

# TESIS DOCTORAL INTERNACIONAL

PROGRAMA DE DOCTORADO EN MEDICINA CLÍNICA Y SALUD PÚBLICA

## **EFECTO DE LAS TERAPIAS COMPLEMENTARIAS EN PACIENTES CON LINFOMA**

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**UNIVERSIDAD  
DE GRANADA**







Doctoral Thesis/Tesis Doctoral

**EFFECT OF COMPLEMENTARY THERAPIES IN PATIENTS WITH  
LYMPHOMA**

**EFFECTO DE LAS TERAPIAS C OMPLEMENTARIAS EN PACIENTES CON LINFOMA**



**UNIVERSIDAD  
DE GRANADA**

PROGRAMA DE DOCTORADO EN MEDICINA CLÍNICA Y SALUD PÚBLICA

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**A mis padres,  
Por ser mi piedra angular en todo el camino.**







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## FINANCIACIÓN Y PROYECTOS DE INVESTIGACIÓN

La presente Tesis Doctoral Internacional se ha realizado en el marco del estudio, Linfoactívate: Mejorando la calidad de vida en pacientes con linfoma financiado por las siguientes organizaciones:

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La doctoranda, **Keyla Vargas Román** ha realizado la presente Tesis Doctoral Internacional como beneficiaria de un contrato con cargo al programa de Formación de Personal Universitario (FPU) del Ministerio de Educación, Cultura y Deporte (Código FPU16/01437) para la realización de la presente Tesis Doctoral Internacional. Por resolución de 31 de agosto de 2017 de la Secretaría de Estado de Educación, Formación Profesional y Universidades, (BOE-B-2017-2646, publicado el 17-01-2017) por la que se conceden ayudas para contratos predoctorales para la formación de profesorado universitario, de los subprogramas de Formación y Movilidad dentro del Programa Estatal de Promoción del Talento y su Empleabilidad.



## RESUMEN

El linfoma no Hodgkin tuvo 544.352 casos nuevos en todo el mundo en 2020 en ambos géneros según la organización mundial de la salud en la categoría de mundial cánceres hemáticos. Ocupa la undécima posición entre otros tipos de cáncer en 2020. En cuanto a su tasa de mortalidad, el cáncer de linfoma no Hodgkin tuvo 259 793 casos en 2020 en ambos géneros en todo el mundo.

En España, en 2020, el linfoma no Hodgkin dentro de los cánceres de la sangre, fue uno de los más alto diagnosticado, ubicándose entre los nueve primeros puestos. El número estimado de casos en España en 2020 fue de 66.733. La mortalidad por este tumor se ha reducido desde finales de la década de 1990, a una tasa del 3% menos de mortalidad cada año, mostrando un claro avance en la eficiencia de tratamientos.

Los tratamientos médicos convencionales para el linfoma no Hodgkin son la quimioterapia y trasplantes de médula ósea o células madre. Estas terapias pueden tener altas consecuencias adversas como la ansiedad, la depresión, la pérdida de la salud física y un alto riesgo de insuficiencia

cardíaca; estas dificultades conducen a un deterioro de la calidad de vida.

La prevención es necesaria para evitar posibles riesgos en el desarrollo del cáncer en general, incluyendo una buena dieta, ejercicio y buena calidad de sueño. Sin embargo, aquellos pacientes que ya están diagnosticados necesitan una estrategia de tratamiento para mitigar los síntomas de su cáncer o su tratamiento.

El nuevo concepto de “Oncología Integrativa”, que utiliza las terapias complementarias junto a los tratamientos convencionales oncológicos para controlar los síntomas asociados al cáncer, está ampliamente aceptado en todo el mundo. Prueba de ello es la aparición de hospitales que basan sus intervenciones en este modelo o la inclusión de estas terapias en diferentes guías clínicas consensuadas por expertos de Asociaciones Oncológicas o Colegios Médicos para tratar síntomas relacionados con el cáncer.

Por lo tanto, los objetivos de la presente Tesis Doctoral Internacional fueron i) comparar, mediante el control de variables de confusión, la HRV de los sobrevivientes de linfoma después de su primer año de

tratamiento finalización con las de sujetos sanos **(estudio I)**. ii) analizar la prevalencia de ansiedad entre pacientes con linfoma de Hodgkin y no Hodgkin; inspeccionar los métodos de recolección de datos, la frecuencia de las intervenciones, los tipos de instrumentos utilizados para reconocer la ansiedad en los pacientes y el propósito de la recolección de datos, tanto en sobrevivientes como en pacientes que están en tratamiento y con diagnóstico de linfoma de Hodgkin y linfoma no Hodgkin **(estudio II)**. iii) detectar los efectos de un programa de Qigong presencial de ocho semanas de 60 min sobre parámetros psicológicos y la actividad del nervio vago con respecto al linfoma no Hodgkin, y comparar los resultados con un grupo control que no participó en el programa **(estudio III)**.

Los resultados de esta Tesis Doctoral Internacional aportan evidencia científica que apoyan el uso de las terapias complementarias como herramienta de apoyo al tratamiento oncológico tradicional con respecto a los pacientes con linfoma. Que ayudan con la mejora de la ansiedad y desbalance cardiovascular provocado por los tratamientos oncológicos y su estado de salud al momento del diagnóstico. Por

último, estos resultados aportan al conocimiento de posibles nuevas formas de ayudar al paciente en su diagnóstico, planteando así la necesidad de incluir dichas terapias complementarias como parte de su rehabilitación oncológica.

## ABSTRACT

Non-Hodgkin lymphoma had 544.352 new cases worldwide in 2020 in both genders according to the world health organization in the category of global blood cancers. It ranks 11th among other cancers in 2020. In terms of its death rate, non-Hodgkin's lymphoma cancer had 259.793 cases in 2020 in both genders worldwide.

In Spain, in 2020, non-Hodgkin's lymphoma within blood cancers was one of the highest diagnosed, ranking among the top nine positions. The estimated number of cases in Spain in 2020 was 66.733. Mortality from this tumor has been reduced since the end of the 1990s, at a rate of 3% less mortality each year, showing a clear advance in the efficiency of treatments.

Conventional medical treatments for non-Hodgkin's lymphoma are chemotherapy and bone marrow or stem cell transplants. These therapies can have adverse consequences such as anxiety, depression, loss of physical health, and a high risk of heart failure; these difficulties lead to a deterioration of the quality of life.

Prevention is necessary to avoid possible risks in the development of cancer in

general, including a good diet, exercise and good quality of sleep. However, those patients who are already diagnosed need a treatment strategy to minimize the symptoms of their cancer or its treatment.

The new concept of "Integrative Oncology", which uses complementary therapies together with conventional cancer treatments to control symptoms associated with cancer, is widely accepted throughout the world. Proof of this is the appearance of hospitals that base their outbreaks on this model or the inclusion of these therapies in different clinical guidelines agreed by experts from Oncology Associations or Medical Colleges to treat symptoms related to cancer.

Therefore, the objectives of this International Doctoral Thesis were i) to compare, by controlling for confounding variables, the HRV of lymphoma survivors after their first year of final treatment with that of healthy subjects (**study I**). ii) to analyze the prevalence of anxiety among patients with Hodgkin's and non-Hodgkin's lymphoma; inspect the methods of data collection, the frequency of interventions, the types of instruments used to recognize anxiety in patients and the purpose of data



collection, both in survivors and in patients who are in treatment and diagnosed with lymphoma Hodgkin's and non-Hodgkin's lymphoma **(study II)**. iii) to detect the effects of an eight-week, 60-minute face-to-face Qigong program on psychological parameters and vagus nerve activity with respect to non-Hodgkin's lymphoma, and compare the results with a control group that did not participate in the program **(study III)**.

The results of this International Doctoral Thesis provide scientific evidence that supports the use of complementary therapies as a support tool for traditional cancer treatment with respect to patients with lymphoma. That helps with the improvement of anxiety and cardiovascular imbalance caused by cancer treatments and their state of health at the time of diagnosis. Finally, these results contribute to the knowledge of possible new ways to help the patient in their diagnosis, thus raising the need to include these complementary therapies as part of their oncological rehabilitation.

## **ABREVIATURAS**

AMA-AC- Ambulatory Medical Assistance - After Cancer

ANCOVA- Analysis of covariance

ANOVA- Analysis of variance

BMI – Body mass index

CI- Confidence Interval

CINAHL - Cumulative Index to Nursing and Allied Health Literature

CCSS -Childhood Cancer Survivor Study

CRCI- Cancer-Related Cognitive Impairment

DLBCL- Diffuse Large B-Cell Lymphoma

ECR- Eindhoven Cancer Registry

FPU- Formación de profesorado universitario

GP General Practitioner

HADS- Hospital anxiety and depression scale

HAM- Hamilton Anxiety Rating Scale

HD- Hodgkin's Disease

HDS - Hodgkin's Disease Survivors

HF- High frequency

HL- Hodgkin Lymphoma

HLS- Hodgkin's Lymphoma Survivors

HRQoL- Health-Related Quality of Life

HRV- Heart rate variability

LF -Low frequency

MECD- Ministerio de educación ciencia y deporte

MR- Maintenance Rituximab

NC- Nurse Coordinator

NHL- Non-Hodgkin lymphoma

NRH- Norwegian Radium Hospital

POMS- Profile of Mood States

PRISMA- Preferred Reporting Items for Systematic Reviews and Meta-Analyses

QoL- Quality of Life

RCT- Randomize clinical trial

RMSSD- The squared root of the mean squared differences of successive R-R intervals

RR- Rituximab Re-treatment

SD- Standard Deviation

SDNN- Standard deviation of the NN interval

SPSS- Statistical Package for the Social Sciences

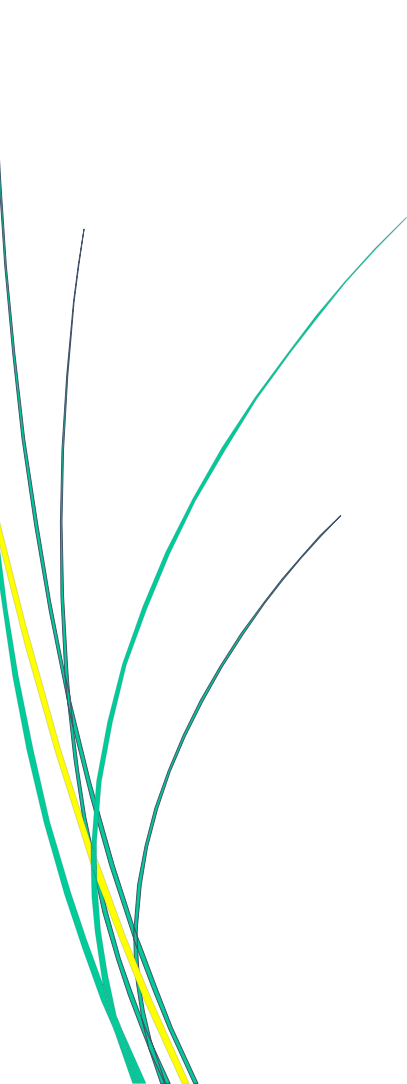
STAI-YI- Spielberger's State Anxiety Inventory

WHO- World health organization



# INTRODUCCIÓN GENERAL

GENERAL INTRODUCTION





## **INTRODUCCIÓN GENERAL**

### **Situación actual del cáncer de linfoma y supervivencia**

El cáncer es un amplio grupo de enfermedades que pueden comenzar en prácticamente cualquier órgano o tejido del cuerpo cuando las células anormales crecen sin control, rompiendo partes adyacentes del cuerpo o escalando a otros órganos <sup>1</sup>. El linfoma no Hodgkin tuvo 544.352 casos nuevos en todo el mundo en 2020 en ambos géneros según la organización mundial de la salud en la categoría de mundial cánceres hemáticos. Ocupa la undécima posición entre otros tipos de cáncer en 2020. En cuanto a su tasa de mortalidad, el cáncer de linfoma no Hodgkin tuvo 259 793 casos en 2020 en ambos géneros en todo el mundo <sup>2</sup>. Cuando se trata de géneros, el linfoma no Hodgkin estuvo presente en 203050 hombres con una proporción de 5,3 en el último año, mientras que en el linfoma de Hodgkin hubo 35483 casos con una proporción de 0,92. En el género femenino los casos de no Hodgkin ha sido un poco menor 161544 con proporciones de 4,3. Linfoma y Linfoma de Hodgkin con 26099 casos con una proporción de

0.69.<sup>3</sup>Centradose en España, en 2020, el linfoma no Hodgkin dentro de los cánceres de la sangre, fue uno de los más diagnosticados, ubicándose entre los nueve primeros puestos. El número estimado de casos en España en 2020 fue de 66.733 <sup>4</sup>. La mortalidad por este tumor se ha reducido desde finales de la década de 1990, a una tasa del 3% menos de mortalidad cada año, mostrando un claro avance en la eficiencia de tratamientos <sup>5</sup>.

### **Terapias complementarias y cáncer**

Tratamientos de medicina complementaria e integradora, incluida la actividad física, el yoga/Tai Chi y la meditación, además del tratamiento oncológico tradicional, pueden tener una influencia beneficiosa en la aflicción psicológica, la ansiedad, el dolor, la fatiga y la interrupción del sueño, lo que conduce a una mejor calidad de vida en pacientes con cáncer<sup>6</sup>. Además de las actividades mencionadas antes, otro ejercicio mente-cuerpo que se está volviendo popular es el Qigong. El Qigong era desarrollado originalmente en China, y está profundamente arraigado en la medicina tradicional china. Eso implica una colección de movimientos precisos y

plácidos, e integra la regulación del control de la respiración y el cuerpo<sup>7</sup>. Los estudios han demostrado los beneficios de practicar Qigong, mejorar la fatiga, la calidad del sueño, la ansiedad, la depresión y la cardiotoxicidad en pacientes con cáncer y linfoma no Hodgkin <sup>7-9</sup>.

### **Cáncer de linfoma, tratamiento, secuelas cardiovasculares y psicológicas**

Los tratamientos médicos convencionales para el linfoma no Hodgkin son la quimioterapia y trasplantes de médula ósea o células madre <sup>10</sup>. Se estima que para el año 2025 habrá un aumento del 16,1% de pacientes oncológicos a los que se les indicará durante su proceso de enfermedad al menos una sesión de radioterapia y en el caso de los linfomas este aumento será del 13,2%<sup>11</sup>. Estas terapias pueden tener altas consecuencias adversas como la ansiedad, la depresión, la pérdida de la salud física y un alto riesgo de insuficiencia cardíaca; estas dificultades conducen a un deterioro de la calidad de vida <sup>12</sup>. Avances en el campo biomédico han hecho mejoras en la comprensión del origen de varios tipos de cáncer, junto con tratamientos y estrategias

de prevención <sup>13</sup>. La prevención es necesaria para evitar posibles riesgos en el desarrollo del cáncer en general, incluyendo una buena dieta, ejercicio y buena calidad de sueño. La atención psicológica, con sus objetivos de aliviar el sufrimiento emocional y promover el bienestar, es central para mejorar la calidad de vida de los pacientes<sup>14</sup>. Mejorar el acceso de los pacientes con cáncer a la atención psicológica sigue siendo un tema crítico. Muchos pacientes que podrían beneficiarse de la atención psicológica no reciben la ayuda que necesitan.<sup>14</sup>

Estos niveles de ansiedad se disparan, cuando llega el momento de hacer una cita de seguimiento, con el temor de que sufra una recaída. Los pacientes sufren la inducción indirecta de ansiedad a través de los procedimientos médicos sin el método psicológico eficaz que ayude al paciente a afrontar los posibles riesgos.<sup>15,16</sup> Además, el cáncer en general es una enfermedad que por las complicaciones que conlleva y la inclusión de una alta tasa de mortalidad, es un problema de salud que a las personas les cuesta sobrellevar.

Anteriormente, el cáncer y las enfermedades cardiovasculares se consideraban dos patologías distintas. Los



datos recientes muestran que comparten múltiples factores de riesgo, lo que sugiere que podría haber una vía biológica<sup>17</sup>. Pacientes con linfoma de Hodgkin que han recibido radiación terapia representan un grupo de alto riesgo de insuficiencia cardíaca, desarrollo de arritmias, isquemia enfermedad cardíaca e insuficiencia cardíaca congestiva<sup>18</sup>. Los síntomas también pueden incluir un desequilibrio en el sistema nervioso autónomo, que está integrado por el simpático y el sistema nervioso parasimpático<sup>19</sup>. Estos son además del nervio vago responsable para la regulación del estado de ánimo, el sistema inmunitario y la frecuencia cardíaca<sup>20</sup>. Ritmo cardíaco la variabilidad es la sinergia entre el sistema nervioso autónomo y el sistema cardiovascular, que sirve como un biomarcador no invasivo de la salud<sup>21</sup>. Ritmo cardíaco disminuido se ha observado que la variabilidad cardíaca (VFC) está relacionada con la disfunción autonómica cardíaca<sup>22</sup>. Estudios previos han mostrado una asociación entre el linfoma no Hodgkin y bajo HRV<sup>23</sup>, que podría ser causado por el tratamiento médico convencional.

## **Psicología para el abordaje de la rehabilitación oncológica**

La intervención psicológica es indudablemente necesaria a la hora de abordar la rehabilitación del cáncer de linfoma. Ayuda a la transición del paciente en ayudarlo a afrontar su diagnóstico. Supervivientes que han tenido un historial de recurrencia con su linfoma tienen mayores niveles de ansiedad que los demás pacientes que no pasan por la misma situación<sup>15</sup>. Pacientes con linfomas Hodgkin y no Hodgkin, estipulan que la mayoría de las necesidades psicológicas quedan insatisfechas en este tipo de cáncer es informar sobre una posible recurrencia, una comprensión más clara de que la supervivencia después del cáncer es un evento condicional puede ayudar a los pacientes con cáncer a obtener evaluaciones más esperanzadoras sobre el futuro, y potencialmente disminuir la ansiedad que a menudo acompaña a la vigilancia posterior al tratamiento, como las entrevistas de seguimiento<sup>24</sup>.

El aspecto psicológico de tener este tipo de cáncer, puede ser desencadenante para el paciente, y es ahí cuando la ayuda

psicológica le vendrá bien. La mayoría de los estudios utilizados sólo recogen este tipo de datos con fines descriptivos. En cambio, esta información debe utilizarse para abordar y tomar conciencia de los riesgos e implementar recomendaciones de vigilancia; que el paciente esté menos ansioso y más consciente de su enfermedad.

Los individuos perciben que la experiencia del cáncer puede influir o ser influenciada por su estado de salud y funcionamiento y calidad de vida que también incluye los aspectos psicológicos.<sup>25</sup> Este hallazgo está de acuerdo con otro artículo que destacó la necesidad de un procedimiento psicológico para que los pacientes hacer frente lentamente a esta enfermedad. El término estrategias de afrontamiento incluye una amplia gama de estrategias cognitivas y conductuales que un individuo utiliza para manejar las demandas internas y externas en respuesta a una situación estresante.<sup>26</sup>

Esta estrategia logra ayudar al paciente a no precipitarse en situaciones que pueden causarle una gran angustia. El personal de atención médica bien preparado, la familia y los amigos, incluso la religión, pueden ser buenas herramientas de afrontamiento sugeridas en las que el paciente puede

confiar. De hecho, un estudio describió cómo el apoyo de proveedores de atención médica, familiares y amigos facilitó la experiencia del paciente con LNH y su régimen de tratamiento correspondiente<sup>27</sup>.

Dado que la sintomatología de este cáncer en particular y la modalidad de tratamiento era diferente, es tratado por otro grupo de especialistas en lugar de los oncólogos, esto hace que los pacientes sientan que se trata más como un problema de salud crónico que como un cáncer específico. Estas diferencias mencionadas anteriormente y tener menos acceso a los servicios de apoyo que tienen otros tipos de cáncer, hacen que los participantes se sientan frustrados y aislados, lo que significa que su experiencia con el cáncer se ve afectada negativamente.<sup>28</sup> De hecho, el Instituto de Medicina (IOM) considera que la mayoría de los sobrevivientes de cáncer son “perdidos en la transición”<sup>29</sup>. Sin embargo, esto puede deberse a la falta de reconocimiento entre los médicos hacia este cáncer en particular. Por lo tanto, existe un modelo creado por el Instituto Nacional para la Salud y la Excelencia Clínica (NICE) que se hizo para ilustrar a los médicos de cualquier nivel para mantener el bienestar psicológico de los

pacientes<sup>52</sup>. Por lo tanto, los proveedores de atención médica y los médicos deben explorar las estrategias de afrontamiento y las necesidades psicológicas de los pacientes y, en consecuencia, junto con el paciente, formular planes de atención individualizados que capaciten al paciente para sobrellevar la quimioterapia de manera eficaz<sup>30</sup>.

