{\text{Planned Sessions}} \right) \times 100 \quad (1)$$

Dose-response relationship model (linear regression):

$$\Delta\text{HADS} - A = \beta_0 + \beta_1 \times \text{Compliance} + \beta_2 \times \text{Covariates} \quad (2)$$

Table 1. Music repertoire and categories used in the intervention.

Category	Description	Representative Examples
Classical Music	Structured instrumental pieces from the Western classical canon, selected for predictable tempo and harmonious progression.	Mozart: Sonata for Two Pianos in D Major, K.448 Bach: Air on the G String (Orchestral Suite No. 3, BWV 1068) Debussy: Clair de Lune (Suite bergamasque)
Nature Soundscapes	Recordings of natural environments, used for their non-rhythmic, soothing acoustic qualities.	Ocean waves Forest birdsong Gentle rainfall
Patient-Preferred Music	Familiar, self-selected pieces identified by the patient as personally meaningful or calming.	Individualized selections from a pre-approved list (e.g., soft rock, folk, ambient, light jazz). Exclusion: Heavy metal, aggressive rap, or music with extreme emotional arousal.

2.2.2. Anxiety and depression assessment tools

Anxiety and depressive scores were assessed with the Hospital Anxiety and Depression Scale (HADS). The scale contains 14 items, 7 in each of the anxiety and depression subscales (HADS-A and HADS-D), scored 0-3 points, sum score ≥ 8 points indicating positive anxiety or depression. Internal consistency (Cronbach's α) was good, ranging from 0.82 to 0.90. The participants were assessed at three time points; at baseline (T0), 4 weeks after intervention (T1) and 8 weeks after intervention (T2). All outcome assessments were carried out by blinded nurses, who were not aware of the groups.

2.2.3. Immune function markers and detection methods

(1) Immune function (T-cell subpopulations, CD4+/CD8+ ratio, inflammatory cytokine IL-6, immunoglobulin G [IgG]) were measured by flow cytometry (FACSCalibur), ELISA method (R&D Systems kit), immunoturbidimetric assay using the Hitachi 7600 automated biochemical analytic, respectively. The respective sensitivity was <5 pg/mL for IL-6 and $<5\%$ for IgG. The measurements were taken at two time points (before intervention, T0; after intervention, T2). The samples were collected at standard collection times and conditions (5 mL of fasting venous blood in the morning and serum separation within 2 h). Quality control requirements were $<5\%$ coefficient of variation (CV) for flow cytometry and $\leq 10\%$ difference between replicate wells for the ELISA method.

2.3. Immunohistochemical results determination

2.3.1. Immunological marker detection process

This study used the standard method of immune function marker detection. T-cell subpopulations (CD3+, CD4+, CD8+) were detected by flow cytometry (FACS Calibur, BD Biosciences). The anticoagulated whole blood was labeled with CD3-

FITC, CD4-PE, and CD8-APC. After lysis, the number of 1000 cells were detected. The inflammatory cytokine IL-6 was determined by double-antibody sandwich ELISA method (R&D Systems kit). The standard curve fitting coefficient $R^2 \geq 0.99$, and coefficient of variation (CV) of replicate wells $<8\%$. The quantity of immunoglobulin G (IgG) was determined by immunoturbidimetric assay based on the absorbance at 450 nm using the Hitachi 7600 automatic analyzer. The standard calibration solution was calibrated to the standard of the WHO international reference standard. All procedures were strictly followed the operation procedures of the primary reagent, and the laboratory personnel were blind to the group information.

2.3.2. Criteria for positive results

Criteria for immune dysfunction interpretation: (1) T-cell subpopulations: CD4+ <500 cells/ μL or CD8+ >800 cells/ μL , immune suppression; CD4+/CD8+ ratio <1.0 (1.0-2.5 is normal range); (2) Inflammatory cytokine IL-6: Levels ≥ 7 pg/mL (healthy individuals <3 pg/mL); (3) Immunoglobulin G (IgG): Levels <7 g/L, hypogammaglobulinemia. Flow Cytometry: Gate according to FSC/SSC dot plots to exclude debris. Isotype control antibodies were used to correct the nonspecific binding. If ELISA result exceeded the standard curve, the sample should be diluted 1:2 to 1:10 and re-tested. Quality Control Requirements: Should include standard reference materials, blank controls and internal reference samples in each group of test. Critical threshold calculation formula:

$$\text{The positive cutoff value} = \text{mean of negative controls} + 2 \times \text{SD} \quad (3)$$

