Universidad de Oviedo

TESIS DOCTORAL

Programa de Doctorado en Ciencias de la Salud

Combinación de aproximaciones biológicas y clínicas para la detección de riesgo de comportamiento suicida en pacientes con depresión mayor

Ángela Velasco Iglesias

Universidad de Oviedo

TESIS DOCTORAL

Programa de Doctorado en Ciencias de la Salud

Combinación de aproximaciones biológicas y clínicas para la detección de riesgo de comportamiento suicida en pacientes con depresión mayor

Ángela Velasco Iglesias

Universidad de Oviedo

RESUMEN DEL CONTENIDO DE TESIS DOCTORAL

1.- Título de la Tesis	
Español/Otro Idioma: **COMBINACIÓN DE APROXIMACIONES BIOLÓGICAS Y CLÍNICAS PARA LA DETECCIÓN DE RIESGO DE COMPORTAMIENTO SUICIDA EN PACIENTES CON DEPRESIÓN MAYOR**	Inglés: **COMBINATION OF BIOLOGICAL AND CLINICAL APPROACHES FOR THE DETECTION OF RISK OF SUICIDAL BEHAVIOR IN PATIENTS WITH MAJOR DEPRESSION**

2.- Autor	
Nombre: **ANGELA VELASCO IGLESIAS**	DNI/Pasaporte/NIE:
Programa de Doctorado: **CIENCIAS DE LA SALUD**	
Órgano responsable: **NEUROCIENCIA EXPERIMENTAL Y CONDUCTA**	

RESUMEN (en español)

El suicidio constituye un problema de salud pública de primer orden. Cerca de 700.000 personas al año mueren por este motivo. A pesar de ser una muerte evitable, la mayoría de las estrategias de prevención del comportamiento suicida se basa en el despistaje de numerosos factores de riesgo. Hasta la fecha, no existen marcadores específicos de la conducta suicida per se. Sin embargo, datos recientes sugieren un posible papel del sistema inmunológico en la fisiopatología del comportamiento suicida.

El presente trabajo de investigación evalúa, mediante la combinación de aproximaciones clínicas y biológicas, la formulación el riesgo de suicidio a través de marcadores periféricos de inflamación. El primer objetivo consiste en determinar la utilidad de los índices periféricos de inflamación, Indice Neutrófilo/Linfocito (INL), Indice Plaqueta/Linfocito (IPL) e Indice Monocito/Linfocito (IML) en la predicción del comportamiento suicida en pacientes con diagnóstico de trastorno depresivo mayor (TDM). El segundo objetivo consiste en determinar la existencia de posibles diferencias en los parámetros hematopoyéticos en TDM, con y sin antecedentes de tentativa suicida (TS), en comparación con personas sanas, así como dilucidar si las diferencias encontradas son más acusadas en aquellos con dichos antecedentes, asi como determinar

si existen diferencias en función del sexo o de la presencia de acontecimientos vitales estresantes, distales o proximales. Finalmente, el tercer objetivo es revisar de modo sistemático si los marcadores periféricos de inflamación previamente mencionados, INL, IPL e IML, son útiles para diferenciar pacientes con TDM con/sin historia de TS, pacientes con DM y TS y controles sanos; y, pacientes con TDM e ideación suicida (IS) antes y después del tratamiento. El principal hallazgo es que los pacientes con TDM y antecedentes de TS presentan un incremento en el INL en comparación con sus iguales sin dichos antecedentes. INL podría establecerse como marcador de riesgo de la conducta suicida en pacientes con depresión mayor. Nuestro trabajo de investigación es el primero que establece un punto de corte óptimo para INL, situándose en 1,30. En el segundo trabajo de investigación, los resultados sugieren que, en comparación con los participantes sanos, los pacientes con depresión mayor (con/sin TS), muestran alteraciones en los parámetros hematológicos que confirman la presencia de inflamación y, por tanto, de estrés hematopoyético. Todos los cambios fueron más pronunciados en aquellos con antecedentes de TS, sexo femenino, y presencia de acontecimientos vitales estresantes en la infancia. Finalmente, INL aparece en la literatura científica como un marcador específico de vulnerabilidad suicida en pacientes con depresión. Este hallazgo solo se asocia a la historia de tentativa suicida previa, y no, a la ideación. Respecto a IPL e IML los resultados no parecen estar del todo claros. En conclusión, los procesos inflamatorios y el estrés hematopoyético podrían tener un papel determinante en la etiopatogenia de la depresión y de la conducta suicida. INL podría establecerse como un marcador de inflamación sistémica, coste-efectivo y fácilmente accesible, capaz de predecir y detectar el riesgo suicida en pacientes con depresión mayor.

Universidad de Oviedo

RESUMEN (en Inglés)

Suicide is a public health problem of the first order. About 700,000 people a year die for this reason. Despite being a preventable death, most suicidal behavior prevention strategies are based on screening for numerous risk factors. To date, there are no specific markers of suicidal behavior per se. However, recent data suggest a possible role of the immune system in the pathophysiology of suicidal behavior.

The present research work evaluates, through the combination of clinical and biological approaches, the formulation of the risk of suicide through peripheral markers of inflammation. The first objective is to determine the usefulness of peripheral inflammation indices, Neutrophil/Lymphocyte Ratio (NLR), Platelet/Lymphocyte Ratio (PLR), and Monocyte/Lymphocyte Ratio (MLR) in predicting suicidal behavior in patients diagnosed with major depressive disorder (MDD). The second objective is to determine the existence of possible differences in hematopoietic parameters in MDD, with and without a history of suicide attempt (SA), compared to healthy people, as well as to elucidate if the differences found are more pronounced in patients with a history of SA, as well as to determine if the differences change depending on the sex or the presence of stressful, distal or proximal life events. Finally, the third objective is to systematically review whether the previously mentioned peripheral markers of inflammation, NLR, PLR, and MLR, are useful to differentiate MDD patients with/without a history of SA, patients with MDD and SA, and healthy controls; and, patients with MDD and suicidal ideation (SI) before and after treatment. The main finding is that patients with MDD and a history of ST have an increase in NLR compared to their peers without such a history. NLR could be established as a risk marker for suicidal behavior in patients with major depression. Our research work is the first to establish an optimal cut-off point for NLR, standing at 1.30. In the second

research paper, the results suggest that, compared to healthy participants, patients with MDD (with/without SA) show alterations in hematological parameters that confirm the presence of inflammation and, therefore, hematopoietic stress. All changes were more pronounced in those with a history of SA, female sex, and the presence of stressful life events in childhood. Finally, NLR appears in the scientific literature as a specific marker of suicidal vulnerability in patients with depression. This finding is only associated with a history of a previous suicide attempt, and not with ideation. Regarding PLR and MLR, the results do not seem to be entirely clear. In conclusion, inflammatory processes and hematopoietic stress could play a determining role in the etiopathogenesis of depression and suicidal behavior. NLR could be established as a cost-effective and easily accessible marker of systemic inflammation, capable of predicting and detecting suicidal risk in patients with major depression.

SR. PRESIDENTE DE LA COMISIÓN ACADÉMICA DEL PROGRAMA DE DOCTORADO EN _____

Universidad de Oviedo

FORMULARIO RESUMEN DE TESIS POR COMPENDIO

1.- Datos personales solicitante	
Apellidos: **VELASCO IGLESIAS**	Nombre: **ÁNGELA**

Curso de inicio de los estudios de doctorado	**2018**

	SI	NO
Acompaña acreditación por el Director de la Tesis de la aportación significativa del doctorando	X	
Acompaña memoria que incluye		
Introducción justificativa de la unidad temática y objetivos	X	
Copia completa de los trabajos *	X	
Resultados/discusión y conclusiones	X	
Informe con el factor de impacto de las publicaciones	X	
Se acompaña aceptación de todos y cada uno de los coautores a presentar el trabajo como tesis por compendio (Art. 32.4.b)	X	
Se acompaña renuncia de todos y cada uno de los coautores no doctores a presentar el trabajo como parte de otra tesis de compendio (Art. 32.4.c)	X	

* Ha de constar el nombre y adscripción del autor y de todos los coautores asi como la referencia completa de la revista o editorial en la que los trabajos hayan sido publicados o aceptados en cuyo caso se aportará justificante de la aceptación por parte de la revista o editorial

FOR-MAT-VOA-033

Artículos, Capítulos, Trabajos

Trabajo, Artículo 1

Titulo (o título abreviado)	**NEUTROPHIL-TO-LYMPHOCYTE RATIO: A POTENTIAL NEW PERIPHERAL BIOMARKER OF SUICIDAL BEHAVIOR**
Fecha de publicación	**17 February 2020**
Fecha de aceptación	**15 December 2019**
Inclusión en Science Citation Index o bases relacionadas por la CNEAI (indíquese)	**JCR – SCIENCE CITATION INDEX**
Factor de impacto	**5.361**

Coautor2 **X** Doctor □ No doctor . Indique nombre y apellidos	**JULIA RODRÍGUEZ REVUELTA**
Coautor3 **X** Doctor □ No doctor . Indique nombre y apellidos	**EMILIE OLIÉ**
Coautor4 □ Doctor **X** No doctor . Indique nombre y apellidos	**ICIAR ABAD**
Coautor5 **X** Doctor □ No doctor . Indique nombre y apellidos	**ABEL FERNÁNDEZ PELÁEZ**
Coautor6 □ Doctor **X** No doctor . Indique nombre y apellidos	**AURÉLIE CAZALS**
Coautor7 **X** Doctor □ No doctor . Indique nombre y apellidos	**SÉBASTIEN GUILLAUME**
Coautor8 **X** Doctor □ No doctor . Indique nombre y apellidos	**LORENA DE LA FUENTE TOMÁS**
Coautor9 **X** Doctor □ No doctor . Indique nombre y apellidos	**LUIS JIMÉNEZ TREVIÑO**
Coautor10 **X** Doctor □ No doctor . Indique nombre y apellidos	**LAURA GUTIÉRREZ**
Coautor11 **X** Doctor □ No doctor . Indique nombre y apellido	**MARIA PAZ GARCÍA PORTILLA**
Coautor12 **X** Doctor □ No doctor . Indique nombre y apellidos	**JULIO BOBES GARCIA**
Coautor13 **X** Doctor □ No doctor . Indique nombre y apellidos	**PHILIPPE COURTET**
Coautor14 **X** Doctor □ No doctor . Indique nombre y apellidos	**PILAR ALEJANDRA SÁIZ**

Trabajo, Artículo 2

Titulo (o título abreviado)	**SEX-DEPENDENT GRADES OF HAEMATOPOIETIC MODULATION IN PATIENTS WITH MAJOR DEPRESSIVE EPISODES ARE ASSOCIATED WITH SUICIDE ATTEMPTS**
Fecha de publicación	**26 June 2020**
Fecha de aceptación	**9 June 2020**
Inclusión en Science Citation Index o bases relacionadas por la CNEAI (indíquese)	**JCR – SCIENCE CITATION INDEX**
Factor de impacto	**4.600**

Coautor2 **X** Doctor □ No doctor . Indique nombre y apellidos	**VALERIA ROLLE**
Coautor3 **X** Doctor □ No doctor . Indique nombre y apellidos	**LUIS JIMÉNEZ TREVIÑO**
Coautor4 **X** Doctor □ No doctor . Indique nombre y apellidos	**LORENA DE LA FUENTE TOMÁS**
Coautor5 □ Doctor **X** No doctor . Indique nombre y apellidos	**ÁNGEL BERNARDO**
Coautor6 □ Doctor **X** No doctor . Indique nombre y apellidos	**TAMARA ARIAS**
Coautor7 **X** Doctor □ No doctor . Indique nombre y apellidos	**MARÍA DEL CARMEN MUÑOZ TURRILLAS**
Coautor8 **X** Doctor □ No doctor . Indique nombre y apellidos	**LETICIA GARCÍA ÁLVAREZ**
Coautor9 **X** Doctor □ No doctor . Indique nombre y apellidos	**LETICIA GONZÁLEZ BLANCO**
Coautor10 **X** Doctor □ No doctor . Indique nombre y apellidos	**JULIA RODRÍGUEZ REVUELTA**
Coautor11 **X** Doctor □ No doctor . Indique nombre y apellidos	**MARIA PAZ GARCÍA PORTILLA**
Coautor12 **X** Doctor □ No doctor . Indique nombre y apellidos	**PHILIPPE COURTET**
Coautor13 **X** Doctor □ No doctor . Indique nombre y apellidos	**JULIO BOBES**
Coautor14 **X** Doctor □ No doctor . Indique nombre y apellidos	**LAURA GUTIÉRREZ**
Coautor15 **X** Doctor □ No doctor . Indique nombre y apellidos	**PILAR ALEJANDRA SÁIZ**

Trabajo, Artículo 3

Titulo (o título abreviado)	**NEUTROPHIL-TO-LYMPHOCYTE RATIO, PLATELET-TO-LYMPHOCYTE RATIO, AND MONOCYTE-TO-LYMPHOCYTE RATIO IN DEPRESSED PATIENTS WITH SUICIDAL BEHAVIOR: A SYSTEMATIC REVIEW**
Fecha de publicación	**16 April 2023**
Fecha de aceptación	**8 March 2023**
Inclusión en Science Citation Index o bases relacionadas por la CNEAI (indíquese)	**JCR – SCIENCE CITATION INDEX**
Factor de impacto	**7.156**

Coautor2	□ Doctor **X** No doctor .	Indique nombre y apellidos	**AISTE LENGVENYTE**
Coautor3	**X** Doctor □ No doctor .	Indique nombre y apellidos	**JULIA RODRÍGUEZ REVUELTA**
Coautor4	**X** Doctor □ No doctor .	Indique nombre y apellidos	**LUIS JIMÉNEZ TREVIÑO**
Coautor5	**X** Doctor □ No doctor .	Indique nombre y apellidos	**PHILIPPE COURTET**
Coautor6	**X** Doctor □ No doctor .	Indique nombre y apellidos	**MARIA PAZ GARCÍA PORTILLA**
Coautor7	**X** Doctor □ No doctor .	Indique nombre y apellidos	**JULIO BOBES**
Coautor8	**X** Doctor □ No doctor .	Indique nombre y apellidos	**PILAR ALEJANDRA SÁIZ**

“No hay más que un problema filosófico verdaderamente serio: el suicidio. Juzgar que la vida vale o no vale la pena de que se la viva es responder a la pregunta fundamental de la filosofía”

El mito de Sísifo (octubre, 1942)
Albert Camus

Agradecimientos

El desarrollo de este trabajo ha sido posible gracias la dirección y apoyo de varias personas que me acompañaron de una u otra forma a lo largo de la elaboración de esta tesis. Aunque me falten líneas de reconocimiento para ellos, me gustaría poder dedicarles unas líneas.

A ti, Prof. Pilar A Sáiz, eres más que una directora de Tesis. Desde el principio apostaste por mí, me has acogido, cuidado y educado como si fuera de la familia. Gracias por tu paciencia, tu tesón, por tu mirar con lupa todo lo habido y por haber, me has hecho más fuerte.

Al Prof. Julio Bobes por confiar en mí y brindarme esta oportunidad que va mucho más allá de esta Tesis Doctoral. Admiro lo que has construido y admiro tus ganas de seguir haciéndolo. Gracias por transmitirme tu conocimiento y experiencia.

Al resto de mis compañeros del Área de Psiquiatría. De todos he aprendido algo, juntos hemos crecido.

A mis abuelos, que suerte teneros a los cuatro en un momento como este. A mis padres, siempre habéis confiado en mí y me habéis enseñado a no rendirme nunca. A mi hermana, que suerte tenerte. Tienes los ingredientes perfectos para triunfar. Al resto de mi escogido círculo cercano, gracias a cada uno de vosotros por ser casa.

Agradecer a la Fundación para el Fomento en Asturias de la Investigación Científica Aplicada y la Tecnología (FICYT) a través del Programa Severo Ochoa de Ayudas predoctorales para la formación en investigación y docencia del Principado de Asturias.

Finalmente, me gustaría mencionar a todos los participantes que han hecho posible este trabajo. Gracias a cada uno de vosotros por seguir ilusionándome en la formación, el conocimiento y la investigación.

Indice de contenidos

Introducción

1. Introducción

1.1. Magnitud e impacto de la conducta suicida

El suicidio constituye un problema de salud pública de primer orden. Los últimos datos de la Organización Mundial de la Salud (OMS) ponen de manifiesto que cerca de 700.000 personas mueren al año por suicidio, siendo la tercera causa de muerte externa en el grupo etario de 15 a 44 años (World Health Organization, 2021). En nuestro país, el suicidio se sitúa como primera causa de muerte externa desde el año 2008 tras haber superado el número de fallecimientos provocados por accidentes de tráfico (Sáiz & Bobes, 2014). Los últimos datos aportados por el Instituto Nacional de Estadística (INE) referentes al año 2021, señalan que, en nuestro país, 4.003 personas han fallecido por suicidio, lo que implica una media de 11 personas diarias (Instituto Nacional de Estadística, 2021).

No obstante, las cifras reales de suicidio podrían ser incluso más elevadas, ya que existe una conocida tendencia a la subnotificación y a la clasificación errónea de casos en la mayoría de los países. En España, se observan claras discrepancias entre los datos aportados por el INE y los Institutos de Medicina Legal, pudiendo alcanzar un infrarregistro alrededor de 450 suicidios anuales (Giner & Guija, 2014). Únicamente, ochenta países disponen de registro civil de buena calidad que se pueden utilizar directamente para estimar tasas de suicidio (World Health Organization, 2021).

Sin embargo, las cifras expuestas sólo representan la punta del iceberg. Se estima que, por cada suicidio consumado, el número de tentativas suicidas (TS) es entre 10 y 20 veces superior (Espandian et al., 2020). A pesar de la gravedad del problema, existe un gran desconocimiento e infranotificación en el cómputo de las TS, lo que nos

impide conocer la magnitud real del mismo debido a la carencia de datos fiables y contrastados (Bobes et al., 2011).

Dada la magnitud y gravedad del problema, el suicidio es uno de los problemas de mayor impacto en la salud pública, y no únicamente en lo que concierne a la salud mental, sino que sus consecuencias se extienden a nivel económico, social y cultural. En los países industrializados, el suicidio constituye una de las principales causas de muerte prematura cuando se tienen presentes los años de vida ajustados por discapacidad (DALYs - *Disability Adjusted Life Years*, por sus siglas en inglés), representando a escala mundial el 1,4% de la carga de morbilidad (Fonseca-Pedrero et al., 2020).

A pesar de ser una muerte evitable, sólo 38 países cuentan con una estrategia nacional de prevención del suicidio (World Health Organization, 2021). Y nuestro país no es uno de ellos, ya que, España se encuentra muy por debajo de otros países europeos con desarrollo similar (Sáiz & Bobes, 2014). Hasta la fecha, la mayoría de las estrategias de prevención del comportamiento suicida se basan en el despistaje de numerosos factores de riesgo, biológicos y clínicos que, sin embargo, no ha demostrado el suficiente poder predictivo (Chang et al., 2016; Franklin et al., 2017; Quinlivan et al., 2016). Por otra parte, la investigación centrada en la potenciación de los factores protectores es más bien limitada. De modo que, la amplificación de los factores protectores, así como la minimización de los factores de riesgo han de constituir las intervenciones sobre dicha conducta (Sanchez-Teruel & Robles-Bello, 2014).

1.2. Factores de riesgo asociados al comportamiento suicida

Los factores de riesgo (FR) asociados a la conducta suicida se dividen clásicamente en dos grupos, los no modificables y los modificables. Los FR no modificables son aquellos inherentes al sujeto que tienden a mantenerse estables en el tiempo. Por el contrario, los FR modificables son aquellos que se asocian a factores sociales, psicológicos y psicopatológicos que pueden alterarse clínicamente.

1.2.1. Factores de riesgo no modificables

Heredabilidad

La herencia de la conducta suicida es un hecho ampliamente estudiado. Se estima que un 43% de la conducta suicida es explicada en base a la carga genética, mientras que el 57% restante se debe a la influencia ambiental (Ayuso-Mateos et al., 2012). Por tanto, la susceptibilidad hacia dicha conducta viene dada por un efecto combinado de genes de efecto menor y diversos factores ambientales (Jiménez-Treviño et al., 2019).

Estudios previos han constatado que aquellas personas con antecedentes familiares de comportamiento suicida presentan una mayor susceptibilidad a desarrollar dichos comportamientos independientemente de la presencia de una enfermedad mental (Carballo et al., 2009; González-Castro et al., 2021). Es decir, la agresividad, la impulsividad y otras variables de personalidad constituyen fenotipos clínicos tanto para el suicidio consumado como para la TS (Cao et al., 2021).

Sexo

En términos generales, son los hombres quienes presentan una mayor tasa de suicidio consumados (12:5), mientras que en las mujeres suele ser más frecuente la realización de TS (World Health Organization, 2021). Esta diferencia, es aún más pronunciada a medida que aumenta la edad (Koo et al., 2017). Los factores de riesgo en común entre hombres y mujeres, para conductas suicidas, suelen ser la presencia de un trastorno mental y/o abuso de sustancias, así como la exposición a la violencia interpersonal. No obstante, atendiendo a los motivos para realizar dicho acto, en los hombres los principales motivos son las dificultades financieras, los problemas legales o laborales, la desesperanza o el acceso a los medios; mientras que, para las mujeres lo serían más frecuentemente los conflictos interpersonales, presencia de síntomas depresivos, el maltrato o la enfermedad de un ser querido (Burón et al., 2016; Miranda-Mendizabal et al., 2019).