En conclusión, teniendo en cuenta que existe una correlación entre la ansiedad y la variabilidad de la frecuencia cardíaca, así como una correlación con la depresión y la variabilidad de la frecuencia cardíaca; vemos la importancia del abordaje psicológico que a su vez ayuda a el mejoramiento cardiovascular de los pacientes mitigando así adicionales riesgos de salud a largo plazo<sup>31</sup>.

## Bibliografía

1. World Health Organization. Cancer. Available online: <https://www.who.int/cancer/en> (accessed on 18 March 2022).
2. World Health Organization WHO. Estimated Number of New Cases in 2020, Worldwide, Both Sexes, All Ages: GLOBOCAN. 2020. Available online: <https://gco.iarc.fr/today/data/factsheets/p>

[populations/900-world-fact-sheets.pdf](https://www.who.int/cancer/en/populations/900-world-fact-sheets.pdf) (accessed on 18 March 2022).

3. World Health Organization (WHO). Latest global cancer data: Cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018 [Cited 2019 July 30]. Available from <https://www.who.int/cancer/PRGlobocanFinal.pdf>
4. World Health Organization WHO. Estimated Number of New Cases in 2020, Europe, Worldwide, Spain, Both Sexes, All Ages: GLOBOCAN. 2020. Available online: <https://gco.iarc.fr/today/online-analysis-table?v=2020> (accessed on 18 March 2022).
5. Bosetti, C.; Levi, F.; Ferlay, J.; Lucchini, F.; Negri, E.; La Vecchia, C. Incidence and mortality from non-Hodgkin lymphoma in Europe: The end of an epidemic? *Int. J. Cancer* 2008, 123, 1917–1923.
6. Adams, M.; Jewell, A.P. The use of complementary and alternative medicine by cancer patients. *Int. Semin. Surg. Oncol.* 2007, 4, 10.
7. Chuang, T.Y.; Yeh, M.L.; Chung, Y.C. A nurse facilitated mind-body interactive exercise (Chan-Chuang Qigong) improves the health status of non-Hodgkin lymphoma

patients receiving chemotherapy: Randomized controlled trial. *Int. J. Nurs. Stud.* 2017, 69, 25–33.

8. Soltero, E.G.; Larkey, L.K.; Kim, W.S.; Rosales Chavez, J.B.; Lee, R.E. Latin dance and Qigong/Tai Chi effects on physical activity and body composition in breast cancer survivors: A pilot study. *Complement. Ther. Clin. Pract.* 2022, 47, 101554.

9. Fong, S.S.; Wong, J.Y.; Chung, L.M.; Yam, T.T.; Chung, J.W.; Lee, Y.; Chow, L.P.; Luk, W.; Ng, S.S. Changes in heart-rate variability of survivors of nasopharyngeal cancer during Tai Chi Qigong practice. *J. Phys. Ther. Sci.* 2015, 27, 1577–1579.

10. Ferlay, J.; Colombet, M.; Soerjomataram, I.; Mathers, C.; Parkin, D.M.; Piñeros, M.; Znaor, A.; Bray, F. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int. J. Cancer* 2019, 144, 1941–1953.

11. Borrás JM, Lievens Y, Barton M, Corral J, Ferlay J, Bray F, et al. How many new cancer patients in Europe will require radiotherapy by 2025? An ESTRO-HERO analysis. *Radiother Oncol* 2016; 119:5-11.

12. Courneya, K.S.; Sellar, C.M.; Trinh, L.; Forbes, C.; Stevinson, C.; McNeely, M.; Peddle-McIntyre, C.; Friedenreich, C.; Reiman, T. Randomized Trial of Aerobic Exercise and Sleep Quality in Lymphoma Patients Receiving Chemotherapy or No Treatments. *Cancer Epidemiol. Biomark. Prev.* 2012, 21, 887–894.

13. Parra, M.T.; Esmeaeli, N.; Kohn, J.; Henry, B.L.; Klagholz, S.; Jain, S.; Pruitt, C.; Vicario, D.; Jonas, W.; Mills, P.J. Greater Well-Being in More Physically Active Cancer Patients Who Are Enrolled in Supportive Care Services. *Integr. Cancer Ther.* 2020, 19, 1534735420921439.

14. Jacobsen PB, Jim, HS. Psychosocial Interventions for Anxiety and Depression in Adult Cancer Patients: Achievements and Challenges. *CA Cancer J Clin* 2008; 58:214-230.

15. Thompson CA, Charlson ME, Schenkein E, Wells MT, Furman RR, Elstrom R, et al. Surveillance CT scans are a source of anxiety and fear of recurrence in long-term lymphoma survivors. *Ann Oncol* 2010; 21:2262-2266.

16. Bestawros A, Foltz L, Srour N, Savage KJ, Connors JM. Patients' and physicians' roles

in detecting recurrent Hodgkin lymphoma following complete remission. *Ann Oncol* 2013; 24:1359-1363.

17. Koene, R.J.; Prizment, A.E.; Blaes, A.; Konety, S.H. Shared Risk Factors in Cardiovascular Disease and Cancer. *Circulation* 2016, 133, 1104–1114.

18. Maraldo, M.V.; Giusti, F.; Vogelius, I.R.; Lundemann, M.; van der Kaaij, M.A.; Ramadan, S.; Meulemans, B.; Henry-Amar, M.; Aleman, B.M.; Raemaekers, J.; et al. Cardiovascular disease after treatment for Hodgkin's lymphoma: An analysis of nine collaborative EORTC-LYSA trials. *Lancet Haematol.* 2015, 2, e492–e502.

19. Teixeira, R.J.; Remondes-Costa, S.; Graça Pereira, M.; Brandão, T. The impact of informal cancer caregiving: A literature review on psychophysiological studies. *Eur. J. Cancer Care* 2019, 28, e13042.

20. Díaz-Rodríguez, L.; Vargas-Román, K.; Sanchez-Garcia, J.C.; Rodríguez-Blaque, R.; Cañadas-De la Fuente, G.A.; De La Fuente-Solana, E.I. Effects of Meditation on Mental Health and Cardiovascular Balance in Caregivers. *Int. J. Environ. Res. Public Health* 2021, 18, 617.

21. Mulcahy, J.S.; Larsson, D.E.O.; Garfinkel, S.N.; Critchley, H.D. Heart rate variability as a biomarker in health and affective disorders: A perspective on neuroimaging studies. *NeuroImage* 2019, 202, 116072.

22. Ha, J.; Baek, H.; Jeong, C.; Yeo, M.; Lee, S.-H.; Cho, J.H.; Baek, K.-H.; Kang, M.I.; Lim, D.-J. Heart Rate Variability in Postoperative Patients with Nonfunctioning Pituitary Adenoma. *Endocrinol. Metab.* 2021, 36, 678–687.

23. Vargas-Román, K.; Cortés-Martín, J.; Sánchez-García, J.C.; Rodríguez-Blaque, R.; De La Fuente-Solana, E.I.; Díaz-Rodríguez, L. Autonomic Imbalance in Lymphoma Survivors. *J. Clin. Med.* 2021, 10, 4391.

24. Baade P, Youlden D, Chambers S. When do I know I am cured? Using conditional estimates to provide better information about cancer survival prospects. *Med J Aust* 2011; 94:73-77.

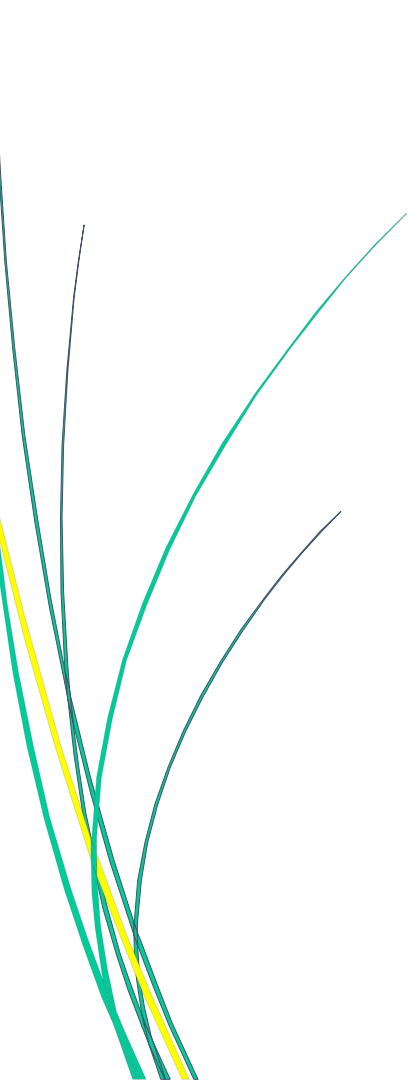
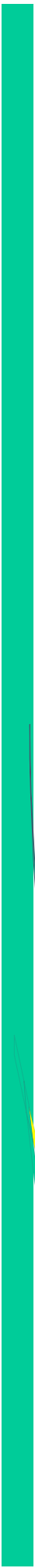
25. Smith SK, Crespi CM, Petersen L, Zimmerman S, Ganz PA. The impact of cancer and quality of life for post-treatment non-Hodgkin lymphoma survivors. *Psychooncology* 2010; 19:1259-1267.

26. Lazarus RS, Folkman S. Stress, appraisal, and coping. New York: Springer Publishing Company; 1984.
27. Chircop D, Scerri J. Coping with non-Hodgkin's lymphoma: a qualitative study of patient perceptions and supportive care needs whilst undergoing chemotherapy. *Support Care Cancer* 2017; 25:2429-2435.
28. Swash B, Hulbert-Williams N, Bramwell R. 'Hematological cancers, they're a funny bunch': A qualitative study of non-Hodgkin's lymphoma patient experiences of unmet supportive care needs. *J. Health Psychol* 2016; 23:1464-1475.
29. Hewitt M, Greenfield S, Stowall E. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, DC: The National Academies Press; 2006.
30. National Institute for Clinical Excellence (NICE). Improving supportive and palliative care for adults with cancer [Cited 2019 August 10]. Available from <https://www.nice.org.uk/guidance/csgsp>
31. Park, H.; Oh, S.; Noh, Y.; Kim, J.Y.; Kim, J.H. Heart Rate Variability as a Marker of Distress and Recovery: The Effect of Brief Supportive Expressive Group Therapy with Mindfulness in Cancer Patients. *Integr. Cancer Ther.* 2018, 17, 825–831.



# OBJETIVOS

AIMS







## OBJETIVOS

El objetivo principal de esta Tesis Doctoral Internacional es evaluar los efectos de un programa presencial de Qigong sobre la calidad de vida de los pacientes supervivientes diagnosticados de linfoma.

Para responder a el objetivo planteado esta Tesis esta segmentada en tres estudios basándose en los siguientes objetivos específicos:

Sección 1: Evaluación de las secuelas del tratamiento oncológico sobre el aspecto psicológico del paciente con linfoma.

- Describir las características psicológicas desarrolladas una vez terminado el tratamiento oncológico.

Sección 2: Evaluación de las secuelas del tratamiento oncológico sobre la cardiotoxicidad en pacientes con linfoma.

- Describir los efectos del tratamiento oncológico sobre la respuesta del sistema nervioso vegetativo, sistema inmuno-secretor y la respuesta proinflamatoria en pacientes con linfoma.

Sección 3: Terapias complementarias como herramienta para la prevención de secuelas psicológicas y cardiacas en pacientes con linfoma.

- Describir los efectos del programa presencial de Qigong sobre la respuesta del sistema nervioso vegetativo, sistema inmuno-secretor y la respuesta proinflamatoria en pacientes con linfoma.
- Analizar el efecto del programa presencial de Qigong en pacientes con linfoma sobre el estado cognitivo y psicológico.



## AIMS

The general aim of this International Doctoral Thesis is to evaluate the effects of a face-to-face Qigong program on the quality of life of surviving patients diagnosed with lymphoma.

To respond to the stated aim, this thesis is segmented into three studies based on the following specific aims:

Section 1: Evaluation of the consequences of cancer treatment on the psychological aspect of the patient with lymphoma.

- Describe the psychological characteristics developed once the oncological treatment is finished.

Section 2: Evaluation of the sequelae of cancer treatment on cardiotoxicity in patients with lymphoma.

- Describe the effects of cancer treatment on the response of the vegetative nervous system, the immunosecretory system and the proinflammatory response in patients with lymphoma.

Section 3: Complementary therapies as a tool for the prevention of psychological and cardiac sequelae in patients with lymphoma.

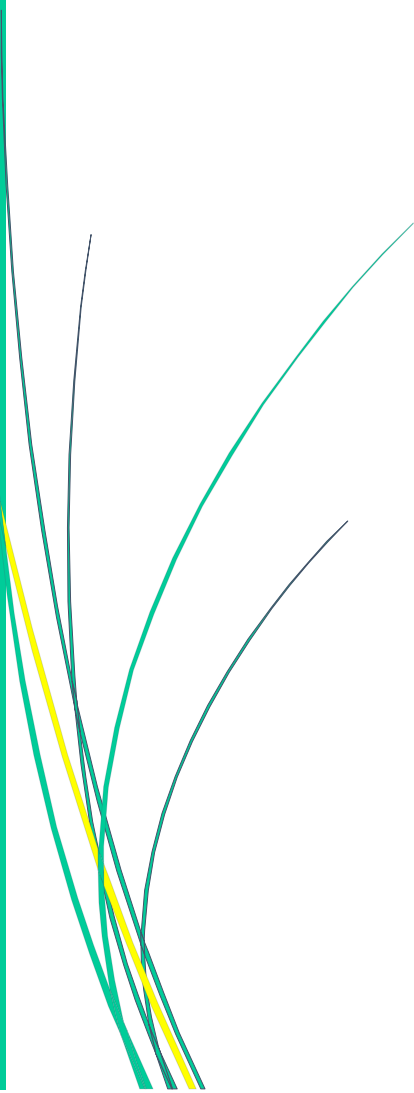
- To know the effects of the face-to-face Qigong program on psychological and cardiac capacity in patients with lymphoma.





# **MATERIAL Y MÉTODOS, RESULTADOS, DISCUSIÓN**

**METHODS, RESULTS, DISCUSSION**





**Table 1. Characteristic of the articles included in the present International Doctoral Thesis.**

Section 1: Evaluation of the consequences of cancer treatment on the psychological aspect of the patient with lymphoma.			
Article	Design	Participants	Outcomes
Anxiety prevalence in Lymphoma: a systematic review and meta-analysis	Systematic review and meta-analysis	n=2566 patients with both type of Hodgkin lymphoma disease	Anxiety levels - HADS - STAI-YI - HAM - POMS
Section 2: Evaluation of the sequelae of cancer treatment on cardiotoxicity in patients with lymphoma.			
Article	Design	Participants	Outcomes
Autonomic Imbalance in Lymphoma Survivors	Descriptive Study	n= 16 Non- Hodgkin Lymphoma Survivors n=16 Healthy Controls	Heart Rate Variability - SDNN - RMSSD - HRV index - LF - HF - LF/HF ratio
Section 3: Complementary therapies as a tool for the prevention of psychological and cardiac sequelae in patients with lymphoma.			
Article	Design	Participants	Outcomes
Effect of a 16-Session Qigong Program in Non-Hodgkin Lymphoma Survivors: A Randomized Clinical Trial	Randomized Clinical Trial	n= 39 non-Hodgkin survivors n=20 Qigong Group n= 19 Control Group	Anxiety & Depression - HADS Heart Rate Variability - SDNN - RMSSD - HRV index - LF - HF - LF/HF ratio



# STUDY I

## ANXIETY PREVALENCE IN LYMPHOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS

Health Psychology

2020

### Journal Citation Report

Impact Factor: 5.55

Category: Psychology

Rank: 12/77 (85.06)



## **STUDY I. Anxiety prevalence in Lymphoma: a systematic review and meta-analysis**

### **ABSTRACT**

**Purpose:** Hodgkin and non-Hodgkin lymphoma patients are at high risk of experiencing anxiety because the clinical processes and therapies they undergo produce strong adverse effects. In this review we discuss the prevalence of anxiety among these patients and examine the methods used for data collection, intervention frequency, types of instruments used to recognize anxiety, and data collection purposes, both in Hodgkin and non-Hodgkin lymphoma survivors and patients being treated or diagnosed with these diseases.

**Materials and Methods:** This systematic review and meta-analysis of the literature was carried out using the following sources: PubMed, Scopus, LILACS, and PsycINFO.

**Results:** The meta-analysis sample was  $n = 2,138$  and the overall prevalence of anxiety was 19% (95% CI [12%, 25%]). According to the Egger test, there were no publication biases and no studies were eliminated after the sensitivity analysis. The  $I^2$  for the heterogeneity analysis was 92.6%.

**Conclusions:** Hodgkin and non-Hodgkin lymphoma patients are vulnerable to suffering anxiety. It is important to focus on the psychological effect of anxiety during remission or current cancer treatments because they can affect patient outcomes.

## INTRODUCTION

Within Hematic cancer types, non-Hodgkin lymphoma is the most frequent worldwide representing 2.7% with a mortality rate of 2.4%.<sup>3</sup> There was 509590 new cases worldwide in 2018 with Non-Hodgkin Lymphoma in both sexes. It ranks the eleventh position in new cases by 2018.[1] On the mortality rates non-Hodgkin cancer had 248724 cases on 2018 both sexes worldwide. In consonance with the lymphoma cancers the Hodgkin type occupied the 26th position on the charts with 79990 new cases by 2018; on the mortality charts worldwide, it had 26167 cases by 2018.[1]

Worldwide, the prevalence by one year was 364594 cases of non-Hodgkin with a proportion of 4.8 and 61582 on the Hodgkin lymphoma with a proportion of 0.81. When it comes to genders the Non-Hodking Lymphoma have been present on 203050 males with a proportion of 5.3 in the past year while on Hodgkin Lymphoma 35483 cases with a proportion of 0.92. On the female gender the cases of Non-Hodking has been a bit lower 161544 with proportions of 4.3. Lymphoma and Hodgkin Lymphoma with 26099 cases with a proportion of 0.69.1

Mortality from this tumor has been declining since the late 1990s, at a rate of 3% less annual mortality reflecting a clear improvement in the efficacy of treatments.[2] The most common treatments for non-Hodgkin lymphoma are chemotherapy, radiotherapy and immunotherapy and in certain special cases bone marrow or stem cell transplants. It is estimated that by 2025 an increase of 16.1% of cancer patients who will be told during their disease process at least one radiotherapy session and in the case of lymphomas this increase will be 13.2%.<sup>[4]</sup> These therapies produce high adverse effects such as fatigue, anxiety, depression, insomnia, loss of physical condition and a high risk of suffering from heart failure that lead to a decrease in their quality of life.<sup>[5]</sup> Psychological care, with its goals of relieving emotional distress and promoting well-being, is central to improve the quality of life in the patients.<sup>[6]</sup>

Improving cancer patients' access to psychological care remains a critical issue. Many patients who could benefit from psychological care do not receive the help they need.<sup>[6]</sup> Although reviews have been conducted regarding Hodgkin and Non-

Hodgkin cancer related to psychological issues, none have focused exclusively on anxiety. We focus this review on anxiety because a considerable body of research has examined the impact of psychological interventions on these outcomes.[6] In

this review, we will discuss the prevalence of anxiety among patients with Hodgkin and Non- Hodgkin lymphoma; inspect the methods for data collection, frequency of interventions, types of instruments used to recognize anxiety in patients, and purpose of data collection, both in survivors, and patients who are under treatment and diagnosed with Hodgkin lymphoma and non-Hodgkin lymphoma. Once the sources, evaluation methods, and prevalence in anxiety in adults with Hodgkin and Non-Hodgkin lymphoma cancer have been described, we revise previous studies and conclude with recommendations on the clinical personnel for possible intervention programs to be used in their work clinics. Ending with a future panorama regarding the development of programs that can help the patient to deal with this illness in a leisurely way and not have future relapses in this psychological aspect.

## **Methods**

### **Literature search and study selection**

The literature search was selected from the databases PubMed, Scopus, LILACS and PsycINFO. Most relevant articles, were written in English, from the beginning 1992 until 2019. The keywords used in the search were "(Hodgkin disease OR lymphoma non-Hodgkin) AND anxiety", which were combined with the words "anxiety." Hodgkin disease "," lymphoma non-Hodgkin "," "by the Boolean "OR" and "AND". The titles and abstracts of the possible elements that could be selected, were examined, and then the full texts of the articles that seemed relevant were read.