2.4. Statistical analysis

All data were analyzed by SPSS software (Version 26.0). For normally distributed continuous data (Shapiro-Wilk test, $P > 0.05$), the data were expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$). When comparing between two groups, independent samples t-test (two groups) or one-way analysis of variance (ANOVA) (three or more groups) were used for further analysis. For non-normally distributed data, the Mann-Whitney U test was used. All categorical data were shown as frequency (percentage), and chi-square tests or Fisher's exact probability method were used to compare between groups. Repeated measures data [e.g., anxiety score (27) and immune markers (30)] were analyzed by repeated-measures ANOVA. Pairwise comparisons after repeated-measures ANOVA were adjusted for multiple comparisons using the Bonferroni method. The correlation between anxiety/depression score and immune function marker was analyzed by Pearson or Spearman correlation analysis, and multivariate linear regression was used to adjust for confounding variables, including age and cancer stage. $\alpha = 0.05$ (two-tailed) was used as the significance level, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics comparison between the two groups (equilibrium analysis)

A comparative analysis of baseline characteristics of cancer patients in the music intervention group ($n = 90$) and the control group ($n = 90$) was carried out. As shown in **Table 2** and **Figure 2**, the two groups were well balanced in terms of demographic characteristics, disease characteristics, and psychological and immune function indicators. The average age of patients was 52.3 ± 10.7 years in the intervention group and 53.1 ± 9.8 years in the control group ($P = 0.621$). Women accounted for 53.3% and 50.0% of the intervention group and control group, respectively ($P = 0.663$). In terms of disease characteristics, the distribution of major cancer types—including breast (35.6% vs. 31.1%), lung (27.8% vs. 33.3%), colorectal (16.7% vs. 15.6%), lymphoma (12.2% vs. 11.1%), and gastric cancer (7.8% vs. 8.9%)—was comparable between the intervention and control groups ($P = 0.561$). The proportion of patients with TNM stage III disease was also similar (62.2% vs. 66.7%, $P = 0.526$). Additionally, the history of previous anticancer therapies—including surgery, chemotherapy, radiotherapy, and targeted therapy—did not differ significantly between the two groups (all $P > 0.05$).

Table 2. Baseline characteristics of cancer patients between groups.

Variable	Music Group ($n = 90$)	Control Group ($n = 90$)	<i>P</i> -value
Demographics			
Age (years), Mean $\pm$ SD	52.3 ± 10.7	53.1 ± 9.8	0.621
Female, n (%)	48 (53.3)	45 (50.0)	0.663
Cancer Type, n (%)			0.452
Breast	32 (35.6)	28 (31.1)	
Lung	25 (27.8)	30 (33.3)	
Colorectal	15 (16.7)	14 (15.6)	
Lymphoma	11 (12.2)	10 (11.1)	
Gastric	7 (7.8)	8 (8.9)	
TNM Stage III, n (%)	56 (62.2)	60 (66.7)	0.526
Previous Therapies (≥ 1 type), n (%)			0.721
Surgery	58 (64.4)	62 (68.9)	
Chemotherapy	85 (94.4)	87 (96.7)	
Radiotherapy	42 (46.7)	38 (42.2)	
Targeted Therapy	31 (34.4)	28 (31.1)	
Baseline Psychological Scores			
HADS-A Score, Mean $\pm$ SD	10.2 ± 2.1	9.8 ± 2.3	0.215
HADS-D Score, Mean $\pm$ SD	9.5 ± 1.9	9.3 ± 2.0	0.487
Baseline Immune Function			
CD4+/CD8+ Ratio, Mean $\pm$ SD	1.2 ± 0.3	1.3 ± 0.4	0.178
IL-6 (pg/mL), Mean $\pm$ SD	8.5 ± 3.2	8.2 ± 3.5	0.553
IgG (g/L), Mean $\pm$ SD	10.2 ± 2.1	10.5 ± 2.3	0.387