Edad

Atendiendo a la edad, los momentos de mayor riesgo suicida se sitúan en la juventud y senectud (Beautrais et al., 2005). En la juventud (15-24 años), las principales razones para realizar una TS son los conflictos interpersonales, incluyendo la separación o divorcio de sus padres, la exposición a violencia con sus iguales o la falta de un ambiente seguro, la presencia de trastornos mentales y/o el abuso de sustancias (Miranda-Mendizabal et al., 2019). En la edad media (45 a 64 años), los principales móviles para realizar una TS son las dificultades financieras, los problemas legales, en el trabajo o los problemas con la pareja (Burón et al., 2016; Koo et al., 2017). Finalmente, en el grupo etario de 65 años o más, los problemas de salud física, la pérdida de alguien cercano, la presencia de deterioro cognitivo, la pérdida de

autonomía, la desconexión social (percepción de carga) y el dolor, son los principales factores de riesgo para realizar un TS (Burón et al., 2016; Conejero et al., 2018).

Antecedentes de tentativa suicida

Múltiples estudios coinciden en señalar la presencia de antecedentes de TS como uno de los factores individuales con mayor capacidad predictiva de posteriores TS, incluyendo el suicidio consumado (Ayuso-Mateos et al., 2012; Hawton et al., 2013; World Health Organization, 2021). Se estima que la probabilidad de reintento aumenta entre 20 y 30 veces dentro del primer año (Hawton et al., 2015) y que, el 80% de los suicidios consumados, se producen dentro del año posterior al intento inicial (Bostwick et al., 2016), siendo las primeras semanas tras el alta hospitalaria las que resultan de especial vulnerabilidad (Larkin et al., 2014).

1.2.2. Factores de riesgo modificables

Presencia de trastornos mentales graves

Estudios epidemiológicos apuntan a una estrecha relación entre suicidio y trastorno mental. Aproximadamente el 90% de las personas que mueren por suicidio tienen al menos un diagnóstico de trastorno mental. Los trastornos más frecuentemente asociados son la depresión mayor (Ribeiro et al., 2018), el abuso de sustancias (Gobbi et al., 2019), los trastornos psicóticos (Barbeito et al., 2021), los trastornos de la personalidad (Mirkovic et al., 2021) y los trastornos de ansiedad (Allan et al., 2023) de acuerdo con la autopsia psicológica (Guía de Práctica Clínica de Prevención y Tratamiento de la Conducta Suicida., 2020).

Presencia de acontecimientos vitales estresantes distales y proximales

Existe un importante cuerpo de investigación que demuestra cómo las experiencias adversas en la primera infancia tienen un significativo impacto en el posterior desarrollo cerebral, asociándose con una mayor probabilidad no solo de ser psicopatológicamente más vulnerable ante situaciones estresantes (desregulación o reactividad anormal), sino de padecer, con más frecuencia, determinados trastornos mentales, como la depresión (Serafini et al., 2015), con un curso más desfavorable de la misma y una peor respuesta a los tratamientos convencionales (Martins-Monteverde et al., 2019).

Las personas que han estado expuestas a experiencias adversas tempranas presentan un mayor riesgo de comportamiento suicida en el futuro (Carballo et al., 2009; Dal Santo et al., 2020; Nanni et al., 2012), siendo la edad de inicio del abuso, el tiempo de duración de este y el sexo, variables moderadoras en la letalidad de dicho acto (Angst et al., 2014). Además, está relación se ve consolida con más fuerza cuánto mayor es el número de eventos traumáticos experimentados (Serafini et al., 2015). En general, el abuso físico, el abuso sexual y la negligencia en edades tempranas, constituyen factores de riesgo para comportamiento suicidas futuros (Zatti et al., 2017), y en particular, es el abuso emocional el más perjudicial de todos ellos (de Araújo & Lara, 2016).

Por otro lado, estar expuesto a situaciones estresantes incrementa el riesgo de suicidio en los 6 meses siguientes (Diaz-Olivan et al., 2021). Pérdidas personales, incluyendo ruptura o muerte, problemas financieros, legales o conflictos en las relaciones interpersonales, presencia de un entorno familiar desestructurado o victimización, pueden ser desencadenantes de un comportamiento suicida en quienes presentan otros factores de riesgo (Beautrais et al., 2005; Liu et al., 2017).

Rasgos psicológicos: agresividad, impulsividad y desesperanza

Las personas con comportamiento suicida suelen tener rasgos de personalidad específicos como son la agresividad, la impulsividad, la desesperanza, la rigidez cognitiva y el perfeccionismo (Brezo et al., 2006; McGirr & Turecki, 2007). Los rasgos de impulsividad forman parte de una cascada de factores que predisponen haca el riesgo suicida (Anestis et al., 2014; Leiva-Murillo et al., 2013). Es decir, la presencia de experiencias traumáticas en la infancia podría reducir el umbral de reactividad y las respuestas adaptativas ante los estresores posteriores, generando en consecuencia, una respuesta al estrés desregulada, que podrían influir en la impulsividad (Dal Santo et al., 2020), en el comportamiento antisocial y violento (Serafini et al., 2015).

La presencia de dolor psíquico o desesperanza es uno de los factores de riesgo principales (Ducasse et al., 2018), ya que la persona que lo padece espera que el suicidio alivie el dolor emocional (Bryan et al., 2019), sugiriendo una solución permanente a un problema temporal. De acuerdo con estas investigaciones, las personas que han sentido alivio al intentar quitarse la vida tienen una mayor probabilidad de realizar un segundo intento, lo que sugiere un aprendizaje basado en la recompensa, ya que tienden a priorizar una recompensa inmediata o corto placista que alivie el malestar, frente a una recompensa de mayor valor, pero demorada en el tiempo (Da Matta et al., 2012).

Abuso de sustancias

Hasta un 40% de los pacientes que buscan tratamiento por dependencia a sustancias informan de antecedentes de tentativa suicida (Onaemo et al., 2022; Yuodelis-Flores & Ries, 2015). Se estima que, entre un 25% y 50% de los suicidios se asocian con el trastorno por abuso de sustancias, siendo un 22% de los mismos,

atribuibles al trastorno por consumo de alcohol. Es decir, uno de cada cinco suicidios podría haberse evitado si no se hubiera consumido alcohol (Onaemo et al., 2022), constituyendo no solo un factor de riesgo sino tratándose también de un factor precipitante hacia dicho comportamiento (Beautrais et al., 2005), ya que, entre otros, la seriedad del intento se asocia con el consumo de alcohol dentro de las 3 horas anteriores al acto suicida (Odds Ratio > 6) (Powell et al., 2001).

Por otro lado, un consumo frecuente de cannabis podría ser un predictor independiente de futuro riesgo de ideación suicida, así como de síntomas depresivos y anhedonia, incrementando la probabilidad de conducta suicida en el futuro (Gobbi et al., 2019). Además, esta relación se ve potenciada en el sexo masculino (Shalit et al., 2016), y en quienes comienzan el abuso a una edad temprana, quienes generan un peor pronóstico, ya que podrían contribuir a otros efectos negativos en el desarrollo cerebral (Borges et al., 2017).

Finalmente, estudios transversales revelan que el uso de otras sustancias como la cocaína, las anfetaminas y los opioides también aumentan el riesgo de suicidio, pero en menor medida, que las mencionadas con anterioridad (Borges et al., 2017; Schneider, 2009).

1.3. La neuroinflamación en el comportamiento suicida

La neuroinflamación es un mecanismo esencial en las enfermedades crónicas (Brundin et al., 2017), que se ha puesto de relieve en enfermedades sistémicas como el cáncer (Zhang et al., 2017) o en las enfermedades cardiovasculares (Misumida et al., 2015). Sin embargo, en los últimos años se ha asociado con diferentes trastornos psiquiátricos, en donde la inflamación sistémica podría dar lugar a un incremento de la respuesta inmune en el sistema nervioso central (SNC) contribuyendo a la patogénesis

de diferentes enfermedades (Canon & Crimmins, 2011) neurológicas, como el Alzheimer o el Parkinson (Wang et al., 2015; Wirth et al., 2013) o psiquiátricas, como la esquizofrenia (Potvin et al., 2008), el trastorno bipolar (Modabbernia et al., 2013) y la depresión (Dowlati et al., 2010; Valkanova et al., 2013).

La desregulación inmunitaria, consecuencia de la falta de homeostasis entre el sistema nervioso central y periférico, se ha propuesto como posible vía subyacente a la fisiopatología de la depresión (Pandey et al., 2018) y del comportamiento suicida (Courtet et al., 2015). Además, investigaciones previas han concluido que: i) existe un mayor riesgo suicida en enfermedades inflamatorias e infecciosas, como son la alergia, el asma y la toxoplasmosis (Postolache et al., 2008; Zhang et al., 2012); ii) existe una asociación entre TS, inflamación y mayor riesgo de morbilidad y mortalidad por causas naturales (cardiometabólicas) (Bergen et al., 2012); y iii) existe un mayor riesgo de suicidio en los pacientes tratados con citoquinas proinflamatorias (Fragoso et al., 2010).

Es por ello que, en los últimos años, los estudios de investigación se dirigen a la búsqueda de biomarcadores válidos, reproductibles, de bajo coste y fácilmente adaptables al entorno clínico, útiles en la prevención del comportamiento suicida. Hasta la fecha, en pacientes con trastorno depresivo mayor (TDM) y comportamiento suicida se han descrito cambios inflamatorios específicos en la periferia, en el líquido cefalorraquídeo (LCR) y en el SNC (Serafini et al., 2020), mostrando cantidades anormalmente elevadas de granulocitos y monocitos, incremento en la Proteína C Reactiva (PCR), quimiocinas, anomalías en las células T y presencia de citocinas inflamatorias (Courtet et al., 2015; Del Giudice & Gangestad, 2018).

En particular, el Indice Neutrófilo-Linfocito (INL) emerge como posible marcador de inflamación periférica de comportamiento suicida en pacientes con TDM. Investigaciones previas describen que, aquellos quienes presentan TDM y antecedentes

de TS tienen cantidades anormalmente elevadas frente a quienes no presentan dichos antecedentes y sus controles sanos (Ekinci & Ekinci, 2017; Ivković et al., 2016; Velasco et al., 2020). El Indice Plaqueta-Linfocito (IPL) se ha descrito como un marcador de gravedad de la depresión (Kayhan et al., 2017; Sunbul et al., 2016). Y el Indice Monocito/Linfocito (IML) fue significativamente mayor en jóvenes con antecedentes de TS (Ucuz & Kayhan, 2020) y conducta autolesiva (Zheng et al., 2022) frente a sus controles sanos. Finalmente, el Volumen Plaquetar Medio (VPM) también se ha asociado con la gravedad de la TS (Orum et al., 2018).

Más allá del estado inflamatorio previamente descrito en otras investigaciones, la combinación de factores biológicos y clínicos podrían subyacer a las alteraciones: i) neuroendocrinas (a través del eje hipotálamo-hipofisiario-adrenal-HPA); ii) neuroquímicas (serotoninérgicas, noradrenérgicas e inmunológicas); y iii) clínicas (pesimismo, desesperanza, impulsividad, agresividad), confiriendo vulnerabilidad haca dicha conducta (Mann et al., 1999). Por lo que, investigaciones recientes señalan que la presencia de estrés constante podría desencadenar la liberación y circulación en plasma de interleucinas proinflamatorias (González-Castro et al., 2021). De este modo, el balance de producción normal de todas las células de la sangre y del sistema inmune (residentes de tejido) se ve alterado, debido a que, dicha producción varía según la demanda fisiológica subyacente (Martínez-Botía et al., 2020), lo que se conoce como estrés hematopoyético.

Recientemente se ha propuesto un modelo comprehensivo (Courtet et al., 2016) que trata de aunar todos estos hallazgos, con el fin de entender la fisiopatología de la conducta suicida a través de la influencia del sistema inmunitario, partiendo de la conceptualización de la conducta suicida como la resultante de la vulnerabilidad suicida y del estrés.

Según este modelo, la presencia de antecedentes de maltrato en la infancia, las alteraciones en el sueño y las infecciones (por ejemplo, por *Toxoplasma Gondii*) podrían conferir vulnerabilidad suicida ya que inducen un estado inflamatorio crónico de bajo grado. En consecuencia, a esta inflamación, el eje Hipotálamo-Hipófisis-Adrenal (HPA) sufriría una desregulación que desencadenaría un aumento en los niveles de cortisol. A su vez, se activa microglía (neuroinflamación), así como, la enzima indolamina 2,3-dioxigenasa (IDO). Dicha enzima, actúa sobre la vía quinurenina-triptófano relacionada con el comportamiento suicida, y aumenta la producción de ácido quinolínico (neurotóxico), disminuyendo la de ácido quinurénico (neuroprotector), generando un incremento, en consecuencia, de la estimulación de receptores glutamatérgicos N-metil-D-aspartato (NMDA). Por otro lado, la sobreactivación de triptófano para la quinurenina, implica la reducción en la producción de serotonina, neurotransmisor relacionado con dimensiones de la personalidad asociadas al comportamiento suicida, tales como la agresividad, la impulsividad o la desesperanza. Finalmente, la presencia de otros estresores, como pueden ser la presencia de trastornos mentales o eventos vitales adversos, pueden actuar sobre la vulnerabilidad suicida para inducir conducta suicida, a través de una respuesta inflamatoria (véase figura 1).

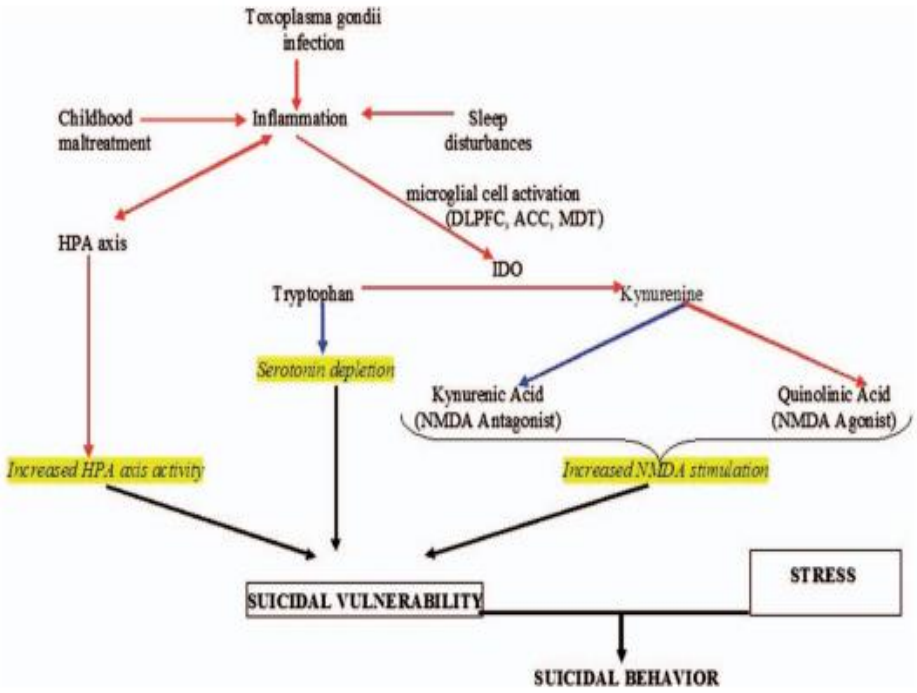


Figura 1. Inflamación y patofisiología del comportamiento suicida. Tomado de Courtet et al. (2016). En rojo se señalan las rutas que están hiperactivas y en azul, las hipoactivas.

1.4. Justificación del estudio

Hasta la fecha, no existen marcadores específicos de la conducta suicida per se. La propia complejidad del comportamiento suicida, la falta de una definición uniforme, el uso de herramientas heterogéneas para su evaluación, la disparidad de resultados o la falta de replicabilidad de los estudios realizados hasta el momento actual dificultan la búsqueda de marcadores potencialmente útiles en la detección del riesgo suicida.

Esta falta de progreso pone de relieve la necesidad de nuevas estrategias de investigación. Una rápida detección y evaluación del riesgo de suicidio ha de ser el objetivo diana que podría contribuir a una mejor prevención de la conducta suicida en los servicios de urgencia y en la práctica clínica habitual. Por tanto, el presente Trabajo de Investigación tiene como objetivo la formulación del riesgo de suicidio en pacientes con depresión a través del uso de los marcadores periféricos inflamatorios accesibles y coste-efectivos.

Hipótesis y objetivos

2. Hipótesis y objetivos

2.1 Hipótesis

1. La neuroinflamación podría tener un papel determinante en la etiopatogenia de la depresión y de la conducta suicida.

2. La formulación del riesgo de suicidio a través de los marcadores periféricos de inflamación permitiría establecer patrones diferenciales que podrían contribuir a una mejor detección y prevención de la conducta suicida en pacientes con depresión.

2.2 Objetivos

1. Determinar la utilidad de determinados marcadores periféricos de inflamación Indice Neutrófilo/Linfocito (INL), Indice Plaqueta/Linfocito (IPL), e Indice Monocito/Linfocito (IML) en la predicción del comportamiento suicida en pacientes con diagnóstico de depresión mayor.

2. Determinar la existencia de posibles diferencias en los parámetros hematopoyéticos de pacientes con depresión mayor, con y sin antecedentes de tentativa suicida, en comparación con personas sanas.

Objetivos secundarios

a) Analizar la posible existencia de estrés hematopoyético asociado a los antecedentes de tentativa suicida en pacientes con depresión mayor.

b) Establecer si existen diferencias en la respuesta de estrés hematopoyético en función del sexo.

c) Examinar la relación entre la exposición a acontecimientos vitales estresantes proximales y distales y el estrés hematopoyético.

3. Revisar de modo sistemático si los marcadores periféricos de inflamación previamente mencionados, Indice Neutrófilo/Linfocito, Indice Plaqueta/Linfocito, e Indice Monocito/Linfocito, son útiles para diferenciar: i) pacientes con depresión mayor con / sin historia de TS; ii) pacientes con depresión mayor con

historia de TS versus controles sanos; y, iii) pacientes con depresión mayor con ideación suicida antes y después de su tratamiento.

Material y método

3. Material y método

La presente Tesis Doctoral se presenta en formato por compendio de publicaciones pertenecientes a un subproyecto multicéntrico financiado por el Ministerio de Sanidad, Servicio Sociales e Igualdad a través del Instituto de Salud Carlos III (Ref. PI14/02029 y Ref. PI17/01433; Investigador Principal: Pilar A. Sáiz), con el título de "Funcionamiento neuropsicológico y perfil inflamatorio en el comportamiento suicida" y "Detección de riesgo de comportamiento suicida mediante la combinación de aproximaciones genómicas y clínicas", respectivamente.

3.1. Aspectos éticos

Los investigadores del presente estudio se comprometieron a respetar la legislación vigente en materia de investigación clínica establecida en la Declaración de Helsinki (World Medical Association, 2013), en el Convenio del Consejo de Europa sobre derechos humanos y biomedicina, en la Declaración Universal de la UNESCO, asi cómo los requisitos establecidos en la legislación española sobre investigación biomédica, protección de datos de carácter personal y bioética, con la Ley 14/2007, de julio, de investigación biomédica y los demás requisitos establecidos por la legislación española al respecto, modificada en la Ley Orgánica 3/2018 de protección de datos personales y garantía de los derechos digitales.

Este trabajo de investigación ha obtenido la aprobación por parte del Comité de Ética e Investigación Clínica del Hospital Universitario Central de Asturias (HUCA) (Ref. 61/14). Tras explicar los objetivos del estudio, los procedimientos que se realizarían, y las condiciones de la participación, se obtuvo el consentimiento informado para la participación en el estudio de todos los participantes (véase Anexo I).

Dada la inocuidad de las pruebas a realizar (evaluaciones clínicas y extracción sanguínea) y la no interferencia en el tratamiento pautado de antemano en el paciente, se considera un estudio de mínimo riesgo.

Publicaciones

4. Publicaciones

La presente Tesis Doctoral se presenta en formato por compendio de publicaciones. Los objetivos e hipótesis planteados se desarrollan detalladamente en los artículos que se incluyen a continuación. Señalar que, todos ellos, han sido publicados en revistas indexadas internacionalmente con Factor de Impacto (FI), en la Journal Citation Reports (JCR), dos de ellos situados en Q1.

En el primer artículo, *Neutrophil-to-lymphocyte ratio: A potential new peripheral biomarker of suicidal behavior* (Velasco et al., 2020) se determina la utilidad de los marcadores periféricos de inflamación INL, IPL e IML en la predicción del comportamiento suicida en pacientes con TDM bajo las siguientes condiciones: i) TS reciente (en la última semana); ii) antecedentes de TS a lo largo de la vida; y iii) sin antecedentes de TS.

En el segundo artículo, *Sex-dependent grades of haematopoietic modulation in patients with major depressive episodes are associated with suicide attempts* (Martínez-Botía et al., 2020), se determina la existencia de posibles diferencias en los parámetros hematopoyéticos en pacientes con TDM (con/sin historia de TS) y controles sanos.

Finalmente, en el tercer artículo, *Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio in depressed patients with suicidal behavior: A systematic review* (Velasco et al., 2023), se revisa de modo sistemático si los marcadores periféricos de inflamación INL, IPL e IML son útiles para diferenciar: i) pacientes con TDM con/sin historia de TS; ii) pacientes con TDM e historia de TS *versus* controles sanos; y, iii) pacientes con TDM e IS antes y después de su tratamiento.

En el apartado de aportaciones científicas, se incluyen otros artículos científicos relacionados con la temática de la Tesis Doctoral, ponencias y comunicaciones

científicas en congresos internacionales y nacionales, colaboraciones en capítulos de libro y dos co-tutorizaciones en trabajos fin de grado.

