The Effectiveness of Music Therapy on Fatigue and Laboratory Values in Acute Myeloid Leukemia Patients undergoing Chemotherapy

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Background

Statistics from the American Cancer Society (ACS) (2020) indicate that the global 5-year survival rate for all types of leukemia ranges from approximately 25% to 85%. For adult Acute Lymphoblastic Leukemia (ALL), the 5-year survival rate is 40%–50%, whereas for Chronic Lymphocytic Leukemia (CLL), it is as high as 85%. Fatigue is the most prevalent symptom reported by leukemia patients (AlFayyad et al., 2020; Schumacher et al., 2002; Wang et al., 2002). Given that leukemia treatment primarily involves chemotherapy and radiation therapy, side effects such as fatigue, nausea, and vomiting are typical (Schumacher et al., 2002). Approximately 60% to 90% of patients experience cancer-related fatigue (CRF) during chemotherapy (Chen & Tang, 2020; Rutkowski et al., 2021). Factors contributing to CRF include cancer stage, treatment-related side effects (e.g., pancytopenia, malnutrition, and poor sleep quality secondary to chemotherapy or radiotherapy), and psychological distress (e.g., tension, anxiety, and fear stemming from uncertainty and stress regarding diagnosis and treatment) (Rau et al., 2020). With advancements in medical resources, cancer patient survival rates are gradually increasing (Miller et al., 2019). Therefore, early detection and timely intervention for fatigue by healthcare professionals are crucial for enhancing patients' quality of life.

As per the 2023 National Comprehensive Cancer Network (NCCN) guidelines, non-pharmacological interventions are the recommended first-line approach for managing CRF. These are broadly categorized into six types: physical activity (Hilfiker et al., 2018; Wu et al., 2019), psychosocial interventions (Wu et al., 2021; Lai, 2015; Lai et al., 2017; Mustian et al., 2017; Poort et al., 2017), energy conservation techniques (Rau et al., 2023; Chou & Tang, 2008; Barsevick et al., 2002), complementary and alternative medicine (CAM) (Chen & Tang, 2020; Rau et al., 2023; Zick et al., 2021), nutritional management (Inglis et al., 2019; Thong et al., 2020), and light therapy (Monteleone et al., 2011; Starreveld et al., 2021; Van Maanen et al., 2016).

Interventions such as acupressure, massage, and art or music therapy fall under the CAM category (Chen & Tang, 2020; Rau et al., 2023; Zick et al., 2021). Considering the specific characteristics of leukemia and the need for practical clinical application, music therapy presents as a non-invasive, safe, comfortable, and easily administered nursing intervention. It can be conveniently implemented by healthcare providers, patients themselves, or family members. Research indicates that music therapy can reduce depression, anxiety, and pain in cancer patients (Köhler et al., 2020; Li et al., 2020; SezgiN & Bektas, 2022). Unfortunately, the application of music therapy for managing CRF in leukemia patients remains limited. Therefore, this study aims to investigate the effects of music therapy on fatigue and clinical laboratory values (e.g.,

White Blood Cell [WBC] count, Hemoglobin [Hb], Albumin) in patients with acute leukemia, to provide a reference for clinical practice.

Section 1: Research Purpose

To investigate the effects of music therapy on fatigue and clinical laboratory values (White Blood Cell count, Hemoglobin, and Albumin) in patients with acute leukemia.

Section 2: Research Hypotheses

1. Patients with acute leukemia who receive music therapy will experience lower levels of fatigue during chemotherapy compared to those receiving standard care.
2. Patients with acute leukemia who receive music therapy will demonstrate improved clinical laboratory values (White Blood Cell count, Hemoglobin, and Albumin) during chemotherapy compared to those receiving standard care.

Literature Review

I. Leukemia and Its Classification

According to the Global Cancer Observatory (GLOBOCAN) (2020), the global incidence of leukemia was 5.4 per 100,000 population, with a mortality rate of 3.3 per 100,000 population (Sung et al., 2021). In Taiwan, statistics from the Ministry of Health and Welfare (2022) indicate that malignant neoplasms have remained the leading cause of death for the past four decades. Leukemia ranked 13th among cancer deaths, with an incidence rate of 2.9 per 100,000 and a mortality rate of 5.0 per 100,000.

Among leukemia cases, Acute Myeloid Leukemia (AML) was the most prevalent, accounting for 32.21% of cases. This was followed by Acute Lymphocytic Leukemia (ALL) at 11.21%, Chronic Myelogenous Leukemia (CML) at 10.30%, and Chronic Lymphocytic Leukemia (CLL) at 8.77%. The median age at diagnosis was 63 years for both sexes. The crude incidence rates for males and females were 13.27 and 10.09 per 100,000 population, respectively, indicating a higher incidence in males (Ministry of Health and Welfare, 2022; Chang, 2021).