### **Inclusion criteria**

The inclusion criteria for this article consisted of original articles written in English, without temporary restriction, they had to be with the theme of the study. Among the exclusion criteria was not using doctoral thesis as an article in the investigation. We have included all the experimental studies written in English, quantitative and qualitative: randomized controlled trials (RCT), controlled trials (CT), studies with only one group (quasi-

experimental studies), longitudinal studies, transversal studies, cohort studies, descriptive studies, protocols, and cross-sectional studies. The subjects mean selected for the study were men and women from 28 to 50 years of age or older, diagnosed with all stages of lymphoma Hodgkin or non-Hodgkin disease. We have selected those studies that used the prevalence associated with anxiety related with this population.

### **Study selection**

The screening of the selected studies was made in several phases. The first selection was made by reading the title and abstract. Continuing with the selection of the articles, the next process was to read the full text and applying the inclusion/exclusion criteria. Lastly, we did a reverse search of the literature to check the possible articles that can be included in the study. This systematic review was prepared in conformity with the PRISMA guidelines is shown in Figure 1 (Preferred report items for systematic reviews and meta-analysis protocols).[7]

### **Data Analysis**

Data analysis was performed by the Stats Direct with the meta-analysis package[8]

that included an analysis of random effects. In addition, an analysis of sensitivity and publication bias with Egger linear regression and heterogeneity test I<sup>2</sup>.

### **Results**

The initial search provided 102 results. After reading the title and abstract of each text, 70 articles were excluded because they did not meet the inclusion criteria. For the remaining 32 articles with full-text, 20 were finally included. Succeeding the critical reading, nine were excluded, remaining eleven articles, because they did not meet the inclusion criteria. Ending with the reverse search, four additional articles were chosen. The ending result, was a sample made of 15 studies.

The sample of the meta-analysis was  $n = 2138$ . The prevalence of anxiety with a 95% confidence interval it was 19% (95% CI 12% 25%). The forest plot is shown in **Figure 2**. There was no publication bias according to the Egger test there were no publication biases and no studies were eliminated after the sensitivity analysis. The  $i^2$  for the heterogeneity analysis was 92.6%.

## Study Characteristics

The complete sample of the review was represented by 2566 patients with both type of Hodgkin lymphoma disease. To categorize the Hodgkin's lymphoma types 1919 (74.78%) were diagnosed with Hodgkin disease while 647 (25.21%) were diagnosed with non-Hodgkin disease. About 1306 (50.89%) of the patients were males and 1260 (49.10%) were females. **Table 1**

In the included articles, the oldest one was published on 1992, the most recent article was published in 2019. Sixty percent of the used articles were published between 2013-2019. All of the used studies were journal articles and published on English language.

In regard to the geographic location of the used studies, four (26.66%) of the fifteen studies were America, ten on Europe (66.66 %) and one in Asia (6.66%).

The studies used were classified into different types such as, Longitudinal study (13.33%), cohort study (6.66%), randomized trials (20%), transversal study (6.66%), descriptive studies (20%), controlled clinical trial (6.66%), study protocol (6.66%), cross-sectional study (13.33%), one arm study (6.66%). The characteristics of the used

studies, related to the prevalence of anxiety on Hodgkin's and Non-Hodgkin's disease are included on **Table 2**.

In addition to these characteristics, the instrument most commonly used was the Hospital Anxiety and Depression Scale (HADS) (80%). [10, 11] Other instruments used were, the Spielberger's State Anxiety Inventory (STAI-YI) [13], Profile of Moods States (POMS) [21] and the Hamilton Anxiety Rating Scale (HAM). [26]

## Prevalence, scales and mean values of anxiety in Hodgkin's and non-Hodgkin's patients

In the articles reviewed, the most used instrument for validating anxiety on patients was the HADS, [10, 11] considering  $\geq 11$  points, moderate-severe anxiety on patients. The prevalence of anxiety on some articles were measured by different timings (baseline, 3 month, 6 months, 9 months and 12 months respectively). Four articles (26.6%), reviewed the anxiety as mentioned. [14, 22, 24, 27] In these four articles the baseline prevalence of anxiety on patients with Hodgkin and Non-Hodgkin's disease was 50 on the 3 month mark the prevalence was 84 patients, on the 6 month mark 73

patients, on the 9 month was 27, and on the 12 month mark was 49 and the 24 month 32 subjects.

The remaining eight articles measured the prevalence of anxiety, by the obtained score on the HADS [10, 11]. Subjects that obtained  $\geq 11$  points are considered with moderate-severe anxiety.[10, 11] Specifically, 305 (11.8%) subjects obtained  $\geq 11$  scores, on the selected instrument of measure, considering this moderate-severe anxiety. Of these 305 cases of anxiety most of the cases were Hodgkin's disease patients.

Three articles about 23%-32% obtained the highest prevalence of anxiety cases in their studies [9, 14, 19]. Consequently, about 14.5%-18% of the mild prevalence was obtained on six of the reviews [14, 16-18, 22, 28]. The remaining three investigations contained the lowest rates on prevalence in anxiety about 6.8%-10% [23, 24, 27] All these papers only used the HADS [10, 11] The rest of the articles that didn't utilize HADS [10, 11] as an instrument of evaluation, however, they used other different test to measure anxiety on Hodgkin and Non-Hodgkin patients. Such test as the HAM [26] was used to rate the severity of the anxiety on Hodgkin's disease patients; obtaining only

4% of prevalence on severe anxiety among patients [25]. Consequently, the STAI-YI 13 was used to measure anxiety among patients, reporting moderate anxiety levels on its patients. Finalizing with the last different instrument used to measure anxiety the POMS [21]; 21% of the patients reported anxiety levels [20].

Not all the articles utilized in this review, reported the same levels of prevalence by time periods, but they did provide descriptive and percentage information about the values of anxiety within the studied population.

### **Description of the interventions**

In most of the articles of this review, the purpose was to access anxiety levels among patients with Hodgkin and Non-Hodgkin disease. Many of the interventions were made by mailing questionnaires to the patients.

Although, most of the research did the same form of gathering the information, there were other papers that did other methods. Other forms of interventions were made by, different forms of therapy, care plans or web help, interviews with clinical personnel, or the combination of the questionnaires with



the interviews and the combination of therapy and questionnaires.

There were studies that utilized the telephone interview or personal interview in combination with the questionnaires. These studies in addition of the participation filling the questionnaires, did a follow-up interview for the monitoring of any psychological, social or medical events the patient may have at the time [9, 14, 16, 23].

In addition to this analysis, three studies made the combination of treatment and questionnaires to gather aspects of anxiety on patients [12, 20, 27]. In addition, Bro et al. and Wagner et al. made the intervention with therapies, such as music therapy and Rituximab induction therapy [12, 27] The remaining intervention, utilized a care plan or web help program, to help the patients with this disease to cope with the future problems related with this condition [20].

Finalizing with the interventions only made by questionnaires, in this particular aspect of the articles, the purpose was to gather all the information as possible to make a descriptive analysis of the studied population. The descriptive part consisted with the sociodemographic data, other

possible psychological problems, social data etc. In this analysis, the psychological data gathered was the aspects of anxiety on this population [15, 17-19, 22, 24, 25, 28].

### **Duration, frequency and intensity of the intervention**

Several of the studies used a period of three months in between to see the prevalence of anxiety in patients. Most of these studies observed a lower anxiety level after time,[ 22, 24] or after a specific intervention like a program that gave follow-up assessments for monitoring any medical, psychological and social events giving the patient or a coping style for managing illness [14, 27] The remaining studies didn't utilize a time frame as to observe the prevalence of the anxiety among patients, it was more an initial collection of data to describe the sample used in their studies. The observation of psychological distress was the most applied method encompassed by the authors; in which anxiety was the main characteristic of observation this is due to the medical procedure that the patient has to go through that brings uncertainty [9, 15, 16-19, 22, 24, 25]. The fatigue was also a main source of observation in combination with the anxiety of the participants [15, 18].

In addition, most of the subjects who participated in the studies were Hodgkin's and Non-Hodgkin's survivors that is 60% of the reviews used [9, 14-16, 18-20, 24, 28]. Other studies 13.33%, used patients that completed a certain treatment for the cancer, chemotherapy or rituximab therapy, for example [25, 27] Finalizing with 26.66% of the studies used was the patients who were diagnosed with the disease with no specific treatment or survivorship status [12, 17, 22, 23].

## **Discussion**

There seems to be an association between Hodgkin and non-Hodgkin cancer patients and anxiety. Specifically in the field of cancer recurrence in individuals, survivors who had a history of recurrent lymphoma had higher levels of anxiety than others, suggesting that this is a population at risk [29]. These levels of anxiety skyrocket, when it was time to make a follow-up appointment, with the fear of it to suffer a relapse. The patients suffer from the indirect induction of anxiety through the medical procedures without the effective psychological method that can help the patient to confront the possible risks [29, 30]. Furthermore, cancer in general, is a disease that due to the complications that

comes with it and the inclusion of a high mortality rate, is a health problem that people have a hard time coping with.

A similar review regarding other psychological aspects among Hodgkin and Non-Hodgkin patients, says that most of the psychological unmet needs in this type of cancer is to report of a possible recurrence, a clearer understanding that survival after cancer is a conditional event may help patients with cancer derive more hopeful appraisals about the future, and potentially decrease the anxiety that often accompanies post-treatment surveillance, such as follow-ups interviews [31]. This can be a useful finding, to start implementing care plans for patients to help them cope and to survey any concern of change on their daily basis. Care plans or web help are instruments that could potentially could help these patients "lost in transition" due to the power that the information can have in patients to feel in control of the situation and how do deal with any particular situation that could come with it. Also, these findings can be utilized as a part of a complementary therapy with the clinical treatment to reduce anxiety or other psychological distress that could affect the quality of life in this population.

In addition to possible solutions on reducing the anxiety in patients, studies have found help on treatments with rituximab, since this may offer some psychological benefit in helping the patients to feel more in control of the situation, rather than wait for a future prognosis of the disease, reducing the anxiety at a long run [32]. On consonance with the therapies that might help the patients, and in agreement with our results, some findings tell that lymphoma patients, go through a lot of anxiety during the treatment [33-36]. In the search for ways of intervening towards anxiety, music has been suggested to relieve this problem [12, 37-42]. Music is related to activity in the brain's reward system, where it may induce emotions, moderate patients; mood, and thereby decrease pain and anxiety levels [43-45] This is a wonderful finding since there are more options for the patients to reduce anxiety levels and have a better quality of life.

Findings suggests that how individuals perceive the cancer experience may influence or be influenced by their health status and functioning and quality of life that also includes the psychological aspects [46] This finding is in agreement with another

article that highlighted the need for a psychological procedure in order for the patients to cope slowly with this disease. The term coping strategies includes a wide range of cognitive and behavioral strategies that an individual uses to manage internal and external demands in response to a stressful situation [47]. This strategy manages to help the patient to not jump into situations that can cause big distress on them. Well prepared healthcare personnel, family and friends even religion can be good suggested coping tools that the patient can rely on. In fact, one study described how the support of health care providers, family and friends facilitated the patient experience of NHL and its corresponding treatment regimen.<sup>48</sup> Other strategies such as care plans can be useful as a tool survival to convey this message and reduce anxiety [29].

Regrettably, those are not the majority of the cases, there are indicators that the hematology patients didn't feel the same treatment as other types of cancer patients. Not surprisingly, most primary care physicians are unfamiliar with this high-risk group and are not cognizant of the surveillance recommendations [49]. Since of the symptomatology of this particular cancer

and the modality of the treatment was different, it is treated by another group of specialists rather than the oncologists, this make the patients feel as it was treated more as a chronic health issue rather than a specific cancer. These differences mentioned before and to have less access to the support services that other types of cancer have, make the participants feel frustrated and isolated, meaning impacted negatively their cancer experience [50]. Indeed, the Institute of Medicine (IOM) considers most cancer survivors “lost in transition” [51]. However, this can be caused to the lack of recognition between the clinicians towards this particular cancer. Thus, there is a created model by the National Institute for Health and Clinical Excellence (NICE) that was made to illustrate clinicians of any level to maintain the psychological well-being of the patients [52]. Hence, healthcare providers and clinicians should explore the coping strategies and the psychological needs of the patients and consequently in conjunction with the patient formulate individualized care plans which empower the patient to cope effectively whilst undergoing chemotherapy [48].

Finalizing, various results of this article, where able by performing psychometric test on patients, to gather information that concludes that there is a presence of anxiety in patients with Hodgkin and non-Hodgkin disease; this performs an additional discomfort in the disease procedure. The data collection used either as a descriptive instrument, clearly shows the presence of this type of mechanism among patients. These types of instruments are a great help to the researchers because they gather first-hand information from the patients. All this data recompilation has been useful to make new advances on anxiety among patients.

### **Study limitations**

This present study shows some limitations. Most of the studies used the HADS for the patients. This test is made in a format that is universal, to any kind of population, however, does not take into consideration specific aspects of this disease. It will be interesting to have an adaptation of this questionnaire with Hodgkin’s and Non-Hodgkin’s anxiety aspects. If such adaptation is possible, future researchers can be able to conclude more detailed concerns of anxiety in Hodgkin and Non-Hodgkin patients. Other limitation was the language, since we only

used written English reviews, other studies might include similar characteristic used on this study; thus, help us to enlarge the population size used on this analysis. Additional research is needed to gather more information on these variables that weren't considered, in order to know what other factors trigger the anxiety among the patients.

### **Clinical implications**

A considerable number of patients suffer from anxiety, due to different reasons. Clinical personnel should be aware of these situations, to start implementing care plans that will help this population in order to, reduce such levels. Such plans should be a complement to the clinical treatment for the disease. The psychological aspect of having his kind of cancer, can be triggering for the patient, and this is when the complementary help will come useful. Most of the studies used, only collect this sort of data for descriptive purposes. Instead, this should be used to address this information for taking conscience of the risks and implement surveillance recommendations; for the patient to be less anxious and more aware of its disease. More research should focus on developing programs or interventions to

identify and reduce anxiety among Hodgkin and Non-Hodgkin's disease patients.

### **Conclusions**

Hodgkin and non-Hodgkin patients are vulnerable to anxiety issues. The prevalence of this psychological aspect, may not seem alarming; however, many patients with this disease may be on risk of developing this trait. The mainly reason anxiety was among patients was because of the fear of relapsing into the cancer again. Most of the recollection of data was to screen possible ways on creating an intervention or to identify predictors of anxiety on survivors. The effect of anxiety during the survival period or the treatment that the patient is using, on a psychological basis, highlights the importance on cancer care of focusing on aspects that psychologically may affect the patient during his period with this disease.

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## Conflict of Interests Statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Data Availability Statement

The data that support the findings of this study are available in the Supplemental Material file.

## References

1. World Health Organization (WHO). Latest global cancer data: Cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018 [Cited 2019 July 30]. Available from <https://www.who.int/cancer/PRGlobocanFinal.pdf>
2. Sociedad Española de Oncología Médica (SEOM). Las Cifras del cáncer en España 2018. [Cited 2019 July 30]. Available from: <https://seom.org/seomcms/images/stories/>

recursos/Las\_Cifras\_del\_cancer\_en\_Espana 2018.pdf

3. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Bray F. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2014; 136:359-386. doi:10.1002/ijc.29210
4. Borrás JM, Lievens Y, Barton M, Corral J, Ferlay J, Bray F, et al. How many new cancer patients in Europe will require radiotherapy by 2025? An ESTRO-HERO analysis. *Radiother Oncol* 2016; 119:5-11. doi:10.1016/j.radonc.2016.02.016
5. Courneya KS, Sellar CM, Trinh L, Forbes CC, Stevinson C, McNeely ML, et al. Randomized Trial of Aerobic Exercise and Sleep Quality in Lymphoma Patients Receiving Chemotherapy or No Treatments. *Cancer Epidemiol Biomarkers Prev* 2012; 21:887-894. doi:10.1158/1055-9965.epi-12-0075
6. Jacobsen PB, Jim, HS. Psychosocial Interventions for Anxiety and Depression in Adult Cancer Patients: Achievements and Challenges. *CA Cancer J Clin* 2008; 58:214-230. doi:10.3322/ca.2008.0003
7. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticre M, et al. Preferred

- reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2012; 4:1-9. doi:10.1186/2046-4053-4-1
8. StatsDirect Statistical Software [website]. United Kingdom: StatsDirect Ltd. [Cited 2019 September 2]. Available from: <https://www.statsdirect.com/>
9. Absolom K, Greenfield D, Ross R, Davies H, Hancock B, Eiser C. Reassurance following breast screening recall for female survivors of Hodgkin's lymphoma. *Breast J* 2007; 16:590-596. doi:10.1016/j.breast.2007.05.001
10. Snaith RP, Zigmond AS. The hospital anxiety and depression scale. *BMJ* 1986; 292:344. doi:10.1136/bmj.292.6516.344
11. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983; 67:361-370. doi:10.1111/j.1600-0447.1983.tb09716.x
12. Bro ML, Johansen C, Vuust P, Enggaard L, Himmelstrup B, Mourits-Andersen T, et al. Effects of live music during chemotherapy in lymphoma patients: a randomized, controlled, multi-center trial. *Support Care Cancer* 2019; 27:3887-3896 doi:10.1007/s00520-019-04666-8
13. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. State-Trait Anxiety ETSY Inventory for Adults (STAI). Mind Garden. 1977. [Cited 2019 July 30]. Available from: <http://growingleadersfoundation.com/wp-content/uploads/2017/03/State-Trait-Anxiety-Inventory.pdf>
14. Compaci G, Rueter M, Lamy S, Oberic L, Recher C, Lapeyre-Mestre M, et al. Ambulatory Medical Assistance - After Cancer (AMA-AC): A model for an early trajectory survivorship survey of lymphoma patients treated with anthracycline-based chemotherapy. *BMC Cancer* 2015; 15:781. doi:10.1186/s12885-015-1815-7
15. Daniëls LA, Oerlemans S, Krol ADG, Creutzberg C L, Van de Poll-Franse LV. Chronic fatigue in Hodgkin lymphoma survivors and associations with anxiety, depression and comorbidity. *British Journal of Cancer* 2014; 110:868-874. doi:10.1038/bjc.2013.779
16. Jensen RE, Arora NK, Bellizzi KM, Rowland JH, Hamilton AS, Aziz NM, et al. Health-related quality of life among survivors of aggressive non-Hodgkin lymphoma. *Cancer* 2013; 119:672-680. doi:10.1002/cncr.27781

17. Loge J, Abrahamsen A, Ekeberg Ø, Hannisdal E, Kaasa S. Psychological distress after cancer cure: a survey of 459 Hodgkin's disease survivors. *Br J Cancer* 1997; 76:791-796. doi:10.1038/bjc.1997.464
18. Loge JH, Abrahamsen AF, Ekeberg Ø, Kaasa S. Fatigue and Psychiatric Morbidity Among Hodgkin's Disease Survivors. *J Pain Symptom Manage* 2000; 19:91-99. doi:10.1016/s0885-3924(99)00148-7
19. Magyari F, Kósa K, Berecz R, Illés A, Miltényi Z, Simon Z, et al. Employment status and health related quality of life among Hodgkin-lymphoma survivors'— results based on data from a major treatment center in Hungary. *Health Qual Life Out* 2017; 15:180. doi:10.1186/s12955-017-0758-x
20. Oeffinger KC, Hudson MM, Mertens AC, Smith SM, Mitby PA, Eshelman-Kent DA, et al. Increasing rates of breast cancer and cardiac surveillance among high-risk survivors of childhood Hodgkin lymphoma following a mailed, one-page survivorship care plan. *Pediatr Blood Cancer* 2011; 56:818-824. doi:10.1002/psc.22696
21. McNair DM, Lorr M, Droppleman LF. Manual for the Profile of Mood States. San Diego, CA: Educational and Industrial Testing Service; 1981.
22. Oerlemans S, Mols F, Nijziel MR, Zijlstra WP, Coebergh JWW, Van de Poll-Franse LV. The course of anxiety and depression for patients with Hodgkin's lymphoma or diffuse large B cell lymphoma: a longitudinal study of the PROFILES registry. *J Cancer Surviv* 2014; 8:555-564. doi:10.1007/s11764-014-0367-1
23. Razavi D, Delvaux N, Bredart A, Paesmans M, Debusscher L, Bron D, et al. Screening for psychiatric disorders in a lymphoma out-patient population. *Eur J Cancer* 1992; 28:1869-1872. doi:10.1016/0959-8049(92)90025-w
24. Roper K, Cooley ME, McDermott K, Fawcett J. Health-Related Quality of Life After Treatment of Hodgkin Lymphoma in Young Adults. *Oncol Nurs Forum* 2013; 40:349-360. doi:10.1188/13.onf.349-360
25. Trachtenberg E, Mashiach T, Ben Hayun R, Tadmor T, Fisher T, Aharon-Peretz J, et al. Cognitive impairment in Hodgkin lymphoma survivors. *Br J Haematol* 2018; 182:670-678. doi:10.1111/bjh.15448
26. Hamilton M. Hamilton Anxiety Rating Scale (HAM-A). *J Med* 1959; 32:50-55.