Artículo 1

Referencia: **Velasco Á**, Rodríguez-Revuelta J, Olié E, Abad I, Fernández-Peláez A, Cazals A, et al. Neutrophil-to-lymphocyte ratio: A potential new peripheral biomarker of suicidal behavior. Eur Psychiatry. 2020;63(1). DOI: 10.1192/j.eurpsy.2019.20

Resumen: Neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) have emerged as important peripheral inflammatory biomarkers. Recent data suggest a possible role of the immune system in the pathophysiology of suicidal behavior (SB). The aim of this study is to evaluate the association among NLR, MLR, and PLR and SB in patients with major depressive disorder (MDD), and to test its validity as a biomarker for suicidality. Methods. We evaluated 538 patients with MDD (mean age [standard deviation] = 43.87 [14.36] years; females: 68.8%). A logistic regression model was estimated to determine the independent factors associated with suicide risk in patients with and without a history of suicide attempt (SA). Results. Three hundred ninety-three patients (74.7%) had a personal history of SA. Patients with a previous SA were more frequently female (71.9% vs. 59.6%; $p = 0.007$), significantly younger (41.20 vs. 51.77 years; $p < 0.001$), had lower depression severity at enrolment (15.58 vs. 18.42; $p < 0.000$), and significantly higher mean NLR and PLR ratios (2.27 vs. 1.68, $p = 0.001$; 127.90 vs. 109.97, $p = 0.007$, respectively). In the final logistic regression model, after controlling for age, sex, and depression severity, NLR was significantly associated with SB ($\beta = 0.489$, $p = 0.000$; odds ratio [95% confidence intervals] = 1.631 [1.266–2.102]). We propose a cut-off value of NLR=1.30 (sensitivity = 75% and specificity = 35%). Conclusions. Our data suggest that NLR may be a valuable, reproducible, easily accessible, and cost-effective strategy to determine suicide risk in MDD.

Factor de impacto JCR 2020: 5.361

European Psychiatry

www.cambridge.org/epa

Neutrophil-to-lymphocyte ratio: A potential new peripheral biomarker of suicidal behavior

Ángela Velasco[1,2,3], Julia Rodríguez-Revuelta[1,3,4], Emilie Olié[5,6], Iciar Abad[4], Abel Fernández-Peláez[1], Aurélie Cazals[5,6], Sébastien Guillaume[5,6], Lorena de la Fuente-Tomás[1,2,3], Luis Jiménez-Treviño[1,2,3,4], Laura Gutiérrez[3,7], Paz García-Portilla[1,2,3,4], Julio Bobes[1,2,3,4], Philippe Courtet[5,6] and Pilar A. Sáiz[1,2,3,4]

[1]Department of Psychiatry, University of Oviedo, Oviedo, Spain; [2]Biomedical Research Networking Centre in Mental Health (CIBERSAM), Oviedo, Spain; [3]Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain; [4]Mental Health Services of Principado de Asturias (SESPA), Oviedo, Spain; [5]Department of Emergency Psychiatry and Post-Acute Care, Lapeyronie Hospital, CHU Montpellier—Inserm U1061, University of Montpellier, Montpellier, France; [6]Fondation FondaMental, Créteil, France and [7]Department of Medicine, University of Oviedo, Oviedo, Spain

Research Article

Cite this article: Velasco Á, Rodríguez-Revuelta J, Olié E, Abad I, Fernández-Peláez A, Cazals A, Guillaume S, de la Fuente-Tomás L, Jiménez-Treviño L, Gutiérrez L, García-Portilla P, Bobes J, Courtet P, Sáiz PA (2020). Neutrophil-to-lymphocyte ratio: A potential new peripheral biomarker of suicidal behavior. *European Psychiatry*, 63(1), e14, 1–6
https://doi.org/10.1192/j.eurpsy.2019.20

Received: 03 May 2019
Revised: 28 October 2019
Accepted: 15 December 2019

Key words:
Major depressive disorder; neutrophil-to-lymphocyte ratio; suicide vulnerability; trait marker

Author for correspondence:
Ángela Velasco Iglesias,
E-mail: angelaig@outlook.com

Abstract

Background. Neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) have emerged as important peripheral inflammatory biomarkers. Recent data suggest a possible role of the immune system in the pathophysiology of suicidal behavior (SB). The aim of this study is to evaluate the association among NLR, MLR, and PLR and SB in patients with major depressive disorder (MDD), and to test its validity as a biomarker for suicidality.

Methods. We evaluated 538 patients with MDD (mean age [standard deviation] = 43.87 [14.36] years; females: 68.8%). A logistic regression model was estimated to determine the independent factors associated with suicide risk in patients with and without a history of suicide attempt (SA).

Results. Three hundred ninety-three patients (74.7%) had a personal history of SA. Patients with a previous SA were more frequently female (71.9% vs. 59.6%; p =0.007), significantly younger (41.20 vs. 51.77 years; $p < 0.001$), had lower depression severity at enrolment (15.58 vs. 18.42; $p < 0.000$), and significantly higher mean NLR and PLR ratios (2.27 vs. 1.68, $p = 0.001$; 127.90 vs. 109.97, $p = 0.007$, respectively). In the final logistic regression model, after controlling for age, sex, and depression severity, NLR was significantly associated with SB ($\beta = 0.489$, $p = 0.000$; odds ratio [95% confidence intervals] = 1.631 [1.266−2.102]). We propose a cut-off value of NLR = 1.30 (sensitivity = 75% and specificity = 35%).

Conclusions. Our data suggest that NLR may be a valuable, reproducible, easily accessible, and cost-effective strategy to determine suicide risk in MDD.

Introduction

Suicide is a pressing public health problem. On an average, 1 million people commit suicide each year worldwide, and suicide is the second leading cause of death in the 15−29-year age group. However, this rate may be even higher since, for each suicide death, it is estimated that there are at least 20 suicide attempts (SAs) [1].

Clinical factors (especially depression and alcoholism), previous SAs, and stressful life events are generally assumed to be the best predictors of suicidal behavior (SB) [2]. Thus, clinical scales are a central component of routine clinical assessment, despite limited evidence of their effectiveness for predicting suicide risk [3]. The short-term variability of suicide ideation may be related to this failure, and some authors have suggested the need for real-time evaluation of interpersonal and psychological variables [4].

A wide range of possible biological risk factors for future SB have also been proposed. However, we are still far from having good biomarkers for SB [5], and prediction of future suicidality is currently a long-range goal. This lack of progress highlights the need for new research strategies.

Neuroinflammatory processes are an essential pathophysiologic mechanism of chronic diseases including severe mental disorders [6,7]. There is now evidence that major depressive disorder (MDD) is characterized by activation of the immune-inflammatory response system, as indicated by increased levels of pro-inflammatory cytokines including interleukin (IL)-6 and IL-10 [8]. A comprehensive model focusing on immune system influence on the pathophysiology of SB has been proposed [9]. In this model, childhood abuse, sleep disturbance, infections, and other stressors induce a chronic inflammatory state, causing dysregulation of the hypothalamic

EUROPEAN PSYCHIATRIC ASSOCIATION

pituitary–adrenal axis. The subsequent cortisol and indolamine 2,3-dioxygenase activation affects serotonin metabolism and increases N-methyl-$_D$-aspartate (NMDA) agonist levels [10]. Thus, inflammatory markers could potentially be used to predict and monitor suicide risk in patients with mental disorder [11,12].

In recent years, neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) have been found to be attractive, convenient, and cost-effective blood indicators of inflammatory status. These ratios have been used as inflammation/immune-based prognostic scores in different systemic diseases such as cancer, coronary heart disease, and pancreatitis [13].

Recently, a few studies have found NLR and PLR to be elevated in MDD [14,15] as well as bipolar disorder [16]. Furthermore, meta-analytic evidence has also shown increased NLR in patients with MDD as compared with healthy controls [17]. Two recent studies even suggest that NLR may be a marker for suicide vulnerability in patients with bipolar disorder or MDD [18,19]. NLR was substantially higher in suicidal depressed patients compared with nonsuicidal depressed patients and healthy controls. One logistic regression model included NLR and previous attempts as predictive variables for suicide status [19].

Our objective is to investigate the association among NLR, MLR, and PLR and history of SAs in patients with MDD, controlling for different potential confounding variables, in order to help determine the possible role of these ratios in predicting SB.

Methods

Participants

A sample of 538 Caucasian patients aged ≥18 years was recruited in the Mental Health Services of Oviedo (Asturias, Spain; $n = 148$) and in the Department of Emergency Psychiatry and Post-Acute Care at the University Hospital of Montpellier (France; $n = 390$) from September 2015 to June 2017.

All patients had a diagnosis of MDD according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria. SA was also defined as a "self-initiated sequence of behaviors by an individual who, at the time of initiation, expected that the set of actions would lead to his or her own death" [20]. All patients were undergoing pharmacological antidepressant treatment at the time of the study. The exclusion criteria were comorbid psychiatric diagnoses, acute infections, active or chronic inflammatory, or autoimmune diseases, smoking ≥20 cigarettes/day, obesity (BMI > 30 kg/m^2), current treatment with anti-inflammatory or immunosuppressive medications, acute coronary syndromes, history of chronic renal, hepatic, or cerebrovascular disease, and significant abnormalities in laboratory test results (anemia, leukocytosis, leukopenia, or thrombocytosis).

Written informed consent was obtained from all patients included in the study. The study was conducted in compliance with applicable legislation in each country and the provisions of the World Medical Association Declaration of Helsinki, and it received institutional approval [21].

Assessments

All participants were assessed by well-trained interviewers using an "ad hoc" protocol for sociodemographic and clinical data (sex, age, pharmacological antidepressant treatment [yes/no], number of SA, and age at first attempt), as well as the Hamilton Depression Rating Scale (HDRS). Hamilton total score was evaluated as follows: 8–16: mild depression; 17–23: moderate depression; and ≥24: severe depression [22].

All the researchers involved in the clinical assessments at both sites received training in order to achieve the same standards.

For the exploratory analysis, patients with a previous SA were divided into two different groups: those with a very recent SA (≤7 days) and those with a less recent lifetime history of SA.

Fasting peripheral blood samples were collected from the cephalic vein between 8:00 and 9:00 a.m. in EDTA tubes. Complete blood counts were performed using a Sysmex XN-10/XN-20 Hematology Analyzer (Norderstedt, Germany). Complete blood counts included total white blood cells, neutrophils, lymphocytes, monocytes, and platelets. NLR, MLR, and PLR were calculated.

Statistical analyses

The data were analyzed using SPSS 15.0 (SPSS, Inc., Chicago, IL). Data are presented as mean (standard deviation [SD]) for numeric variables and as frequencies and percentages for categorical variables.

A Kolmogorov–Smirnov normality test was used to determine if variables were normally distributed. A chi-square (χ^2) test was used to compare categorical variables and frequencies. Continuous variables were expressed as mean (SD). Normally and abnormally distributed variables were analyzed. A Student's *t*-test and one-way analysis of variance with post hoc Duncan test was used to compare normally distributed variables between two and three groups, respectively. However, a Mann–Whitney *U* test or Kruskal–Wallis test was performed to analyze any abnormally distributed variables. Bivariate correlations were performed to determine differences according to previous SA based on sociodemographic and clinical data. A logistic regression model (forward stepwise selection) was estimated to determine the independent factors associated with suicide risk in patients with and without a history of SA. A multinomial logistic regression model (main effects model) was used to determine factors linked to suicidality in patients with MDD ("never attempted" was used as the category of reference). A receiver operating characteristic (ROC) curve analysis was performed to determine the cut-off level for biomarkers to detect the SA. The level of statistical significance was set at $\alpha = 0.05$ (two-sided).

Results

The final sample included 538 patients with a DSM-5 MDD diagnosis (mean age [SD] = 43.87 [14.36] years; females: 370 [68.8%]). All patients included in the study were experiencing an active episode of depression with a score of 7 or more on the HDRS scale. Severity of depression was moderate/severe in 44.8% of patients according to the HDRS score. An average NLR ratio (SD) of 2.12 (1.98) was observed in the total sample, whereas the mean MLR and PLR ratios (SD) were 0.27 (0.14) and 123.37 (55.68), respectively (Table 1).

There were 402 patients (74.7%) with a personal history of SA (mean age [SD] = 41.20 [13.78] years; females: 289 [71.9%]). Mean age (SD) at first SA was 32.62 (14.20) years and mean number (SD) of SA was 2.62 (3.13). Patients with no history of SA were more frequently males (40.4% vs. 28.6 and 27.9%; χ^2 [df] = 7.214 [2], $p = 0.027$), were significantly older (51.77 [13.10] vs. 39.99 [14.64] and 41.75 [13.37] years; $F = 31.397$, $p < 0.001$), had higher depression severity (HDRS score: 18.42 [5.21] vs. 14.33 [4.07] and 16.15 [5.14];

Table 1. Sociodemographic and clinical characteristics of the study group

	Total sample n = 538	Recent SA (≤7 days) n = 126	Lifetime SA (≥8 days) n = 276	No history of SA n = 136	χ^2/ANOVA[a]/Student's t-test[b]/Kruskal–Wallis test[b]	p
Sociodemographic data						
Sex (n [%])]						
Males	168 (31.2%)	36 (28.6%)	77 (27.9%)	55 (40.4%)	7.214	0.027
Females	370 (68.8%)	90 (71.4%)	199 (72.1%)	81 (59.6%)		
Age (mean [SD])	43.87 (14.36)	39.99 (14.64)[1]	41.75 (13.37)[2]	51.77 (13.10)[1,2]	31.397[a]	0.000
Clinical characteristics						
Severity of depression (mean [SD])	16.30 (5.13)	14.33 (4.07)[1,2]	16.15 (5.14)[1,3]	18.42 (5.21)[2,3]	22.803[a]	0.000
HDRS 8–16 (mild) (n [%])	297 (55.2%)	96 (76.2%)	154 (55.8%)	47 (34.6%)	52.996	0.000
HDRS 17–23 (moderate) (n [%])	188 (34.9%)	26 (20.6%)	100 (36.2%)	62 (45.6%)		
HDRS ≥24 (severe) (n [%])	53 (9.9%)	4 (3.2%)	22 (8.0%)	27 (19.9%)		
Number of SA (mean [SD])	–	2.79 (3.89)	2.53 (2.72)	–	0.769[b]	0.443
Age of first SA (mean [SD])	–	32.33 (14.93)	32.75 (13.87)	–	–0.273[b]	0.785
NLR (mean [SD])	2.12 (1.98)	2.37 (2.36)[1]	2.22 (2.17)[2]	1.68 (0.80)[1,2]	10.630[c]	0.005
MLR (mean [SD])	0.27 (0.14)	0.28 (0.16)	0.27 (0.15)	0.25 (0.10)	1.114[c]	0.573
PLR (mean [SD])	123.37 (55.68)	128.20 (61.65)	127.76 (58.91)[1]	109.97 (38.75)[1]	7.487[c]	0.024
Leukocytes (mean [SD])	7.15 (4.05)	7.12 (2.65)	7.24 (5.17)	6.97 (2.03)	0.061[c]	0.970
Neutrophils (mean [SD])	4.01 (2.14)	4.22 (2.79)	4.05 (2.10)	3.75 (1.39)	1.024[c]	0.599
Monocytes (mean [SD])	0.53 (0.19)	0.52 (0.20)	0.51 (0.19)[1]	0.56 (0.18)[1]	8.993[c]	0.011
Lymphocytes (mean [SD])	2.22 (0.91)	2.15 (1.10)[1]	2.16 (0.87)[2]	2.42 (0.77)[1,2]	14.482[c]	0.001
Platelets (mean [SD])	243.02 (67.19)	236.34 (60.64)	245.36 (74.31)	244.49 (57.00)	1.584[c]	0.453

Abbreviations: HDRS, Hamilton Depression Rating Scale; MLR, monocyte-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SA, suicide attempt; SD, standard deviation; χ^2, chi-square test.
Note: Superscript numerals represent statistically different groups after post hoc Duncan test.
[a]One-way analysis of variance (ANOVA).
[b]Student's t-test.
[c]Kruskal–Wallis test.

χ^2 [df] = 32.168 [2], $p < 0.001$), and had significantly lower mean NLR and PLR ratios (1.68 [0.80] vs. 2.37 [2.36] and 2.22 [2.17], H = 10.630, p = 0.005; 109.97 [38.75] vs. 128.20 [61.65] and 127.76 [58.91], H = 7.487, p = 0.024, respectively; Table 1).

No association was found between NLR or PLR and age (r = 0.002, p = 0.957 and r = 0.046, p = 0.290, respectively), number of SA (r = –0.062, p = 0.222 and r = 0.041, p = 0.422), or age at first SA (r = 0.060, p = 0.242 and r = –0.004, p = 0.942). No association was found between NRL and depression severity (r = –0.015, p = 0.730), whereas PRL was significantly associated with depression severity (r = –0.113, p = 0.009). However, both ratios were associated with sex with NLR higher in men (2.37 vs. 1.99; U = 26,730, p = 0.009) and PLR higher in women (127.25 vs. 114.80; U = 35,248.50, p = 0.013). Conversely, MLR was associated with age (r = 0.096, p = 0.026) and age at first SA (r = 0.119, p = 0.020), whereas no association was found between MLR and depression severity (r = –0.045, p = 0.298), number of SA (r = –0.048, p = 0.344), or sex (U = 28,107, p = 0.094). A significant correlation was found between NLR and PLR (r = 0.462, p < 0.001), NLR and MLR (r = 0.518, p < 0.001), and MLR and PLR (r = 0.607, p < 0.001).

Since no statistically significant differences were found between the two SA subgroups, we used SA (yes/no) as a dependent variable for the stepwise logistic regression model. The model was run to assess the potential predictive value of NLR and PLR on SA. After controlling for age, sex, and depression severity, only NLR (β = 0.489, p < 0.001; odds ratio [OR] [95% confidence intervals (CI)] = 1.631 [1.266–2.102]) was included in the final model.

The multinomial regression analysis shows no differences in NLR or PLR between recent and past attempters, while patients with MDD who never attempted suicide exhibited significantly lower NRL compared with recent attempters (β = 0.471, p = 0.003; OR [95% CI] = 1.602 [1.177–2.179]) and past attempters (β = 0.423, p = 0.006; OR [95% CI] = 1.526 [1.131–2.059]; Table 2).

According to the ROC curve analysis (Figure 1), the optimal cut-off value for NLR in predicting SA was 1.59 (area under the curve = 0.593 [95% CI = 0.540–0.646], sensitivity = 60%, and specificity = 58%). However, in order to reduce the large number of false negatives, we suggest a cut-off of 1.30 (sensitivity = 75%, specificity = 35%, positive predictive value = 77%, and negative predictive value = 32%).

Discussion

Inflammation and suicidality

In the present study, we suggest a role of inflammation in SB that may be detected by white blood cell count. NLR was higher in suicidal versus nonsuicidal depressive patients and may represent a marker of

Table 2. Variables associated with never attempted versus recent attempt or past attempt

	β	SE	Wald	df	*p*	OR	95% CI
Recent attempt							
Intersection	4.943	0.786	39.540	1	0.000		
PLR	0.001	0.003	0.107	1	0.743	1.001	0.995–1.008
NLR	0.471	0.157	8.999	1	0.003	1.602	1.177–2.179
HDRS	−0.165	0.029	32.703	1	0.000	0.847	0.801–0.897
Age	−0.068	0.011	41.394	1	0.000	0.934	0.915–0.954
Sex (male)	−0.638	0.302	0.035	1	0.035	0.528	0.292–0.955
Past attempt							
Intersection	4.034	0.676	35.583	1	0.000		
PLR	0.002	0.003	0.522	1	0.470	1.002	0.996–1.008
NLR	0.423	0.153	7.655	1	0.006	1.526	1.131–2.059
HDRS	−0.081	0.023	12.861	1	0.000	0.922	0.882–0.964
Age	−0.059	0.009	41.833	1	0.000	0.943	0.926–0.960
Sex (male)	−0.592	−0.249	5.641	1	0.018	0.553	0.340–0.902

Abbreviations: CI, confidence interval; df, degrees of freedom; HDRS, Hamilton Depression Rating Scale; NLR, neutrophil-to-lymphocyte ratio; OR, odds ratio; PLR, platelet-to-lymphocyte ratio; SE, standard error.

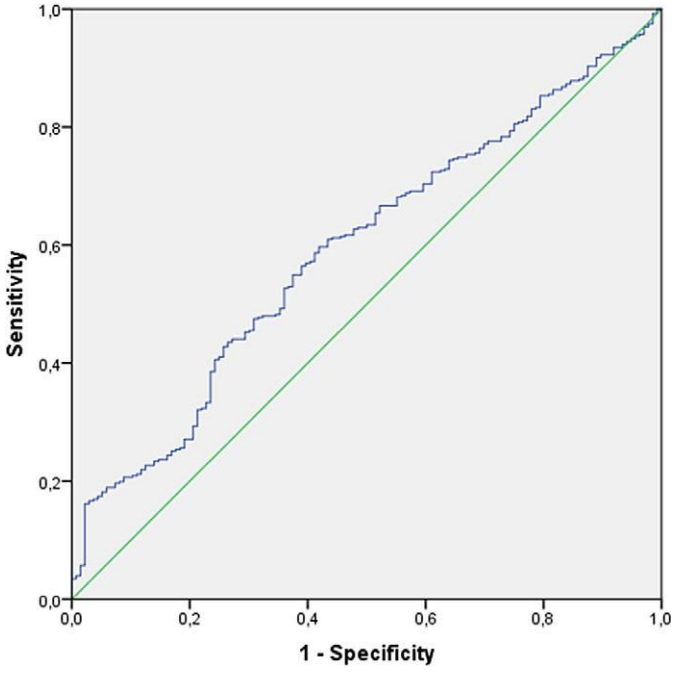


Figure 1. Receiver operating characteristic (ROC) curve of neutrophil-to-lymphocyte ratio for prediction of suicide attempt.

SA in patients with MDD. Interestingly, NLR was associated with SA after controlling for age, sex, and depression severity.