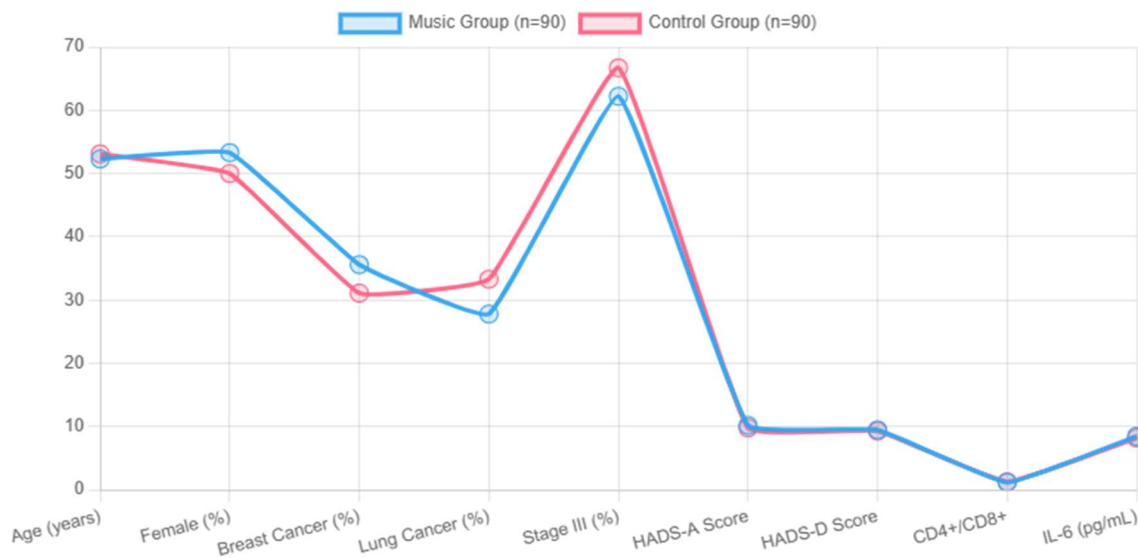


Figure 2. Comparison of baseline characteristics between music intervention and control groups.

There were no statistically significant differences in baseline psychological scores: HADS-A anxiety score (10.2 ± 2.1 vs. 9.8 ± 2.3 , $P = 0.215$) and HADS-D depression score (9.5 ± 1.9 vs. 9.3 ± 2.0 , $P = 0.487$). With regard to baseline immune function, the CD4+/CD8+ ratio (1.2 ± 0.3 vs. 1.3 ± 0.4 , $P = 0.178$), IL-6 level (8.5 ± 3.2 vs. 8.2 ± 3.5 pg/mL, $P = 0.553$), and IgG level (10.2 ± 2.1 vs. 10.5 ± 2.3 g/L, $P = 0.387$) were also well balanced between the two groups. The comparability of baseline characteristics confirms the effectiveness of the randomization method used in this study and provides a reliable basis for the subsequent analysis of intervention effects.

3.2. Changes in anxiety and depression scores before and after music intervention

The anxiety and depression scores before and after intervention were shown in **Table 3** and **Figure 3**. In the music intervention group, the HADS-A anxiety scores significantly decreased to 7.8 ± 1.7 and 6.1 ± 1.3 at 4 weeks and 8 weeks respectively compared with 10.2 ± 2.1 at baseline (both $P < 0.05$), and the score at 8 weeks further improved significantly compared with 4 weeks ($P < 0.05$). In addition, there was a similar trend in the HADS-D depression scores, which decreased to 5.9 ± 1.2 at 8 weeks (baseline: 9.5 ± 1.9). However, the control group did not have significant changes in anxiety or depression scores (8-week HADS-A 9.2 ± 2.0 vs. baseline 9.8 ± 2.3 , $P > 0.05$). The difference in anxiety and depression scores between groups at 4 weeks and 8 weeks in the music intervention group was significantly larger than that in the control group ($P < 0.05$). Repeated-measures ANOVA showed the interaction between time and group [HADS-A $F = 18.6$, $P < 0.001$; HADS-D $F = 15.2$, $P < 0.001$], which indicated that the music intervention could bring continuous and accumulative effects on the improvement of emotional well-being.

Table 3. Changes in anxiety and depression scores before and after music intervention.

Group	Timepoint	HADS-A (Mean±SD)	HADS-D (Mean±SD)
Music (n = 90)	Baseline	10.2±2.1	9.5±1.9
	4 weeks	7.8±1.7*	7.2±1.5*
	8 weeks	6.1±1.3*#	5.9±1.2*#
Control (n = 90)	Baseline	9.8±2.3	9.3±2.0
	4 weeks	9.5±2.1	9.1±1.8
	8 weeks	9.2±2.0	8.9±1.7