Under normal conditions, hematopoietic stem cells in the bone marrow differentiate and mature into two major lineages: the myeloid lineage and the lymphoid lineage. The pathogenesis of leukemia involves the uncontrolled proliferation of abnormal blood cells during hematopoiesis, which may result from genetic abnormalities such as translocation, deletion, point mutation, or epigenetic alterations. The precise etiology remains unclear, but potential risk factors include: advanced age, male sex, exposure to radiation, prior radiotherapy or chemotherapy, exposure to chemical agents (e.g., formaldehyde, building material coatings, industrial disinfectants),

lifestyle factors (e.g., smoking, alcohol consumption), viral infections such as Epstein-Barr virus (EBV) and human immunodeficiency virus (HIV), heredity, and genetic mutations (Chang, 2021; Bispo et al., 2020; Vogado et al., 2018; Dohner et al., 2015).

Leukemia is classified based on cell origin and morphological features into lymphoblastic leukemia and myeloid leukemia. It is further categorized by cancer cell maturity and the clinical speed of progression into acute (excess immature blast cells) and chronic (excess mature blood cells). This results in the four main types: AML, CML, ALL, and CLL (Bispo et al., 2020; Dohner et al., 2015).

II. Diagnostic Methods for Leukemia

Diagnostic methods include blood tests, peripheral blood smears, and bone marrow aspiration and biopsy to observe the infiltration of leukemia cells in the blood and marrow. Imaging studies, such as computed tomography (CT) or magnetic resonance imaging (MRI), are used to assess for lymphadenopathy (swollen lymph nodes) or hepatosplenomegaly (enlarged liver and spleen). Genetic testing is also employed for disease classification (Wang et al., 2020).

III. Treatment Modalities for Leukemia

Currently, there are four primary treatment modalities for leukemia: chemotherapy, radiation therapy, hematopoietic stem cell transplantation (HSCT), and supportive therapy (Wang et al., 2020; Bispo et al., 2020).

1. **Chemotherapy:** This is the primary treatment for leukemia, typically divided into three phases: 1) Induction: Short-term, intensive, high-dose therapy, usually lasting 1–2 months; 2) Consolidation/Intensification: High-dose therapy continued for several months; and 3) Maintenance/Post-consolidation: Low-dose therapy, typically continued for about two years. Common side effects include alopecia (hair loss), oral mucositis (mouth sores), anorexia (loss of appetite), nausea, vomiting, diarrhea or constipation, and pancytopenia (Wang et al., 2020; Turcotte et al., 2022).
2. **Radiation Therapy:** This modality utilizes high-energy radiation to eliminate abnormal cells. It may be used for leukemia that has infiltrated the central nervous system (CNS) or to reduce tumor size. Side effects include fatigue, pancytopenia, skin reactions in the treatment area (ranging from mild redness or burning to desquamation [peeling]), and hair loss in the treated area. Depending on the irradiated zone, side effects such as nausea and vomiting (if the head or abdomen is treated) or diarrhea (if the abdomen or pelvis is treated) may occur (Wang et al., 2020; Turcotte et al., 2022).
3. **Hematopoietic Stem Cell Transplantation (HSCT):** This is divided into allogeneic hematopoietic stem cell transplantation (allo-HSCT) and peripheral

blood stem cell transplantation (PBSCT). PBSCT is commonly used today. Because hematopoietic stem cells are scarce in peripheral blood, granulocyte-colony stimulating factor (G-CSF) is administered for 3–5 days to accelerate stem cell growth and mobilize them into the peripheral blood. These cells are then collected, separated, cryopreserved, and stored for transplantation (Wang et al., 2020).

4. **Supportive Therapy:** This involves symptomatic treatment, such as administering antibiotics for fever or providing blood transfusions for low hemoglobin or platelet counts (Wang et al., 2020).

II Overview of Cancer-Related Fatigue

Fatigue is the most prevalent symptom reported by leukemia patients (AlFayyad et al., 2020; BIKMAZ & ÜNSAR, 2021; Schumacher et al., 2002; Wang et al., 2002). As leukemia treatment primarily involves chemotherapy and radiation therapy, side effects such as fatigue, nausea, and vomiting are typical (BIKMAZ & ÜNSAR, 2021; Großek et al., 2023; Schumacher et al., 2002). Approximately 80% of patients receiving chemotherapy and 90% receiving radiation therapy experience cancer-related fatigue (CRF) post-treatment. For some patients, this fatigue may persist for years after completing cancer therapy. Compared to other side effects like nausea and vomiting, fatigue is one of the most common and distressing issues. Factors contributing to CRF include cancer stage, treatment-related side effects (e.g., pancytopenia, malnutrition, and poor sleep quality secondary to chemotherapy or radiotherapy), and psychological distress, such as fatigue caused by tension, anxiety, and fear stemming from uncertainty and stress regarding the diagnosis and treatment (Rau et al., 2020).

1. Definition of Cancer-Related Fatigue

According to the National Comprehensive Cancer Network (NCCN) (2023), CRF is defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that interferes with daily functioning (Son, 2019; Piper, 1989; Aistars, 1987). Aistars (1987) defined fatigue as a subjective feeling of tiredness, weakness, exhaustion, and lack of energy resulting from long-term stress, which directly or indirectly impacts the disease process. Even with adequate sleep, the individual experiences an overwhelming sense of exhaustion, accompanied by reduced physical and mental capacity. Aaronson et al. (1999) defined fatigue as an imbalanced state in the availability, utilization, and restoration of an individual's resources, leading to a perceived reduction in physical or psychological capacity.