A relationship between different chronic inflammatory states and depression or SB has already been suggested in previous research. First, autoimmune disorders such as multiple sclerosis and systemic lupus erythematosus have been associated with a twofold increase in risk of death by suicide [23] and higher prevalence of suicidal ideation [24]. Second, the prevalence of suicidal ideation and SA is higher in HIV patients and chronic hepatitis C patients [25], and *Toxoplasma gondii* infection has been associated with SB [26]. It is worth noting that infections activate neuroinflammatory mechanisms associated with the pathophysiology of SB. Third, acute-phase inflammatory markers such as C-reactive protein (CRP) have been associated with SB [27,28]. Fourth, the therapeutic benefit of ketamine for reducing suicidal ideation may be related, at least in part, to its NMDA antagonist effect [29]. It is also noteworthy that increased NMDA agonist levels seem to be affected by inflammatory processes [10].

Interoceptive signaling of inflammation also plays a role in human depression. Cumulative meta-analyses now provide convincing evidence for elevated peripheral inflammatory markers, particularly IL-6 and CRP, in a subset of depressed patients [30]. Interoceptive pathways link these central and peripheral immune changes and make a powerful contribution to maladaptive stress responses such as SB.

Altogether, these studies support the hypothesis that inflammation may be a critical factor in the etiology of mood disorders and suicide risk. Thus, immunomodulatory therapies may be effective treatment options. To develop individualized therapeutic strategies, some authors point out the need for identifying subgroups of patients with psychiatric disorders and signs of immune dysregulation [31], hence the need for inflammation markers in SB.

NLR as a biological marker of SB

Our results confirm previous findings by Ekinci and Ekinci also in a sample of MDD patients [19]. These authors suggest that NLR may be a trait marker for suicide vulnerability in MDD.

Previous studies had already shown that the NLR is significantly higher in patients with MDD [14] and bipolar disorder [16] than in healthy controls. In addition, it has recently been suggested that NLR may be useful in predicting risk of SA in the subpopulation of bipolar disorder patients with a family history of SA [18] or in differentiating violent SAs and nonviolent SAs [32]. The only negative study, to the best of our knowledge, regarding an association between NLR and suicidality is the one by Gundogdu Meydaneri and Meydaneri [33]. However, the small sample size in the study may have led to a type II error.

White blood cell and subtype counts are some of the predictors of chronic inflammation. It has been suggested that stress and depression increase leukocyte and neutrophil levels, whereas they decrease lymphocytes [34]. However, it has also been suggested that NLR is a more reliable and stable peripheral-blood biomarker of inflammation than CRP levels or lipid profile for predicting suicidality [19]. Our results strengthen this association and extend it to suicidality, as depressed patients with a lifetime history of SA showed higher neutrophil and lower lymphocyte levels than depressed patients without a history of suicidality.

In contrast, our study did not show any differences in PLR index between MDD patients with or without a history of SA. PLR has previously been correlated with severity of MDD. More specifically, patients who had MDD with psychotic features had higher PLR scores than other MDD patients [15]. The latter research, along with recent studies conducted in other areas, have reported that PLR may be better than NLR for determining severity of inflammation [35]; thus the lack of association between PLR and suicide risk found in our study was unexpected.

NLR cut-off value

To date, this is the first study suggesting a NLR cut-off value associated with SA. Our data suggest that NLR is significantly associated with SA in MDD patients with an optimal cut-off value of 1.59 (sensitivity 60% and specificity 58%). However, after evaluating our results, we suggest that a more suitable cut-off point for evaluation of suicide risk would be 1.30. With this cut-off point, at least in our sample, there is a major increase in sensitivity (75%), although specificity falls to 35%. Nevertheless, given the consequences of the event, we wish to predict and the possibility of using NLR to screen for suicide risk in situations where time is of the essence, such as hospital emergency room or primary care settings, it is clear that good sensitivity must take priority over specificity. It should be noted that Orum et al. [32] proposed 2.22 as the optimal cut-off for NLR in order to differentiate violent from nonviolent SA (sensitivity 68.8% and specificity 60.6%).

Strengths and limitations

Our study has some strengths and limitations. On the one hand, we collected a large cohort from two independent institutions with a sample size large enough to find a significant association between NLR and lifetime SA in patients with MDD. In addition, the fact that we used a sample from two different countries may contribute to the generalizability of our results in Caucasian populations. Patients with chronic illnesses and those treated with anti-inflammatory drugs were excluded. Finally, we controlled for age, sex, and depression severity to ensure reliable results.

One limitation of the present study is its cross-sectional design, which limits conclusions regarding causal relationships between history of SA and inflammation. Other limitations may include potential confounding factors such as tobacco use, number of previous MDD episodes, antidepressant psychiatric treatment, including dosage and time on treatment, or the lack of a healthy control group. However, we consider these partial limitations, since our study is aimed at assessing the power of NLR, PLR, and MLR to separate MDD patients based on SA, and if strong enough, to define a cut-off with prognostic value. We have observed no differences based on tobacco use or treatment among MDD patient subgroups and therefore conclude that the potential use of NLR as a prognostic biomarker should not be biased by these variables.

In conclusion, our data confirm that using NLR may be a valuable, reproducible, easily accessible, and cost-effective strategy in clinical practice for detecting suicide vulnerability in patients with MDD. To date, there is no strong biomarker associated with suicidality. In particular, it is more probable that a combination of different biomarkers could predict the risk of SBs [36]. However, prospective studies are needed in order to determine causal relationships. Studies that include other psychiatric diagnoses are also needed in order to test the specificity of our findings.

Acknowledgments. The authors thank Sharon Grevet for her English assistance, which was sponsored by research grants.

Financial Support. This research was partially supported by grants FIS PI14/02029 and PI17/01433 (PI: P.A.S.) from the Instituto de Salud Carlos III, Spanish Ministry of Economy and Competitiveness, and Fondos Europeos de Desarrollo Regional (FEDER), by the Government of the Principality of Asturias PCTI-2018-2022 IDI/2018/235, and by an RYC fellowship (RYC-2013-12587) and an I+D 2017 grant (SAF2017-85489-P) to L.G. Finally, L.d.l.F.-T. and Á.V. received Severo Ochoa grants (PA-17-PF-B16-179 and PA-18-PF-BP17-177, respectively) from the Government of the Principality of Asturias. The funders played no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflict of Interest. All authors declare that they have no conflict of interest relative to this study.

Authorship Contributions. All authors contributed equally to and approved the final manuscript.

Data Availability Statement. There are no linked research data sets. Data will be made available on request.

Abbreviations

CRP	C-reactive protein
HDRS	Hamilton Depression Rating Scale
HIV	human immunodeficiency virus
MDD	major depressive disorder
MLR	monocyte-to-lymphocyte ratio
NLR	neutrophil-to-lymphocyte ratio
NMDA	N-methyl-$_D$-aspartate
PLR	platelet-to-lymphocyte ratio
ROC	receiver operating characteristic
SA	suicide attempt

References

[1] World Health Organization. Public health action for prevention of suicide: a framework. Geneva, Switzerland: World Health Organization Press; 2012.

[2] Blasco-Fontecilla H, Delgado-Gómez D, Ruiz-Hernández D, Aguado D, Baca-García E, López-Castroman J. Combining scales to assess suicide risk. J Psychiatr Res. 2012;46:1272−7.

[3] Quinlivan L, Cooper J, Davies L, Hawton K, Gunnell D, Kapur N. Which are the most useful scales for predicting repeat self-harm? A systematic review evaluating risk scales using measures of diagnostic accuracy. BMJ Open. 2016;6:e009297.

[4] Hallensleben N, Glaesmer H, Forkmann T, Rath D, Strauss M, Kersting A, *et al*. Predicting suicidal ideation by interpersonal variables, hopelessness and depression in real-time. An ecological momentary assessment study in psychiatric inpatients with depression. Eur Psychiatry. 2019;56:43−50.

[5] Chang BP, Franklin JC, Ribeiro JD, Fox KR, Bentley KH, Kleiman EM, *et al*. Biological risk factors for suicidal behaviours: a meta-analysis. Transl Psychiatry. 2016;6:e887.

[6] Couzin-Frankel J. Inflammation bares a dark side. Science. 2010;330:16−21.

[7] García-Álvarez L, Caso JR, García-Portilla MP, De la Fuente-Tomás L, González-Blanco L, Sáiz-Martinez P, *et al*. Regulation of inflammatory pathways in schizophrenia: a comparative study with bipolar disorder and healthy controls. Eur Psychiatry. 2018;47:50−9.

[8] Al-Fadhel SZ, Al-Hakeim HK, Al-Dujaili AH, Maes M. IL-10 is associated with increased mu-opioid receptor levels in major depressive disorder. Eur Psychiatry. 2019;57:46−51.

[9] Courtet P, Giner L, Seneque M, Guillaume S, Olié E, Ducasse D. Neuroinflammation in suicide: toward a comprehensive model. World J Biol Psychiatry. 2016;17:564−86.

[10] Brundin L, Bryleva EY, Thirtamara Rajamani K. Role of inflammation in suicide: from mechanisms to treatment. Neuropsychopharmacology. 2017;42:271−83.

[11] Chang CC, Tzeng NS, Kao YC, Yeh CB, Chang HA. The relationships of current suicidal ideation with inflammatory markers and heart rate variability in unmedicated patients with major depressive disorder. Psychia- try Res. 2017;258:449−56.

[12] Messaoud A, Mensi R, Douki W, Neffati F, Najjar MF, Gobbi G, *et al*. Reduced peripheral availability of tryptophan and increased activation of the kynurenine pathway and cortisol correlate with major depression and suicide. World J Biol Psychiatry. 2018;23:1−9.

[13] Isaac V, Wu C, Huang C, Baune BT, Tseng C, McLachlan CS. Elevated neutrophil to lymphocyte ratio predicts mortality in medical inpatients with multiple chronic conditions. Medicine. 2016;95:e0916.

[14] Demir S, Atli A, Bulut M, Ibiloglu AO, Gunes M, Kaya MC, *et al*. Neutrophil-lymphocyte ratio in patients with major depressive disorder undergoing no pharmacological therapy. Neuropsychiatr Dis Treat. 2015; 11:2253−8.

[15] Kayhan F, Gunduz S, Ersoy SA, Kandeger A, Annagur BB. Relationships of neutrophil-lymphocyte and platelet-lymphocyte ratios with the severity of major depression. Psychiatry Res. 2017;247:332−5.

[16] Cakir U, Tuman TC, Yildirim O. Increased neutrophil/lymphocyte ratio in patients with bipolar disorder: a preliminary study. Psychiatr Danub. 2015; 27:180−4.

[17] Mazza MG, Lucchi S, Tringali AGM, Rossetti A, Botti ER, Clerici M. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in mood dis- orders: a meta-analysis. Prog Neuropsychopharmacol Biol Psychiatry. 2018;84:229−36.

[18] Ivkovic M, Pantovic-Stefanovic M, Dunjic-Kostic B, Jurisic V, Lackovic M, Totic-Poznanovic S, *et al*. Neutrophil-to-lymphocyte ratio predicting suicide risk in euthymic patients with bipolar disorder: moderatory effect of family history. Compr Psychiatry. 2016;66:87−95.

[19] Ekinci O, Ekinci A. The connections among suicidal behaviour, lipid profile and low-grade inflammation in patients with major depressive disorder: a specific relationship with the neutrophil-to-lymphocyte ratio. Nord J Psychiatry. 2017;71:574−80.

[20] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.

[21] World Medical Association. Declaration of Helsinki. 41st World Medical Association General Assembly. Hong Kong: World Medical Association; 1989.

[22] Zimmerman M, Martinez JH, Young D, Chelminski I. Severity classification on the Hamilton Depression Rating Scale. J Affect Disord. 2013;150:384−8.

[23] Bronnum-Hansen H, Stenager E, Nylev Stenager E, Koch-Henriksen N. Suicide among Danes with multiple sclerosis. J Neurol Neurosurg Psychiatry. 2005;76:1457−9.

[24] Zakeri Z, Shakiba M, Narouie B, Mladkova N, Ghasemi-Rad M, Khosravi A. Prevalence of depression and depressive symptoms in patients with systemic lupus erythematosus: Iranian experience. Rheumatol Int. 2012;32:1179−87.

[25] Alavi S, Valeshabad A, Sharifi Z, Nourbakhsh K, Arzanian MT, Navidinia M, *et al*. Torque teno virus and hepatitis C virus co-infection in Iranian pediatric thalassemia patients. Turk J Haematol. 2012;29:156−61.

[26] Postolache TT, Komarow H, Tonelli LH. Allergy: a risk factor for suicide? Curr Treat Options Neurol. 2008;10:363−76.

[27] Courtet P, Jaussent I, Genty C, Dupuy AM, Guillaume S, Ducasse D, *et al*. Increased CRP levels may be a trait marker of suicidal attempt. Eur Neuropsychopharmacol. 2015;25:1824−31.

[28] Gibbs HM, Davis L, Han X, Clothier J, Eads LA, Cáceda R. Association between C-reactive protein and suicidal behaviour in an adult inpatient population. J Psychiatr Res. 2016;79:28−33.

[29] Price RB, Iosifescu DV, Murrough JW, Chang LC, Al Jurdi RK, Iqbal SZ, *et al*. Effects of ketamine on explicit and implicit suicidal cognition: a randomized controlled trial in treatment-resistant depression. Depress Anxiety. 2014;31:335−43.

[30] Savitz J, Harrison NA. Interoception and inflammation in psychiatric disorders. Biol Psychiatry Cogn Neurosci Neuroimag. 2018;3:514−24.

[31] Pape K, Tamouza R, Leboyer M, Zipp F. Immunoneuropsychiatry—novel perspectives on brain disorders. Nature Rev Neurol. 2019;15:317−28.

[32] Orum MH, Kara MZ, Egilmez OB. Mean platelet volume and neutrophil to lymphocyte ratio as parameters to indicate the severity of suicide attempt. J Immunoassay Immunochem. 2018;39:647−59.

[33] Gundogdu Meydaneri G, Meydaneri S. Can neutrophil lymphocyte ratio predict the likelihood of suicide in patients with major depression? Cureus. 2018;10:e2510.

[34] Tuglu C, Kara SH, Caliyurt O, Vardar E, Abay E. Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. Psychopharmacology. 2003;170:429−33.

[35] Turkmen K, Erdur FM, Ozcicek F, Ozcicek A, Akbas EM, Ozbicer A, *et al*. Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in end-stage renal disease patients. Hemo- dial Int. 2013;17:391−6.

[36] Sudol K, Mann JJ. Biomarkers of suicide attempt behaviour: towards a biological model of risk. Curr Psychiatry Rep. 2017;19:31−44.

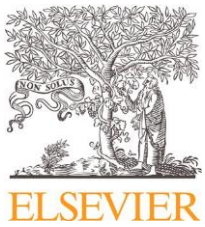
Artículo 2

Referencia: Martínez-Botía P, **Velasco A**, Rolle V, Jiménez-Trevino L, De la Fuente-Tomás L, Bernardo Á, et al. Sex-dependent grades of haematopoietic modulation in patients with major depressive episodes are associated with suicide attempts. Eur Neuropsychopharmacol. 2020 Nov 1;40: 17–30. DOI: 10.1016/j.euroneuro.2020.06.006

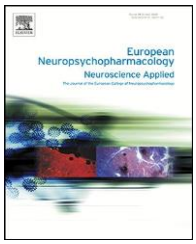
Resumen: Suicide is the leading cause of non-natural death worldwide, and major depressive disorder (MDD) is the mood disorder with the highest prevalence among individuals with suicidal behaviour (SB). The role of inflammation and immunomodulation in mood disorders has raised interest in recent years, as inflammation biomarkers have been reported to be increased in mood disorder patients, suggesting a role of inflammation in their pathogenesis. The influence of inflammation on the haematopoietic production is well known; however, a comprehensive study of the haematopoietic production in patients with major depressive episodes (MDE) is lacking. We examined global haematopoietic parameters from complete blood counts (CBC) of patients with MDE, in search of prognostic patterns. MDE patients presented differences in several CBC parameters, differences that were clearly pronounced and/or significant in concur- rence with suicide attempts (SA). Red and white blood cell lineage parameters were affected, suggesting general haematopoietic modulation or imbalance. We observed distinct haematological parameter changes in women versus men, with men presenting milder alterations than women. Interestingly, we found that the List of Threatening Experiences (LTE) score, but not the Childhood Trauma Questionnaire (CTQ), was associated with the haematopoietic alterations observed exclusively in women and, more importantly, served as a parameter to stratify fe- male MDE patients based on concurrence or non-concurrence with SA. In conclusion, grades of haematopoietic modulation in MDE patients are associated with absence or presence of SA. Haematopoietic manifestations differ between men and women and, in the latter, are markedly influenced by late, and not early, traumatic events.

Factor de impacto JCR 2020: 4.600

European Neuropsychopharmacology (2020) 40, 17–30



www.elsevier.com/locate/euroneuro



Sex-dependent grades of haematopoiec modulation in patients with major depressive episodes are associated with suicide attempts

Patricia Martínez-Botía[a,b,1], *Angela Velasco*[a,c,d,1], *Valeria Rolle*[a], *Luis Jiménez-Trevino*[a,c,d,e], *Lorena De la Fuente-Tomás*[a,c,d], *Ángel Bernardo*[a,f], *Tamara Arias*[a,g], *María del Carmen Muñoz-Turrillas*[a,g], *Leticia García-Alvarez*[a,d], *Leticia González-Blanco* [a,c,d,e], *Julia Rodríguez-Revuelta*[a,c,e], *Maria Paz Garcia-Portilla*[a,c,d,e], *Philippe Courtet*[h,i], *Julio Bobes*[a,c,d,e], *Laura Gutiérrez*[a,b,*], *Pilar Alejandra Sáiz*[a,c,d,e,*]

[a] *Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain*
[b] *Department of Medicine, Universidad de Oviedo, Spain*
[c] *Department of Psychiatry, Universidad de Oviedo, Spain*
[d] *Biomedical Research Networking Centre in Mental Health (CIBERSAM), Oviedo, Spain*
[e] *Servicio de Salud del Principado de Asturias (SESPA), Oviedo, Spain*
[f] *Hospital Universitario Central de Asturias, Laboratorio de Diagnóstico Clínico Hematología, Oviedo, Spain*
[g] *Centro Comunitario de Sangre y Tejidos de Asturias, Oviedo, Spain*
[h] *Department of Emergency Psychiatry & Post-Acute Care, Lapeyronie Hospital, CHU Montpellier - Inserm U1061, University of Montpellier, Montpellier, France*
[i] *Fondation FondaMental, Créteil, France*

Received 19 December 2019; received in revised form 8 May 2020; accepted 9 June 2020

* Corresponding authors at: Instituto de Investigación Sanitaria del Principado de Asturias (ISPA) and Universidad de Oviedo, Oviedo, Spain.
E-mail addresses: gutierrezglaura@uniovi.es (L. Gutiérrez), frank@uniovi.es (P.A. Sáiz).
[1]These authors contributed equally to this work.

https://doi.org/10.1016/j.euroneuro.2020.06.006

KEYWORDS
Major depressive episode;
Haematopoiesis;
Suicide;
Inflammation;
Sex;
LTE

Abstract
Suicide is the leading cause of non-natural death worldwide, and major depressive disorder (MDD) is the mood disorder with the highest prevalence among individuals with suicidal behaviour (SB). The role of inflammation and immunomodulation in mood disorders has raised interest in recent years, as inflammation biomarkers have been reported to be increased in mood disorder patients, suggesting a role of inflammation in their pathogenesis. The influence of inflammation on the haematopoietic production is well known; however, a comprehensive study of the haematopoietic production in patients with major depressive episodes (MDE) is lacking. We examined global haematopoietic parameters from complete blood counts (CBC) of patients with MDE, in search of prognostic patterns. MDE patients presented differences in several CBC parameters, differences that were clearly pronounced and/or significant in concurrence with suicide attempts (SA). Red and white blood cell lineage parameters were affected, suggesting general haematopoietic modulation or imbalance. We observed distinct haematological parameter changes in women versus men, with men presenting milder alterations than women. Interestingly, we found that the List of Threatening Experiences (LTE) score, but not the Childhood Trauma Questionnaire (CTQ), was associated with the haematopoietic alterations observed exclusively in women and, more importantly, served as a parameter to stratify female MDE patients based on concurrence or non-concurrence with SA. In conclusion, grades of haematopoietic modulation in MDE patients are associated with absence or presence of SA. Haematopoietic manifestations differ between men and women and, in the latter, are markedly influenced by late, and not early, traumatic events.

1. Introduction

Suicide is the leading cause of non-natural death worldwide and the second leading cause of mortality in individuals aged 15–29 years (World Health Organization, 2018), psychiatric disorders and substance abuse being the acknowledged risk factors. Major depressive disorder (MDD) is the most prevalent mood disorder in individuals with suicidal behaviour (SB), depression itself being associated with a 20-fold increase in suicide mortality rate (Osby et al., 2001). Stressors in childhood and adulthood have been associated with suicide attempts (SA), and there is ongoing debate whether early events have a stronger association with SB in comparison with late or recent events (Liu et al., 2017; Ludwig and Dwivedi, 2018). Importantly, individuals who have attempted suicide are at higher risk for future attempts, and a large proportion of them experience self-inflicted injuries or long-term disability, requiring medical attention and follow-up. It is therefore of interest to health systems to develop and rely on more precise personalised algorithms and biomarkers to better predict and prevent SA (Barrigon and Baca-Garcia, 2018). In this direction, efforts have been made to identify different novel biomarkers using high-throughput technologies (GWAS, metabolomics), highlighting the importance of transversal or multidisciplinary approaches to understand mood disorders.