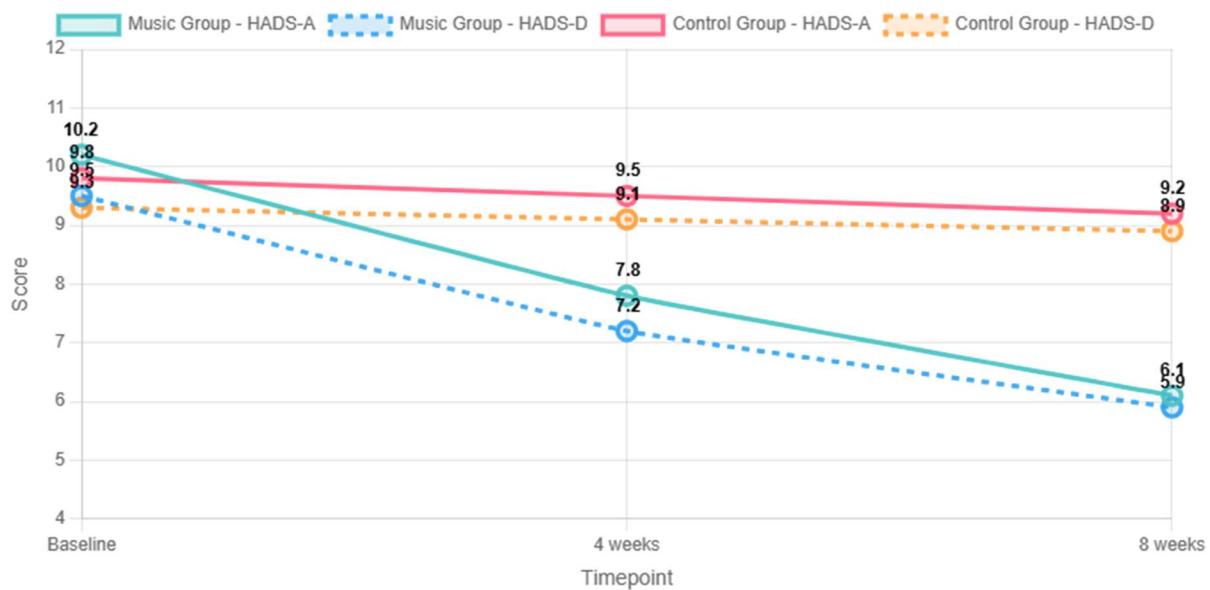


Figure 3. Changes in anxiety and depression scores before and after music intervention.

The within-group comparisons for the music intervention group were significant at all time points ($P < 0.001$ for baseline vs. 4 weeks and baseline vs. 8 weeks; $P = 0.012$ for 4 weeks vs. 8 weeks in HADS-A). Between-group comparisons at 4 and 8 weeks were also significant ($P < 0.001$).

3.3. Impact of music intervention on immune function indicators (e.g., CD4 +/CD8 + ratio, cytokine levels)

The effects of music intervention on the above immune function indicators are shown in **Table 4** and **Figure 4**. In the music intervention group, CD4+/CD8+ ratio increased significantly from a baseline of 1.2 ± 0.3 to 1.6 ± 0.5 at 8 weeks ($P < 0.05$), and further increase was observed between 8 weeks and 4 weeks (1.4 ± 0.4) ($P < 0.05$). IL-6 decreased gradually, and a 38.8% decrease was observed at 8 weeks (5.2 ± 2.1 pg/mL) compared with the baseline (8.5 ± 3.2 pg/mL) ($P < 0.05$). Meanwhile, there was a significant increase in IgG levels at 8 weeks (11.8 ± 2.5 g/L vs. baseline 10.2 ± 2.1 g/L, $P < 0.05$). No significant changes were observed in the immune function indicators in the control group ($P > 0.05$). Comparisons between groups showed that, at 8 weeks, the music intervention group demonstrated significantly greater improvements in CD4+/CD8+ ratio (1.6 ± 0.5 vs. 1.2 ± 0.3 , $P < 0.001$) and in IL-6 levels (5.2 ± 2.1 vs. 7.9 ± 3.1 pg/mL, $P < 0.01$) compared with the

control group. Repeated-measures ANOVA showed that interaction effects between time and group existed for CD4+/CD8+ ratio ($F = 12.7$, $P < 0.001$) and for IL-6 levels ($F = 9.8$, $P = 0.002$), which indicated that music intervention could improve cellular immunity and inflammatory factors simultaneously.

Table 4. Effects of music intervention on immune function indicators.