27. Wagner LI, Zhao F, Hong F, Williams ME, Gascoyne RD, Krauss JC., et al. Anxiety and Health-Related Quality of Life Among Patients With Low-Tumor Burden Non-Hodgkin Lymphoma Randomly Assigned to Two Different Rituximab Dosing Regimens: Results From ECOG Trial E4402 (RESORT). *J Clin Oncol* 2015; 33:740-748. doi:10.1200/jco.2014.57.6801
28. Wettergren L, Björkholm M, Axdorph U, Langius-Eklöf A. Determinants of Health-Related Quality of Life in Long-Term Survivors of Hodgkin's Lymphoma. *Qual Life Res* 2004; 13:1369-1379. doi:10.1023/b:qure.0000040790.43372.69
29. Thompson CA, Charlson ME, Schenkein E, Wells MT, Furman RR, Elstrom R, et al. Surveillance CT scans are a source of anxiety and fear of recurrence in long-term lymphoma survivors. *Ann Oncol* 2010; 21:2262-2266. doi:10.1093/annonc/mdq215
30. Bestawros A, Foltz L, Srour N, Savage KJ, Connors JM. Patients' and physicians' roles in detecting recurrent Hodgkin lymphoma following complete remission. *Ann Oncol* 2013; 24:1359-1363. doi:10.1093/annonc/mds606
31. Baade P, Youlden D, Chambers S. When do I know I am cured? Using conditional estimates to provide better information about cancer survival prospects. *Med J Aust* 2011; 94:73-77. doi:10.5694/j.1326-5377.2011.tb04171.x
32. Ardeschna KM, Qian W, Smith P, Braganca N, Lowry L, Patrick P, et al. Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial. *Lancet Oncol* 2014; 15:424-435. doi:10.1016/s1470-2045(14)70027-0
33. Andrade V, Sawada NO, Barichello E. Quality of life in hematologic oncology patients undergoing chemotherapy. *Rev Esc Enferm USP*, 2013; 47:355-361. doi:10.1590/s0080-62342013000200012
34. Merli F, Bertini M, Luminari S, Mozzana R, Berte R, Trottini M, et al. Quality of life assessment in elderly patients with aggressive non-Hodgkin's Lymphoma treated with anthracycline-containing regimens. Report of a prospective study by the Intergruppo Italiano Linfomi [Cited 2019 August 22]. Available from:

<http://www.haematologica.org/content/89/8/973.long>

35. Poe JK, Hayslip JW, Studts JL. Decision Making and Distress Among Individuals Diagnosed with Follicular Lymphoma. *J Psychosoc Oncol* 2012; 30:426-445. doi:10.1080/07347332.2012.684853

36. Rueda A, Alba E, Ribelles N, Sevilla I, Ruiz I, Miramón J. Six cycles of ABVD in the treatment of stage I and II Hodgkin's lymphoma: a pilot study. *J Clin Oncol* 1997; 15:1118-1122. doi:10.1200/jco.1997.15.3.1118

37. Archie P, Bruera E, Cohen L. Music-based interventions in palliative cancer care: a review of quantitative studies and neurobiological literature. *Support Care Cancer* 2013; 21:2609-2624. doi:10.1007/s00520-013-1841-4

38. Boyde C, Linden U, Boehm K, Ostermann T. The Use of Music Therapy during the Treatment of Cancer Patients: A Collection of Evidence. *Glob Adv Health Med* 2012; 1:24-29. doi:10.7453/gahmj.2012.1.5.009

39. Bradt J, Dileo C, Magill L, Teague A. Music interventions for improving psychological and physical outcomes in cancer patients. *Cochrane Database Syst Rev* 2016;

15:CD006911.

doi:10.1002/14651858.cd006911.pub3

40. Nightingale CL, Rodríguez C, Carnaby G. The Impact of Music Interventions on Anxiety for Adult Cancer Patients. *Integr Cancer Ther* 2013; 12:393-403. doi:10.1177/1534735413485817

41. Tsai HF, Chen YR, Chung MH, Liao YM, Chi MJ, Chang CC, et al. Effectiveness of Music Intervention in Ameliorating Cancer Patients' Anxiety, Depression, Pain, and Fatigue. *Cancer Nurs* 2014; 37:35-50. doi:10.1097/ncc.0000000000000116

42. Zhang J, Wang P, Yao J, Zhao L, Davis MP, Walsh D, et al. Music interventions for psychological and physical outcomes in cancer: a systematic review and meta-analysis. *Support Care Cancer* 2012; 20:3043-3053. doi:10.1007/s00520-012-1606-5.

43. Garza EA, Brattico E, Leino S, Østergaard L, Vuust P. Distinct neural responses to chord violations: A multiple source analysis study. *Brain Res* 2011; 1389:103-114. doi:10.1016/j.brainres.2011.02.089

44. Gebauer L, Kringelbach ML, Vuust P. Ever-changing cycles of musical pleasure: The role of dopamine and anticipation.

Psychomusicology 2012; 22:152-167.  
doi:10.1037/a0031126

45. Vuust P, Kringelbach, ML. The Pleasure of Making Sense of Music. *Interdiscipl Sci Rev* 2010; 35:166-182.  
doi:10.1179/030801810x12723585301192

46. Smith SK, Crespi CM, Petersen L, Zimmerman S, Ganz PA. The impact of cancer and quality of life for post-treatment non-Hodgkin lymphoma survivors. *Psychooncology* 2010; 19:1259-1267.  
doi:10.1002/pon.1684

47. Lazarus RS, Folkman S. Stress, appraisal, and coping. New York: Springer Publishing Company; 1984.

48. Chircop D, Scerri J. Coping with non-Hodgkin's lymphoma: a qualitative study of patient perceptions and supportive care needs whilst undergoing chemotherapy. *Support Care Cancer* 2017; 25:2429-2435.  
doi:10.1007/s00520-017-3649-0

49. Bober SL, Recklitis CJ, Campbell EG, Park ER, Kutner JS, Najita J.S, et al. Caring for cancer survivors. *Cancer* 2009; 115:4409–4418. doi: 10.1002/cncr.24590

50. Swash B, Hulbert-Williams N, Bramwell R. 'Haematological cancers, they're a funny

bunch': A qualitative study of non-Hodgkin's lymphoma patient experiences of unmet supportive care needs. *J. Health Psychol* 2016; 23:1464-1475.  
doi:10.1177/1359105316660179

51. Hewitt M, Greenfield S, Stowall E. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, DC: The National Academies Press; 2006.

52. National Institute for Clinical Excellence (NICE). Improving supportive and palliative care for adults with cancer [Cited 2019 August 10]. Available from <https://www.nice.org.uk/guidance/csgsp>

## Supplementary Material

Table 1. Study Characteristics

Number of cases = 2566 (both Lymphoma types)

Gender (Both lymphoma types)

Male = 1306

Female = 1260

Lymphoma type (both gender)

Hodgkin's disease= 1919

Non-Hodgkin's disease = 647

**TABLE 2. Characteristics of Included Studies (N = 15)**

Author, Year	Study Design	Participants	Intervention and duration	Instruments
Absolom et al., 2007. <sup>9</sup>	Cross-sectional study	56 Female survivors of HL treated with mantle radiotherapy experience increased breast cancer risk related to radiation dose and age at diagnosis	The aims of this paper are to describe women's emotional responses and knowledge of their personal risk following the recall.	HADS <sup>10,11</sup>
Bro et al., 2019. <sup>12</sup>	Randomized, control trial	143 participants with NHL and HL	Examine whether live or pre-recorded music listening decreases anxiety during chemotherapy in newly diagnosed lymphoma patients.	STAI-YI <sup>13</sup>
Compaci et al., 2015. <sup>14</sup>	Cohort Study	115 participants in survivorship stage of lymphoma cancer.	The AMA-AC program consisted of quarterly follow-up assessments for monitoring any medical, psychological and social events. It encompassed GP appointments, self-perceived evaluation of HRQoL and mental health, and phone calls conducted by the NC. It was a 12 month process.	HADS <sup>10,11</sup> Phone calls on the 3, 6, 9 and 12 months follow-up.
Daniels et al., 2014. <sup>15</sup>	Cross-sectional study	In total, 180 (68%) of the 267 HL survivors completed and returned the questionnaires.	The purpose of this study was to investigate the prevalence of clinically relevant fatigue in HL survivors and the relation between fatigue and anxiety and depression	HADS <sup>10,11</sup>
Jensen et al., 2013. <sup>16</sup>	Cross-sectional study	The cases were adult survivors of aggressive NHL selected in 2003. Analyzed for 319 survivors of aggressive NHL. Survivors, 2–5 years after diagnosis, were selected from the Los Angeles County Cancer Registry	To obtain knowledge of HRQoL and its correlates among aggressive NHL survivors is limited	HADS <sup>10,11</sup>
Loge et al., 1997. <sup>17</sup>	Cross-sectional study	459 participants patients admitted to the NRH between 1971 and 1991 with HD and known to be alive by the end of 1993 were approached by post	To assess the levels of psychological distress and identify predictors of anxiety/depression after caseness cancer cure.	HADS <sup>10,11</sup>
Loge et al., 2000. <sup>18</sup>	Cross-sectional study	421 patients HDS	This cross-sectional study examined how fatigue related to psychiatric morbidity.	HADS <sup>10,11</sup>
Magyari et al., 2017. <sup>19</sup>	Controlled Clinical Trial	140 participants HLS	Evaluate psychological distress and its risk factors among our HLS	HADS <sup>10,11</sup>
Oeffinger et al., 2011. <sup>20</sup>	Cohort Study	62 HL survivors, ages 27 to 55, participating in the CCSS who were at increased risk for breast cancer and/or cardiomyopathy and had not had a screening mammogram or echocardiogram, respectively, within the prior two years.	HLS face substantially elevated risks of breast cancer and cardiovascular disease. They and their physicians are often unaware of these risks and surveillance recommendations.	POMS <sup>21</sup>
Oerlemans et al., 2014. <sup>22</sup>	Longitudinal study	This study is part of a longitudinal population-based survey among HL and DLBCL patients registered by the ECR 150 Started as subjects in the study.	The purpose of this study is to prospectively assess anxiety and depression among patients with HL and DLBCL	HADS <sup>10,11</sup>
Razavi et al., 1992. <sup>23</sup>	Cross-sectional study	117 HL and NHL consecutive out-patients.	This makes it possible to choose an optimal cut-off score that takes into account the costs and benefits of treatment of psychiatric disorders (mainly adjustment, depressive and anxiety disorders) in a lymphoma out-patient population.	HADS <sup>10,11</sup>
Roper et al., 2013. <sup>24</sup>	Crossover Study	The final sample consisted of 40 young adult survivors of HL	To describe changes in HRQoL and to identify supportive care services used after treatment for HL in young adults.	HADS <sup>10,11</sup>
Trachtenberg et al., 2018. <sup>25</sup>	Cross-sectional study	51 Patients, aged 18–50 years, diagnosed with HLS, who completed first-line (chemotherapy radiation) therapy and remained in complete remission for 6 months to 5 years from therapy end, were evaluated	The current study aimed to objectively assess CRCI incidence and characteristics in HLS.	HAM <sup>26</sup> Is a questionnaire used to rate the severity of anxiety.
Wagner et al., 2015. <sup>27</sup>	Randomized Control Trial	253 participants NHL who achieved complete or partial response after 4-week rituximab induction therapy completed patient-reported outcome measures	The purpose of this study was to compare illness-related anxiety among trial participants randomly assigned to MR versus RR. A secondary objective was to examine superiority of MR versus RR with regard to illness-related anxiety given participant coping style for managing illness (active v avoidant).	HADS <sup>10,11</sup>
Wettergren et al., 2003. <sup>28</sup>	Randomized Control Trial	121 long-term survivors of HL in Stockholm	A better understanding of the relationships between the variables explaining HRQoL may improve care and rehabilitation of HL patients.	HADS <sup>10,11</sup>

† Ambulatory Medical Assistance - After Cancer (AMA-AC); Childhood Cancer Survivor Study (CCSS); Cancer-Related Cognitive Impairment (CRCI); Diffuse Large B-Cell Lymphoma (DLBCL); Eindhoven Cancer Registry (ECR); General Practitioner (GP); Hamilton Anxiety Rating Scale (HAM); Health-Related Quality of Life (HRQoL); Hodgkin's Disease (HD); Hodgkin's Disease Survivors (HDS); Hodgkin's Lymphoma (HL); Hodgkin's Lymphoma Survivors (HLS); Hospital Anxiety and Depression Scale (HADS); Maintenance Rituximab (MR); Non-Hodgkin Lymphoma (NHL); Norwegian Radium Hospital (NRH); Nurse Coordinator (NC); Profile of Mood States (POMS); Rituximab Re-treatment (RR); Spielberger's State Anxiety Inventory (STAI-YI).

# STUDY II

## AUTONOMIC IMBALANCE IN LYMPHOMA SURVIVORS

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## STUDY II. Autonomic Imbalance in Lymphoma Survivors

### ABSTRACT

**Purpose:** Among the types of blood cancers, non-Hodgkin lymphoma is the most common. The usual treatments for this type of cancer can cause heart failure.

**Materials and Methods:** A descriptive observational study was conducted that included 16 non-Hodgkin lymphoma survivors and 16 healthy controls matched by age and sex. Vagal tone was evaluated in the short term with a three-channel Holter device, and the time and frequency domains were analyzed following a previously accepted methodology to evaluate cardiac autonomic balance.

**Results:** The results of the analysis revealed that the standard deviation of the NN interval ( $F = 6.25$ ,  $p = 0.021$ ) and the square root of the mean of the sum of the differences between NN intervals ( $F = 9.74$ ,  $p = 0.004$ ) were significantly higher in healthy subjects than in lymphoma survivors. In the heart rate variability (HRV) index, there were no significant differences between the groups ( $F = 0.03$ ,  $p = 0.85$ ), nor in the parameters of the frequency domains

LF ( $F = 1.94$ ,  $p = 0.17$ ), HF ( $F = 0.35$ ,  $p = 0.55$ ), and the ratio LF/HF ( $F = 3.07$ ,  $p = 0.09$ ).

**Conclusions:** HRV values were lower in non-Hodgkin lymphoma survivors in the first year after treatment, resulting in autonomic imbalance compared to healthy paired subjects.

## Introduction

According to the World Health Organization, cancer is the leading cause of death worldwide and there are around 18.1 million new cases every year, expected to increase to 24 million cases by 2035 [1,2]. Within the World Health Organization's global hematic cancers, non-Hodgkin lymphoma had 509,590 (2.8%) new cases worldwide in 2018 in both genders. It ranks eleventh in new cases for 2018 [1]. In terms of mortality rate, non-Hodgkin lymphoma cancer caused 248,724 deaths in 2018 in both genders worldwide.

In Spain, in 2020, non-Hodgkin lymphoma was one of the most diagnosed blood cancers (9188), being in the top 10 positions [2]. Worldwide, it is the most frequent, accounting for 3.0% with a mortality rate of 2.6% [3]. Mortality from this tumor type has decreased since the late 1990s at a rate of 3% annually, reflecting a clear improvement in the effectiveness of treatments [2].

The most common treatments for non-Hodgkin lymphoma include chemotherapy, radiation therapy, immunotherapy, and, in certain special cases, bone marrow or stem cell transplants. It is estimated that by 2025,

the number of cancer patients that undergo at least one session of radiation therapy will have increased by 16.1% [4]. These therapies produce highly adverse effects such as fatigue, anxiety, depression, insomnia, loss of physical condition, and a high risk of suffering heart failure that leads to a decrease in quality of life [5].

Cancer and cardiovascular disease were previously considered two distinct pathologies. Recent data show that they share multiple risk factors, suggesting that there might be a biological pathway [6]. Patients with Hodgkin lymphoma who have received radiation therapy represent a high-risk group for heart failure, developing arrhythmias, ischemic heart disease, and congestive heart failure [7]. Another study found that in patients undergoing chemotherapy for non-Hodgkin lymphoma, especially with anthracyclines, cardiovascular risk is increased [8]. With increased survival, attention to the adverse effects of treatments received during cancer becomes increasingly important [9].

Heart rate variability (HRV) is a noninvasive biomarker of health that reflects vagal activity and it may be a useful test for autonomic imbalance [10,11]. It results from



interaction between the autonomous nervous system and the cardiovascular system. [12]

Vagal nerve activity is very strongly correlated with HRV [13] and it is an independent predictor of prognosis after myocardial infarctions [14] and in cancer [15].

No HRV-related studies have been found in patients with non-Hodgkin lymphoma. This is why the objective of this descriptive study is to compare, by controlling the confounding variables, the HRV of lymphoma survivors after their first year of treatment completion with those of healthy subjects.

## **Materials and Methods**

### **Subjects**

A descriptive observational study was conducted that included 16 non-Hodgkin lymphoma survivors and 16 healthy controls matched by age and sex. Short-term vagal tone was evaluated with a three-channel Holter device, and the time and frequency domains were analyzed to evaluate cardiac autonomic balance. The patients were recruited from the oncology department of the Spanish hospital Virgen de las Nieves in

Granada, and the healthy controls matched by age and sex were recruited from the general community. Inclusion criteria were a primary diagnosis of non-Hodgkin lymphoma cancer (Grades I-IIIa), age between 18 and 65 years, and the primary part of cancer treatment (surgery, chemotherapy, radiation therapy, and/or immunotherapy) having been completed 6 months to 1 year earlier. Exclusion criteria for this study were the presence of metastasis and/or active cancer, history of cardiovascular disease, and administration of medications known to alter vagus nerve activity. The contact procedure was telephone. Once the patients were cited, the informed consent document was signed, their medical history was completed, a questionnaire was completed for epidemiological data, and the procedure of obtaining HRV was started.

### **HRV Measurements**

The Holter device (NoravHolter DL 800, Braemar, Burnsville, MN, USA) and analysis through NH300 Software (Norav, v. 2.70) were used. The variables that collect the time domain and heart rate were evaluated in the short term. The participants adopted a supine position for 10 minutes in a room

with a temperature of 22–25 C, without external stimulation. ECG signals were acquired using a Holter device for 5 minutes and a modified lead channel II system.

HRV was calculated from ECG records as the time interval between consecutive heartbeats (RR interval). In the time domain, we analyzed the standard deviation of the average from normal-to-normal interval (NN) (SDNN), the square root of the mean of the differences squared of successive NN intervals (RMSSD), and the number of all NN intervals divided by the maximum of all NN intervals (HRV Index). The main spectral components analyzed in the frequency domain were the low frequency band (LF) (0.04–0.15 Hz), as sympathetic and parasympathetic measure, occupations; high frequency band (HF) (0.15–0.40 Hz), associated with vagal-parasympathetic activity; and the LF/HF ratio, indicating sympathovagal equilibrium. We followed the recommendations from the working group of the European society of cardiology and the American Society of Stimulation and Electrophysiology (Task Force, 1996) [16].

## **Statistical Analysis**

The results were expressed through means with standard deviation for continuous variables and as percentages for categorical variables. A confidence interval of 95% was obtained. Parametric and non-parametric tests were applied after the Shapiro–Wilk test to verify the normal distribution of the data. When necessary, the data were logarithmically transformed to achieve homogeneity of variances. Unidirectional analysis of variance (ANCOVA) was used with the group (healthy and lymphoma) as and between subjects.

The variables of heart rate, SDNN, RMSSD, HRV index, HF, LF, and HF/LF ratio were evaluated considering the following covariates: age, studies, marital status, work, smoking, alcohol consumption, menopause, height, weight, and body mass index (BMI). IBM-SPSS 26.0 was used for data analysis, and  $p < 0.05$  in the tests was considered statistically significant.

## **Results**

### **Demographic and Clinical Data**

The study sample of 32 subjects who met the eligibility criteria comprised of 19 females (59.4%) and 13 males (40.6%), the vast

majority were Caucasians (96.9%) with a mean (SD) age of 43.13 (7.14) years.

The mean BMI in the group of survivors was 25.81 (5.66), which did not differ significantly from that of the healthy subjects, 24.69 (3.50). The consumption of tobacco was higher with the healthy group, of which 56.3% of them smoked, contrary to the lymphoma group, 62.6% of which were non-smokers. Of the lymphoma group, 68.8% did not consume alcohol while, in the healthy group, 56.3% did not consume alcohol. The statistically significant differences between groups were educational level and occupational status, with higher educational levels (68.8%) and more frequent employment (87.5%) in healthy subjects, versus 18.8% and 12.5%, respectively, in the lymphoma survivors' group (**Table 1**).