The role of inflammation and immunomodulation in different conditions or pathologies, including mood disorders, has raised interest recently (Pariante, 2017). Inflammation-related biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR) (Ekinci and Ekinci, 2017; Ivkovic et al., 2016; Velasco et al., 2020) and C-reactive protein (CRP) (Courtet et al., 2015; Gibbs et al., 2016), have been reported to be increased in mood disorder patients, suggesting a role of inflammation in their pathogenesis and a potential use for these biomarkers as predictors of SB. More recently, NLR and mean platelet volume (MPV) have been related to the severity of SA (Orum et al., 2018). Inflammatory and infectious diseases, including allergy, asthma, and toxoplasmosis, have been associated with SB (Postolache et al., 2008; Zhang et al., 2012). Furthermore, an association has been established between SA, inflammation, and increased risk of morbidity and mortality from natural (cardiometabolic) causes (Bergen et al., 2012). Interestingly, patients treated with pro-inflammatory cytokines demonstrated increased risk of suicidal ideation or SA (Fragoso et al., 2010).

A comprehensive model focusing on the influence of the immune system in the pathophysiology of SB has been proposed (Courtet et al., 2016), where childhood abuse, sleep disturbance, infections, and other stressors induce a chronic inflammatory state causing dysregulation of the hypothalamic-pituitary-adrenal axis, increasing cortisol levels and indolamine 2,3-dioxygenase activation, which results in increased N-methyl-D-aspartate (NMDA) agonist and decreased serotonin levels. All these mechanisms may lead to psychological vulnerability and SB. However, the cause-consequence relationship between psychiatric disorders, SB, and systemic inflammation response and feedback is still largely unknown.

Haematopoiesis occurs in an inter-lineage equilibrium, where production of the different haematopoietic cell types that circulate in the blood is tightly regulated, as they need to be constantly replenished due to their short lifespan. A complete blood count (CBC) test measures a number of variables related to the different circulating blood cell-types, and is a *bona fide* portrait of an individual's health status. Hence, complete blood count (CBC) variables follow a given correlation in healthy individuals. When haematopoietic distress, imbalance, or modulation occurs, those correlations are disrupted, because the haematopoietic output shifts depending on the underlying physiological demand. It is well known that in response to external cues (e.g. cytokines during inflammation), the steady state output of the different types of blood cells shifts, usually towards producing higher numbers of innate immune cells (e.g. basophils, neutrophils, etc.), at the expense of erythropoiesis, megakaryopoiesis, and lymphopoiesis (Zhao and Baltimore, 2015). For example, anaemia of inflammation occurs when the body feels a need to increase white blood cell (WBC) production in response to infection, at the expense of red blood cell (RBC) production; in this case, the anaemia is caused by a rise in IL-6 and hepcidin levels, with subsequent inhibition of iron absorption, ultimately resulting in hampered erythropoiesis (Nemeth and Ganz, 2014). In a transgenic mouse model of anaemia of chronic disease, characterised by enhanced CD27-mediated co-stimulation and a strong increase in the production of IFN-γ-producing effector T cells, progressive anaemia is due to inhibition of erythropoiesis through the IRF-1-dependent activation of PU.1 transcription factor in haematopoietic precursors (Libregts et al., 2011). This exemplifies how this balance is self-regulated through transcriptional reprogramming of haematopoietic precursors. Contrariwise, recurrent infections are typical of chronic anaemia patients, as, in these cases, the necessity to increase RBC production negatively influences the commitment and differentiation of lymphoid precursors (Jonker et al., 2017). It has been reported that inflammation influences haematopoiesis at the haematopoietic stem cell level (King and Goodell, 2011). Hence, it is plausible that the sub-clinical inflammation (Köhler et al., 2017) reported in patients with MDE may be accompanied by other alterations in the haematopoietic production, which, we hypothesise, will manifest at different levels depending on SA co-occurrence, sex, and early or late stressors.

In the present study, we examine global haematopoietic parameters from CBCs of MDE patients, with or without SA, and evaluate potential haematopoietic imbalance based on SA co-occurrence, sex, and early or late stressors, with the objective of defining clinical patterns that would contribute to a better prognosis and SB management in these patients.

2. Experimental procedures

2.1. Study sample

We performed a cross-sectional study, including 172 Caucasian participants aged $\geq$18 years recruited in the area of Oviedo, Spain, from April 2016 to September 2018. All participants gave informed consent. The study was conducted according to the Declaration of Helsinki (World Medical Association, 2013).

The cohort consisted of 79 patients recruited at the Mental Health Services of Oviedo, diagnosed with MDE according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association, 2013). The exclusion criteria were comorbid psychiatric diagnoses, acute infection, active or chronic inflammatory or autoimmune diseases, smoking $\geq$ 20 cigarettes/day, obesity (BMI > 30 kg/m^2), current treatment with anti-inflammatory or immunosuppressant drugs, acute coronary syndrome, history of chronic renal, hepatic, or cerebrovascular disease, and reported haematological disorders.

Our control population consisted of 93 healthy active blood donors approved by the regional blood bank (Centro Comunitario de Sangre y Tejidos de Asturias, CCSTA).

2.2. Clinical assessment

Patients were assessed by well-trained interviewers using an *ad hoc* protocol for sociodemographic and clinical data. Psychometric evaluation included the Spanish versions of different scales and questionnaires. We employed the Hamilton Depression Rating Scale (HDRS) (Bobes et al., 2003) to determine severity of depression; the Childhood Trauma Questionnaire-Short Form (CTQ-SF) (Hernandez et al., 2013), a self-report questionnaire, to detect early life stressors (emotional, physical and sexual abuse, and emotional and physical neglect); the List of Threatening Experiences (LTE) to detect twelve stressful life events in the six months prior to the evaluation (Motrico et al., 2013), and the Medical Damage Scale (MDS) (Beck et al., 1975) to score medical damage due to SA, ranging from 0 (none) to 8 (dead).

SA was defined as a "self-initiated sequence of behaviours by an individual who, at the time of initiation, expected that the set of actions would lead to his or her own death" (American Psychiatric Association, 2013).

For every patient, seven days prior to assessment, mean daily antidepressant doses were calculated and standardised to fluoxetine equivalents (Hayasaka et al., 2015).

2.3. CBC analysis

Fasting blood samples were collected in the morning in EDTA tubes. CBCs were performed the same day using a Sysmex XN-10/XN-20 haematology analyser.

2.4. Statistical analysis

Descriptive parameters were shown as mean and standard deviation. In addition, normal distribution was assessed by the Shapiro-Wilk test. A Chi-square test was used for comparison of categorical variables, whereas an unpaired Mann-Whitney *U* test or a Kruskal-Wallis test were used to compare continuous variables among two or more groups, respectively. False discovery rate (FDR) correction was applied to account for multiple comparisons. Correlation analyses were performed by Spearman correlation, followed by FDR correction. Statistical significance was considered p (or q value in the case of FDR correction) < 0.05. All data were analysed using R version 3.6 (R Core Team, 2019), and figures were produced using the ggplot2 package (Wickham, 2009). Principal component analysis (PCA) was performed after scale-to-interval normalisation of variable values using Perseus Software version 1.5.2.6.

3. Results

3.1. Patient cohort: socio-demographics and psychiatric evaluation

The study population consisted of 79 MDE patients [mean age (SD): 52.28 (10.56) years; females: 46 (58.2%)], most with MDD [$n = 71$ (89.9%)]. MDE patients were stratified into two major groups based on history of SA (MDE SA) [$n = 48$ (60.8%)] or absence of SA (MDE noSA) [$n = 31$ (39.2%)]. The control group consisted of 93 healthy active blood donors [mean age (SD): 48.22 (11.44) years; females: 40 (43.0%)]. No significant differences between patient groups were identified with regard to sociodemographic characteristics or sex. Age differed considerably between patient and control groups, although *post-hoc* pairwise analysis (Duncan) revealed significant differences only in the MDE noSA group compared with the control group (Table 1 and Supplementary Table 1).

3.2. CBC of MDE patients: grades of haematopoietic modulation associated with SA

The CBCs of all patients were within normal range for all variables analysed, including WBC and differential count (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), RBC count, mean corpuscular volume (MCV), red cell distribution width (RDW), haematocrit (HCT), and haemoglobin-related variables (haemoglobin (Hb), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC)), and platelets and mean platelet volume (PLT, MPV). From these data, the neutrophil-to-lymphocyte (NLR), monocyte-to-lymphocyte (MLR), and platelet-to-lymphocyte (PLR) ratios were calculated (Table 2 and Supplementary Table 1).

Principal component analysis (PCA) was performed on the CBC variables as presented in Supplementary Table 1 (taking into consideration only the WBC differential counts and not the percentages) in order to visualise the clustering of the patients in the different groups and the controls. This analysis revealed that while the clusters of MDE patients without SA (MDE noSA) and the controls overlapped to a large extent, the cluster of MDE patients with SA (MDE SA) presented only a partial overlap with the cluster of controls, with a number of MDE SA patients located very distant from the nucleus (or centre) of the control cluster (Fig. 1). Of note, the MDE SA patients who clearly separated from the control cluster nucleus were females. This data suggests differential clustering of MDE patients, in concurrence with or without SA, based on their CBC measurements.

To identify the variables responsible for this differential clustering, we next compared potential haematological differences in blood samples between the two major subgroups of MDE patients (SA and noSA) and controls. Descriptive analysis revealed significant changes in RBC lineage-related parameters, e.g. RBC count (reduced), MCV (increased), RDW (reduced), MCH (increased), and MCHC (reduced), with no Hb or HCT changes, suggesting signs of stress erythropoiesis in MDE patients. There were no significant changes in WBC counts; however, there was a significant reduction in monocytes and an increase in eosinophils and basophils, suggestive of systemic inflammation. Platelet-related parameters showed a tendency toward thrombocytosis (not significant) with a significant reduction in MPV in MDE patients versus controls. The difference in these variables was significant and/or greater in MDE patients in concurrence with SA, supporting the PCA results. Furthermore, a tendency toward increased NLR and significantly reduced MLR were observed in MDE SA patients (Tables 2 and 3 and Fig. 2).

3.3. Disruption of haematopoietic equilibrium in MDE patients

We next evaluated the haematological equilibrium of CBC variables by studying their correlations in MDE patients versus controls, with the hypothesis that the identified differences and differential clustering observed in the PCA analysis could be explained by the loss of canonical or appearance of *de novo* correlations, supporting the notion of haematopoietic distress or production imbalance.

In fact, the significant correlations identified in the control group, and thus, the normal equilibrium of haematopoietic production, were gradually disrupted in MDE patients, with increasing severity associated with concurrence of SA (Fig. 3). Interestingly, we observed new significant correlations of haematopoietic variables that would indicate an imbalance of haematopoiesis not present in the control group. This imbalance would suggest an incipient shift favouring WBC lineage at the expense of RBC lineage production (Fig. 3).

3.4. Sex and haematopoietic modulation in MDE

It is well known that some haematological parameters from a CBC depend on age and sex (Cheng et al., 2004; Qiao et al., 2014); therefore we performed multiple regression analyses, which allowed us to identify the haematological parameters dependent on or influenced by these variables in our cohort of patients and controls (Table 2). As is already known, females presented slightly reduced RBC count, Hb, HCT, and MCH compared with males. Contrariwise, females displayed significantly higher platelet numbers. This also explains the differential clustering of male and female individuals in the PCA (Fig. 1). Additionally, we observed age-related differences that, although small, were still significant; i.e. the RDW % was higher in older individuals while the opposite was true for lymphocyte counts (Table2).

It was therefore important to study whether the haematopoietic imbalance observed in our cohort was maintained when the sexes were studied separately and whether it would impact males and females equally. Therefore, we next performed the same comparative analysis after stratification of our cohort based on sex. Of note, the difference observed in age in the global population (MDE noSA vs controls) disappeared in women after stratifying our cohort, but persisted in men (data not shown).

We observed increased SA-associated haematopoietic imbalance both in men and women; however, both sexes presented particularities and separate haematopoietic modulation profiles. While females experienced the most evi-

Table 1 Sociodemographic and clinical data. SD: Standard deviation; HDRS: Hamilton Depression Rating Scale; MDE: Major Depressive Episode; SA: Suicide attempt; noSA: No suicide attempt; MDS: Medical Damage Score; LTE: List of Threatening Experiences; CTQ: Childhood Trauma Questionnaire; SSRI: Selective Serotonin Reuptake Inhibitor; SNRI: Serotonin and Norepinephrine Reuptake Inhibitor; NDRI: Norepinephrine Dopamine Reuptake Inhibitor;[1] Statistically different (Post-hoc Duncan test).

	MDE	MDE SA	MDE noSA	Healthy controls	MDE	MDE + Controls
	$n = 79$	$n = 48$	$n = 31$	$n = 93$	X^2 */ T test (p)	X^2 */ANOVA (p)
Sex [n (%)]						
Males	33 (41.8%)	18 (37.5%)	15 (48.4%)	53 (57.0%)	0.918* (0.338)	4.849* (0.089)
Females	46 (58.2%)	30 (62.5%)	16 (51.6%)	40 (43.0%)	1.414 (0.162)	**3.810 (0.024)**
Age [Mean (SD)]	52.28 (10.56)	50.94 (9.71)	54.35 (11.61) [1]	48.22 (11.44)[1]		
Diagnosis [n (%)]						
Major Depressive Disorder	71 (89.9%)	43 (89.6%)	28 (90.3%)		0.011* (0.915)	
Bipolar Disorder	8 (10.1%)	5 (10.4%)	3 (9.7%)			
HDRS [Mean (SD)]	21.15 (4.21)	21.04 (4.56)	21.32 (3.67)		0.288 (0.774)	
Number of SA [Mean (SD)]	-	2.58 (2.53)	-		-	
Age of 1st SA [Mean (SD)]	-	39.71 (13.64)	-		-	
MDS [Mean (SD)]	-	3.17(1.45)	-		-	
LTE [Mean (SD)]	2.99 (2.44)	3.25 (2.99)	2.58 (1.12)		−1.193 (0.237)	
CTQ Total Score [Mean (SD)]	51.09 (17.90)	53.94 (19.93)	46.77 (13.45)		−1.894 (0.062)	
CTQ Physical Abuse [Mean (SD)]	6.64 (3.39)	7.13 (4.07)	5.90 (1.78)		−1.817 (0.074)	
CTQ Sexual Abuse [Mean (SD)]	6.82 (4.34)	7.32 (4.81)	6.06 (3.42)		−1.344 (0.183)	
CTQ Emotional Abuse [Mean (SD)]	8.88 (4.62)	9.45 (4.86)	8.03 (4.16)		−1.331 (0.187)	
CTQ Physical Neglect [Mean (SD)]	8.41 (3.83)	8.85 (3.71)	7.74 (3.98)		−1.256 (0.213)	
CTQ Emotional Neglect [Mean (SD)]	11.03 (5.40)	11.64 (5.48)	10.10 (5.21)		−1.239 (0.219)	
Pharmacological Treatment [n (%)]	74 (93.7%)	46 (95.8%)	28 (90.3%)		0.965* (0.326)	
Antidepressant equivalent to fluoxetine 40 mg/day [Mean (SD)]	45.21 (19.08)	45.74 (20.71)	44.36 (16.41)		−0.316 (0.766)	
SSRI [n (%)]	26 (32.9%)	17 (35.4%)	9 (29.0%)		0.348* (0.555)	
SNRI [n (%)]	36 (45.6%)	21 (43.6%)	15 (48.4%)		0.163* (0.686)	
NDRI [n (%)]	7 (8.9%)	4 (8.3%)	3 (9.7%)		0.042* (0.837)	
Others [n (%)]	36 (45.6%)	23 (47.9%)	13 (41.9%)		0.272* (0.602)	
Mood Stabilisers [n (%)]	10 (12.7%)	7 (14.6%)	3 (9.7%)		0.410* (0.522)	
Antipsychotics [n (%)]	32 (40.5%)	23 (47.9%)	9 (29.0%)		2.787* (0.095)	
Benzodiazepines [n (%)]	67 (84.8%)	43 (89.6%)	24 (77.4%)		2.163* (0.141)	
Others [n (%)]	12 (15.18%)	6 (12.5%)	6 (19.4%)		0.687* (0.407)	
Tobacco consumption [n (%)]						
Yes	36 (45.6%)	20 (41.7%)	16 (51.6%)		0.751* (0.386)	
No	43 (54.4%)	28 (58.3%)	15 (48.4%)			
No. of cigarettes/day [Mean (SD)]	15.19 (9.56)	13.35 (5.76)	17.50 (12.70)		1.307 (0.200)	

dent changes, these were not always significantly altered in males (Table 3). Regarding RBC lineage, a significant increase in RBC count with no change in RDW was observed in MDE females; however, in males, the MCV and RDW changes were significant only in concurrence with SA (Fig. 4). RDW is affected by age, as our analysis showed (Table 2), but since age was different in the MDE noSA group and the significant difference was detected in the MDE SA group, we consider our results valid. These data suggest that females with MDE are more prone to experience haematological imbalance, affecting both the RBC and WBC lineages, while men present overall milder alterations.

3.5. CTQ and LTE scores and haematopoietic modulation in MDE

Further analyses were conducted to evaluate the associations between stressors during childhood and adulthood, as assessed using CTQ and LTE scores, respectively, and the

Table 2 Complete blood parameters in the patient and control groups. Variables are summarised as mean (standard deviation). Differences between the MDE SA and MDE noSA groups and the healthy controls were assessed by one-way Kruskal-Wallis test. Variables with significant differences ($p < 0.05$) are highlighted in bold. MDE: Major Depressive Episode; SA: Suicide attempt; noSA: No suicide attempt; WBC: white blood cell count; RBC: red blood cell count; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; RDW: red cell distribution width; MPV: mean platelet volume; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio.

	MDE	MDE SA	MDE noSA	Healthy controls	One-way Kruskal-Wallis	Sex adjusted	Age adjusted
	N = 79	*N* = 48	*N* = 31	*N* = 93	*p*	*p*	*p*
WBC (10^3/µL)	7.47 (2.25)	7.82 (2.38)	6.93 (1.94)	7.11 (1.66)	0.205	1	1
RBC (10^6/µL)	4.73 (0.46)	4.69 (0.43)	4.79 (0.49)	4.90 (0.38)	**0.017**	**< 0.001**	1
Haemoglobin (g/dL)	14.31 (1.54)	14.17 (1.60)	14.51 (1.44)	14.56 (1.11)	0.460	**< 0.001**	1
Haematocrit (%)	42.49 (4.03)	42.25 (4.12)	42.86 (3.93)	42.34 (2.79)	0.945	**< 0.001**	1
MCV (fL)	89.76 (5.22)	89.87(6.35)	89.59 (2.75)	86.52 (3.94)	**< 0.001**	1	1
MCH (pg)	31.83 (9.84)	32.80 (12.54)	30.33 (1.29)	29.73 (1.50)	**0.006**	**< 0.001**	1
MCHC (g/dL)	33.73 (1.29)	33.65 (1.45)	33.85 (1.00)	34.37 (1.00)	**0.003**	1	1
RDW (%)	13.39 (1.24)	13.41 (1.41)	13.36 (0.96)	13.70 (1.01)	**0.022**	1	**< 0.001**
Neutrophils (10^3/µL)	4.23 (1.84)	4.54 (2.02)	3.74 (1.39)	3.95 (1.29)	0.109	1	1
Lymphocytes (10^3/µL)	2.38 (0.84)	2.41 (0.87)	2.35 (0.81)	2.31 (0.78)	0.835	1	**< 0.001**
Monocytes (10^3/µL)	0.56 (0.17)	0.57 (0.16)	0.55 (0.19)	0.64 (0.18)	**0.012**	1	1
Eosinophils (10^3/µL)	0.24 (0.15)	0.25 (0.15)	0.21 (0.14)	0.19 (0.12)	0.043	1	1
Basophils (10^3/µL)	0.05 (0.02)	0.06 (0.02)	0.05 (0.02)	0.03 (0.01)	**< 0.001**	1	1
Platelets (10^3/µL)	252.16 (68.97)	260.08 (80.56)	239.90 (44.09)	244.25 (60.63)	0.540	**< 0.001**	1
MPV (fL)	10.83 (0.80)	10.80 (0.81)	10.89 (0.78)	11.29 (0.94)	**0.008**	1	1
NLR	1.97 (1.35)	2.17 (1.66)	1.68 (0.57)	1.87 (0.80)	0.510	1	1
PLR	117.26 (53.49)	122.39 (64.51)	109.30 (28.50)	117.99 (54.77)	0.952	1	1
MLR	0.26 (0.11)	0.26 (0.12)	0.25 (0.08)	0.30 (0.13)	**0.017**	1	1

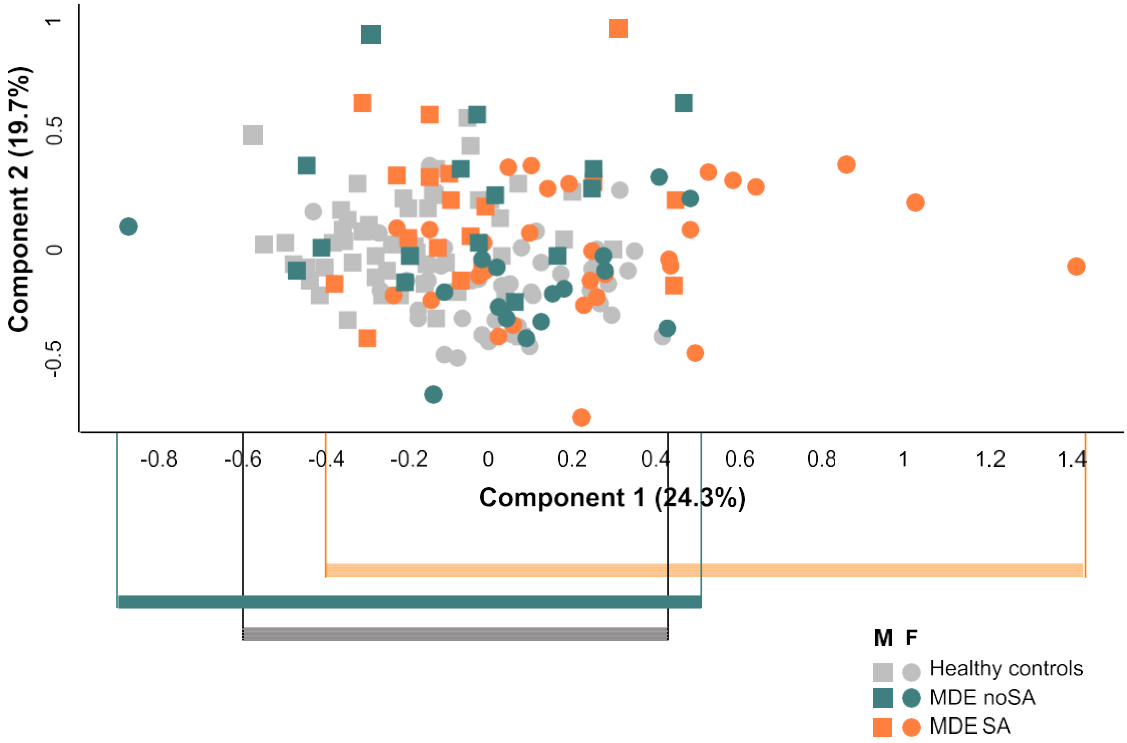


Fig. 1 Principal component analysis (PCA) of haematological parameters in MDE patients and healthy controls shows distinct clustering of samples depending on co-occurrence of SA.
PCA of haematological parameters performed on MDE patients (MDE noSA, MDE SA, and controls) is depicted.