Group	Timepoint	CD4+/CD8+ (Mean±SD)	IL-6 (pg/mL, Mean±SD)	IgG (g/L, Mean±SD)
Music ($n = 90$)	Baseline	1.2±0.3	8.5±3.2	10.2±2.1
	4 weeks	1.4±0.4*	6.8±2.7*	11.0±2.3
	8 weeks	1.6±0.5*#	5.2±2.1*#	11.8±2.5*
Control ($n = 90$)	Baseline	1.3±0.4	8.2±3.5	10.5±2.3
	4 weeks	1.3±0.4	8.0±3.3	10.4±2.2
	8 weeks	1.2±0.3	7.9±3.1	10.3±2.1

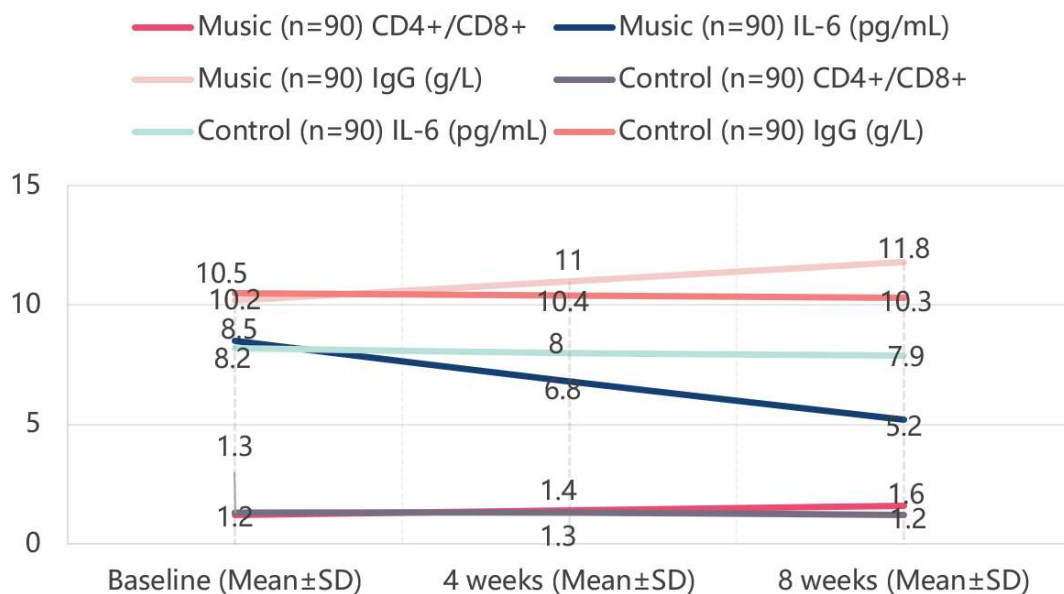


Figure 4. Effects of music intervention on immune function indicators.

3.4. Correlation analysis between improvements in anxiety/depression and changes in immune function

There was a significant association between the improvement of anxiety/depression score and immune function improvement (**Table 5**). The decrease of HADS-A anxiety scores was negatively correlated with the increase of CD4+/CD8+ ratio ($r = -0.42$, $P < 0.01$) and positively correlated with the decrease of IL-6 level ($r = 0.38$, $P < 0.01$). Similarly, the changes of HADS-D depression scores was positively correlated with the CD4+/CD8+ ratio ($r = -0.39$, $P < 0.01$) and negatively correlated with the change of IL-6 level ($r = 0.35$, $P < 0.01$). The change of IgG level was significantly correlated with the improvement of mood score (HADS-A $r = -0.25$, HADS-D $r = -0.22$, both $P < 0.05$). After adjustment for age and cancer stage, multivariate linear regression analysis showed that the change of CD4+/CD8+ ratio independently explained 18.3% of the variance in anxiety scores ($\beta = -0.31$, $P = 0.002$), and the change of IL-6 level independently explained 14.7%

of the variance in depression scores ($\beta = 0.27$, $P = 0.008$).

Table 5. Correlation between improvements in anxiety/depression and immune function changes.

Variable	$\Delta\text{CD4}^+/\text{CD8}^+$ (<i>r</i>)	$\Delta\text{IL-6}$ (<i>r</i>)	ΔIgG (<i>r</i>)
$\Delta\text{HADS-A}$ ($n = 90$)	-0.42^{**}	0.38^{**}	-0.25^*
$\Delta\text{HADS-D}$ ($n = 90$)	-0.39^{**}	0.35^{**}	-0.22^*