Domestic scholar Liu (2001) described fatigue as: an individual's subjective perception, an unpleasant experience, and an overwhelming, persistent sense of exhaustion. Li and Lin (2002) proposed fatigue as: persistent physical and psychological weakness, reduced capacity for physical or mental activity, and an imbalanced state of energy preventing the attainment of comfort.

Synthesizing the definitions from domestic and international scholars, fatigue is a subjective experience (Li & Lin, 2002; Liu, 2001; Aistars, 1987; NCCN, 2023). Its assessment dimensions should encompass physical, psychological, activity, and cognitive aspects (Li & Lin, 2002; Liu, 2001; Aistars, 1987; Aaronson et al., 1999; Charalambous & Kouta, 2016; Bennett et al., 2016; NCCN, 2023). Therefore, to comprehensively measure a patient's fatigue, multidimensional assessment tools are necessary.

2. Theoretical Basis of CRF: The Proinflammatory Cytokine Dysregulation Hypothesis

The pathogenic mechanism of CRF is not yet fully understood. However, many scholars suggest that CRF results from the interaction of multiple factors. The most widely accepted theory is the proinflammatory cytokine dysregulation hypothesis (Bower, 2014; Chao et al., 2011). When the body's immune response is affected by cancer cells or related treatments (e.g., chemotherapy, radiotherapy), it triggers the abnormal secretion of proinflammatory cytokines. This increases the inflammatory response, which in turn interferes with the central nervous system (CNS), leading to symptoms such as fever, sleep disturbances, headaches, reduced activity, and fatigue. This process can also impact the hypothalamic–pituitary–adrenal (HPA) axis, causing abnormal secretion of cortisol, hematopoietic cells, and serotonin, thereby disrupting circadian rhythms and resulting in physical and psychological fatigue (Taiwanese Society of Cancer Palliative Medicine, 2017; Bower, 2014; Hart & Reviews, 1988; Rau et al., 2023; Thong et al., 2020).

3. Clinical Laboratory Values Associated with CRF

The occurrence of CRF may be associated with clinical laboratory values. Common indicators are discussed in three parts below:

1. White Blood Cell (WBC) Count (Leukocyte) An elevated WBC count is a key indicator of systemic inflammation. Influenced by the leukemia disease process and treatment side effects like chemotherapy, pancytopenia is a common adverse event. When patients develop pancytopenia and their WBC count drops, they become susceptible to infection (Oun et al., 2018; Tenold et al., 2021; Wei & Li, 2018).

In a 2007 study of 65 leukemia patients, Alibhai et al. found a negative correlation between WBC count and fatigue severity ($r = –0.34$, $p < 0.01$) (Alibhai et al., 2007). Conversely, a domestic study by Tsai (2007) on 42 terminal cancer patients found a

moderate positive correlation between WBC count and fatigue ($r = 0.63$, $p < 0.05$). However, other studies, including those on post-operative colorectal cancer patients and leukemia patients, reported no significant correlation between fatigue severity and WBC count ($\beta = -0.037$, $p = 0.588$; $\beta = 0.16$, $p = 0.29$, respectively) (Addisia et al., 2022; Wei & Li, 2018).

The possible reasons for these discrepant findings may relate to cancer type and stage. Different cancer types and stages necessitate different treatment dosages, leading to varying degrees of myelosuppression (Anand et al., 2023; Kuter, 2015). Furthermore, the timing of fatigue assessment is relevant. If assessed during chemotherapy, patients are likely experiencing side effects, including leukopenia. If survivors are assessed, the decrease in WBCs may be less pronounced. The week following chemotherapy is the period of peak side effects (Chen & Tang, 2020). Therefore, research designs should collect blood laboratory values concurrently with fatigue assessments during the patient's chemotherapy process to accurately monitor the fatigue problem. Study designs must reflect the clinical reality, synchronizing the collection of laboratory data and fatigue assessments to effectively capture the correlation between fatigue and WBC count.

2. Hemoglobin (Hb) According to the World Health Organization (WHO) and the American Association of Blood Banks (AABB), anemia is defined as Hb < 12 g/dl for females and < 13 g/dl for males (Lotterman & Sharma, 2022; Safiri et al., 2021). Anemia (Hb < 12 g/dl) can result from the cancer itself, treatments (chemo/radiotherapy), malnutrition, bone marrow infiltration, or hemorrhage (Madeddu et al., 2018; Wang et al., 2002). Chemotherapy side effects cause myelosuppression, inhibiting erythropoiesis (red blood cell production) (Jhamb et al., 2008; Thong et al., 2020). This leads to insufficient hemoglobin, which impairs systemic oxygen delivery and subsequently causes fatigue (Thong et al., 2020; Wang, 2008). While 0% to 67% of chemotherapy patients may develop anemia, some studies note that fatigue can occur even in non-anemic cancer patients (Gaston-Johansson et al., 1999).