**Table 1.** Participant characteristics by study group.

Variable	Healthy Controls (n = 16)	Lymphoma Cancer (n = 16)	p Value
Age (years), mean + SD (range) **	43.13 ± 6.51 (34–56)	43.13 ± 7.94 (32–58)	1
Sex(%) *			0.072
Female	75.0	43.7	
Male	25.0	56.2	
Marital Status (%) *			0.146
Single	0.0	25.0	
Married	75.0	50.0	
Living together	0.0	18.8	
Widowed	6.3	0.0	
Divorced	18.8	6.3	
Educational Level (%) *			0.001 *
Primary Studies	0.0	25.0	
Secondary Studies	31.3	56.3	
High school	68.8	18.8	
Occupational status (%) *			0.008 *
Homemaker	12.5	18.8	
Employed	87.5	12.5	
Sick Leave	0.0	50.0	
Not working due to the disease	0.0	12.5	
Retired	0.0	6.3	

**Table 1. Cont.**

Variable	Healthy Controls (n = 16)	Lymphoma Cancer (n = 16)	p Value
Smoking Status (%) *			0.797
Nonsmoker	18.8	62.5	
Smoker	56.3	12.5	
Ex-smoker	25.0	25	
Alcohol status (%) *			0.325
No consumption	56.3	68.8	
Consume monthly	18.8	25.0	
Consume weekly	25.0	6.3	
Menopausal status (%) *			0.075
No	93.8	68.8	
Yes	6.3	31.3	
Weight (kg), mean + SD (range) **	68.59 ± 15.24 (56–105)	74.84 ± 18.21 (45–108.8)	0.301
Height (cm), mean + SD (range) **	165.75 ± 7.01 (158–179)	169.94 ± 9.18 (150–183)	0.157
BMI (kg/m <sup>2</sup> ), mean + SD (range) **	24.69 ± 3.50 (21–32.8)	25.82 ± 5.66 (17.8–40.0)	0.505

Note: Values are expressed as means ± standard deviation (95% confidence interval). Chi-square test \* and Student *t*-test \*\* for between group comparisons; \* *p* < 0.05.

The dominant type of treatment was chemotherapy, used in 75% of cases. Combination radiation therapy and chemotherapy was used in 6%, and combination immunotherapy and

chemotherapy in 19%. The most frequent chemotherapy administered in 80% of cases was a regimen of four drugs known as “CHOP”: cyclophosphamide, doxorubicin, vincristine and prednisone. The CHOP treatment plus the monoclonal antibody

rituximab, known as “R-CHOP”, was administered in 20% of cases.

Regarding transplants, 87.5% of patients received none, compared to 6% who received auto transplantation and another 6% who received allotransplantation. Among patients, stage VI disease was predominant in 37.5% of cases (**Table 2**).

**Table 2.** Clinical characteristics of participating non-Hodgkin lymphoma cancer patients.

Variable	Cancer Patients ( <i>n</i> = 16)
Diagnosis type of lymphoma (%) Non-Hodgkin	16
Tumor Stage (%)	
I	18.8
II	18.8
III	25.0
IV	37.5
Type of medical treatment (%)	
Radiotherapy	0.0
Chemotherapy	75.0
Radiotherapy and Chemotherapy	6.3
Chemotherapy and Immunotherapy	18.8
Type of medical transplant (%)	
Allotransplant	6.3
Autotransplant	6.3
None	87.5

Note: Values are expressed as percentages in the variables referring the lymphoma cancer patients.

## HRV Analysis

HRV analysis revealed no significant values between the lymphoma survivors' group and the healthy subjects in HRV index ( $p = 0.859$ ). (Table 3).

and educational level ( $p = 0.000$ ), alcohol ( $p = 0.032$ ), and menopausal status ( $p = 0.002$ ) for SDNN values. In the same way, the type of treatment (RMSSD  $p = 0.041$ ) and the type of medical transplant

Table 3. Comparison of the dependent variables of heart rate variability (HRV) between the study groups.

Variable	Healthy Controls ( $n = 16$ ) Mean + SD (95%CI)	Non-Hodgkin Cancer ( $n = 16$ ) Mean + SD (95%CI)	$p$ Value
Time domain			
SDNN (ms)	52.63 ± 17.05 (43.54–61.71)	38.97 ± 13.65 (31.69–46.24)	0.018 *
RMSSD (ms)	50.40 ± 18.36 (40.62–60.19)	30.72 ± 17.30 (21.5–39.94)	0.006 *
HRV index	5.81 ± 1.42 (5.05–6.57)	5.73 ± 1.14 (5.12–6.34)	0.859
Frequency domain			
LF (ms)	134.69 ± 41.51 (112.57–156.81)	168.87 ± 88.70 (121.60–216.14)	0.177
HF (ms)	138.62 ± 0.23 (121.44–155.8)	128.77 ± 57.49 (98.13–159.4)	0.555
LF/HF ratio	1.04 ± 0.464 (0.794–1.29)	1.36 ± 0.583 (1.05–1.67)	0.090

Note: ANCOVA for comparisons between interventions \*  $p < 0.05$ , SDNN = standard deviation of the normal-to-normal interval; RMSSD = root mean square of successive differences; LF = low frequency; HF = high frequency; and ANCOVA = analysis of covariance.

Significant differences were found between groups in the time domain: RMSSD ( $F = 9.74$ ,  $p = 0.004$ ) and SDNN ( $F = 6.25$ ,  $p = 0.018$ ). In the frequency domain parameters, the results were not significant: LF ( $F = 1.94$ ,  $p = 0.17$ ), HF ( $F = 0.35$ ,  $p = 0.55$ ), and LF/HF ratio ( $F = 3.07$ ,  $p = 0.09$ ).

There were statistically significant differences between groups when controlling for covariates like height (RMSSD  $p = 0.001$ ; SDNN  $p = 0.003$ ), weight (RMSSD  $p = 0.021$ ; SDNN  $p = 0.002$ ), BMI (RMSSD  $p = 0.027$ ; SDNN  $p = 0.002$ ), occupational status (RMSSD  $p = 0.045$ ; SDNN  $p = 0.015$ ), and tobacco (RMSSD  $p = 0.029$ ; SDNN  $p = 0.001$ ),

(RMSSD  $p = 0.047$ ; SDNN  $p = 0.009$ ) influenced HRV parameters. The RMSSD values in combination chemotherapy and immunotherapy treatment were higher ( $49.08 ± 17.41$ ) than in chemotherapy ( $26.76 ± 3.27$ ) or a combination of radiation therapy and chemotherapy ( $23.13 ± 0.00$ ) treatments. The allotransplant patients showed higher scores (SDNN =  $54.14 ± 0.00$ ; RMSSD =  $52.90 ± 0.00$ ) than non-transplant (SDNN =  $38.18 ± 3.73$ ; RMSSD =  $29.79 ± 4.63$ ) or auto transplant patients (SDNN =  $34.80 ± 0.00$ ; RMSSD =  $21.48 ± 0.00$ ).

## Discussion

The main finding in this study was the presence of autonomic imbalance in non-Hodgkin lymphoma survivors during their first year after completing treatment compared to healthy paired subjects, evidenced by the lower values of time domain measures in heart rate variability (SDNN and RMSSD). This imbalance could be related to either the cancer treatment received or remnants of the cancer itself in the survival stage and lifestyle (problems with cholesterol, blood pressure, obesity, among other factors) [17]. Based on the evidence, we estimate that approximately 30 to 50% of deaths caused by cancer could be avoided if risk factors such as tobacco consumption, low dietary consumption of healthy foods such as fruit and vegetables, and excess alcohol consumption, among others, had been modified or prevented [18]. One study found that among breast cancer patients treated with chemotherapy who were obese, there was a relationship between cardiovascular problems and obesity [19]. The influence of these factors is beyond the scope of this study, but deserves further research in the future in order to

prevent possible factors that could affect the survival of this population.

In consonance with the evidence presented above, our study found an influence of covariates such as height, weight, BMI, occupational status, tobacco, educational level, alcohol and menopausal status as factors significantly affecting the time domain values comparing non-Hodgkin lymphoma survivors with healthy subjects. This may reinforce the previous evidence stating the risk factors in cancer deaths, although it has shown the lifestyle, genetic or psychological state influence on HRV [20] mainly HRV reflects the cardiac vagal tone [21]. This could be the significant difference between healthy groups and those with non-Hodgkin lymphoma cancer. In terms of cancer survival, a study shows how cancer survivors are more likely to have cardiovascular risk factors, such as excess bodyweight and hypertension, compared to healthy patients [22]. Following this line of research, another study found a high incidence of cardiovascular disease in patients with breast cancer, lung cancer, and non-Hodgkin lymphoma compared to the healthy population. Patients with pre-existing cardiovascular problems did worse

compared to cancer patients without any heart disease over time [23].

Our findings show a significant difference between groups in terms of time domain in heart rate variability (HRV), thus demonstrating a sympathovagal imbalance. This connects with previous studies, where, in the first year of survival, patients with breast cancer obtained high HRV values [24]. Further research on HRV in cancer patients is needed to establish its potential for clinical follow-up in this population. Based on the results of a previous meta-analysis, HRV is a viable noninvasive tool for assessing prognoses in cancer patients [25].

We recognize that there are some limitations to this study. First, the time taken to measure HRV was 5 min instead of a 24 h observation. However, the Task Force of the Union Society of Cardiology and the American Society of Stimulation and Electrophysiology (1996) recommends the short-term method of measuring HRV as it is the most commonly used non-invasive approach in cancer patients. Second, breathing rhythm was not controlled, suggesting that simultaneous measurement of respiratory rates may provide important additional results in resting HRV [26]. Finally,

the small sample size and the uncommon gender (female) and mean age (43) of our population, limits the interpretation and the extrapolation of HRV results. Studies with large samples and a typical mean of age and sex within this population are required to establish references in cancer survivors and determine that the usefulness of HRV in the monitoring of cardiovascular health in patients with non-Hodgkin lymphoma cancer. This would greatly help to use non-pharmacological therapies such as meditation or qigong in combination with traditional medicine to correct the balance of the autonomic nervous system and further improve the prognosis of non-Hodgkin lymphoma survivors [27].

## **Conclusions**

Thus, the sample size of studied patient is too small to extrapolate a conclusion to a bigger population. Heart rate variability values were lower in non-Hodgkin lymphoma survivors in the first year after treatment than in healthy controls, suggesting a sympathovagal imbalance compared to healthy paired subjects.

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methodology design, and writing—review and editing. K.V.-R., J.C.-M. and R.R.-B.: investigation, data curation, and formal analysis. All authors have read and agreed to the published version of the manuscript.

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## References

1. World Health Organization. Latest Global Cancer Data: Cancer Burden Rises to 18.1

million New Cases and 9.6 million Cancer Deaths in 2018: GLOBOCAN. 2018. Available online:<https://www.who.int/cancer/PRGlobocanFinal.pdf> (accessed on 1 June 2021).

2. Spanish Society of Medical Oncology SEOM. Cancer Figures in Spain 2020. Available online: [https://seom.org/seomcms/images/stories/recursos/Cifras\\_del\\_cancer\\_2020.pdf](https://seom.org/seomcms/images/stories/recursos/Cifras_del_cancer_2020.pdf) (accessed on 1 June 2021).

3. World Health Organization (WHO). Estimated Number of Deaths in 2018, Spain, both Sexes, All Ages. GLOBOCAN. 2018. Available online: [https://gco.iarc.fr/today/online-analysis-table?v=2018&mode=cancer&mode\\_population=countries&population=900&populations=724&key=asr&sex=0&cancer=39&type=1&statistic=5&prevalence=0&population\\_group=16&ages\\_group%5B%5D=0&ages\\_group%5B%5D=17&group\\_cancer=1&include\\_nmssc=1&include\\_nmssc\\_other=1#collapse-group-0-4](https://gco.iarc.fr/today/online-analysis-table?v=2018&mode=cancer&mode_population=countries&population=900&populations=724&key=asr&sex=0&cancer=39&type=1&statistic=5&prevalence=0&population_group=16&ages_group%5B%5D=0&ages_group%5B%5D=17&group_cancer=1&include_nmssc=1&include_nmssc_other=1#collapse-group-0-4) (accessed on 1 June 2021).

4. Ferlay, J.; Colombet, M.; Soerjomataram, I.; Mathers, C.; Parkin, D.M.; Piñeros, M.; Znaor, A.; Bray, F. Estimating the global cancer

incidence and mortality in 2018: GLOBOCAN sources and methods. *Int. J. Cancer* 2019, 144, 1941–1953.

5. Courneya, K.S.; Sellar, C.M.; Trinh, L.; Forbes, C.C.; Stevinson, C.; McNeely, M.L.; Peddle-McIntyre, C.J.; Friedenreich, C.M.; Reiman, T. Randomized Trial of Aerobic Exercise and Sleep Quality in Lymphoma Patients Receiving Chemotherapy or No Treatments. *Cancer Epidemiol. Biomarkers Prev.* 2012, 21, 887–894.

6. Koene, R.J.; Prizment, A.E.; Blaes, A.; Konety, S.H. Shared Risk Factors in Cardiovascular Disease and Cancer. *Circulation* 2016, 133, 1104–1114.

7. Maraldo, M.V.; Giusti, F.; Vogelius, I.R.; Lundemann, M.; van der Kaaij, M.A.; Ramadan, S.; Meulemans, B.; Henry-Amar, M.; Aleman, B.M.; Raemaekers, J.; et al. Cardiovascular disease after treatment for Hodgkin's lymphoma: An analysis of nine collaborative EORTC-LYSA trials. *Lancet Haematol.* 2015, 2, e492–e502.

8. Mizia-Stec, K.; Elz'bieciak, M.; Wybraniec, M.T.; Róz' ewicz, M.; Bodys, A.; Braksator, W.; Ga\_sior, Z.; Gos'ciniak, P.; Hryniewiecki, T.; Kasprzak, J.; et al. Chemotherapy and echocardiographic indices in patients with

non-Hodgkin lymphoma: The ONCO-ECHO study. *Med. Oncol.* 2017, 35, 14.

9. Chang, H.M.; Okwuosa, T.M.; Scarabelli, T.; Moudgil, R.; Yeh, E.T.H. Cardiovascular Complications of Cancer Therapy: Best Practices in Diagnosis, Prevention, and Management: Part 2. *J. Am. Coll. Cardiol.* 2017, 70, 2552–2565.

10. Mulcahy, J.S.; Larsson, D.E.O.; Garfinkel, S.N.; Critchley, H.D. Heart rate variability as a biomarker in health and affective disorders: A perspective on neuroimaging studies. *Neuroimage* 2019, 202, 116072.

11. Guo, Y.; Palmer, J.L.; Strasser, F.; Yusuf, S.W.; Bruera, E. Heart rate variability as a measure of autonomic dysfunction in men with advanced cancer. *Eur. J. Cancer Care (Engl.)* 2013, 22, 612–616.

12. Malik, M.; Bigger, J.T.; Camm, A.J.; Kleiger, R.E.; Malliani, A.; Moss, A.J.; Schwartz, P.J. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur. Heart J.* 1996, 17, 354–381.

13. Kuo, T.B.; Lai, C.J.; Huang, Y.T.; Yang, C.C.H. Regression analysis between heart rate variability and baroreflex-related vagus nerve activity in rats. *J. Cardiovasc. Electrophysiol.* 2005, 16, 864–869.
14. Buccelletti, E.; Gilardi, E.; Scaini, E.; Galiuto, L.; Persiani, R.; Biondi, A.; Basile, F.; Silveri, N.G. Heart rate variability and myocardial infarction: Systematic literature review and metanalysis. *Eur. Rev. Med. Pharmacol. Sci.* 2009, 13, 299–307.
15. Zhou, X.; Ma, Z.L.; Zhang, L.F.; Zhou, S.Z.; Wang, J.L.; Wang, B.Y.; Fu, W. Heart rate variability in the prediction of survival in patients with cancer: A systematic review and meta-analysis. *J. Psychosom. Res.* 2016, 89, 20–25.
16. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: Standards of measurements, physiological interpretation and clinical use. *Eur. Heart J.* 1996, 17, 354–381.
17. Al-Khatib, S.M.; Stevenson, W.G.; Ackerman, M.J.; Bryant, W.J.; Callans, D.J.; Curtis, A.B.; Deal, B.J.; Dickfeld, T.; Field, M.E.; Fonarow, G.C.; et al. 2017 AHA/ACC/HRS Guideline for Management of patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J. Am. Coll. Cardiol.* 2018, 72, e91–e220.
18. Salas, D.; Peiró, R. Evidence on the prevention of cancer. *Rev. Esp. Sanid. Penit.* 2013, 15, 66–75.
19. Aeschbacher, S.; Bossard, M.; Ruperti Repilado, F.J.; Good, N.; Schoen, T.; Zimny, M.; Probst-Hensch, N.M.; Schmidt-Trucksäss, A.; Risch, M.; Risch, L.; et al. Healthy lifestyle and heart rate variability in young adults. *Eur. J. Prev. Cardiol.* 2016, 23, 1037–1044.
20. Thayer, J.F.; Ahs, F.; Fredrikson, M.; Sollers, J.J., III; Wager, T.D. A meta-analysis of heart rate variability and neuroimaging studies: Implications for heart rate variability as a marker of stress and health. *Neurosci. Biobehav. Rev.* 2012, 36, 747–756.
21. Kaboré, E.G.; Guenancia, C.; Vaz-Luis, I.; Di Meglio, A.; Pistilli, B.; Coutant, C.; Cottu, P.; Lesur, A.; Petit, T.; Dalenc, F.; et al. Association of body mass index and cardiotoxicity related to anthracyclines and

trastuzumab in early breast cancer: French CANTO cohort study. *PLoS Med.* 2019, 16, e1002989.

22. Armenian, S.H.; Lacchetti, C.; Barac, A.; Carver, J.; Constine, L.S.; Denduluri, N.; Dent, S.; Douglas, P.S.; Durand, J.B.; Ewer, M.; et al. Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J. Clin. Oncol.* 2017, 35, 893–911.

23. Armenian, S.H.; Xu, L.; Ky, B.; Sun, C.; Farol, L.T.; Pal, S.K.; Douglas, P.S.; Bhatia, S.; Chao, C. Cardiovascular Disease Among Survivors of Adult-Onset Cancer: A Community-Based Retrospective Cohort Study. *J. Clin. Oncol.* 2016, 34, 1122–1130.

24. Caro-Morán, E.; Fernández-Lao, C.; Galiano-Castillo, N.; Cantarero-Villanueva, I.; Arroyo-Morales, M.; Díaz-Rodríguez, L. Heart Rate Variability in Breast Cancer Survivors After the First Year of Treatments: A Case-Controlled Study. *Biol. Res. Nurses.* 2016, 18, 43–49.

25. Kloter, E.; Barrueto, K.; Klein, S.D.; Scholkmann, F.; Wolf, U. Heart Rate Variability as a Prognostic Factor for Cancer

Survival—A Systematic Review. *Front. Physiol.* 2018, 9, 623.

26. Druschky, K.; Lorenz, J.; Druschky, A. Effects of Respiratory Rate on Heart Rate Variability in Neurological Outpatients with Epilepsies or Migration: A Preliminary Study. *Med. Pract.* 2020, 29, 318–325.

27. Díaz-Rodríguez, L.; Vargas-Román, K.; Sanchez-Garcia, J.C.; Rodríguez-Blanco, R.; Cañadas-De la Fuente, G.A.; De La Fuente-Solana, E.I. Effects of Meditation on Mental Health and Cardiovascular Balance in Caregivers. *Int. J. Environ. Res. Public Health* 2021, 18, 617.

# STUDY III

EFFECT OF A 16-SESSION QIGONG PROGRAM IN  
NON-HODGKIN LYMPHOMA SURVIVORS: A RANDOMIZED  
CLINICAL TRIAL

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## **STUDY III. Effect of a 16-Session Qigong Program in Non-Hodgkin Lymphoma Survivors: A Randomized Clinical Trial**

### **ABSTRACT**

**Purpose:** The treatment associated with non-Hodgkin lymphoma patients may cause adverse effects on their physical and psychological condition. The aim of this study is to detect the response to an eight-week, 16-session, 60-min presential Qigong program in anxiety, depression and vagal nerve activity alongside a control group.

**Materials and Methods:** A randomized controlled clinical trial was managed. Randomization was carried out by generating a numerical sequence of three cycles through the software EPIDAT 4.1. Numbers were placed in sealed opaque envelopes for assignment to the different groups.