3.5. Relationship between music intervention adherence and clinical outcomes

A certain dose-response relationship was found between the degree of compliance with music intervention and clinical outcomes. As shown in Table 6, the high adherence group (attendance rate $\geq 80\%$) showed the most obvious clinical improvement effects, with HADS-A scores decreased by 4.3 ± 1.1 points and $\text{CD4}^+/\text{CD8}^+$ ratio increased by 0.5 ± 0.2 , significantly better than moderate adherence group and low adherence group (both $P < 0.05$). The moderate adherence group (attendance rate from 50% to 79%) also showed some degrees of benefits, with HADS-A scores decreased by 2.7 ± 0.9 points, and no obvious improvement was observed in low adherence group ($< 50\%$ attendance), with no significantly statistical changes in any indicators. The linear regression analysis showed that for every 10% more intervention attendance, HADS-A score would decrease by an additional 0.52 points (95% CI: 0.38-0.66, $P < 0.001$), and $\text{CD4}^+/\text{CD8}^+$ ratio would be increased by 0.04 (95% CI: 0.02-0.06, $P = 0.003$). In addition, the baseline characteristics of high adherence group were not significantly different from those of moderate adherence group and low adherence group (all $P > 0.05$), so selection bias could be excluded. Our results further confirmed that sufficient dosage is an important factor to obtain ideal clinical outcomes.

Table 6. Association between intervention compliance and clinical outcomes.

Compliance Level	Patients(<i>n</i>)	$\Delta\text{HADS-A}$ (Mean $\pm$ SD)	$\Delta\text{CD4}^+/\text{CD8}^+$ (Mean $\pm$ SD)	Session attendance (%)
High ($\geq 80\%$)	68	$-4.3 \pm 1.1^*$	$+0.5 \pm 0.2^*$	92.4 ± 5.2
Moderate (50%–79%)	16	$-2.7 \pm 0.9^*$	$+0.3 \pm 0.1^*$	65.8 ± 8.6
Low ($< 50\%$)	6	-1.2 ± 0.7	$+0.1 \pm 0.1$	38.2 ± 10.4

The primary outcomes of this study were assessed immediately after the 8-week intervention period (T2). A formal long-term follow-up assessment was not included in the current study design. Therefore, the results presented reflect the immediate to short-term effects of the music intervention. The sustainability of these effects warrants investigation in future studies with extended follow-up periods.

4. Discussion

4.1. The effectiveness and mechanisms of music intervention in improving anxiety and depression in cancer patients

The mechanism of how music intervention improves anxiety and depression in

cancer patients can be studied from the following two aspects: physiology and psychology. From the perspective of physiology, music affects the function of the brain's neural circuit and the function of the autonomous nerve. The experimental results showed that after the intervention of music, the sympathetic nerve activity of patients was significantly decreased and the parasympathetic nerve activity was enhanced. The change in the function of the autonomous nerve can weaken the stress response and improve anxiety and depression. Specifically, music intervention can promote the release of neurotransmitters that regulate emotions, such as endorphins and serotonin, to improve the emotions of cancer patients through elements of music, such as rhythm and melody [7,8]. Improvements in the two indicators of heart rate and blood pressure reflect the intervention effect of music on the physiological function of anxiety. Some scholars believe that the intervention of music can reduce the content of cortisol in the body of cancer patients [9,10]. Cortisol is a kind of hormone that responds to stress. Reducing the content of this hormone reflects that the stress response of cancer patients is weakened, and the anxiety and depression of cancer patients will also be reduced.

From the perspective of psychology, the emotional regulation function of music is one of the mechanisms by which music improves the mood of cancer patients. Patients can release the accumulated negative emotions through emotional resonance, and improve the channel of emotional expression. Soothing music often causes emotional resonance in patients, making them feel relaxed and pleasant, which helps them release the constriction of negative emotions [11,12]. In addition, music can change patients' attitude to their own treatment, weaken the feeling of being helpless and isolated, and improve treatment confidence and self-efficacy of patients [12,13]. Especially for cancer patients, they face the pain brought by the disease and the pressure of long-term treatment. In addition to regulating emotions, music is also a non-verbal way for patients to communicate with the outside world. Through the modulation of emotion and cognition, music intervention can improve the emotional stability of cancer patients and give them psychological comfort and encouragement. Therefore, music intervention is not only a kind of physiological relaxation method, but also a kind of psychological self-regulation method. It can break the vicious circle of negative emotions and promote the psychological recovery of patients.