Oswald et al. (2021) found that low hemoglobin and low platelets were strongly associated with fatigue in leukemia patients ($\beta = 0.56$, 95% CI = 0.12 to 0.99, $p = 0.013$; $\beta = 0.18$, 95% CI = 0.08 to 0.28, $p = 0.001$, respectively). Shafqat et al. (2005) and Blair et al. (2008), in studies of 228 leukemia patients and 40 breast cancer patients, respectively, found a low-to-moderate negative correlation between hemoglobin and fatigue ($r = 0.332$, $p < 0.001$; $r = 0.71$, $p = 0.002$, respectively) (Blair et al., 2008; Shafqat et al., 2005).

In contrast, Dimeo et al. (2004), studying 71 leukemia survivors who were relapse-free and had not received treatment (chemo, radiotherapy, or

immunomodulators) for at least 3 months, found fatigue was unrelated to the degree of anemia ($r < 0.20$, $p = 0.79$). This may be because data collection did not occur during active chemo/radiotherapy; the patients' anemia was not pronounced (mean Hb = 12 ± 1.0 g/dl) and did not meet the criteria for anemia treatment (transfusion or erythropoietin-stimulating agents) (Dimeo et al., 2004).

The literature suggests a negative correlation between Hb and fatigue. As CRF peaks within one week post-chemotherapy (Chen & Tang, 2020), fatigue-related studies must ensure appropriate data collection timing to accurately monitor the CRF-Hb relationship. Considering the clinical situation, a single-item scale (e.g., Numerical Rating Scale) can simplify the burden of questionnaire completion, thereby enhancing internal validity and reducing attrition. Synchronizing the collection of laboratory data and fatigue assessments is essential to truly reflect the correlation between fatigue and hemoglobin.

3. Albumin In the human body, albumin is not only a key nutritional marker but also reflects the body's inflammatory response. Studies indicate that as C-reactive protein (CRP) levels increase, albumin levels tend to decrease (McGovern et al., 2022; McMillan & Care, 2009; Schvartsman et al., 2017). Beyond the cancer process itself, treatment side effects (chemo/radiotherapy), such as nausea and vomiting leading to malnutrition, can also indirectly cause fatigue (McGovern et al., 2022; Schvartsman et al., 2017).

Wang et al. (2002) and Shafqat et al. (2005), in studies of 174 mixed-cancer patients (lung, breast, leukemia, renal, etc.) and 228 leukemia patients, respectively, found a low-to-moderate negative correlation between albumin and fatigue ($r = -0.22$, $P = 0.004$; $r = -0.396$, $p < 0.001$, respectively) (Shafqat et al., 2005; Wang et al., 2002). However, Schvartsman et al. (2017) (222 cancer patients) and Dimeo et al. (2004) (71 leukemia survivors >3 months post-treatment) found no significant correlation between albumin and fatigue ($p = 0.171$; $p = 0.99$, respectively). Dimeo et al. noted that treatment side effects are a primary cause of fatigue; because their study enrolled patients who had not received recent cancer-related treatment, the associated side effects were absent, preventing the detection of a correlation between albumin and fatigue (Dimeo et al., 2004; Schvartsman et al., 2017).

The literature thus suggests a negative correlation between albumin and fatigue, and indicates that data collection and fatigue measurement should be conducted while the patient is undergoing chemotherapy to accurately monitor the fatigue problem.

III **Overview of Music Therapy**

Section 1. Definition of Music Therapy (MT)

The American Music Therapy Association (AMTA) defined music therapy in 2005 as

a clinical and evidence-based intervention implemented by a qualified and certified music therapist. This therapeutic interaction utilizes the rich diversity of music to achieve individualized treatment goals for the client (AMTA, 2005). In the United States, certification for music therapists requires completion of a music therapy bachelor's degree, including an internship, passing the national certification board examination, and engaging in continuing education. In addition to the US, regions such as Canada, the UK, Australia, Germany, Japan, and Korea also have the professional designation of music therapist (Liu, 2021; AMTA, 2005).

However, music therapy is still in its developmental stage in Taiwan; therefore, its definition is broader. It encompasses measures conducted by a music therapist, or music-related therapeutic activities conducted by healthcare personnel certified by the domestic Ministry of Health and Welfare (MOHW). These activities are implemented within their professional scope, following a systematic assessment of the patient's physical, psychological, and spiritual state, and are applicable for promoting or maintaining the patient's holistic health (Wu & Huang, 2006; Shih, 2006; Lin et al., 2011). Music therapy utilizes musical elements to design activities appropriate for the client, thereby enhancing and maintaining their physiological, psychological, and spiritual balance and health. Healthcare professionals trained in music therapy can apply these techniques systematically and skillfully in clinical practice to help patients improve their physical, mental, and spiritual well-being (Lin et al., 2011; Hung & Wang, 1999).