**Results:** Anxiety levels were substantially decreased in the experimental group, with a large effect size ( $F = 30.38, p < 0.00$ ). Depression levels had an improvement in the experimental group in contrast to the control group, reaching statistical significance ( $F = 19.19, p < 0.00$ ). Heart Rate Variability unveiled significant results in terms of between-group differences, with a

large effect size in the HRV Index ( $F = 15.80, p < 0.00$ ), SDNN ( $F = 8.82, p < 0.00$ ), and RMSSD ( $F = 6.72, p < 0.01$ ) in the time domain, and a medium effect size in the HF ( $F = 9.78, p < 0.003$ ), LF ( $F = 9.78, p < 0.00$ ), and LF/HF Ratio ( $F = 18.44, p < 0.00$ ) in the frequency domain, which were all bettered in the experimental group, after the Qigong program.

**Conclusions:** Qigong therapy can be an effective therapeutic activity in consonance with traditional medicine to improve psychological health and autonomic nervous system balance in non-Hodgkin lymphoma survivors.

## Introduction

Cancer is a broad group of illnesses that can start in practically any organ or tissue of the body when abnormal cells grow uncontrollably, breaching adjacent parts of the body or escalating to other organs [1]. Non-Hodgkin lymphoma had 544,352 new cases worldwide in 2020 in both genders according to the world health organization in the category of global hematic cancers. It ranks in the eleventh position among other types of cancers in 2020. In terms of its fatality rate, non-Hodgkin lymphoma cancer had 259,793 cases in 2020 in both genders worldwide [2].

In Spain, in 2020, non-Hodgkin lymphoma within blood cancers, was one of the highest diagnosed, being in the top nine positions. The estimated number of cases in Spain in 2020 was 66,733 [3]. Mortality from this tumor has reduced since the late 1990s, at a rate of 3% less mortality each year, showing a clear advancement in the efficiency of treatments [4].

The conventional medical treatments for non-Hodgkin lymphoma are chemotherapy and mother cells or bone marrow transplants [5]. These therapies may have

high inimical consequences such as anxiety, depression, the loss of physical health, and a high risk of heart failure; these difficulties lead to a deteriorating quality of life [6]. Advances in the biomedical field have made improvements in the understanding of the origin of various cancers, along with treatments and prevention strategies [7]. Prevention is necessary in order to avoid possible risks in the development of cancer in general, including a good diet, exercise, and good sleep quality.

However, those patients who are already diagnosed need a treatment strategy to mitigate the symptoms of their cancer or its treatment. Symptoms may also include an imbalance in the autonomic nervous system, which is integrated by the sympathetic and parasympathetic nervous systems [8]. These are in addition to the vagus nerve responsible for the regulation of mood status, the immune system and heart rate [9]. Heart rate variability is the synergy between the autonomic nervous system and the cardiovascular system, which serves as a noninvasive biomarker of health [10]. Diminished heart rate variability (HRV) has been noted to be related to cardiac autonomic dysfunction [11].



Previous studies have shown an association between non-Hodgkin lymphoma and low HRV [12], which could be caused by the conventional medical treatment.

Complementary and integrative medicine treatments, including physical activity, yoga/Tai Chi, and meditation, in addition to traditional oncology treatment, may have a beneficial influence on psychological affliction, anxiety, pain, fatigue, and sleep disruption, leading to a bettered QoL in cancer patients [13]. In addition to the activities mentioned before, another mind–body exercise that is becoming popular is the Qigong. Qigong was originally developed in China, and is deeply rooted in traditional Chinese medicine. It involves a collection of precise and placid movements, and integrates the regulation of the breath and body control [14]. Studies have shown the benefits of practicing Qigong, improving fatigue, sleep quality, anxiety, depression and cardiotoxicity in cancer patients and non-Hodgkin lymphoma [14–16].

To our best knowledge, presently, there is no Qigong study that has targeted survivors with non-Hodgkin lymphoma for the betterment of patient heart rate variability (HRV), anxiety and depression outcomes.

Therefore, the aim of the present study was to detect the effects of an eight-week presential Qigong program of 60 min on psychological parameters and vagal nerve activity with regard to non-Hodgkin lymphoma, and to compare the results with a control group that did not participate in the program.

## **Materials and Methods**

### **Study Design**

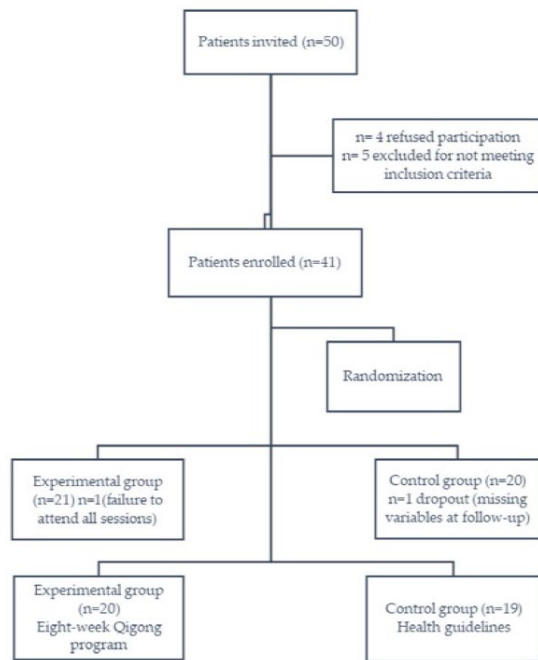
A randomized, single-blinded, controlled trial was conducted on non-Hodgkin lymphoma survivors. Randomization was carried out by generating a numerical sequence of 3 cycles through the software EPIDAT 4.1. The numbers were placed in sealed opaque envelopes for assignment to the different groups. Informed consent was collected from all of the candidates in the study, which was authorized by the local research ethics committee (CEI-GRC-9) and ensued the principles of the Declaration of Helsinki. The trial protocol is registered at ClinicalTrials.gov (NCT04701554).

### **Setting and Selection of the Participants**

Patients from the Oncology Unit in the University Hospital Virgen de las Nieves in

the province of Granada city was reached by the researchers face-to-face, by telephone, and by social media (Facebook, Instagram and Twitter). The inclusion criteria were a primary diagnosis of non-Hodgkin lymphoma cancer (Grades I–IIIa), being of any gender, being 18 years old or older, and having completed the primary section of traditional cancer treatment (chemotherapy, radiotherapy, surgery

the patients to the control or intervention groups. The flow of the participants through the study is shown in **Figure 1**. A single researcher (K.V.-R.) reached the participants by telephone, in order to collect epidemiological data related to their medical history and demographic characteristics, including their age, gender, race, social status, education level, occupation, alcohol and smoking customs, menopause status, type of cancer treatment, transplantation situation, cancer stage, weight, and height.



**Figure 1.** Flow of the participants. and/or immunotherapy) previously within 6 months to 1 year. The exclusion criteria for this study were the existence of metastasis and/or active cancer, a history of cardiovascular disease, and taking medications known to alter vagus nerve activity. Randomization was used to allocate

### Control Group

The control group obtained advice on healthy habits, physical activity and dietary suggestions.

### Experimental Group

The experimental group took part in the Qigong course over an interim of 2 months, for 16 sessions, with a total of 16 h.

### Qigong Training Program

A meditation coach with more than a decade of knowledge ran a Qigong program at the Wudang Shan Center in Granada city. The non-Hodgkin survivors had an initial encounter with the instructor to talk about the Qigong program, emphasizing the

concentration techniques, coordinated musculoskeletal movements, and diaphragmatic breathing.

Over an eight-week period, two times a week, 60-min sessions—for a total of 16 h—were conducted each Tuesday and Friday in the afternoon. Ultimately, the objective was to learn how to focus attention on the breathing techniques and improving physical function.

Each 60-min session started with a confirmation sheet, and a brief consultation session of about 10 min to answer questions related to the Qigong practice. This was followed by 20 min of mild elongation and body motion in standing postures to trigger the body along the energy channels, and 10 min of motion in a seated posture (a Nei Yang Gong exercise for inner nurture, relaxing the head, neck, shoulders, waist, lower back, legs, and feet, and imagining an inner smile while in this posture). This concluded with 20 min of meditation, including breathing exercises, starting with abdominal breathing, chest breathing to bring energy regulation, relaxation, and the feeling of the Qi (vital energy). The researcher (K.V.-R.) reached the candidates weekly, by telephone, to send the

participants reminders of their Qigong practices.

### **Sample Size Calculation**

In order to estimate the sample size for statistical power, the EPIDAT 4.1 software (Xunta de Galicia, Santiago, Spain) was used. This was 80% with a 5% level of significance, based on formerly divulged data [14]. A margin sample size of 20 individuals per group was determined.

### **Outcome Measures**

The data collection took place between week zero and the eighth week after the Qigong program. Both data collections were carried out by a single researcher (K.V.-R).

### **Hospital Anxiety and Depression Scale (HADS) Score**

This authorized self-administered questionnaire is intended to detect the potential existence of anxiety and depression. It contains 14 items that equally measure anxiety and depression, with responses on a 4-point Likert scale (0–3); the responses are related to how the patient felt in the previous week [17].

### **Short-Term HRV**

The participants first lay reclined in a quiet room (22–25 C) for 10 min of cessation with normal breathing timed by a 0.2 Hz metronome. ECG signals were then acquired for 5 min using a Holter monitor with a fitted shunt channel II system (Norav Holter NR302, Braemar, Brunsville, MN, USA). Heart Rate Variability was computed from ECG recordings as the time interval between successive heart beats (RR interval). The following time-domain parameters were determined: the standard deviation of the mean normal-to-normal (NN) interval (SDNN), the square root mean square differences of successive NN intervals (RMSSD), and the number of all NN intervals divided by the maximum of all NN intervals (HRV index). The following spectral components were determined in the frequency domain: the low-frequency (LF) band (0.04–0.15 Hz), as a measure of sympathetic and parasympathetic activities; the high-frequency (HF) band (0.15 to 0.40 Hz), which is associated with vagal-parasympathetic activity; and the LF/HF ratio, which indicates sympathovagal balance. Spectral analysis was performed with the NH301-4 software (Norav, version

2.70), using fast Fourier transform algorithms. All of this procedure followed the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, as published by Kuppussamy (2020) [18,19].

### **Statistical Analysis**

For the statistical analysis, IBM-SPSS 26.0 was used. The results were defined as means with standard deviations for continuous variables, and percentages with 95% confidence intervals for categorical variables. t-tests and chi-square tests were performed for the continuous and categorical variables' between-group differences at the baseline. The Shapiro–Wilk test was used to verify the data distribution normality. An ANCOVA test was performed to measure possible influences between covariates and baseline variables during the pre- and post-interventions, including the control and experimental groups.

### **Results**

Initially, fifty patients enrolled in this study, and eleven survivors didn't finalize the program. This left a final sample of 39 non-

Hodgkin survivors, with 19 females and 20 males, with a mean (SD) age of 44.49 (10.60) years, a mean height of 170.21 (8.22) cm, a mean weight of 65.55 (9.06) kg, and therefore a mean BMI of 24.75 (4.21) kg/m<sup>2</sup>. All of the candidates except one were Caucasian, 51.3% were married, 48.7% had completed middle education, 43.6% were unemployed, 69.2% were non-smokers, 66.7% did not consume alcohol, 43.6% were in cancer stage II, 74.4% received chemotherapy, and only two patients had received transplants (Allotransplant). The only statistically significant difference in the above variables among the experimental (n = 20) and control (n = 19) groups was in the BMI, with a higher index in the control group versus the experimental group (**Table 1**).

Table 1. Sample characteristics and comparison between the study groups.

Variables	Control Group (n = 19)	Qigong Group (n = 20)	p
Age (y) Mean (SD) **	43.74 ± 10.53 (22–60)	45.20 ± 10.88 (23–68)	0.67
Gender (%) *			0.86
Female	47.4	50.0	
Male	52.6	50.0	
Ethnicity (%) *			0.32
Caucasian	100	95.0	
Other	0	5.0	
Marital status (%) *			0.83
Single	21.1	20.0	
Married	52.6	50.0	
Divorced	10.5	5.0	
Lives with partner	15.8	20.0	
Widowed	0	5.0	
Educational level (%) *			0.52
Primary studies	15.8	25.0	
Secondary studies	57.9	4.0	
Higher education	26.3	35.0	
Occupational status (%) *			0.20
Homemaker	10.5	0	
Employed	42.1	20.0	
Unemployed	31.6	55.0	
Retired	15.8	20.0	
Other	0	5.0	
Smoking Status (%) *			0.14
Smoker	0	10.0	
Non-smoker	63.2	75.0	
Ex-smoker	36.8	15.0	
Alcohol status (%) *			0.26
Don't consume	57.9	75.0	
Consume monthly	31.6	25.0	
Consume weekly	10.5	0	
Menopausal status (%) *			0.93
NO	78.9	80.0	
YES	21.1	20.0	
Type of treatment (%) *			0.31
Chemotherapy	68.4	80.0	
Radiotherapy	10.5	15.0	
Immunotherapy	21.1	5.0	
Cancer Stage (%) *			0.74
I	15.8	20.0	
II	36.8	50.0	
III	15.8	10.0	
IV	31.6	20.0	
Transplants (%) *			0.97
Autologous transplant	0	0	
Allotransplant	5.3	5.0	
No transplant	94.7	95.0	
Weight (kg) Mean (SD) **	72.04 ± 8.94 (56–84)	67.18 ± 8.74 (45–81)	0.09
Height (cm) Mean (SD) **	172.47 ± 7.60 (159–186)	168.05 ± 8.40 (150–180)	0.09
Body Mass Index Mean ** (Kg/m <sup>2</sup> ) (SD)	26.48 ± 4.23 (18–40)	23.10 ± 3.55 (17.8–32.4)	0.01 *

Values are expressed as means ± standard deviation (95% confidence interval). The Chi-square test \* and Student *t*-test \*\* were used for between-group comparisons; \* *p* < 0.05.

In the experimental group, the anxiety levels were substantially decreased, with a large effect size ( $F = 30.38, p < 0.00$ ) (Table 2). The depression levels had an improvement in the experimental group in contrast to the control group, reaching statistical significance ( $F = 19.19, p < 0.00$ ). Heart Rate Variability unveiled significant results in terms of between group differences, with a

large effect size in the HRV Index ( $F = 15.80, p < 0.000$ ), SDNN ( $F = 8.82, p < 0.00$ ), and RMSSD ( $F = 6.72, p < 0.01$ ), in the time domain, and a medium effect size in the HF ( $F = 9.78, p < 0.00$ ), LF ( $F = 9.78, p < 0.00$ ), and LF/HF Ratio ( $F = 18.44, p < 0.00$ ) in the frequency domain, which were all bettered in the experimental group, after the Qigong

**Table 2.** Before- and after-treatment comparison between the outcomes.

Outcomes	Control Group ( $n = 19$ )	Qigong Group ( $n = 20$ )	F	<i>p</i>
<b>Hospital Anxiety Depression Scale values</b>				
Anxiety				
Baseline	6.32 ± 4.30	8.35 ± 4.67	30.38	0.00 *
Post-treatment	7.0 ± 4.35	4.00 ± 3.8		
Depression				
Baseline	3.47 ± 2.59	4.55 ± 3.28	19.19	0.00 *
Post-treatment	3.47 ± 2.93	2.65 ± 2.79		
<b>Heart Rate Variability</b>				
SDNN				
Baseline	68.92 ± 49.21	61.86 ± 44.56	8.82	0.00 *
Post-treatment	67.99 ± 66.54	123.40 ± 92.71		
RMSSD				
Baseline	50.87 ± 34.62	72.60 ± 47.33	6.72	0.01 *
Post-treatment	54.31 ± 35.81	140.53 ± 107.19		
HRV index				
Baseline	11.67 ± 3.88	9.80 ± 4.89	15.80	0.00 *
Post-treatment	10.14 ± 4.63	15.26 ± 4.98		
LF				
Baseline	308.64 ± 313.33	1016.76 ± 1148	11.77	0.00 *
Post-treatment	553.76 ± 399.26	405.29 ± 427.22		
HF				
Baseline	497.38 ± 476.11	268.13 ± 345.10	9.78	0.00 *
Post-treatment	380.44 ± 445.67	609.25 ± 448.42		
LF/HF RATIO				
Baseline	1.48 ± 1.93	6.27 ± 6.67	18.44	0.00 *
Post-treatment	5.25 ± 6.60	1.11 ± 1.38		

For comparisons between the interventions, \*  $p < 0.05$  SDNN = standard deviation of the normal-to-normal interval; RMSSD = root mean square of successive differences; LF = low frequency; HF = high frequency. ANCOVA = analysis of covariance was performed.

program (**Table 2**). Covariates had no influence on these results.

## **Discussion**

To our understanding, this is the first controlled trial to evidence the progression of the cardiovascular balance and psychological health of non-Hodgkin survivors after an eight-week Qigong program of 60 min per session twice a week (16 sessions in total), in contrast to a control group. Once the program ended, the non-Hodgkin lymphoma survivors demonstrated a decrease in anxiety and depression, and higher heart rate variability markers.

All of these compiled data add weight to past studies that demonstrated the effectiveness of complementary therapies by improving the heart rate variability in cancer survivors [16]. Regarding mental health, including anxiety and depression, other study emphasized the use of meditation therapies like mindfulness, which lowered these parameters in cancer patients [20]. It was previously found that an eight-week Qigong program reduced anxiety and depression in breast cancer survivors [15]. This confirmed that with traditional medical treatment and complementary therapies, patients can

reduce their levels of anxiety and depression, and better their cardiovascular balance caused by the stress of the disease itself or the impact of medical treatments in the patients.

Moreover, past studies have shown that vagal activity in cancer patients tends to be impaired in comparison to healthy people [21]. Additionally, a previous case-controlled study described the cardiovascular imbalance in breast cancer survivors compared to gender-matched controls [22]. This difference might be explained by the emotional distress associated with the cancer [23]. In a recent published meta-analysis, it was shown that lymphoma patients are liable to suffer anxiety, mainly due to the remission stage of their disease or caused by the treatment itself [24]. This can explain the studies showcasing the fact that people are turning to non-pharmacological and non-conventional interventions [21] to battle the mental outcomes and physical problems that cancer diseases might cause.

Our results indicated that our non-Hodgkin survivors had reduced anxiety and depression levels after the Qigong sessions; this is in consonance with a previous study showing that an intervention with medical



Qigong led to better mood status, specifically decreasing the anxiety and depression in cancer patients [25]. In the present research, the existence of anxiety correlated with a lower HRV value. Another significant finding is that a correlation between depression and HRV was present: the higher the depression, the lower the HRV values, confirming the relationship between good mental health and HRV. In the time domain, the SDNN, RMSSD, and HRV index values were substantially larger after the Qigong program, in comparison to controls who didn't participated. Similar findings were reported in previous studies with cancer patients and a mindfulness therapy [20].

The positive effects of Qigong therapy regarding the improvement of mental health and HRV were previously described [14–16,26]. However, this is the first controlled clinical trial that demonstrated the improvement of psychological health and cardiovascular balance produced by a Qigong program in lymphoma patients, with a significant reduction in anxiety and depression, and an improvement in heart rate variability values.

Some study limitations that need to be included are, firstly, the sample size of the subjects, which reduces the extent to which the results can be extrapolated. The follow-up was quite short, and it is unknown whether the patients followed the therapeutic practice alone. The ethnicity was, in the majority, Caucasian in both groups; given the high diversity of ethnicities in Spain, the sample should have been more diverse. We should finalize with the stipulation that a larger sample size might confirm the improvement, such that the results can be extrapolated to a bigger population in future research.

## **Conclusions**

An eight-week Qigong program of 60 min per session twice a week with a total of 16 sessions might be an effective way to improve the psychological health and cardiovascular balance in non-Hodgkin lymphoma survivors. This would work by reducing anxiety, depression, and heart rate variability parameters. Future clinical trials are assured to certify the effectiveness of a Qigong program to improve the quality of life of non-Hodgkin lymphoma survivors.

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**Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki, and was approved by the local research ethics committee (CEI-GRC-9).

**Informed Consent Statement:** Informed consent was obtained from all of the subjects involved in the study.

**Data Availability Statement:** Data is contained within the article.

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## References

1. World Health Organization. Cancer. Available online: <https://www.who.int/cancer/en> (accessed on 18 March 2022).
2. World Health Organization WHO. Estimated Number of New Cases in 2020, Worldwide, Both Sexes, All Ages: GLOBOCAN. 2020. Available online: <https://gco.iarc.fr/today/data/factsheets/populations/900-world-fact-sheets.pdf> (accessed on 18 March 2022).
3. World Health Organization WHO. Estimated Number of New Cases in 2020, Europe, Worldwide, Spain, Both Sexes, All Ages: GLOBOCAN. 2020. Available online: <https://gco.iarc.fr/today/online-analysis-table?v=2020> (accessed on 18 March 2022).
4. Bosetti, C.; Levi, F.; Ferlay, J.; Lucchini, F.; Negri, E.; La Vecchia, C. Incidence and mortality from non-Hodgkin lymphoma in

Europe: The end of an epidemic? *Int. J. Cancer* 2008, 123, 1917–1923.