Table 3 Differences between patient groups, stratified by severity of MDE (SA/noSA) and sex, and healthy controls were evaluated by the Mann–Whitney *U* test, and the False Discovery Rate (FDR, *q* value) is indicated. Variables with significant differences are highlighted in bold. Ratios show the relationship between the means of each patient group and the healthy controls for each haematological parameter. MDE: Major Depressive Episode; SA: Suicide attempt; noSA: No suicide attempt; WBC: white blood cell count; RBC: red blood cell count; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; RDW: red blood cell distribution width; MPV: mean platelet volume; NLR; neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio.

	Global				Male				Female			
	MDE SA		MDE noSA		MDE SA		MDE noSA		MDE SA		MDE noSA	
	q	Ratio	*q*	Ratio	*q*	Ratio	*q*	Ratio	*q*	Ratio	*q*	Ratio
WBC (10^3/μL)	0.236		0.722		0.687		0.811		0.726		0.134	**0.85**
RBC (10^6/μL)	**0.02**	**0.96**	0.218		0.638		0.811		0.190		0.309	
Haemoglobin (g/dL)	0.342		0.676		0.856		0.914		0.797		0.630	
Haematocrit (%)	0.884		0.947		0.687		0.811		0.698		0.576	
MCV (fL)	**< 0.001**	**1.04**	**< 0.001**	**1.04**	**0.04**	**1.03**	0.153		**0.005**	**1.04**	**0.003**	**1.04**
MCH (pg)	**0.02**	**1.10**	0.125		0.056		0.365		0.182		0.409	
MCHC (g/dL)	**0.02**	**0.98**	0.077		0.130		0.811		0.190		**0.02**	**0.98**
RDW (%)	**0.02**	**0.98**	0.218		**0.04**	**0.96**	0.351		0.660		0.630	
Neutrophils (10^3/μL)	0.193		0.558		0.587		0.811		0.726		0.128	
Lymphocytes (10^3/μL)	0.656		0.947		0.995		0.811		0.732		0.521	
Monocytes (10^3/μL)	**0.03**	**0.88**	0.089		0.587		0.860		0.153		**0.031**	**0.71**
Eosinophils (10^3/μL)	**0.03**	**1.34**	0.558		0.242		0.365		0.190		0.978	
Basophils (10^3/μL)	**< 0.001**	**2.05**	**< 0.001**	**1.81**	**0.001**	**1.87**	**0.009**	**1.88**	**< 0.001**	**2.27**	**0.031**	**1.78**
Platelets (10^3/μL)	0.386		0.993		0.812		0.994		0.726		0.921	
MPV (fL)	**0.020**	**0.96**	0.111		0.242		0.145		0.153		0.693	
NLR	0.545		0.676		0.812		0.811		0.855		0.309	
PLR	0.998		0.917		0.964		0.811		0.883		0.921	
MLR	**0.02**	**0.88**	0.218		0.638		0.990		0.112		0.128	

haematopoietic modulation observed in MDE patients, with or without stratification based on sex.

First, we studied the distribution of CTQ and LTE scores in our patient cohort. Although there was a tendency towards a progressive increase in those scores from lower in MDE noSA patients to higher in MDE SA patients, there were no significant changes in CTQ nor LTE scores (data not shown). In order to analyse the association of CTQ and LTE scores with the haematopoietic imbalance observed in MDE patient subgroups, we generated new ratio variables calculated as "haematopoietic parameter value vs CTQ or LTE score" per patient (Table 4) in the global MDE cohort and after stratification based on sex. This analysis showed that LTE (and not CTQ) was associated with the haematological alterations observed in females only, and that the ratios calculated with all the RBC lineage parameters and those calculated with lymphocytes and monocytes as part of the WBC differential clearly separated SA from noSA in females (Fig. 5). These results suggest that females are more susceptible to developing signs of haematopoietic distress, that this imbalance is more severe in concurrence with SA, and that the correlation of all RBC lineage parameters and some of the WBC parameters with the LTE score clearly separates SA from noSA in female patients with MDE.

4. Discussion

We examined global haematological parameters from CBCs of MDE patients, with or without SA, and evaluated potential haematopoietic modulation, imbalance or distress due to co-occurrence of SA, and how sex and early or late stressors may influence potential haematopoietic modulation manifestations in MDE patients.

We suggest that the haematopoietic imbalance observed in these patients goes beyond the inflammatory status previously reported by others (Courtet et al., 2016, 2015; Ekinci and Ekinci, 2017; Gibbs et al., 2016; Glaus et al., 2018a, b; Ivkovic et al., 2016; Kayhan et al., 2017; Liu et al., 2012; Mazza et al., 2019; Miller and Raison, 2016; Orum et al., 2018). Haematopoietic imbalance, modulation, or distress refers to the physiological response of the haematopoietic system to a certain stimulus, which causes loss of the haematopoietic production equilibrium. This loss of equilibrium may not affect single variables (as the normal ranges for some of them are considerably wide), and hence, CBCs as such may be within the normal range. However, since the haematopoietic production is so tightly regulated, correlations amongst variables start to be lost even when shifts of variables are still present within the normal range, but deviate from the values and correlations measured in a given individual under healthy conditions. A simple cold, which is transitory, will induce such distress. Furthermore, studying a given variable, like the red blood cell count, in a certain patient cohort, such as the one as we present in this manuscript, may show a skewed distribution towards a minimum threshold -still within the normal range-, while in healthy donors, the distribution is evenly dispersed within the top and bottom limits. While it is important to ac-

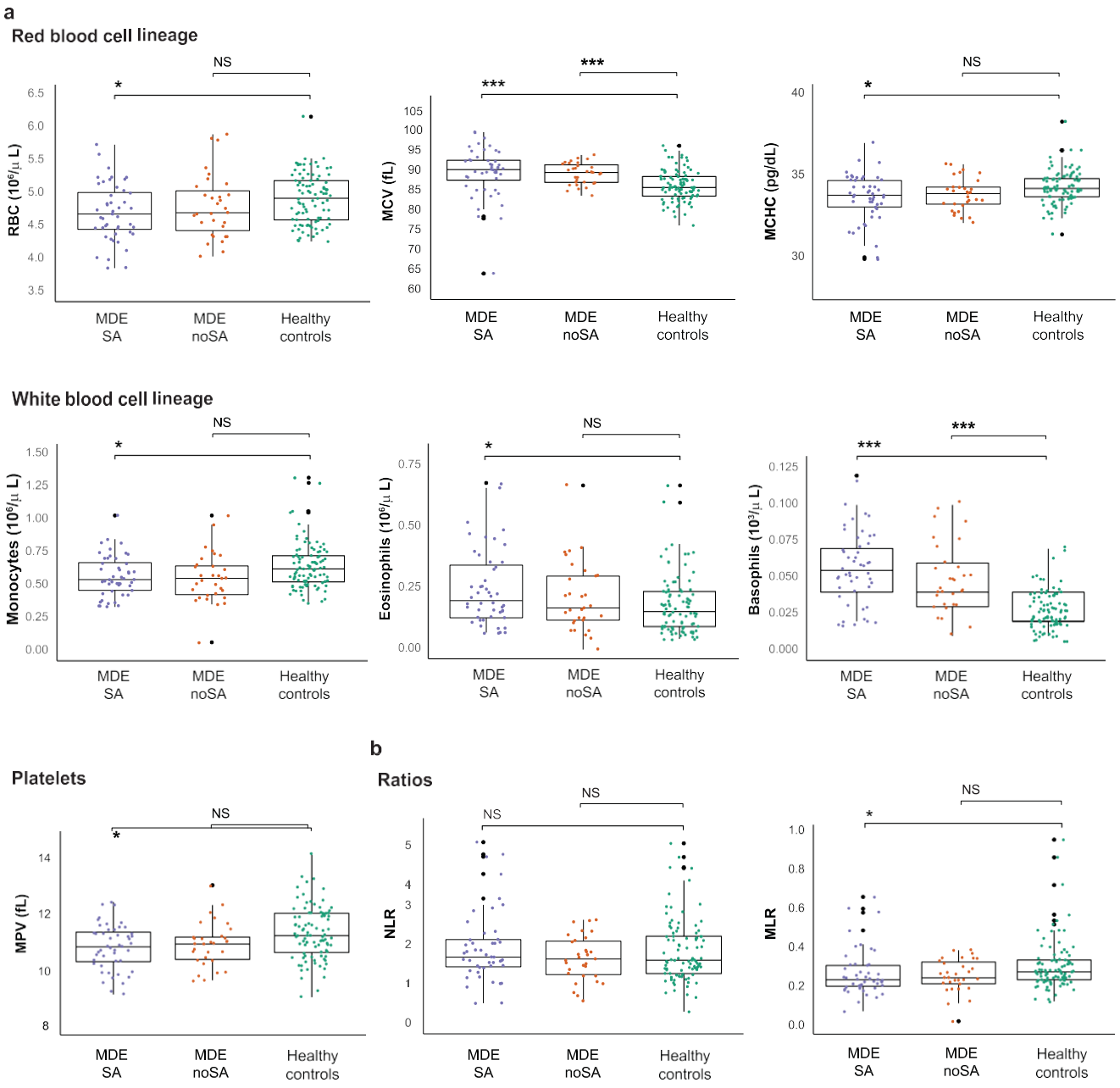


Fig. 2 Haematological parameters are affected in MDE patients and changes are more pronounced in co-occurrence with SA. (a) Box plots of selected haematological parameters from the CBCs of MDE patients (SA and noSA) and healthy controls. Top row depicts some parameters of the RBC lineage. Middle row depicts some parameters of the WBC lineage differential. Lower row depicts the mean platelet volume. (b) Box plots of calculated ratios. RBC, red blood cell; MCV, mean corpuscular volume; MCHC, mean corpuscular haemoglobin concentration; MPV, mean platelet volume; NLR, neutrophil-lymphocyte ratio; and MLR, monocyte-lymphocyte ratio. $*p < 0.05$ and $*** p < 0.001$. NS: not significant.

knowledge that CBCs of all patients were within the normal range, we observed clear signs of stress erythropoiesis (reduced RBC and RDW with increased MCV) accompanying inflammation (decreased monocytes and increased basophils and eosinophils). The tendency toward increased platelet counts, although not significant, along with reduced MPV, are suggestive of reactive thrombocytosis and platelet vesiculation, which is normally present in acute phase response or systemic inflammation. All these changes were more pronounced or significant in MDE patients in co-occurrence with SA. Furthermore, the equilibrium of the haematopoietic production, as exemplified by haematological variable correlation matrixes, showed a disappearance of many correlations and the appearance of *de novo* correlations in MDE patients versus controls. These data, taken together, suggest increasing grades of haematopoietic modulation/distress in MDE patients (associated with SA), indicative of inflammation (as previously reported), but also

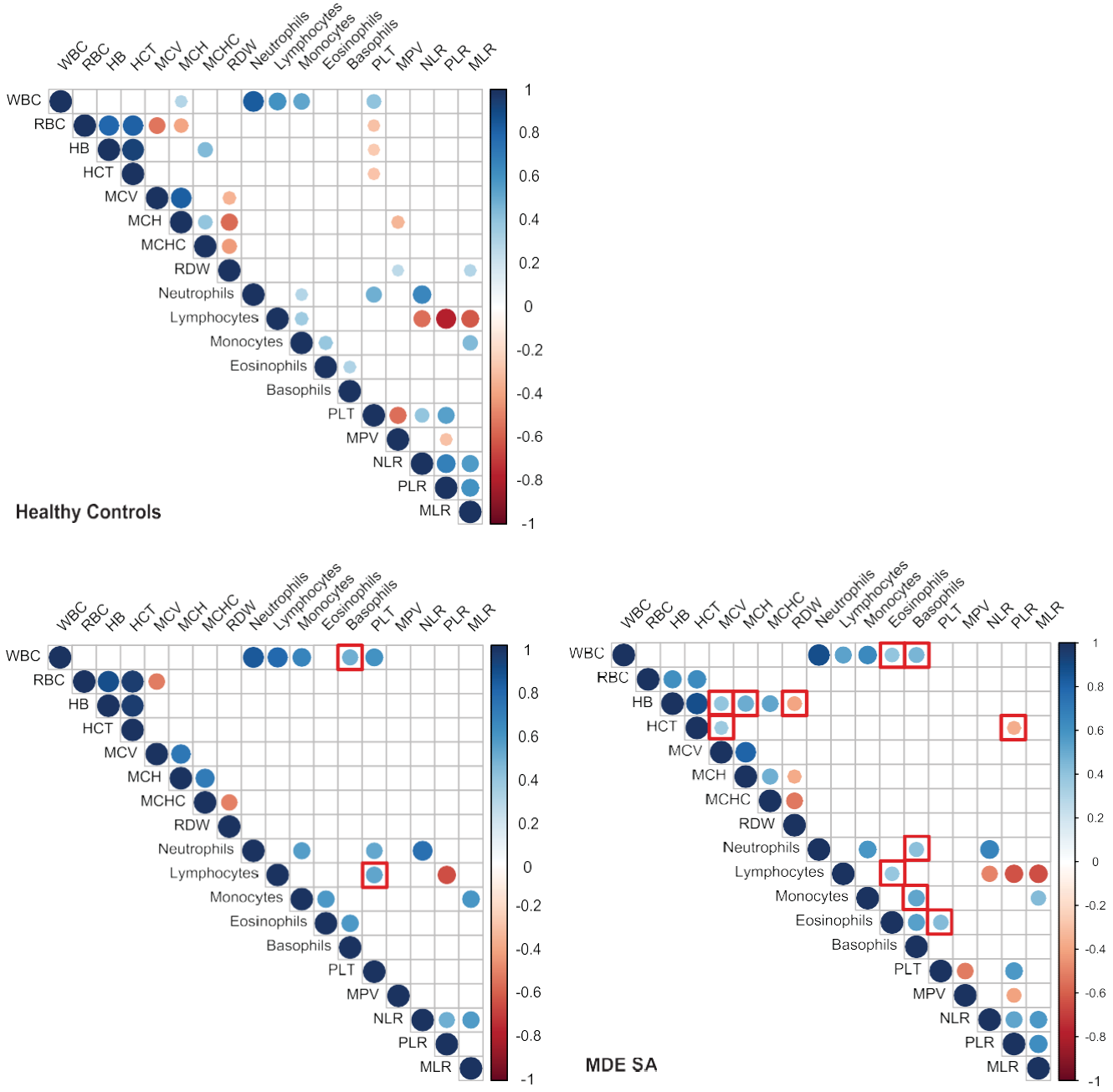


Fig. 3 Correlation of haematological parameters is disturbed in MDE patients.
Correlation matrixes of haematological parameters in MDE patients (noSA and SA) and healthy controls are depicted. Significant correlations are shown by different sized circles, indicating the strength of the slope. Direct correlations are coloured blue, while negative correlations are coloured red. Note that many correlations identified in the healthy control group disappear in MDE patients. *De novo* correlations are framed in a red-line square. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

indicative of underlying or onset of stress erythropoiesis. Changes in haematological parameters in mood disorders have been previously reported, including the appearance of specific correlations as we report in this study (Wysokinski and Szczepocka, 2016, 2018). In some reports, the tendencies observed are the opposite (increased RDW vs decreased RDW as we observed) (Demircan et al., 2016). Heterogeneity among study cohorts (probably due to sociodemographic and environmental factors) and sample size may condition this discrepancy, separating inflammation-associated erythroid stress due to iron deficiency (or malabsorption) from other types of dyserythropoiesis. Furthermore, the variables affected by sex (i.e. RBC, HB, HCT, MCH, and PLT) or by age (RDW and lymphocyte count) suggest that correction or

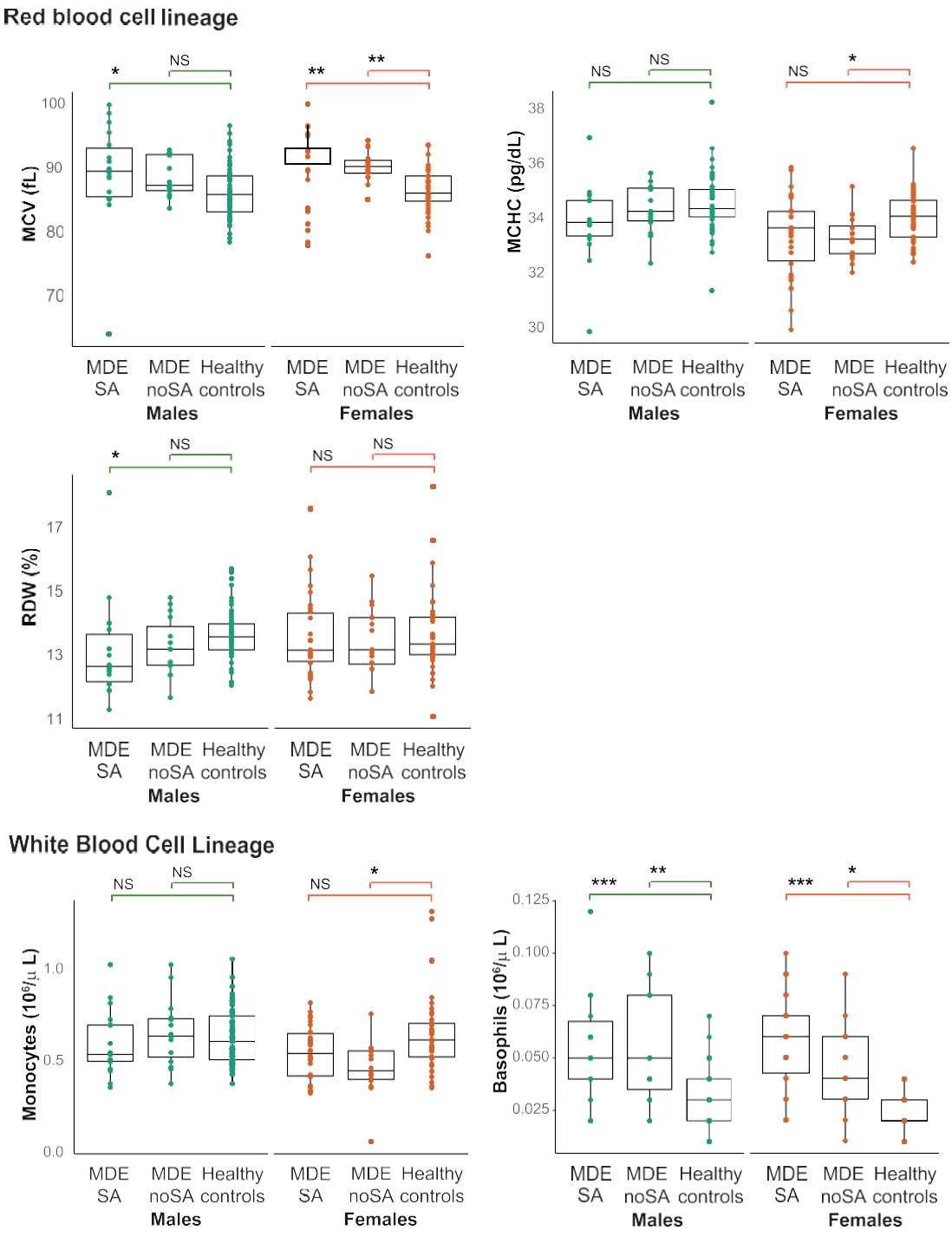


Fig. 4 Sex associates with a distinct haematopoietic modulation response in MDE patients.
Box plots depicting MCV (mean corpuscular volume), MCHC (mean corpuscular haemoglobin concentration), RDW (red cell distribution width), and monocyte and basophil counts in MDE patients with or without SA (SA and noSA, respectively) compared with healthy controls, stratified by sex. $*p < 0.05$, $**p < 0.005$ and $***p < 0.001$. NS, not significant.

stratification should be done to study the haematological component rigorously.

Our data highlight reduced monocytes and reduced MLR as potential markers that separate SA from noSA MDE. A possible explanation of the reduced peripheral blood monocyte counts and percentages in our cohort is the recruitment of activated monocytes to the central nervous system, becoming active players in the described neuro-inflammation of mood disorders (Weber et al., 2017).