2. Mechanisms of Music Therapy

After music enters the brain via the ear and auditory nerve, it can activate the limbic system and reduce the activity of the neuroendocrine and sympathetic nervous systems. It is then transmitted via the hypothalamus, reducing the secretion of adrenocorticotropic hormone (ACTH), which in turn decreases cortisol secretion. This alleviates the release of the body's stress-related chemical substances and promotes muscle relaxation (Lin et al., 2011; Beck, 1991; Cook, 1986; Suda et al., 2008).

Music can also activate the ventral tegmental area (VTA) in the midbrain, promoting dopamine secretion, which induces feelings of pleasure and positivity (Tsai & Chou, 2015; Gerdner, 2000; Menon & Levitin, 2005). Scholars note that song selection for MT must align with the client's background and personal preferences. Through appropriate assessment and selection of music that corresponds to the client's current emotional state, the therapeutic effects of music can be achieved (Tsai & Chou, 2015; Browning, 2000; Gerdner, 2000).

Section II: Research on Music Therapy for Cancer-Related Fatigue

Music therapy is currently widely used in populations such as older adults with dementia (Gassner et al., 2022; Lam et al., 2020; McDermott et al., 2013;

Moreno-Morales et al., 2020), psychiatric patients (Carr et al., 2013; Gassner et al., 2022; Gold et al., 2009; Köhler et al., 2020; Marquez-Garcia et al., 2021), and children with autism (Mayer-Benarous et al., 2021). Research by Sezgin et al. (2022) indicates that interventions—including the use of instruments, classical, modern, or personalized music therapy—typically last between 20–45 minutes, are conducted 1–2 times per week, and continue for 1–2 months (Burns et al., 2008; Sezgin & Bektas, 2022).

Although many studies have found that music therapy can reduce depression, anxiety, and pain in cancer patients, its application for managing fatigue is less common. This review identified six clinical trials that utilized music therapy as an intervention for fatigue in leukemia patients. The frequency, duration, intervention methods, and outcomes of these studies are summarized below (see Table 2-4).

All six studies involved leukemia patients aged 18 or older undergoing chemotherapy. Four of these clinical trials reported significant differences (Burns et al., 2008; Cassileth et al., 2003; Reimnitz et al., 2020; Miladinia et al., 2021), finding small to large effect sizes (ES, $d = 0.12–1.95$).

- **Burns et al. (2008)** randomized 49 patients into a music therapy (MT) group (N=25) and a standard care group (N=24). The MT group received 20-minute sessions twice weekly for one month (eight sessions total). Using The Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) scale, they found a significant difference in fatigue between the groups, showing a small effect (Cohen's $d = 0.12$, $p < 0.001$).
- **Cassileth et al. (2003)** randomized 62 patients undergoing autologous stem cell transplantation (ASCT) into an MT group (N=34) and a standard care group (N=28). The MT group received 20-minute sessions of individualized live music (vocal and instrumental, based on patient preference) for 3–7 weeks. Fatigue, measured by the POMS-Fatigue subscale, decreased significantly in the MT group (Cohen's $d = 0.21$, $p = 0.03$).
- **Reimnitz et al. (2020)** randomized 35 leukemia patients to an MT group (N=18) or a standard care group (N=17). The MT group received two 30-minute individual sessions of live music. The Visual Analogue Scale - Fatigue (VAS-F) showed a significant difference between groups, demonstrating a moderate effect (Cohen's $d = 0.78$, $p = 0.004$).
- **Miladinia et al. (2021)** randomized 104 acute leukemia patients (with pain and fatigue scores ≥3) into three groups: light massage (N=34), MT (N=33), and standard care (N=37). Interventions were 15 minutes, 3 times/week for 4 weeks. The MT group listened to self-selected instrumental music via headphones. Results showed significant inter-group differences in fatigue for

both the MT group (vs. standard care) (Cohen's $d = 1.95$, $p = 0.001$, large effect) and the massage group (vs. standard care) (Cohen's $d = 2.42$, $p = 0.001$, large effect). Fatigue in both intervention groups decreased progressively, with no significant difference between them ($p = 0.148$).

Conversely, two studies showed no significant benefit of music therapy on fatigue (Bates et al., 2017; Rosenow & Silverman, 2014).

- **Rosenow and Silverman (2014)** assigned 18 acute leukemia patients to an MT group (N=8) or standard care (N=10). The MT group received only one 30–45 minute session. The Brief Fatigue Inventory (BFI) showed no significant difference ($p = 0.173$).
- **Bates et al. (2017)** randomized 82 patients (multiple myeloma or lymphoma) undergoing ASCT to an MT group (N=37) or standard care (N=45). The MT group received two 30-minute sessions (chemo day 1 and day 5). The POMS, measured at baseline and day 5, showed no significant difference ($p = 0.173$). According to the literature, the peak of chemotherapy side effects often occurs one week *after* its completion (Chen & Tang, 2020). Therefore, conducting assessments on day 1 and day 5 may have occurred before patients reached their peak fatigue levels.