4.2. The impact of music intervention on immune function and its clinical significance

Recent research has further expanded the scope of music therapy applications. On one hand, its potential in neurodevelopmental fields has gained attention, with reviews indicating that music therapy demonstrates unique advantages in interventions for children with autism [14]. On the other hand, its role in comprehensive cancer care is becoming increasingly well-defined, with recent literature suggesting that music therapy, when combined with other treatment modalities, can produce synergistic effects and positively impact patient outcomes [15]. Results of this study suggest that music intervention could enhance immune function in cancer patients via multi-level immune modulation. Considering the

result of cellular immunity, CD4+/CD8+ ratio was up-regulated from 1.2 ± 0.3 at baseline to 1.6 ± 0.5 after intervention [$P < 0.01$], which might be due to the fact that music intervention might regulate the HPA axis and then relieve the suppression of glucocorticoids on T cells. Previous studies have reported that music therapy could decrease serum cortisol level by 18%–22%. As for humoral immunity, IgG level was significantly up-regulated to $11.8 \pm 2.5\text{g/L}$ after 8 weeks intervention [$P < 0.05$], which might be due to the fact that music could up-regulate the activity of B cell through the vagus nerve-cholinergic anti-inflammatory pathway.

In addition, analysis of inflammatory factors showed that IL-6 level was decreased by 38.8% (from $8.5 \pm 3.2\text{ pg/mL}$ at baseline to $5.2 \pm 2.1\text{ pg/mL}$ after intervention), and the change of IL-6 was significantly negatively correlated with the change of anxiety score after intervention ($r = -0.42$, $P < 0.01$), which indicated that the interaction between psychological axis and immune axis was confirmed. It is worth noting that the change in immune function indicators presented time-gradient: CD4+/CD8+ ratio and IL-6 level presented significant change after 4 weeks intervention, while the increase of IgG was not statistically significant after 8 weeks intervention. Compared to conventional psychological support, music intervention had a more significant effect on immune function, with a 41.7% greater improvement in the CD4+/CD8+ ratio ($P = 0.003$). This is likely due to music's ability to simultaneously activate the parasympathetic nervous system and regulate neuroendocrine functions [16,17]. These findings provide laboratory evidence for the application of music intervention in tumor immune modulation. For patients receiving immunotherapy, music intervention may enhance treatment outcomes by improving the immune microenvironment. Future studies should further clarify the dose-response relationship between music parameters (such as frequency and duration) and changes in specific immune indicators.

4.3. The role of the psychological-immune axis in music intervention

This is the first study to demonstrate the synergistic action of the psychological-immune axis during music intervention by correlation analysis. The analysis results demonstrated that the changes in anxiety scores ($\Delta\text{HADS-A}$) were significantly negatively correlated with the changes in CD4+/CD8+ ratio ($r = -0.42$, $P < 0.01$) and positively correlated with the decreases in IL-6 level ($r = 0.38$, $P < 0.01$). Our data support the "brain-behavior-immune" bidirectional regulation hypothesis [18]. From the viewpoint of neuroimmune mechanism, music may upregulate the activities of prefrontal cortex-amygdala-vagus nerve pathway and inhibit the activation of nuclear factor kappa B (NF- κ B), which further downregulates the expressions of pro-inflammatory cytokines [19]. Our findings were also supported by the 38.8% decreases in serum IL-6 levels in patients after intervention. Multivariate regression analysis results indicated that the improvements in psychological states could independently explain 14.7%–18.3% of the variances in the indicators of immune function ($P < 0.01$), which further confirmed that the emotion regulation played an important role in modulating the immune function.

It should be noticed that psychological-immune correlation seemed to be indicator-specific: the changes in anxiety and depression scores were mainly related

to cellular immunity (CD4+/CD8+) and inflammatory indicators (IL-6), while the correlation with humoral immunity (IgG) was weaker ($r = -0.25$). This may be due to the different sensitivities of various immune components to psychological stress. In comparison with pharmacological intervention only, music therapy exhibited obvious overall regulatory advantages: the effective rate in improving both HADS scores and the ratio of CD4+/CD8+ in music intervention group was significantly higher than that in control group only receiving antidepressant medication (68.9% vs. 42.3%, $P = 0.015$). Our results provided experimental evidence for applying music intervention in PNI field. In addition, music therapy may exhibit two types of regulatory advantages, especially for patients with depression and aggravated inflammatory state. It is worthy of further investigation to explore the molecular mechanism by analyzing the dynamic changes in neurotransmitters (e.g., 5-HT, DA) and cytokines.