We next assessed whether sex may condition a distinct response regarding the identified haematopoietic modulation in MDE patients. This is relevant, since many of the

Table 4 Differences between the CBC vs CTQ/LTE ratios of patient groups, stratified by severity of MDE (SA/noSA) and sex, and healthy controls were evaluated by the Mann-Whitney *U* test, and the False Discovery Rate (FDR, *q* value) is indicated. Variables with significant differences are highlighted in bold. Ratios show the relationship between the means of each patient group and the healthy controls for each haematological parameter. MDE: Major Depressive Episode; SA: Suicide attempt; noSA: No suicide attempt; WBC: white blood cell count; RBC: red blood cell count; MCV: mean corpuscular volume; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; RDW: red blood cell distribution width; MPV: mean platelet volume; NLR; neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; MLR: monocyte-to-lymphocyte ratio.

	Global				Male				Female			
	CTQ		LTE		CTQ		LTE		CTQ		LTE	
	q	Ratio	*q*	Ratio	*q*	Ratio	*q*	Ratio	*q*	Ratio	*q*	Ratio
WBC (10^3/μL)	0.943		0.288		0.841		1		0.802		0.305	
RBC (10^6/μL)	0.460		0.108		0.740		1		0.802		**0.022**	**0.631**
Haemoglobin (g/dL)	0.460		0.108		0.662		1		0.802		**0.026**	**0.630**
Haematocrit (%)	0.460		0.108		0.662		1		0.802		**0.022**	**0.633**
MCV (fL)	0.460		0.117		0.662		1		0.802		**0.022**	**0.642**
MCH (pg)	0.623		0.136		0.797		1		0.802		**0.022**	**0.644**
MCHC (g/dL)	0.460		0.127		0.662		1		0.802		**0.022**	**0.645**
RDW (%)	0.491		0.108		0.662		1		0.802		**0.024**	**0.641**
Neutrophils (10^3/μL)	0.623		0.219		0.797		1		0.802		0.118	
Lymphocytes (10^3/μL)	0.460		0.063		0.662		1		0.802		**0.011**	**0.565**
Monocytes (10^3/μL)	0.219		0.063		0.662		1		0.802		**0.011**	**0.587**
Eosinophils (10^3/μL)	0.797		0.621		0.810		1		0.872		0.591	
Basophils (10^3/μL)	0.623		0.244		0.797		1		0.802		0.157	
Platelets (10^3/μL)	0.797		0.621		0.882		1		0.802		0.592	
MPV (fL)	0.623		0.127		0.662		1		0.915		0.090	
NLR	0.623		0.159		0.662		1		0.991		0.283	
PLR	0.943		0.987		0.797		1		0.802		0.831	
MLR	0.943		0.521		0.797		1		0.872		0.540	

symptoms associated with mood disorders suggest an autoimmune background, and women have a higher prevalence of autoimmune disorders (Rainville and Hodes, 2019). Sex-related differences in levels of inflammation markers have been previously reported (Majd et al., 2018). Indeed, we observed that changes were more pronounced in women versus men, and some of the variables followed a different pattern. Our analyses suggest that MDE females are prone to develop a cumulative increase in haematological changes, which indicate or are associated with systemic inflammation. The increase in MCV could be a reflection of haematopoietic imbalance due to a consolidated systemic immune response, which induces haematopoietic production compensation shifts at the expense of RBC production. On the other hand, our data suggest that MDE males have reduced haematopoietic alterations compared to MDE females, with signs of mild ineffective erythroid production (extrapolated from RDW values) and mild signs of systemic inflammation in association with SA.

Next, we evaluated whether the identified haematopoietic imbalance in MDE associates with early or late stressors, as there is a long-standing debate about how traumatic events in childhood may confer vulnerability to SB in MDE patients (Liu et al., 2017; Nelson et al., 2017). Interestingly, despite not finding an association of CTQ or LTE with MDE regardless of the presence of SA, we observed an association of alterations in haematopoietic parameters with the LTE score in females only. All these results suggest that stressors during adulthood seem to be a major factor contributing to the severity of the haematopoietic modulation observed in MDE patients, which associates with SA in females.

The study was performed in Caucasians, which limits the extrapolation of our observations to other ethnicities. However, our MDE cohort excluded individuals with severe chronic illness and those treated with anti-inflammatory drugs, to prevent confounders in the analysis. In addition, we performed the analysis on MDE patients and evaluated the impact of changes and correlations of haematological parameters versus a healthy control group, which adds power to the clinical significance of the haematopoietic modulation of interest. However, this study is of exploratory nature, and the cross-sectional design and reduced N of the cohort may compromise our conclusions. Along this line, we did not see a significant increase in the NLR in MDE SA patients (although there was a tendency), while the MLR was significantly reduced in concurrence with SA. We recently postulated NLR as a biomarker of suicidal behaviour, however in a much larger cohort (Velasco et al., 2020).

We conclude from our observations that grades of haematopoietic modulation in MDE patients associate with co-occurrence of suicide attempts. Interestingly, haematopoietic manifestations differed between men and women and were markedly influenced by late but not early

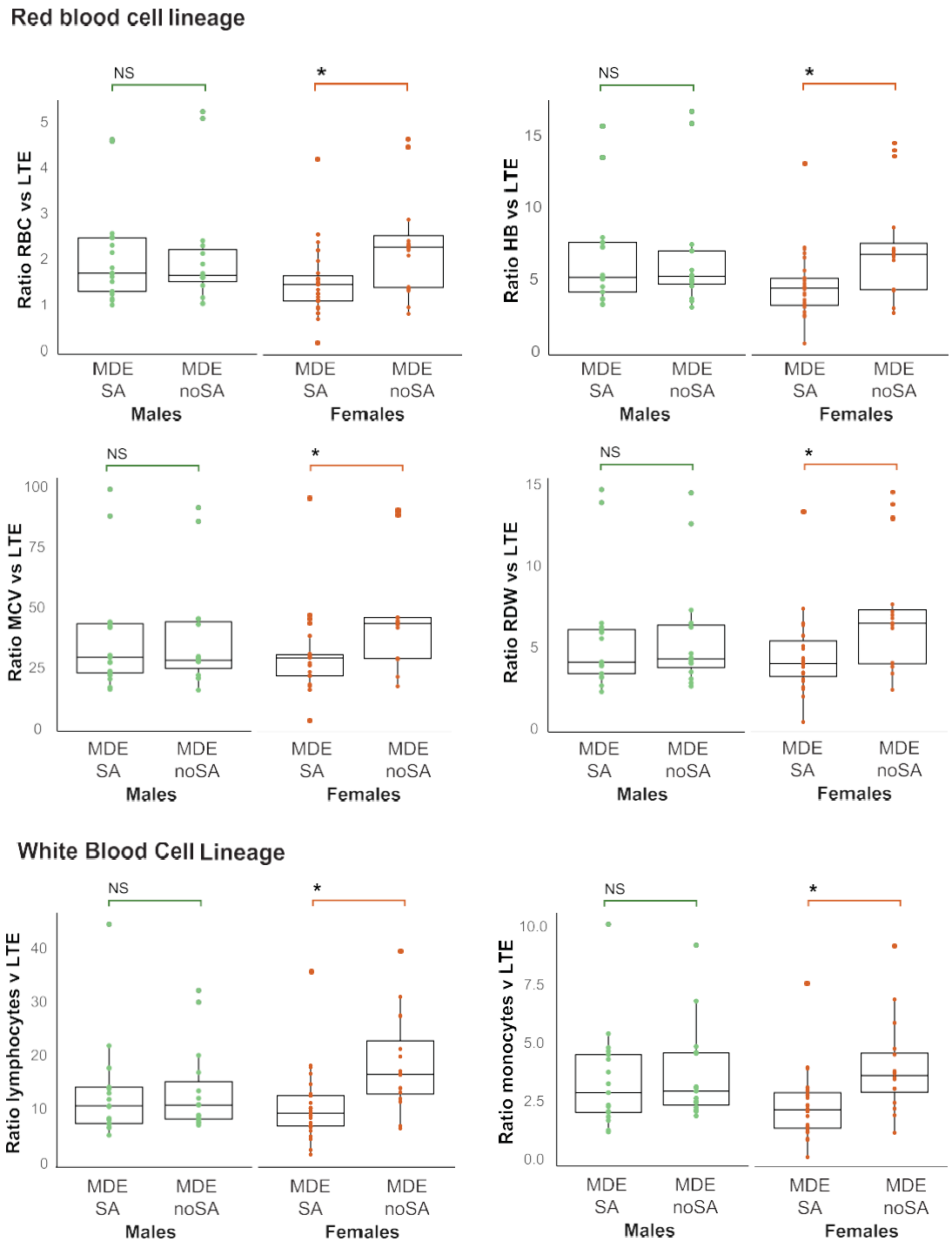


Fig. 5 Stressors and sex association with haematopoietic modulation in MDE patients.
Box plots depicting ratios of CBC parameters vs LTE scores are depicted, stratified by sex. In the upper half of the figure, the ratios calculated with red blood cell lineage parameters are depicted, and in the bottom, those calculated with white blood cell parameters are depicted. $*p < 0.05$. NS, not significant.

traumatic events exclusively in females. We hypothesise that haematopoietic imbalance could be an underlying basis for systemic changes, including those affecting the immune response and inflammation. How these haematological arms regulate each other in the context of mood disorders remains to be elucidated, a question that we will pursue by studying larger independent cohorts and implementing a mathematical model of CBC variables, in combination with molecular and cell biology studies.

Conflict of interest

All authors declare no conflict of interest relative to this study.

Role of funding source

This research was partially supported by grants FIS PI14/02029 and PI17/01433 (PI: P. A. S.) of the Instituto de Salud Carlos III, Spanish Ministry of Economy and Competitiveness, and Fondos Europeos de Desarrollo Regional (FEDER), by the Government of the Principality of Asturias PCTI-2018-2022 IDI/2018/235, by an RYC fellowship (RYC-2013-12587) to L.G., and an I+D 2017 grant (SAF2017-85489-P) to L. G. and P. M.-B. Finally, L. F.-T, A. V., and P. M.-B. received a Severo Ochoa grant (PA-17-PF-B16-179, PA-18-PF-BP17-177, and PA-20-PF-BP19-014, respectively) supported by the Principado de Asturias government. La Fundación para la Investigación e Innovación Biosanitaria del Principado de Asturias (FINBA) partially supported this study. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Contributors

PMB, AV, and VR analysed and interpreted the data and wrote the manuscript; AV, LJT, LFT, LGA, LGB, JRR, MPGP, JB, and PAS followed up patients and performed/assisted in evaluations; AB, TA, and MCMT performed CBC counts of blood samples and assessed the haematological analysis and data interpretation of the study; LG and PAS designed the study, analysed data, contributed to data interpretation, and wrote the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We thank Lorena Rodríguez Lorenzo and Begoña García Méndez for their technical support and Sharon Grevet for her assistance with English editing.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.euroneuro.2020.06.006.

References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. American Psychiatric Publishing, Arlington, VA.

Barrigon, M.L., Baca-Garcia, E., 2018. Current challenges in research in suicide. Rev. Psiquiatr. Salud Ment. 11, 1–3.

Beck, A.T., Beck, R., Kovacs, M., 1975. Classification of suicidal behaviors: I. Quantifying intent and medical lethality. Am. J. Psychiatry 132, 285–287.

Bergen, H., Hawton, K., Waters, K., Ness, J., Cooper, J., Steeg, S., Kapur, N., 2012. Premature death after self-harm: a multicentre cohort study. Lancet 380, 1568–1574.

Bobes, J., Bulbena, A., Luque, A., Dal-Re, R., Ballesteros, J., Ibarra, N.Grupo de Validacion en Espanol de Escalas, P., 2003. [A comparative psychometric study of the Spanish versions with 6, 17, and 21 items of the Hamilton depression rating scale]. Med. Clin. Barc 120, 693–700.

Cheng, C.K., Chan, J., Cembrowski, G.S., van Assendelft, O.W., 2004. Complete blood count reference interval diagrams derived from NHANES III: stratification by age, sex, and race. Lab. Hematol. 10, 42–53.

Courtet, P., Giner, L., Seneque, M., Guillaume, S., Olie, E., Ducasse, D., 2016. Neuroinflammation in suicide: toward a comprehensive model. World J. Biol. Psychiatry 17, 564–586.

Courtet, P., Jaussent, I., Genty, C., Dupuy, A.M., Guillaume, S., Ducasse, D., Olie, E., 2015. Increased CRP levels may be a trait marker of suicidal attempt. Eur. Neuropsychopharmacol. 25, 1824–1831.

Demircan, F., Gozel, N., Kilinc, F., Ulu, R., Atmaca, M., 2016. The impact of red blood cell distribution width and neutrophil/lymphocyte ratio on the diagnosis of major depressive disorder. Neurol. Ther. 5, 27–33.

Ekinci, O., Ekinci, A., 2017. The connections among suicidal behavior, lipid profile and low-grade inflammation in patients with major depressive disorder: a specific relationship with the neutrophil-to-lymphocyte ratio. Nord. J. Psychiatry 71, 574–580.

Fragoso, Y.D., Frota, E.R., Lopes, J.S., Noal, J.S., Giacomo, M.C., Gomes, S., Goncalves, M.V., da Gama, P.D., Finkelsztejn, A., 2010. Severe depression, suicide attempts, and ideation during the use of interferon beta by patients with multiple sclerosis. Clin. Neuropharmacol. 33, 312–316.

Gibbs, H.M., Davis, L., Han, X., Clothier, J., Eads, L.A., Caceda, R., 2016. Association between C-reactive protein and suicidal behavior in an adult inpatient population. J. Psychiatr. Res. 79, 28–33.

Glaus, J., von Kanel, R., Lasserre, A.M., Strippoli, M.F., Vandeleur, C.L., Castelao, E., Gholam-Rezaee, M., Marangoni, C., Wagner, E.N., Marques-Vidal, P., Waeber, G., Vollenweider, P., Preisig, M., Merikangas, K.R., 2018a. The bidirectional relationship between anxiety disorders and circulating levels of inflammatory markers: results from a large longitudinal population-based study. Depress. Anxiety 35, 360–371.

Glaus, J., von Kanel, R., Lasserre, A.M., Strippoli, M.F., Vandeleur, C.L., Castelao, E., Gholam-Rezaee, M., Marangoni, C., Wagner, E.N., Marques-Vidal, P., Waeber, G., Vollenweider, P., Preisig, M., Merikangas, K.R., 2018b. Mood disorders and circulating levels of inflammatory markers in a longitudinal population-based study. Psychol. Med. 48, 961–973.

Hayasaka, Y., Purgato, M., Magni, L.R., Ogawa, Y., Takeshima, N., Cipriani, A., Barbui, C., Leucht, S., Furukawa, T.A., 2015. Dose equivalents of antidepressants: evidence-based recommendations from randomized controlled trials. J. Affect. Disord. 180, 179–184.

Hernandez, A., Gallardo-Pujol, D., Pereda, N., Arntz, A., Bernstein, D.P., Gaviria, A.M., Labad, A., Valero, J., Gutierrez-Zotes, J.A., 2013. Initial validation of the Spanish childhood trauma questionnaire-short form: factor structure, reliability and association with parenting. J. Interpers. Violence 28, 1498–1518.

Ivkovic, M., Pantovic-Stefanovic, M., Dunjic-Kostic, B., Jurisic, V., Lackovic, M., Totic-Poznanovic, S., Jovanovic, A.A., Damjanovic, A., 2016. Neutrophil-to-lymphocyte ratio predicting suicide risk in euthymic patients with bipolar disorder: moderatory effect of family history. Compr. Psychiatry 66, 87–95.

Jonker, F.A.M., Te Poel, E., Bates, I., Boele van Hensbroek, M., 2017. Anaemia, iron deficiency and susceptibility to infection in children in sub-Saharan Africa, guideline dilemmas. Br. J. Haematol. 177, 878–883.

Kayhan, F., Gunduz, S., Ersoy, S.A., Kandeger, A., Annagur, B.B., 2017. Relationships of neutrophil-lymphocyte and platelet-lymphocyte ratios with the severity of major depression. Psychiatry Res. 247, 332–335.

King, K.Y., Goodell, M.A., 2011. Inflammatory modulation of HSCs:

viewing the HSC as a foundation for the immune response. Nat. Rev. Immunol. 11, 685–692.
Köhler, C.A., Freitas, T.H., Maes, M., de Andrade, N.Q., Liu, C.S., Fernandes, B.S., Stubbs, B., Solmi, M., Veronese, N., Herrmann, N., Raison, C.L., Miller, B.J., Lanctôt, K.L., Carvalho, A.F., 2017. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatr. Scand. 135, 373–387.
Libregts, S.F., Gutierrez, L., de Bruin, A.M., Wensveen, F.M., Papadopoulos, P., van Ijcken, W., Ozgur, Z., Philipsen, S., Nolte, M.A., 2011. Chronic IFN-gamma production in mice induces anemia by reducing erythrocyte life span and inhibiting erythropoiesis through an IRF-1/PU.1 axis. Blood 118, 2578–2588.
Liu, J., Fang, Y., Gong, J., Cui, X., Meng, T., Xiao, B., He, Y., Shen, Y., Luo, X., 2017. Associations between suicidal behavior and childhood abuse and neglect: a meta-analysis. J. Affect. Disord. 220, 147–155.
Liu, Y., Ho, R.C., Mak, A., 2012. Interleukin (IL)-6, tumour necrosis factor alpha (TNF-alpha) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-regression. J. Affect. Disord. 139, 230–239.
Ludwig, B., Dwivedi, Y., 2018. The concept of violent suicide, its underlying trait and neurobiology: a critical perspective. Eur. Neuropsychopharmacol. 28, 243–251.
Majd, M., Graham-Engeland, J.E., Smyth, J.M., Sliwinski, M.J., Lipton, R.B., Katz, M.J., Engeland, C.G., 2018. Distinct inflammatory response patterns are evident among men and women with higher depressive symptoms. Physiol. Behav. 184, 108–115.
Mazza, M.G., Tringali, A.G.M., Rossetti, A., Botti, R.E., Clerici, M., 2019. Cross-sectional study of neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratios in mood disorders. Gen. Hosp. Psychiatry 58, 7–12.
Miller, A.H., Raison, C.L., 2016. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat. Rev. Immunol. 16, 22–34.
Motrico, E., Moreno-Kustner, B., de Dios Luna, J., Torres-Gonzalez, F., King, M., Nazareth, I., Monton-Franco, C., Gilde Gomez-Barragan, M.J., Sanchez-Celaya, M., Diaz-Barreiros, M.A., Vicens, C., Moreno-Peral, P., Bellon, J.A., 2013. Psychometric properties of the List of Threatening Experiences-LTE and its association with psychosocial factors and mental disorders according to different scoring methods. J. Affect. Disord. 150, 931–940.
Nelson, J., Klumparendt, A., Doebler, P., Ehring, T., 2017. Childhood maltreatment and characteristics of adult depression: meta-analysis. Br. J. Psychiatry 210, 96–104.
Nemeth, E., Ganz, T., 2014. Anemia of inflammation. Hematol. Oncol. Clin. N. Am. 28, 671–681 vi.
Orum, M.H., Kara, M.Z., Egilmez, O.B., 2018. Mean platelet volume and neutrophil to lymphocyte ratio as parameters to indicate the severity of suicide attempt. J. Immunoass. Immunochem. 39, 647–659.
Osby, U., Brandt, L., Correia, N., Ekbom, A., Sparén, P., 2001. Excess mortality in bipolar and unipolar disorder in Sweden. Arch. Gen. Psychiatry 58, 844–850.
Pariante, C.M., 2017. Why are depressed patients inflamed? A reflection on 20 years of research on depression, glucocorticoid resistance and inflammation. Eur. Neuropsychopharmacol. 27, 554–559.
Postolache, T.T., Komarow, H., Tonelli, L.H., 2008. Allergy: a risk factor for suicide? Curr. Treat. Options Neurol. 10, 363–376.
Qiao, R., Yang, S., Yao, B., Wang, H., Zhang, J., Shang, H., 2014. Complete blood count reference intervals and age- and sex-related trends of North China Han population. Clin. Chem. Lab. Med. 52, 1025–1032.
R. Core Team, 2019. R: A Language Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.
Rainville, J.R., Hodes, G.E., 2019. Inflaming sex differences in mood disorders. Neuropsychopharmacology 44, 184–199.
Velasco, Á., Rodríguez-Revuelta, J., Olié, E., Abad, I., Fernández-Peláez, A., Cazals, A., Guillaume, S., de la Fuente-Tomás, L., Jiménez-Treviño, L., Gutiérrez, L., García-Portilla, P., Bobes, J., Courtet, P., Sáiz, P.A., 2020. Neutrophil-to-lymphocyte ratio: a potential new peripheral biomarker of suicidal behavior. Eur. Psychiatry 63, e14.
Weber, M.D., Godbout, J.P., Sheridan, J.F., 2017. Repeated social defeat, neuroinflammation, and behavior: monocytes carry the signal. Neuropsychopharmacology 42, 46–61.
Wickham, H., 2009. Ggplot2: Elegant Graphics For Data Analysis. Springer, New York.
World Health Organization, 2018. Suicide Prevention: Toolkit For Engaging Communities, Switzerland.
World Medical Association, 2013. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 310, 2191–2194.
Wysokinski, A., Szczepocka, E., 2016. Platelet parameters (PLT, MPV, P-LCR) in patients with schizophrenia, unipolar depression and bipolar disorder. Psychiatry Res. 237, 238–245.
Wysokinski, A., Szczepocka, E., 2018. Red blood cells parameters in patients with acute schizophrenia, unipolar depression and bipolar disorder. Psychiatr. Danub. 30, 323–330.
Zhang, Y., Traskman-Bendz, L., Janelidze, S., Langenberg, P., Saleh, A., Constantine, N., Okusaga, O., Bay-Richter, C., Brundin, L., Postolache, T.T., 2012. Toxoplasma gondii immunoglobulin G antibodies and nonfatal suicidal self-directed violence. J. Clin. Psychiatry 73, 1069–1076.
Zhao, J.L., Baltimore, D., 2015. Regulation of stress-induced hematopoiesis. Curr. Opin. Hematol. 22, 286–292.