Synthesizing these articles, the **dosage** (frequency and duration) of the MT intervention is a critical consideration. The two studies with non-significant results (Bates et al., 2017; Rosenow & Silverman, 2014) had methodological limitations. The Rosenow et al. (2014) RCT had a small sample size (N=18) and a low intervention dosage (one session), which was likely insufficient. Furthermore, Bates et al. (2017) did not set an inclusion criterion for moderate-to-severe baseline fatigue (e.g., ≥4 points); thus, the enrolled patients may not have had significant fatigue issues at the outset.

Literature Summary

Based on the literature review, CRF is a significant and distressing problem for leukemia patients. Due to the disease itself, considerations for hemoglobin, platelets, and patient activity safety severely limit the available intervention options for fatigue. Music therapy is a non-invasive, safe, comfortable, and easily administered nursing intervention. Following appropriate assessment and selection of resonant music based on client preferences, it can be implemented by healthcare providers or by the patients' families.

Discrepancies exist between domestic (Taiwanese) and international music therapy practices, primarily in education systems, professional certification, legal regulations, and cultural factors. Currently, Taiwan lacks a formal certification system for music

therapists, unlike many other countries. Compounded by financial constraints that often preclude hiring therapists with foreign qualifications, the implementation of standardized MT is challenging.
Therefore, this study aims to recruit patients newly diagnosed with leukemia who are undergoing conventional chemotherapy. It will utilize music therapy as an intervention to investigate its effects on fatigue and clinical laboratory values.

Research Methods

This chapter is divided into nine sections, detailing the methods and procedures of this study. It includes: (1) research framework, (2) research design, (3) research setting and participants, (4) sample size, (5) the music therapy protocol, (6) research instruments and reliability/validity, (7) research procedures, (8) ethical considerations, and (9) data processing and analysis.

Research Framework

Based on the aforementioned literature review, the research framework for this study was developed as illustrated in Figure 3-1.
The primary purpose of this study is to investigate the effects of music therapy on fatigue and clinical laboratory values (e.g., White Blood Cell [WBC] count, Hemoglobin [Hb], Albumin) in patients with acute leukemia undergoing chemotherapy. The study is designed to provide music therapy to this patient population, utilizing fatigue severity and clinical laboratory values as the primary outcome variables. This framework will be used to compare the differences in these key outcome variables between the music therapy group and the standard care group.

Research Design

This study employs an **experimental research design** utilizing **randomized assignment** and **repeated measures**. Participants who consent to the study will be allocated to either the experimental group (Group A) or the control group (Group B). Group A participants will listen to self-selected music in addition to receiving standard care. Group B participants will receive standard care only. The objective is to evaluate the effectiveness of music therapy in alleviating fatigue. A total of 44 patients with leukemia undergoing their initial chemotherapy will be recruited, with 22 participants allocated to each group.
The measurement process will be conducted in two parts:

1. **Primary Data Collection:** Data will be collected at two main time points: upon admission for initial chemotherapy (Baseline, T0) and on Day 21 of the

chemotherapy cycle (T1). On Day 21, the researcher will visit the ward to collect the required data, including the Tang's Fatigue Scale, the Fatigue Numerical Rating Scale (NRS), and clinical laboratory data. If a participant has been discharged, data will be collected via telephone interview or an online questionnaire.

2. **Symptom Diary:** Participants will record their fatigue levels using the Fatigue NRS immediately following each music therapy session.

Baseline demographic data will be collected only at T0. The measurement time points and the application of corresponding instruments are detailed in Table 3-2.

Table 1: Schedule of Research Measurements

Time	Before Chemo (T0)	Chemo Day 7	Chemo Day 14	Chemo Day 21 (T1)
Tang's Fatigue Scale	○			○
Numerical Rating Scale (NRS)	○	○	○	○
WBC	○			○
Hemoglobin	○			○
Albumin	○			○
Demographic Data	○			

Note: ○ = Data to be collected

Research Setting and Participants

This study will be conducted in the hematology-oncology ward of a medical center located in Northern Taiwan. Participants must meet the following inclusion criteria:

1. Clinically diagnosed with Acute Myeloid Leukemia (AML) by a specialist physician.
2. Scheduled to receive initial (first-time) chemotherapy.
3. Aged 20 years or older.
4. Able to communicate in Mandarin or Taiwanese.
5. Possess normal hearing ability.
6. No history of psychiatric illness and clear consciousness.
7. No prior participation in any fatigue management intervention study.
8. Understands the research purpose, voluntarily agrees to participate, and has signed the informed consent form.
9. Willing to cooperate with all study procedures during the research period.

Participants will be **excluded** from the study if they meet the following criteria:

1. Severe hearing impairment.

2. Unstable vital signs or unclear consciousness.

III: Sample Size Calculation

The sample size was estimated based on the **Generalized Estimating Equations (GEE)** approach for repeated measures. The analysis will control for baseline demographic and disease characteristics as covariates (e.g., age, sex, education level, occupation, perceived economic status, marital status, religious beliefs, and metastasis). The dependent variables are fatigue, White Blood Cell (WBC) count, hemoglobin, and albumin.