5. Ferlay, J.; Colombet, M.; Soerjomataram, I.; Mathers, C.; Parkin, D.M.; Piñeros, M.; Znaor, A.; Bray, F. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int. J. Cancer* 2019, 144, 1941–1953.

6. Courneya, K.S.; Sellar, C.M.; Trinh, L.; Forbes, C.; Stevinson, C.; McNeely, M.; Peddle-McIntyre, C.; Friedenreich, C.; Reiman, T. Randomized Trial of Aerobic Exercise and Sleep Quality in Lymphoma Patients Receiving Chemotherapy or No Treatments. *Cancer Epidemiol. Biomark. Prev.* 2012, 21, 887–894.

7. Parra, M.T.; Esmeaeli, N.; Kohn, J.; Henry, B.L.; Klagholz, S.; Jain, S.; Pruitt, C.; Vicario, D.; Jonas, W.; Mills, P.J. Greater Well-Being in More Physically Active Cancer Patients Who Are Enrolled in Supportive Care Services. *Integr. Cancer Ther.* 2020, 19, 1534735420921439.

8. Teixeira, R.J.; Remondes-Costa, S.; Graça Pereira, M.; Brandão, T. The impact of informal cancer caregiving: A literature review on psychophysiological studies. *Eur. J. Cancer Care* 2019, 28, e13042.

9. Díaz-Rodríguez, L.; Vargas-Román, K.; Sanchez- Garcia, J.C.; Rodríguez-Blaque, R.; Cañadas-De la Fuente, G.A.; De La Fuente-Solana, E.I. Effects of Meditation on Mental Health and Cardiovascular Balance in Caregivers. *Int. J. Environ. Res. Public Health* 2021, 18, 617.

10. Mulcahy, J.S.; Larsson, D.E.O.; Garfinkel, S.N.; Critchley, H.D. Heart rate variability as a biomarker in health and affective disorders: A perspective on neuroimaging studies. *NeuroImage* 2019, 202, 116072.

11. Ha, J.; Baek, H.; Jeong, C.; Yeo, M.; Lee, S.-H.; Cho, J.H.; Baek, K.-H.; Kang, M.I.; Lim, D.-J. Heart Rate Variability in Postoperative Patients with Nonfunctioning Pituitary Adenoma. *Endocrinol. Metab.* 2021, 36, 678–687.

12. Vargas-Román, K.; Cortés-Martín, J.; Sánchez-García, J.C.; Rodríguez-Blaque, R.; De La Fuente-Solana, E.I.; Díaz-Rodríguez, L. Autonomic Imbalance in Lymphoma Survivors. *J. Clin. Med.* 2021, 10, 4391.

13. Adams, M.; Jewell, A.P. The use of complementary and alternative medicine by cancer patients. *Int. Semin. Surg. Oncol.* 2007, 4, 10.

14. Chuang, T.Y.; Yeh, M.L.; Chung, Y.C. A nurse facilitated mind-body interactive exercise (Chan-Chuang Qigong) improves the health status of non-Hodgkin lymphoma patients receiving chemotherapy: Randomized controlled trial. *Int. J. Nurs. Stud.* 2017, 69, 25–33.
15. Soltero, E.G.; Larkey, L.K.; Kim, W.S.; Rosales Chavez, J.B.; Lee, R.E. Latin dance and Qigong/Tai Chi effects on physical activity and body composition in breast cancer survivors: A pilot study. *Complement. Ther. Clin. Pract.* 2022, 47, 101554.
16. Fong, S.S.; Wong, J.Y.; Chung, L.M.; Yam, T.T.; Chung, J.W.; Lee, Y.; Chow, L.P.; Luk, W.; Ng, S.S. Changes in heart-rate variability of survivors of nasopharyngeal cancer during Tai Chi Qigong practice. *J. Phys. Ther. Sci.* 2015, 27, 1577–1579.
17. Hyland, K.A.; Hoogland, A.; Gonzalez, B.D.; Nelson, A.M.; Lechner, S.; Tyson, D.M.; Barata, A.; Gomez, M.F.; Antoni, M.H.; Small, B.; et al. Evaluation of the Psychometric and Structural Properties of the Spanish Version of the Hospital Anxiety and Depression Scale in Latina Cancer Patients. *J. Pain Symptom Manag.* 2019, 58, 289–296.e2.
18. Kuppusamy, M.; Kamaldeen, D.; Pitani, R.; Amaldas, J.; Ramasamy, P.; Shanmugam, P.; Vijayakumar, V. Effects of yoga breathing practice on heart rate variability in healthy adolescents: A randomized controlled trial. *Integr. Med. Res.* 2020, 9, 28–32.
19. Malik, M.; Bigger, J.T.; Camm, A.J.; Kleiger, R.E.; Malliani, A.; Moss, A.J.; Schwartz, P.J. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Eur. Heart J.* 1996, 17, 354–381.
20. Park, H.; Oh, S.; Noh, Y.; Kim, J.Y.; Kim, J.H. Heart Rate Variability as a Marker of Distress and Recovery: The Effect of Brief Supportive Expressive Group Therapy with Mindfulness in Cancer Patients. *Integr. Cancer Ther.* 2018, 17, 825–831.
21. De Couck, M.; Gidron, Y. Norms of vagal nerve activity, indexed by Heart Rate Variability, in cancer patients. *Cancer Epidemiol.* 2013, 37, 737–741.
22. Caro-Morán, E.; Fernández-Lao, C.; Galiano-Castillo, N.; Cantarero-Villanueva, I.; Arroyo-Morales, M.; Díaz-Rodríguez, L.

Heart Rate Variability in Breast Cancer Survivors After the First Year of Treatments: A Case-Controlled Study. *Biol. Res. Nurs.* 2016, 18, 43–49.

23. Renna, M.E.; Shrouf, M.R.; Madison, A.A.; Bennett, J.M.; Malarkey, W.B.; Emery, C.F.; Kiecolt-Glaser, J.K. Distress disorder histories predict HRV trajectories during and after stress. *Psychoneuroendocrinology* 2022, 135, 105575.

24. Vargas-Román, K.; Díaz-Rodríguez, C.L.; Cañadas-De la Fuente, G.A.; Gómez-Urquiza, J.L.; Ariza, T.; De la Fuente-Solana, E.I. Anxiety prevalence in lymphoma: A systematic review and meta-analysis. *Health Psychol.* 2020, 39, 580–588.

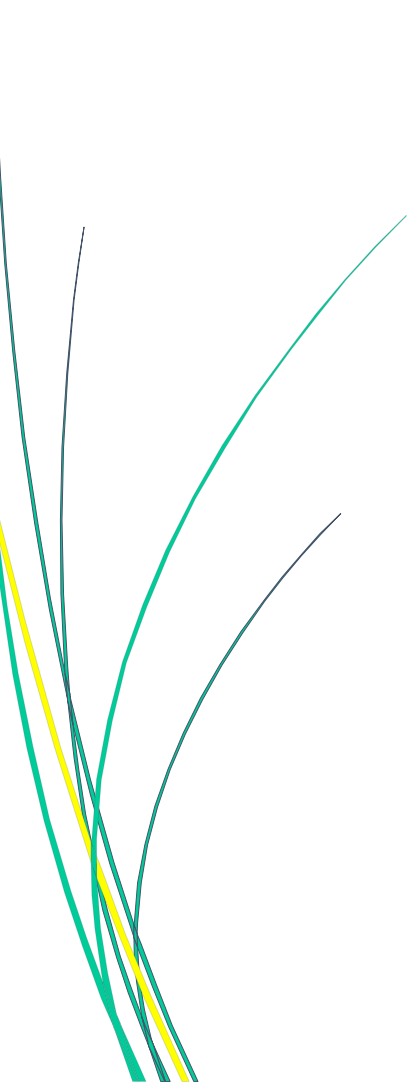
25. Saeed, S.A.; Cunningham, K.; Bloch, R.M. Depression and Anxiety Disorders: Benefits of Exercise, Yoga, and Meditation. *Am.Fam. Physician* 2019, 99, 620–627.

26. Oh, B.; Butow, P.; Mullan, B.; Clarke, S.; Beale, P.; Pavlakis, N.; Kothe, E.; Lam, L.; Rosenthal, D. Impact of medical Qigong on quality of life, fatigue, mood and inflammation in cancer patients: A randomized controlled trial. *Ann. Oncol.* 2010, 21, 608–614.



# LIMITACIONES GLOBALES

GLOBAL LIMITATIONS







## LIMITACIONES GLOBALES

Esta Tesis Doctoral presenta una serie de limitaciones que se fueron planteando a lo largo de los diferentes estudios propuestos. Las mismas se han mencionado con anterioridad, pero es necesario resumirlas en este apartado para que los resultados sean apreciados en este ámbito.

Primeramente, la revisión sobre la prevalencia de ansiedad en pacientes con linfoma, la mayoría de los estudios utilizaron el HADS para los pacientes. Esta prueba se realiza en un formato que es universal, a cualquier tipo de población, sin embargo, no toma en consideración aspectos específicos de esta enfermedad. Será interesante tener una adaptación de este cuestionario con aspectos de ansiedad Hodgkin y No Hodgkin. Si tal adaptación es posible, los futuros investigadores podrán concluir preocupaciones más detalladas sobre la ansiedad en pacientes Hodgkin y no Hodgkin. Otra limitación fue el idioma, ya que solo utilizamos revisiones escritas en inglés, otros estudios podrían incluir características similares utilizadas en este estudio; así ayudarnos a ampliar el tamaño de la población utilizada en este análisis. Se

necesita investigación adicional para recopilar más información sobre estas variables que no se consideraron, para saber qué otros factores desencadenan la ansiedad entre los pacientes.

Respecto al estudio descriptivo de la variabilidad de la frecuencia cardíaca en pacientes con linfoma Reconocemos que existen algunas limitaciones en este estudio. En primer lugar, el tiempo necesario para la medida HRV fue de 5 min en lugar de una observación de 24 h. Sin embargo, el Grupo de Trabajo de la Unión Sociedad de Cardiología y Sociedad Americana de Estimulación y Electrofisiología (1996) recomienda el método a corto plazo para medir la HRV, ya que es el más utilizado método no invasivo en pacientes con cáncer. En segundo lugar, no se controló el ritmo de la respiración, lo que sugiere que la medición simultánea de las frecuencias respiratorias puede proporcionar resultados adicionales en la VFC en reposo [26]. Finalmente, el pequeño tamaño de la muestra y el poco común género (femenino) y edad media (43) de nuestra población, limita la interpretación y la extrapolación de los resultados de HRV. Estudios con muestras grandes y una media típica de edad y sexo

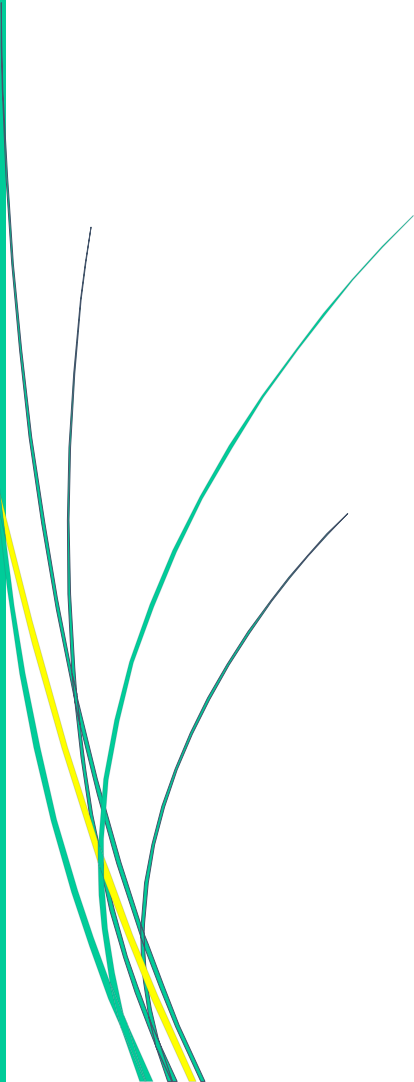
dentro de esta población son necesarios para establecer referencias en sobrevivientes de cáncer y determinar que la utilidad de la HRV en el seguimiento de la salud cardiovascular en pacientes con cáncer de linfoma no Hodgkin. Esto sería de gran ayuda para el uso no farmacológico terapias como la meditación o el Qigong en combinación con la medicina tradicional para corregir el equilibrio del sistema nervioso autónomo y mejorar aún más el pronóstico de no sobrevivientes de linfoma de Hodgkin [27].

Concluyendo con el estudio aleatorizado controlado del efecto del Qigong en supervivientes con linfoma, algunas

limitaciones del estudio que es necesario incluir son, en primer lugar, el tamaño de la muestra de los sujetos, lo que reduce el grado de extrapolación de los resultados. el seguimiento fue bastante breve, y se desconoce si los pacientes siguieron la práctica terapéutica solo. La etnia fue, en su mayoría, caucásica en ambos grupos; dada la gran diversidad de etnias en España, la muestra debería haber sido más diversa. Debemos finalizar con la estipulación de que un tamaño de muestra más grande podría confirmar la mejora, de modo que el los resultados pueden extrapolarse a una población más grande en futuras investigaciones.

# FUTURAS LÍNEAS DE INVESTIGACIÓN

FUTURE RESEARCH DIRECTIONS





## **FUTURAS LÍNEAS DE INVESTIGACIÓN**

A partir de los resultados obtenidos en esta Tesis Doctoral, se plantean diferentes líneas de investigación, dirigidas a mejorar la calidad de vida de los pacientes con linfoma, ayudando con la prevención de las secuelas provocadas por los tratamientos oncológicos actuales.

- Describir las características físicas y psico-neuroendocrino-inmunológicas de los pacientes con linfoma tras finalizar el tratamiento coadyuvante. Añadiendo biomarcadores como la saliva para medir los niveles de cortisol, el cual es un índice clave para analizar el estrés en los pacientes.
- Incluir pacientes con linfoma Hodgkin con el fin de ampliar el

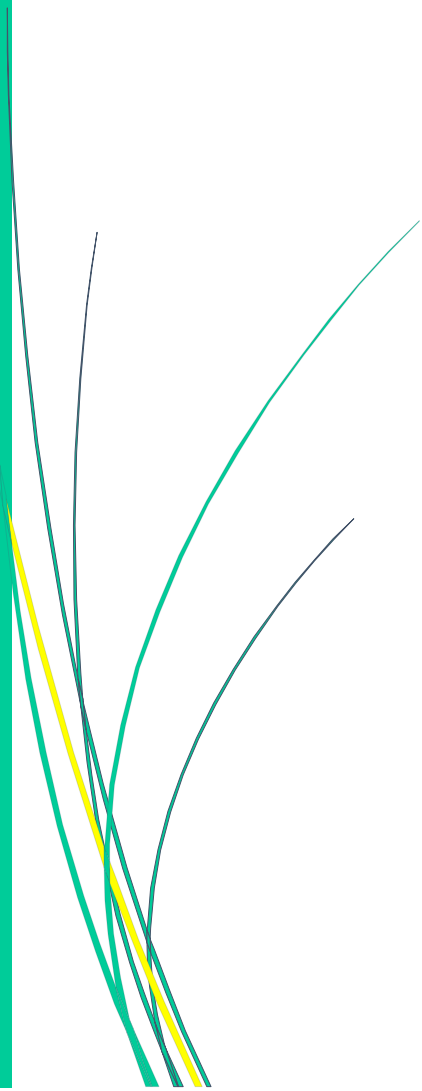
conocimiento de si el Qigong puede ser de ayuda para mejorar también las secuelas del tratamiento oncológico en esta población.

- Un programa longitudinal donde se vean los efectos a largo plazo de el Qigong en los pacientes con linfoma, motivando a los pacientes que lo practiquen de forma independiente y rutinario.
- Facilitar la práctica del Qigong a través de una aplicación móvil que motive a los pacientes el poder realizar los ejercicios en su propio hogar. Así con esto, cumplimos con el objetivo anterior de lograr que hagan el Qigong de forma independiente y rutinaria.



# CONCLUSIONES

## CONCLUSIONS







## **CONCLUSIONES**

### **Conclusiones Generales**

Esta Tesis Doctoral Internacional presenta una solución a los pacientes con linfoma en complemento con el tratamiento oncológico tradicional para combatir las secuelas presentadas por los tratamientos oncológicos. De igual manera, este programa presentó un beneficio psicológico, ayudando en la ansiedad y depresión de los supervivientes de linfoma, en adición, a una mejoría a nivel cardiovascular. Los resultados de este programa presencial muestran un beneficio a nivel general de la calidad de vida de estos pacientes.

### **Conclusiones Específicas**

Sección I: Evaluación de las secuelas del tratamiento oncológico sobre el aspecto psicológico del paciente con linfoma.

Los pacientes Hodgkin y No Hodgkin son vulnerables a problemas de ansiedad. La prevalencia de este aspecto psicológico, puede no parecer alarmante; sin embargo, muchos pacientes con esta enfermedad pueden estar en riesgo de desarrollar este rasgo. La razón principal por la que la ansiedad estaba entre los pacientes era por el miedo a recaer en el cáncer nuevamente. La mayor parte de la recopilación de datos

fue para evaluar posibles formas de crear una intervención o para identificar predictores de ansiedad en los sobrevivientes. El efecto de la ansiedad durante el período de supervivencia o el tratamiento que el paciente está realizando, sobre una base psicológica, resalta la importancia en la atención del cáncer de centrarse en los aspectos que psicológicamente pueden afectar al paciente durante su período con esta enfermedad.

Sección II: Evaluación de las secuelas del tratamiento oncológico sobre la cardiotoxicidad en pacientes con linfoma.

Por lo tanto, el tamaño de la muestra de los pacientes estudiados es demasiado pequeño para extrapolar una conclusión a una población más grande. Los valores de variabilidad de la frecuencia cardíaca fueron más bajos en los sobrevivientes de linfoma no Hodgkin en el primer año después del tratamiento que en los controles sanos, lo que sugiere un desequilibrio simpátovagal en comparación con sujetos sanos emparejados.

Sección III: Terapias complementarias como herramienta para la prevención de secuelas

psicológicas y cardíacas en pacientes con linfoma.

Un programa de Qigong de ocho semanas de 60 minutos por sesión dos veces por semana con un total de 16 sesiones podría ser una forma efectiva de mejorar la salud psicológica y el equilibrio cardiovascular en los sobrevivientes de linfoma no Hodgkin. Esto funcionaría al reducir la ansiedad, la depresión y los parámetros de variabilidad

de la frecuencia cardíaca. Se asegura que futuros ensayos clínicos certifiquen la efectividad de un programa de Qigong para mejorar la calidad de vida de los sobrevivientes de linfoma no Hodgkin.

## **CONCLUSIONS**

### **General Conclusions**

This International Doctoral Thesis presents a solution for patients with lymphoma in addition to traditional oncological treatment to combat the sequelae presented by oncological treatments. Similarly, this program presented a psychological benefit, helping in the anxiety and depression of lymphoma survivors, in addition to an improvement at the cardiovascular level. The results of this face-to-face program show a general benefit in the quality of life of these patients.

### **Specific Conclusions**

Section I: Evaluation of the consequences of cancer treatment on the psychological aspect of the patient with lymphoma.

Hodgkin and non-Hodgkin patients are vulnerable to anxiety issues. The prevalence of this psychological aspect, may not seem alarming; however, many patients with this disease may be on risk of developing this trait. The main reason anxiety was among patients was because of the fear of relapsing into the cancer again. Most of the recollection of data was to screen possible

ways on creating an intervention or to identify predictors of anxiety on survivors. The effect of anxiety during the survival period or the treatment that the patient is using, on a psychological basis, highlights the importance on cancer care of focusing on aspects that psychologically may affect the patient during his period with this disease.

Section II: Evaluation of the sequelae of cancer treatment on cardiotoxicity in patients with lymphoma.

Thus, the sample size of studied patient is too small to extrapolate a conclusion to a bigger population. Heart rate variability values were lower in non-Hodgkin lymphoma survivors in the first year after treatment than in healthy controls, suggesting a sympathovagal imbalance compared to healthy paired subjects.