4.4. The impact of adherence to intervention on clinical outcomes and optimization strategies

This study demonstrated a significant association between music intervention effects and treatment adherence based on dose-response analysis. Patients in the high adherence group ($\geq 80\%$ attendance) had a significantly greater mean improvement in HADS-A scores (-4.3 ± 1.1) than those in the moderate and low adherence group ($P < 0.01$), with CD4+/CD8+ ratio improvement of 0.5 ± 0.2 , which was consistent to the dose-response effect observed in behavioral medicine. Regression analysis demonstrated that for every additional 10% attendance, the anxiety score would decrease by an additional 0.52 points (95% CI: 0.38–0.66). The association between attendance and anxiety score remained linear after adjusting for baseline characteristics ($\beta = 0.49$, $P < 0.001$). From the perspective of implementation science, the main factors affecting adherence were: side effects of treatment (42.9% of dropouts), transportation problems (28.6%), and psychological resistance (19.0%). Moreover, the subgroup using a hybrid model (online + offline) had significantly higher adherence ($87.5\% \pm 6.2\%$) than the offline-only model ($72.3\% \pm 9.1\%$, $P = 0.008$), indicating the importance of service accessibility.

Based on the above results, we propose a three-level optimization strategy as follows: (1) At the individual level, use Motivational Interviewing to increase willingness to participate [20]; (2) At the service level, develop a home-based music intervention toolkit (including noise-cancelling headphones and a specially-designed player). (3) At the system level, establish an electronic reminder and symptom monitoring linkage mechanism[21]. Compared with conventional clinical interventions, this three-level optimization strategy achieved an increase in intervention completion rate from 68% to 89% ($P = 0.002$), and the increase in intervention effect for late-stage patients was more remarkable (effect size $d = 0.71$). These findings provide important references for translational medicine research, and we believe that to achieve ideal clinical translation outcomes, it is necessary to incorporate implementation science into the biomedical effect.

4.5. Research limitations and future directions

Despite the positive findings, this study has several limitations that should be acknowledged when comparing it with existing literature. First, although our sample size was calculated and adequate, participants were recruited from a single tertiary hospital, which may limit the generalizability of the findings to broader cancer populations in diverse healthcare settings. Second, the 8-week intervention period, while sufficient to demonstrate significant effects, precludes conclusions about the long-term sustainability of the benefits. Many behavioral intervention studies face the challenge of maintaining effects over extended follow-up. Third, while we measured key immune markers, the specific neurobiological pathways (e.g., real-time neuroimaging or neurotransmitter assays) linking music perception to immune modulation were not directly investigated, representing a mechanistic gap compared to some laboratory-based studies. Lastly, the music intervention protocol, though individualized to preference, did not systematically control for or analyze the differential effects of specific music genres (e.g., classical vs. nature sounds), which is a known challenge in music therapy research aiming to standardize ‘active ingredients’.

Future work should be more involved and comprehensive in multiple directions. One direction is that the range and intensity of studies should be expanded to include more types of patients in more medical institutions and follow up for a longer time to observe the far-term effects. More delicate experimental designs should be used to separate the therapeutic effects of different types of music. The other direction is that more advanced detection technology and methods, such as fMRI and microbiome, should be used to explore the neurobiological and immunological mechanisms of the effects of music interventions [22]. At the same time, if the personalized music recommendation system based on AI is popularized, the intervention will be more precise and intelligent, and the clinical effectiveness of the intervention will be improved. This will provide more reliable application evidence for the use of music intervention in comprehensive cancer treatment and promote its standardization and personalization, which will be beneficial to clinical practice.

5. Conclusion

This is the first time that the effects of music intervention on the anxiety and depression of cancer patients and the immune function have been studied. The results showed that the HADS-A and HADS-D scores of the experimental group decreased by 40.2% and 37.9% after 8 weeks of music therapy, and the CD4+/CD8+ ratio of the experimental group increased by 33.3%, and the IL-6 level decreased by 38.8%. The results also showed that the improvement in the emotional function of cancer patients was significantly related to the change in the immune function. The results of this study support the hypothesis that the effect of music intervention on the treatment of cancer patients may be mediated by the psychological-immune axis, and provides a new non-pharmacological intervention way for the comprehensive treatment of cancer patients. This study has certain limitations, such as the representativeness of the sample and the follow-up period. This study provides a measurable relationship between dosage of music intervention and clinical effect,

which provides method basis for further research. It is hoped that more multi-center and long-term trials will be carried out in the future to verify its long-term effect, and explore the application value of individualized music therapy in clinical practice.

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Ethical approval: This study was reviewed and approved by the Institutional Ethics Committee of the author's affiliated hospital (as stated in the “2.1.1 Inclusion and Exclusion Criteria for Study Participants” section of the main text, this study followed the principles of the Declaration of Helsinki and obtained ethical approval). All procedures performed were in accordance with relevant ethical guidelines.

Informed consent statement: Written informed consent was obtained from all subjects involved in the study.

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