The calculation was performed using G*Power software (version 3.1.9.7). Parameters were set as follows: a significance level (α) of 0.05, statistical power (1-β) of 0.80, a 95% confidence interval, and an anticipated **effect size of 0.21**. This calculation yielded a required sample size of 34 participants (as shown in Figure 3-2). To account for a potential attrition rate of 30%, the study aims to recruit a total of **44 participants** (n=22 for Group A, n=22 for Group B).

Music Therapy Protocol

1. Music Selection, Dosage, and Headphone Use

According to the literature, a music therapy duration of 15–30 minutes is effective for fatigue alleviation (Burns et al., 2008; Cassileth et al., 2003; Miladinia et al., 2021; Reimnitz et al., 2020; Sezgin & Bektas, 2022). Music selection will be based on individual preferences and cultural background (Tsai & Chou, 2015; Browning, 2000; Gerdner, 2000).

To ensure data integrity while considering the patient's length of stay, physical burden during chemotherapy, and protocol adherence, the music therapy intervention in this study will be administered **once daily for 21 consecutive days**. The **30-minute intervention** will commence at the start of the chemotherapy infusion. During the study, participants will be provided with a chemotherapy symptom tracking diary to confirm adherence to the music therapy protocol in the experimental group.

For reasons of personal hygiene, preference, and potential patient discharge, participants will be asked to use their own headphones. If a participant does not have headphones, a set will be provided by the researcher.

Research Instruments and Psychometric Properties

1. Participant Demographic Data Sheet Data will be collected using Google Forms or paper questionnaires, as appropriate. This sheet includes demographic information such as age, sex, education level, occupation, perceived economic status, marital status, and religious beliefs, to be completed by the participant. The questionnaire also

includes items regarding the participant's prior musical training, frequency of daily music listening, motivations for listening, typical timing and methods of listening, and preferred activities during rest.

2. Leukemia-Related Treatment Data Sheet This data will be extracted from the patient's medical records by the researcher. It includes information on chemotherapy drugs and dosages, as well as laboratory values—specifically Absolute Neutrophil Count (ANC), Hemoglobin (Hb), and Albumin—from before chemotherapy (T0) and on Day 21 (T1).

3. Tang Fatigue Rating Scale (TFRS) While many reliable and valid fatigue scales exist globally, many have limitations. Considering that fatigue assessment should encompass physical, psychological, and activity dimensions, the TFRS was selected as the primary outcome measure for this study.

The TFRS contains 37 items across three subscales: Physical (15 items), Psychosocial (12 items), and Daily-Living (10 items). It uses a 10-point rating scale, where higher scores indicate greater fatigue severity. The TFRS underwent content validity testing by three PhD-level experts in fatigue theory and psychometrics. It was validated in a sample of 107 patients with chronic heart failure. The internal consistency (Cronbach's α) was 0.96 for the total scale, and 0.83 (Physical), 0.92 (Psychosocial), and 0.97 (Daily-Living) for the subscales. The TFRS demonstrated excellent validity: **convergent validity** with the Visual Analogue Scale for Fatigue (VAS-F) was 0.87, and **construct validity** with The Beck Depression Inventory-Second Edition (BDI-II) was 0.77 (Tang et al., 2010).

In the study by Tang et al. (2010), the TFRS also showed a significant positive correlation with the New York Heart Association (NYHA) functional class ($r = 0.75$, $p < 0.01$) and significant negative correlations with Ejection Fraction (EF) ($r = -0.46$, $p < 0.01$) and Hemoglobin (Hb) ($r = -0.27$, $p < 0.01$) (Tang et al., 2010).

4. G-8 Geriatric Screening Tool (G-8) The G-8 consists of 8 items, including three related to nutritional status (Item A: food intake, Item B: weight loss, Item F: Body Mass Index), motor skills (Item C), psychological status (Item E), number of medications (Item H), and self-perception of health (Item P).

Bellera et al. (2012), in a study of 364 cancer patients aged >70 receiving chemotherapy, found that a G-8 **cut-off value** of 14 had good **sensitivity** (85%) and **specificity** (65%) for vulnerability. In 2022, Chen et al. studied 755 newly diagnosed cancer patients in Taiwan (aged >20) and found a cut-off value of ≤13 was more suitable for screening vulnerability in both elderly and non-elderly Taiwanese cancer patients (Sensitivity=68.4%, Negative Predictive Value=76.8%). They recommended stratifying patients by age (<65 and ≥65) to differentiate the effect of age on vulnerability (Chen et al., 2022).

5. Numeric Rating Scale (NRS) for Fatigue This is an 11-point Likert-type scale (0–10) that serves as a simple and convenient single-item tool for assessing subjective fatigue (Gladman et al., 2020; Nordin et al., 2016; Whitehead, 2009). A score of 0 indicates "no fatigue at all," and 10 indicates "the worst fatigue imaginable," with higher scores representing greater fatigue severity. Numerous studies have demonstrated that the fatigue NRS possesses good **construct validity** when correlated with other internationally recognized psychological and fatigue assessment tools, such as the Profile of Mood States (POMS), Visual Analogue Scale - Fatigue (VAS-F), Medical Outcomes Study Short Form-20 (MOS SF-20), and Functional Assessment of Cancer Therapy–Anemia (FACT-An) (Aaronson et al., 1999; de Boer et al., 2004; Gladman et al., 2020; Kirsh et al., 2001; Lee et al., 1991; Van Hooff et al., 2007; Youngblut & Casper, 1993).