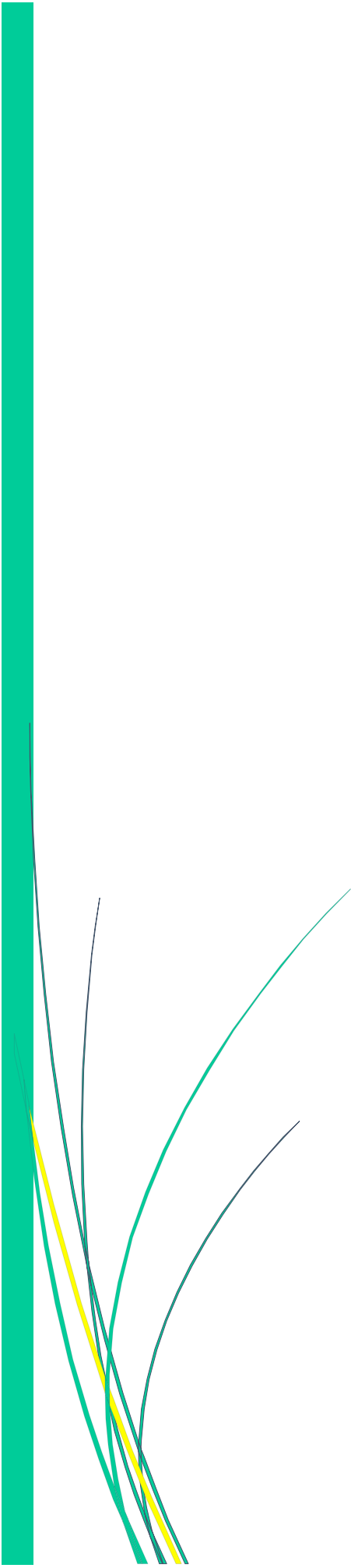
Section III: Complementary therapies as a tool for the prevention of psychological and cardiac sequelae in patients with lymphoma.

An eight-week Qigong program of 60 min per session twice a week with a total of 16 sessions might be an effective way to improve the psychological health and cardiovascular balance in non-Hodgkin lymphoma survivors. This would work by

reducing anxiety, depression, and heart rate variability parameters. Future clinical trials are assured to certify the effectiveness of a Qigong program to improve the quality of life of non-Hodgkin lymphoma survivors.

# ANEXOS

ANEXES





## **ARTÍCULOS DERIVADOS DE LA TESIS DOCTORAL INTERNACIONAL**

A continuación, se presentan las publicaciones derivadas de la presente Tesis Doctoral Internacional ya incluidos previamente en la sección de material, métodos, resultados y discusión. Se incluyen los tres trabajos que al día de hoy están publicados (portada y última página) y dos que se encuentra en la fase de preparación y no están aceptado aún a fecha de la elaboración de tesis.

1. Vargas-Román K, Díaz-Rodríguez CL, Cañadas-De la Fuente GA, Gómez-Urquiza JL, Ariza T, De la Fuente-Solana EI. Anxiety prevalence in lymphoma: A systematic review and meta-analysis. *Health Psychol.* 2020;39(7):580-588.

[doi:10.1037/hea0000869](https://doi.org/10.1037/hea0000869)

2. Vargas-Román K, Cortés-Martín J, Sánchez-García JC, Rodríguez-Blanco R, De la Fuente-Solana EI, Díaz-Rodríguez L. Autonomic Imbalance in Lymphoma Survivors. *Journal of Clinical Medicine.* 2021; 10(19):4391.

<https://doi.org/10.3390/jcm10194391>

3. Vargas-Román K, De la Fuente-Solana EI, Cortés-Martín J, Sánchez-García JC,

González-Vargas CJ, Díaz-Rodríguez L. Effect of a 16-Session Qigong Program in Non-Hodgkin Lymphoma Survivors: A Randomized Clinical Trial. *Journal of Clinical Medicine.* 2022; 11(12):3421. <https://doi.org/10.3390/jcm11123421>

4. Vargas-Román K, Suleiman-Martos N, Díaz-Rodríguez L, Cañadas-De la Fuente GA, Ortega-Campos E, Ariza T, De la Fuente-Solana EI. Prevalence of Depression in Patients with Hodgkin and Non-Hodgkin: A Systematic Review and Meta-Analysis. En preparación.

5. Vargas-Román K et al. Qigong program effects in Non-Hodgkin Lymphoma Survivors in happiness, resilience and heart rate variability: A Randomize Clinical Trial. En preparación.





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### Abstract

**Objective:** Hodgkin and non-Hodgkin lymphoma patients are at high risk of experiencing anxiety because the clinical processes and therapies they undergo produce strong adverse effects. In this review we discuss the prevalence of anxiety among these patients and examine the methods used for data collection, intervention frequency, types of instruments used to recognize anxiety, and data collection purposes, both in Hodgkin and non-Hodgkin lymphoma survivors and patients being treated or diagnosed with these diseases. **Methods:** This systematic review and meta-analysis of the literature was carried out using the following sources: PubMed, Scopus, LILACS, and PsycINFO. **Results:** The meta-analysis sample was  $n = 2,138$  and the overall prevalence of anxiety was 19% (95% CI [12%, 25%]). According to the Egger test, there were no publication biases and no studies were eliminated after the sensitivity analysis. The I<sup>2</sup> for the heterogeneity analysis was 92.6%. **Conclusions:** Hodgkin and non-Hodgkin lymphoma patients are vulnerable to suffering anxiety. It is important to focus on the psychological effect of anxiety during remission or current cancer treatments because they can affect patient outcomes. (PsycInfo Database Record (c) 2020 APA, all rights reserved)

Article

# Autonomic Imbalance in Lymphoma Survivors

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**Abstract:** Among the types of blood cancers, non-Hodgkin lymphoma is the most common. The usual treatments for this type of cancer can cause heart failure. A descriptive observational study was conducted that included 16 non-Hodgkin lymphoma survivors and 16 healthy controls matched by age and sex. Vagal tone was evaluated in the short term with a three-channel Holter device, and the time and frequency domains were analyzed following a previously accepted methodology to evaluate cardiac autonomic balance. The results of the analysis revealed that the standard deviation of the NN interval ( $F = 6.25$ ,  $p = 0.021$ ) and the square root of the mean of the sum of the differences between NN intervals ( $F = 9.74$ ,  $p = 0.004$ ) were significantly higher in healthy subjects than in lymphoma survivors. In the heart rate variability (HRV) index, there were no significant differences between the groups ( $F = 0.03$ ,  $p = 0.85$ ), nor in the parameters of the frequency domains LF ( $F = 1.94$ ,  $p = 0.17$ ), HF ( $F = 0.35$ ,  $p = 0.55$ ), and the ratio LF/HF ( $F = 3.07$ ,  $p = 0.09$ ). HRV values were lower in non-Hodgkin lymphoma survivors in the first year after treatment, resulting in autonomic imbalance compared to healthy paired subjects.

**Keywords:** lymphoma cancer; HRV; autonomic nervous system; non-Hodgkin lymphoma



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## 1. Introduction

According to the World Health Organization, cancer is the leading cause of death worldwide and there are around 18.1 million new cases every year, expected to increase to 24 million cases by 2035 [1,2]. Within the World Health Organization's global hematic cancers, non-Hodgkin lymphoma had 509,590 (2.8%) new cases worldwide in 2018 in both genders. It ranks eleventh in new cases for 2018 [1]. In terms of mortality rate, non-Hodgkin lymphoma cancer caused 248,724 deaths in 2018 in both genders worldwide.

In Spain, in 2020, non-Hodgkin lymphoma was one of the most diagnosed blood cancers (9188), being in the top 10 positions [2]. Worldwide, it is the most frequent, accounting for 3.0% with a mortality rate of 2.6% [3]. Mortality from this tumor type has decreased since the late 1990s at a rate of 3% annually, reflecting a clear improvement in the effectiveness of treatments [2].

The most common treatments for non-Hodgkin lymphoma include chemotherapy, radiation therapy, immunotherapy, and, in certain special cases, bone marrow or stem cell transplants. It is estimated that by 2025, the number of cancer patients that undergo at least one session of radiation therapy will have increased by 16.1% [4]. These therapies produce highly adverse effects such as fatigue, anxiety, depression, insomnia, loss of physical

26. Druschky, K.; Lorenz, J.; Druschky, A. Effects of Respiratory Rate on Heart Rate Variability in Neurological Outpatients with Epilepsies or Migration: A Preliminary Study. *Med. Pract.* **2020**, *29*, 318–325.
27. Díaz-Rodríguez, L.; Vargas-Román, K.; Sanchez-Garcia, J.C.; Rodríguez-Blanco, R.; Cañadas-De la Fuente, G.A.; De La Fuente-Solana, E.I. Effects of Meditation on Mental Health and Cardiovascular Balance in Caregivers. *Int. J. Environ. Res. Public Health* **2021**, *18*, 617. [[CrossRef](#)] [[PubMed](#)]



Article

# Effect of a 16-Session Qigong Program in Non-Hodgkin Lymphoma Survivors: A Randomized Clinical Trial

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**Abstract:** Background: The treatment associated with non-Hodgkin lymphoma patients may cause adverse effects on their physical and psychological condition. The aim of this study is to detect the response to an eight-week, 16-session, 60-min presential Qigong program in anxiety, depression and vagal nerve activity alongside a control group. Methods: A randomized controlled clinical trial was managed. Randomization was carried out by generating a numerical sequence of three cycles through the software EPIDAT 4.1. Numbers were placed in sealed opaque envelopes for assignment to the different groups. Results: Anxiety levels were substantially decreased in the experimental group, with a large effect size ( $F = 30.38, p < 0.00$ ). Depression levels had an improvement in the experimental group in contrast to the control group, reaching statistical significance ( $F = 19.19, p < 0.00$ ). Heart Rate Variability unveiled significant results in terms of between-group differences, with a large effect size in the HRV Index ( $F = 15.80, p < 0.00$ ), SDNN ( $F = 8.82, p < 0.00$ ), and RMSSD ( $F = 6.72, p < 0.01$ ) in the time domain, and a medium effect size in the HF ( $F = 9.78, p < 0.003$ ), LF ( $F = 9.78, p < 0.00$ ), and LF/HF Ratio ( $F = 18.44, p < 0.00$ ) in the frequency domain, which were all bettered in the experimental group, after the Qigong program. Conclusions: Qigong therapy can be an effective therapeutic activity in consonance with traditional medicine to improve psychological health and autonomic nervous system balance in non-Hodgkin lymphoma survivors.

**Keywords:** lymphoma cancer; HRV; autonomic nervous system; non-Hodgkin lymphoma; anxiety; depression



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## 1. Introduction

Cancer is a broad group of illnesses that can start in practically any organ or tissue of the body when abnormal cells grow uncontrollably, breaching adjacent parts of the body or escalating to other organs [1]. Non-Hodgkin lymphoma had 544,352 new cases worldwide in 2020 in both genders according to the world health organization in the category of global hematic cancers. It ranks in the eleventh position among other types of cancers in 2020. In terms of its fatality rate, non-Hodgkin lymphoma cancer had 259,793 cases in 2020 in both genders worldwide [2].

In Spain, in 2020, non-Hodgkin lymphoma within blood cancers, was one of the highest diagnosed, being in the top nine positions. The estimated number of cases in Spain in 2020 was 66,733 [3]. Mortality from this tumor has reduced since the late 1990s,

22. Caro-Morán, E.; Fernández-Lao, C.; Galiano-Castillo, N.; Cantarero-Villanueva, I.; Arroyo-Morales, M.; Díaz-Rodríguez, L. Heart Rate Variability in Breast Cancer Survivors After the First Year of Treatments: A Case-Controlled Study. *Biol. Res. Nurs.* **2016**, *18*, 43–49. [[CrossRef](#)]
23. Renna, M.E.; Shrout, M.R.; Madison, A.A.; Bennett, J.M.; Malarkey, W.B.; Emery, C.F.; Kiecolt-Glaser, J.K. Distress disorder histories predict HRV trajectories during and after stress. *Psychoneuroendocrinology* **2022**, *135*, 105575. [[CrossRef](#)]
24. Vargas-Román, K.; Díaz-Rodríguez, C.L.; Cañadas-De la Fuente, G.A.; Gómez-Urquiza, J.L.; Ariza, T.; De la Fuente-Solana, E.I. Anxiety prevalence in lymphoma: A systematic review and meta-analysis. *Health Psychol.* **2020**, *39*, 580–588. [[CrossRef](#)] [[PubMed](#)]
25. Saeed, S.A.; Cunningham, K.; Bloch, R.M. Depression and Anxiety Disorders: Benefits of Exercise, Yoga, and Meditation. *Am. Fam. Physician* **2019**, *99*, 620–627. [[PubMed](#)]
26. Oh, B.; Butow, P.; Mullan, B.; Clarke, S.; Beale, P.; Pavlakis, N.; Kothe, E.; Lam, L.; Rosenthal, D. Impact of medical Qigong on quality of life, fatigue, mood and inflammation in cancer patients: A randomized controlled trial. *Ann. Oncol.* **2010**, *21*, 608–614. [[CrossRef](#)] [[PubMed](#)]

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## **Publications:**

1. Keyla Vargas-Román; Emilia I. De la Fuente-Solana; Jonathan Cortés-Martín; Juan Carlos Sánchez-García; Christian J. González-Vargas; Lourdes Díaz-Rodríguez. Effect of a 16-Session Qigong Program in Non-Hodgkin Lymphoma Survivors: A Randomized Clinical Trial. *Journal of Clinical Medicine*. DOI: 10.3390/jcm11123421
2. Lourdes Díaz-Rodríguez; Keyla Vargas-Román; María del Mar Díaz-Rodríguez; Juan Carlos Sánchez-García; Antonio Liñán-González; Raquel Rodríguez-Blanche Using “Diraya” System as a Complementary Tool in Nursing Process Education: A Controlled Clinical Study. *Journal of Clinical Medicine*. DOI: 10.3390/jcm11102771
3. Keyla Vargas-Román; María Isabel Tovar-Gálvez; Antonio Liñán-González; Guillermo Arturo Cañadas de la Fuente; Emilia Inmaculada de la Fuente-Solana; Lourdes Díaz-Rodríguez Coping Strategies in Elderly Colorectal Cancer Patients. *Cancers*. DOI: 10.3390/cancers14030608
4. Keyla Vargas-Román; Jonathan Cortés-Martín; Juan Carlos Sánchez-García; Raquel Rodríguez-Blanche; Emilia Inmaculada De La Fuente-Solana; Lourdes Díaz-Rodríguez Autonomic Imbalance in Lymphoma Survivors. *Journal of Clinical Medicine*. DOI: 10.3390/jcm10194391
5. Carolina Ruiz Hernández, José L. Gómez-Urquiza, Laura Pradas-Hernández, Keyla Vargas Roman, Nora Suleiman-Martos, Luis Albendín-García, Guillermo A. Cañadas-De la Fuente. Effectiveness of nursing interventions for preoperative anxiety in adults: A systematic review with meta-analysis. *Journal of advanced nursing*. DOI: 10.1111/jan.14827
6. Lourdes Díaz-Rodríguez; Keyla Vargas-Román; Juan Carlos Sanchez-Garcia; Raquel Rodríguez-Blanche; Guillermo Arturo Cañadas-De la Fuente; Emilia I. De La Fuente-Solana. Effects of Meditation on Mental Health and Cardiovascular Balance in Caregivers. *International Journal of Environmental Research and Public Health*. DOI: 10.3390/ijerph18020617
7. Sonia Ortega Romero; Almudena Velando-Soriano; José Luis Romero-Bejar; Keyla Vargas-Román; Luis Albendín-García; Nora Suleiman-Martos; Guillermo Arturo Cañadas-De la

- Fuente. Nurses Training and Capacitation for Palliative Care in Emergency Units: A Systematic Review. *Medicina*. DOI: 10.3390/medicina56120648
8. Emilia I. De La Fuente-Solana; Elena Ortega-Campos; Keyla Vargas-Roman; Gustavo R. Cañadas-De la Fuente; Tania Ariza C.; Raimundo Aguayo-Extremera; Luis Albendín-García. Study of the Predictive Validity of the Burnout Granada Questionnaire in Police Officers. *International Journal of Environmental Research and Public Health*. DOI: 10.3390/ijerph17176112
  9. María José Godino-láñez; María Begoña Martos-Cabrera; Nora Suleiman-Martos; José Luis Gómez-Urquiza; Keyla Vargas-Román; María José Membrive-Jiménez; Luis Albendín-García. Play Therapy as an Intervention in Hospitalized Children: A Systematic Review. *Healthcare*. DOI: 10.3390/healthcare8030239
  10. Elvira Ortiz-Sánchez; Almudena Velando-Soriano; Laura Pradas-Hernández; Keyla Vargas-Román; Jose L. Gómez-Urquiza; Guillermo A. Cañadas-De la Fuente; Luis Albendín-García. Analysis of the Anti-Vaccine Movement in Social Networks: A Systematic Review. *International Journal of Environmental Research and Public Health*. DOI: 10.3390/ijerph17155394
  11. Keyla Vargas-Román; C. Lourdes Díaz-Rodríguez; Guillermo A. Cañadas-De la Fuente; José Luis Gómez-Urquiza; Tania Ariza; E. Inmaculada De la Fuente-Solana. Anxiety prevalence in lymphoma: A systematic review and meta-analysis. *Health Psychology*. DOI: 10.1037/hea0000869
  12. Membrive-Jiménez, María J., Laura Pradas-Hernández, Nora Suleiman-Martos, Keyla Vargas-Román, Guillermo A. Cañadas-De la Fuente, José L. Gomez-Urquiza, and Emilia I. De la Fuente-Solana. Burnout in Nursing Managers: A Systematic Review and Meta-Analysis of Related Factors, Levels and Prevalence. *International Journal of Environmental Research and Public Health*. DOI: 10.3390/ijerph17113983
  13. Nora Suleiman-Martos; Luis Albendín-García; José L. Gómez-Urquiza; Keyla Vargas-Román; Lucia Ramirez-Baena; Elena Ortega-Campos; Emilia I. De La Fuente-Solana. Prevalence and Predictors of Burnout in Midwives: A Systematic Review and Meta-



Analysis. International Journal of Environmental Research and Public Health. DOI: 10.3390/ijerph17020641

14. Elena Ortega-Campos; Keyla Vargas-Román; Almudena Velando-Soriano; Nora Suleiman-Martos; Guillermo Arturo Cañadas-De la Fuente; Luis Albendín-García; Jose Luis Gómez Urquiza Compassion Fatigue, Compassion Satisfaction, and Burnout in Oncology Nurses: A Systematic Review and Meta-Analysis. Sustainability. DOI: 10.3390/su12010072

## **Congress Communications**

The PhD Candidate will only highlight the communications pertaining with the doctoral thesis:

Effects of Chikung on Non-Hodgkin Lymphoma Survivors. 12<sup>th</sup> European Congress of Integrative Medicine. Barcelona, Spain. 13-15, September 2019.

Desequilibrio vegetativo en supervivientes de linfoma. I CONGRESO DE INVESTIGADORES DEL PTS. Granada, Spain. February 2, 2019.

EFFECTOS DE LAS TERAPIAS ENERGÉTICAS SOBRE LA VARIABILIDAD DE LA FRECUENCIA CARDÍACA: REVISIÓN SISTEMÁTICA. II Congreso Internacional y VII Encuentros Hispano-cubanos en Ciencias de la Salud. Cienfuegos, Cuba. May, 05, 2018.

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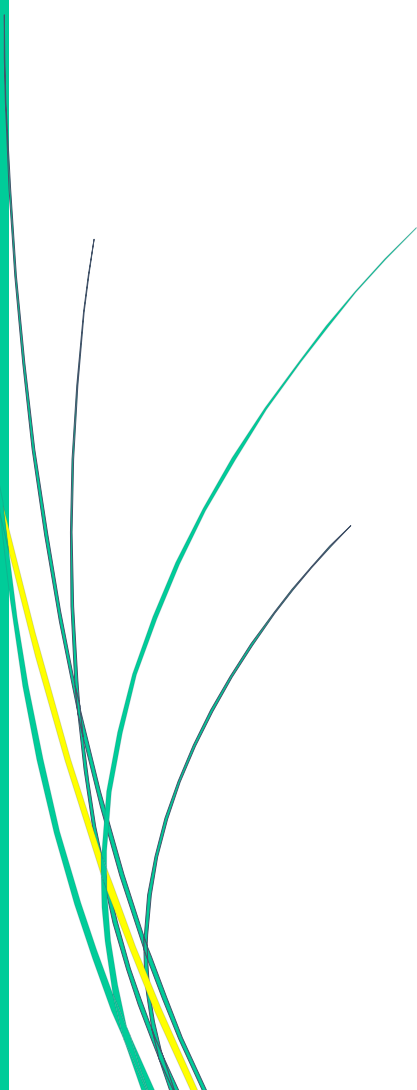
2020-2021 Description and exploration od data in psychology (1,5 ECTS Credits).

Analysis Techniques in Psychological Research (2,5 ECTS Credits).

Research Seminar (2,0 ECTS Credits).

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