Research Procedures

Prior to study commencement, approval will be obtained from the Institutional Review Board (IRB). Following IRB approval, and after explaining the study to and receiving consent from the attending physicians and ward nursing staff, the researcher will conduct participant recruitment in the inpatient wards and outpatient clinics. Individuals who meet the inclusion criteria will be identified as potential participants. The researcher will explain the study's purpose and methodology to these individuals. After obtaining informed consent and a signed consent form, the researcher will administer the pre-test (T0) questionnaires. This packet includes the Demographic Data Sheet, the Tang Fatigue Rating Scale (TFRS), the G-8 screening tool, and the symptom diary. This self-administration process is expected to take approximately 10 minutes. If a participant is unable or unwilling to self-report (e.g., due to advanced age or fatigue), the researcher will conduct a structured interview to complete the questionnaires, which is estimated to take 30–40 minutes. Concurrently, all participants will be invited to join the study's official LINE group for communication. Following the collection of baseline questionnaires, a computer-generated randomization sequence will be implemented by personnel not directly involved in the study (i.e., someone other than the principal investigator) to allocate participants to either the experimental group (Group A) or the control group (Group B). Participants in Group A, after confirming their chemotherapy infusion line is properly connected, will begin listening to 30 minutes of self-selected music while concurrently receiving standard care. Participants in Group B will receive standard care only. A total of **60 participants** with Acute Myeloid Leukemia (AML) undergoing chemotherapy are expected to be recruited (n=30 per group).
Both groups will be required to complete the symptom diary throughout the 21-day

study period (est. 1 minute per entry). Group A will complete the Fatigue Numerical Rating Scale (NRS) immediately following each music therapy session. Group B will complete the Fatigue NRS 30 minutes after the commencement of their chemotherapy infusion.

On Day 21 (T1), the researcher will collect the post-test data (TFRS, NRS, and G-8) in the ward. If a participant has been discharged, data will be collected via telephone interview or an online questionnaire.

The laboratory data required for this study (WBC, Hb, Albumin) will be obtained by the researcher through a medical record review. Data from blood samples drawn as part of standard clinical care, taken before chemotherapy (T0) and on Day 21 (±3 days) (T1), will be utilized. **No additional blood draws will be required for this study.**

Throughout the study period, participants may ask questions at any time via the official LINE group, and the researcher will provide responses.

Ethical Considerations

This study will be initiated only after obtaining approval from the Institutional Review Board (IRB) and securing consent from the nursing administrators and attending physicians of the recruitment site. Prior to formal enrollment, the researcher will personally explain the study's purpose, procedures, and methodology to each potential participant.

The researcher will address all participant inquiries. Participants will be explicitly informed that their participation is voluntary, that they may withdraw from the study at any time without penalty, and that their decision will not affect the quality of their medical treatment or nursing care in any way.

All research data collected from participants will be processed using anonymous coding. The data will be securely stored by the researcher and used exclusively for academic purposes. Confidentiality will be strictly maintained, and data will not be publicly disclosed or used for other purposes, ensuring the protection of participant privacy.

Data Processing and Statistical Analysis

1. Data Management The researcher will review all questionnaires for completeness. All collected data will be coded and entered into the Statistical Packages for the Social Sciences (SPSS) version 26.0 for data processing and management.

2. Statistical Analysis In accordance with the study's objectives, data analysis will be divided into descriptive and inferential statistics, as outlined in Table 3-3.

- **a. Descriptive Statistics:** Based on the characteristics of the variables, data

will be categorized into four measurement scales: nominal, ordinal, interval, and ratio (Kaur et al., 2018). Nominal and ordinal scale data are considered **categorical variables** (e.g., sex, education level, occupation, perceived economic status, marital status, religious beliefs, and chemotherapy drug names) and will be presented as frequencies (n) and percentages (%). Interval and ratio scale data are considered **continuous variables** (e.g., age, fatigue severity, Absolute Neutrophil Count [ANC], hemoglobin, and albumin) and will be presented using means, standard deviations (SD), and ranges (minimum and maximum) (Kaur et al., 2018).

- **b. Inferential Statistics:** This study utilizes an experimental design with longitudinal follow-up and repeated measures, analyzed on an **intention-to-treat (ITT)** basis. It will compare the differences in fatigue severity and clinical laboratory values between the music therapy and control groups. During the study, data attrition may occur due to factors such as disease progression or a participant's personal decision to withdraw, leading to unequal sample sizes at different measurement points. Therefore, this study will employ **Generalized Estimating Equations (GEE)** to analyze the relationship between the independent and dependent variables. GEE will be used to compare pre- and post-test values (fatigue severity, Absolute Neutrophil Count [ANC], hemoglobin, and albumin) between the experimental and control groups. A p-value of < 0.05 will be considered the standard for statistical significance (Ziegler & Vens, 2010).