Artículo 3

Referencia: **Velasco A**, Lengvenyte A, Rodríguez-Revuelta J, Jiménez-Treviño L, Courtet P, García-Portilla MP, et al. Neutrophil-to-lymphocyte ratio, platelet-to-lymphocte ratio, and monocyte-to-lymphocyte ratio in depressed patients with suicidal behavior: A systematic review. Eur Psychiatry. 2023; 1-25. DOI: 10.1192/j.eurpsy.2023.18. Online ahead of print.

Resumen: Inflammatory biomarkers are reportedly increased in depressed patients. Several studies have been conducted using neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR). The objective of this systematic review was to study the relationship between these peripheral biomarkers and suicidality in depressed patients with/without suicidal behavior, including suicide attempts and ideation, and healthy controls. Methods: We searched the following relevant terms in the PubMed, Web of Science, and Scopus databases published in the last five years. We assessed the methodological quality of included studies using the Oxford criteria and reviewed the evidence following PRISMA guidelines. Results: Eleven studies were retained for the data synthesis, with a total sample of 1,701 participants, of which the majority (819) were patients with depression and suicidal behavior, 494 were depressed patients without suicidal behavior, and only 388 were healthy participants. Our results reinforce the idea that NLR could be an attractive, convenient, and cost-effective trait marker of suicidal vulnerability in patients with major depressive disorder (MDD). Conclusion: Future large-scale replication studies are needed to examine the apparently understudied role of PLR and MLR in depressed patients in greater depth.

Factor de impacto JCR 2023: 7.156

Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio in depressed patients with suicidal behavior: A systematic review

Velasco A[a,b,c,d], Lengvenyte A[e,f,g], Rodriguez-Revuelta J[a,d,h], Jimenez-Treviño L[a,d,h], Courtet P[e,f,], Garcia-Portilla MP[a,b,c,d,h], Bobes J[a,b,c,d], Sáiz PA[a,b,c,d,h]

a. Department of Psychiatry, University of Oviedo, Oviedo, Spain

b. Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM). Spain

c. Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Spain

d. Instituto de Neurociencias del Principado de Asturias (INEUROPA), Spain

e. Department of Emergency Psychiatry and Acute Care, CHU Montpellier, France

f. IGF, University of Montpellier, CNRS, INSERM, Montpellier, France

g. Psychiatric Clinic, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

h. Mental Health Services of the Principality of Asturias (SESPA), Oviedo, Spain

Corresponding author:

María Paz García-Portilla

Department of Psychiatry, School of Medicine, University of Oviedo

Av. Julian Claveria, 6, 33006, Oviedo, Asturias – Spain

albert@uniovi.es

This peer-reviewed article has been accepted for publication but not yet copyedited or typeset, and so may be subject to change during the production process. The article is considered published and may be cited using its DOI.

Short title:

NLR, PLR, and MLR in depression and suicidal behavior

Abstract

Background: Inflammatory biomarkers are reportedly increased in depressed patients. Several studies have been conducted using neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and monocyte/lymphocyte ratio (MLR). The objective of this systematic review was to study the relationship between these peripheral biomarkers and suicidality in depressed patients with/without suicidal behavior, including suicide attempts and ideation, and healthy controls.

Methods: We searched the following relevant terms in the PubMed, Web of Science, and Scopus databases published in the last five years. We assessed the methodological quality of included studies using the Oxford criteria and reviewed the evidence following PRISMA guidelines.

Results: Eleven studies were retained for the data synthesis, with a total sample of 1,701 participants, of which the majority (819) were patients with depression and suicidal behavior, 494 were depressed patients without suicidal behavior, and only 388 were healthy participants. Our results reinforce the idea that NLR could be an attractive, convenient, and cost-effective trait marker of suicidal vulnerability in patients with major depressive disorder (MDD).

Conclusion: Future large-scale replication studies are needed to examine the apparently understudied role of PLR and MLR in depressed patients in greater depth.

Keywords: Neutrophil/lymphocyte ratio; Platelet/lymphocyte ratio; Monocyte/lymphocyte ratio; Suicidal behavior; Depression

1. Introduction

Suicidal behavior (SB) is a serious public health concern. More than 700,000 people die by suicide every year, representing one death every 40 seconds on average (1). Factors contributing to increased risk of suicidal behaviors are diverse and complex, but epidemiological studies indicate that the vast majority of attempted and completed suicides occur in people with mental disorders with mood disorders being the most frequently associated with SB (2,3).

Understanding the pathophysiology of suicide is still a long-term goal. The evidence increasingly indicates a possible role of the immune-inflammatory response in the development and maintenance of depression and SB (4). Inflammation has been associated with increased risk of suicidal behaviors above and beyond the risk associated with depression (5). Neuroinflammatory processes are a pathophysiological mechanism that is essential for understanding SB in depressed patients. To explain the role of the immune system in the pathophysiology of suicide, a comprehensive model has been proposed. In this model, sleep disturbances, stress, childhood abuse, and infections induce dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis that is associated with a chronic low-grade inflammatory state and increased risk of suicidal behaviors (6). It has therefore been suggested that inflammatory biomarkers are potentially useful in predicting and monitoring suicide risk in patients with depression (7).

Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) indexes are convenient and cost-effective blood indicators of inflammatory status (8).

NLR is the most studied hematological parameter (9). Neutrophils are the first defense cells of the innate immune system, representing an active nonspecific inflammatory mediator of

phagocytosis and apoptosis functions (10), and lymphocytes represent the regulatory or protective component of the immune system (11,12,13). NLR is the ratio between two different immune pathways reflecting the intensity of chronic stress. It may be more informative and perhaps less changed by unknown factors. PLR index is related to stress. The presence of stress activates the sympathetic nervous system, increases platelets, and induces endothelial permeability. When this permeability occurs, neutrophils and macrophages appear, generating peripheral inflammation (14). Some studies suggest that PLR could be a better predictor than NLR for determining the severity of inflammation (15,16). An elevated level of MLR is associated with an overexpression of immunological genes that increases the production of cytokines related to monocytes and, as a consequence, activates microglia in the brain, causing neuroinflammation (14).

These indexes have been suggested as new indicators of low-grade inflammation and have been used as systemic inflammation prognostic scores in diseases such as cancer, coronary heart disease, and pancreatitis (17) and are also being investigated in neuropsychiatric disorders such as Alzheimer’s disease, schizophrenia, bipolar disorder, and major depressive disorder (MDD) (11,18). Recently, a meta-analysis (18) reported that inflammatory activation occurs in mood disorders and that NLR and PLR may be useful to detect this activation. NLR has been found to increase in depressed patients compared with healthy controls (HC) (15,19) and in depressed patients with SB. Moreover, studies have suggested that NLR may be a significant predictor of SB in MDD (4,20) and could be more elevated in patients with recent Suicide Attempt (SA) (21). In parallel, increased PLR levels have also been associated with diagnosis and severity of depression (15,22). Finally, MLR was significantly higher in adolescents with SA than in HC (23).

However, potential mechanisms underlying inflammatory processes in depression and suicidal behavior have yet to be fully elucidated. Biomarkers would provide more

personalized methods for their assessment and treatment and would help to enhance our understanding of suicidal pathophysiology and improve prevention (24). No previous reviews have examined NLR, PLR, and MLR in depressed patients with/without SA and Suicidal Ideation (SI) and HC. Therefore, we aimed to explore if there are significant differences in NLR, PLR, and MLR in i) depressed patients with or without a lifetime history of SA; ii) depressed patients with a lifetime history of SA vs healthy controls; and iii) depressed patients with SI before and after treatment.

2. Materials and methods

A systematic literature search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (25). The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42022361238).

2.1. Search criteria

We systematically searched PubMed, Web of Science, and Scopus databases in September 2022. A single search strategy has been used for each of the databases:

Studies of neutrophil-to-lymphocyte ratio were systematically searched using the terms "(NLR OR neutrophil-to-lymphocyte ratio OR neutrophil-to-lymphocyte index OR neutrophil-to-lymphocyte rate OR neutrophil to lymphocyte ratio OR neutrophil to lymphocyte index OR neutrophil to lymphocyte rate OR neutrophil lymphocyte ratio OR neutrophil lymphocyte index OR neutrophil lymphocyte rate OR neutrophil/lymphocyte ratio OR neutrophil/lymphocyte index OR neutrophil/lymphocyte rate) AND (depressive disorder OR depressive disorders OR depression OR mood disorder OR mood disorders OR major depression) AND (suicide OR suicidal behavior OR suicide attempt OR suicidal thoughts OR self-mutilation)."

In the same way, studies of platelet-to-lymphocyte ratio were systematically searched using the terms "(PLR OR platelet-to-lymphocyte ratio OR platelet-to-lymphocyte index OR platelet-to-lymphocyte rate OR platelet to lymphocyte ratio OR platelet to lymphocyte index OR platelet to lymphocyte rate OR platelet lymphocyte ratio OR platelet lymphocyte index OR platelet lymphocyte rate OR platelet/lymphocyte ratio OR platelet/lymphocyte index OR platelet/lymphocyte rate) AND (depressive disorder OR depressive disorders OR depression OR mood disorder OR mood disorders OR major depression) AND (suicide OR suicidal behavior OR suicidal attempt OR suicidal thoughts OR self-mutilation)."

Finally, studies of monocyte-to-lymphocyte ratio were systematically searched using the terms "(MLR OR monocyte-to-lymphocyte ratio OR monocyte-to-lymphocyte index OR monocyte-to-lymphocyte rate OR monocyte to lymphocyte ratio OR monocyte to lymphocyte index OR monocyte to lymphocyte rate OR monocyte lymphocyte ratio OR monocyte lymphocyte index OR monocyte lymphocyte rate OR monocyte/lymphocyte ratio OR monocyte/lymphocyte index OR monocyte/lymphocyte rate) AND (depressive disorder OR depressive disorders OR depression OR mood disorder OR mood disorders OR major depression) AND (suicide OR suicidal behavior OR suicidal attempt OR suicidal thoughts OR self-mutilation)."

We reviewed titles and abstracts to select potentially relevant papers. After this screening process, we reviewed the full texts and checked the references in the included studies, meta-analyses, and systematic reviews to identify additional studies. Some data was extracted from previous meta-analyses and systematic reviews.

2.2. Eligibility criteria

Case-control studies and cross-sectional data from longitudinal studies that compared NLR, PLR, and/or MLR indexes among depressed patients with SB, depressed patients without SB,

and healthy controls were included, based on the following criteria: (i) patients with MDD according to standardized diagnostic criteria; (ii) measurement of NLR, PLR, and/or MLR in young people and adults; (iii) patients with current SI and history of SB. Only articles in English published in the last 5 years were included. Conference and meeting abstracts, meta-analyses, reviews, and pilot studies were excluded (see Supplementary Table).

2.3. Data extraction and assessment of methodological quality

Data were extracted by two independent authors (A.V. and P.A.S.) and verified by the other two (J.R. and L.J.). Extracted data included author, year of publication, country, diagnosis, study population, sample size, age, ratios of females, depression and suicide scales, type of outcome (SI/SA), and type and quality of the study. Results were ordered according to indexes (Table 1). The methodological quality of the included studies was assessed using the Oxford criteria (26). Only medium- and high-quality papers were included in the final review. Any disagreements between reviewers were resolved by discussion and consensus.

3. Results

3.1. Study selection and characteristics

A total of 86 studies were identified from electronic databases and, after removing duplicates, there were 37 single records to be screened. After reading titles and abstracts, we identified 21 full-text articles to be assessed for eligibility but excluded 10 studies after the full text was read (the inclusion and exclusion process is depicted in Figure 1). Of those, 11 studies met the inclusion and quality criteria and were selected for this review.

A total of 10 papers were rejected for the following reasons: (i) type of article (review, letter, meeting abstract): 2 articles were meeting abstracts and 2 articles were letters to the editor; (ii) 2 articles did not include a study of suicidal behavior, 2 articles did not specify depressed

patients, and 1 study included parameters of peripheral inflammation other than NLR, PLR, and MLR; and (iii)1 article was published in the Turkish language (see Supplementary Table).

All included studies were published between August 2017 and September 2022. Five studies were conducted in Turkey (8,20,27–29), one in India (30), two in Spain (4,31), one in Sweden (32), one in Israel (33), and one in Thailand (9).

The 11 records included in the review yielded a total sample of 1,701 participants, of which 819 were patients with MDD and suicidal behavior (including current SI and lifetime SA), 494 were control patients (MDD without SB), and 388 were healthy controls.

We included data from (i) six studies of NLR, PLR, and/or MLR in depressed patients with or without SB (4,20,27,31–33); (ii) six studies of NLR, PLR, and/or MLR in depressed patients with SB vs HC (9,20,28,29,31,32); (iii) two studies of NLR in depressed patients with SI before (with or without monotherapy 4 weeks prior) and after pharmacotherapy (2 to 12 weeks after treatment), one of which also explored PLR (8,30), respectively (Table 1).

3.2. Patients with major depressive disorder with or without suicidal behavior

In three studies with patients with moderate to severe depression, NLR was reported to be higher in suicide attempters compared with depressed patients without a history of SA (4,20,33). NLR could be potentially used as a biomarker to predict recent and past SA (4). However, these results were not confirmed in other studies. First, in two studies there was a (non-significant) tendency towards an increase in NLR in patients with a history of SA vs without any (27,31). One study examining the association between current SI and NLR in patients with MDD found no differences between patients with and without current SI in NLR (32) (Table 2).

Regarding the PLR index in patients with MDD, two studies reported PLR to be higher in patients with a history of SA vs those without any (4,33). Conversely, this difference was not observed in three other studies (20,27,31) (Table 2).

Finally, only two studies explored the MLR index in relation to SB in MDD, with no reported statistically significant differences between depressed patients with and without SB (4,31) (Table 2)..

3.3. Patients with major depressive disorder and suicidal behavior vs healthy controls

In three studies, NLR was reported to be higher in depressed patients with a history of SA vs HC (9,20,28). However, three other studies reported no statistically significant differences (29,31,32) (Table 3).

Regarding the PLR index, two studies reported that PLR was higher in depressed patients (including SA, SI and nSI) vs HC (28,23). Conversely, in two studies, this difference was not observed (20,31) (Table 3).

MLR was investigated in only two out of six studies, with inconsistent results. MLR was reported to be higher in depressed patients with SA vs HC (9). However, MLR was reported to be decreased in depressed patients with SB vs HC (31) (Table 3).

3.4. Depressed patients with suicidal ideation before and after treatment for depression

There were two studies that evaluated NLR before and after antidepressant treatment. First, Demirkol et al. (2019) studied depressed patients (n = 74) with monotherapy four weeks before treatment and found a decrease in NLR during and after treatment with antidepressant therapy (AD) and bright light therapy (BLT), with a greater decrease compared with AD monotherapy [NLR mean (SD) = 2.31(1.05) pretreatment vs 2.25 (0.96) after treatment vs 1.9 (0.9) 2 weeks after treatment; $p < 0.001$]. In addition, HDRS scores and SI were also

significantly decreased after treatment [HDRS mean (SD) = 20.69 (4.21) pretreatment vs 16.69 (5.96) after treatment vs 15.14 (5.33) 2 weeks after treatment; $p < 0.001$; and SI median (Q1-Q3): 5 (3-10) pretreatment vs 5 (1-9) after treatment vs 3.5 (0-7) 2 weeks after treatment; $p < 0.001$] (8). However, in a sample of 50 depressed patients without antidepressant treatment the previous month, Adhikari et al. (2018) found a significant increase in NLR after 12 weeks of antidepressant treatment only in females [NLR mean in females (SD) = 2.55 (0.87) pretreatment vs 2.85 (0.89) 12 weeks after treatment; $p < 0.001$] (30).

Regarding PLR, only one study examined PLR levels in depressed patients with SI before and after treatment and concluded there was no significant change in PLR during AD treatment [PLR mean (SD) = 118.61 (39.01) pretreatment vs 118.16 (40.57) after treatment vs 117.96 (40.82) 2 weeks after treatment; $p = 0.985$] (8).

None of the studies included MLR.

4. Discussion

SB is a leading cause of death and disability worldwide (34). Detecting and identifying potential biomarkers of peripheral inflammation in suicidal behavior has the potential to provide the knowledge needed to understand the pathophysiology of SB, develop personalized therapies, and improve prevention. To date, this is the first review that has examined NLR, PLR, and MLR in depressed patients with and without SA and current SI versus healthy controls.

NLR, PLR, and MLR indexes emerge as relatively stable biomarkers of systemic inflammation (35), which, in turn, is cost-effective and easily accessible. Perhaps, for this reason, most of the studies included in this systematic review were conducted in low-income countries, which seem to be interested in this option given the potential value for clinical application.

According to our review, in depressed patients, NLR was higher in patients with a history of SA, suggesting that, if confirmed in larger studies, it could be a biomarker of suicidal vulnerability in these patients. Although this result was not observed in all studies, in the majority there was a tendency for increased NLR. To the best of our knowledge, only one study that examined the differences in patients with and without SI did not find this association (32). However, it has been previously suggested that SA and SI are different phenomena with different explanations and predictors (36), and it seems that the relationship between the increase in NLR and suicidality occurs only in SA and not in SI (32). In addition, NLR was higher in depressed patients with SA vs HC. However, these differences were not observed in depressed patients with SI vs HC. Mounting evidence indicates that activation of the immune-inflammatory response is linked to the development and maintenance of depression and SB (4,7,18).

Some studies suggest that PLR could be a better predictor than NLR for determining the severity of inflammation (15,16). Our review shows inconsistent results regarding PLR in MDD patients (including SB). However, when compared with HC, the difference in the PLR index is observed more clearly in depressed patients. This phenomenon might be explained by the fact that platelets are one of the first cells to start an inflammatory cascade (cytokines, chemokines, the serotonin pathway), and patients with depression had a loss of equilibrium in hematopoietic production, resulting in an imbalance or distress in modulation (31).

The present review found no evidence for the link between MLR and SB in depressed patients, in contrast to some studies than showed MLR was higher in the manic episodes of bipolar disorder compared with euthymic states (37). However, despite not being related to suicidal behavior, high MLR in young people appears to be associated with self-harm when compared with young people without this behavior (14).

Finally, discrepant, and limited results were found regarding SI changes and inflammatory indexes following antidepressant treatment. These results may indicate that: (i) not all depressed patients show changes in inflammatory response (30); (ii) the mechanisms underlying the relationship between inflammation and suicide are still unclear (38): and (iii) it has not been determined whether inflammation is a causative factor or a consequence of depression (11). However, we also need to keep in mind that inflammatory response is influenced by multiple factors, such as body mass index, use of tobacco and other psychoactive substances, duration and severity of illness, resistance to antidepressant treatment, other psychiatric comorbidities, unbalanced diet, lack of exercise, and stress or traumatic life events in childhood or adulthood (30,31,39).

5. Limitations

First, our results are mostly based on cross-sectional studies, and a causal relationship between NLR and SI and SB in patients with MDD cannot be inferred. Second, other inflammatory parameters were not assessed in the review, precluding us from concluding whether increased NLR is an independent biomarker or is related to other immune and inflammatory changes in depressed patients. Third, the studies included in the systematic review are very heterogeneous (i.e., sample characteristics, small sample sizes, recruitment, and assessment of depression and suicidality), and therefore results remain preliminary and cannot be generalized to any specific population. Finally, due to the small number and small scale of studies included, we cannot exclude publication and reporting bias in those studies, possibly biasing the results of the systematic review.

6. Conclusion

In conclusion, the present review found preliminary evidence for an association between NLR and SB in patients with MDD. Our results reinforce the idea that neuroinflammatory

processes may be important in the pathophysiology of suicidal behavior in depressed patients. NLR could be an attractive, convenient, and cost-effective trait marker of suicidal vulnerability in patients with MDD. Future large-scale replication studies are needed to confirm the observed associations and to examine the apparently understudied role of PLR and MLR in depressed patients in greater depth.

7. Acknowledgment

The authors wish to thank Sharon Grevet for her English assistance.

8. Conflict of interest

All authors declare no conflict of interest relative to this study.

9. Funding source

This research was partially supported by the Government of the Principality of Asturias PCTI-2021-2023 IDI/2021/111, the Fundación para la Investigación e Innovación Biosanitaria del Principado de Asturias (FINBA), and Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud Carlos III, Ministerio de Ciencia e Innovación. The funders had no role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript.

10. References

1. World Health Organization. Suicide worldwide in 2019: global health estimates. World Health Organization. 2021. Licence: CC BY-NC-SA 3.0 IGO. Available from: https://apps.who.int/iris/rest/bitstreams/1350975/retrieve

2. Bachmann S. Epidemiology of Suicide and the Psychiatric Perspective. Int J Environ Res Public Health. 2018 Jul 6;15(7). DOI: 10.3390/ijerph15071425

3. Dong M, Wang SB, Wang F, Zhang L, Ungvari GS, Ng CH, et al. Suicide-related behaviours in schizophrenia in China: a comprehensive meta-analysis. Epidemiol Psychiatr Sci. 2019 Jun 1;28(3):290. DOI: 10.1017/S2045796017000476

4. Velasco Á, Rodríguez-Revuelta J, Olié E, Abad I, Fernández-Peláez A, Cazals A, et al. Neutrophil-to-lymphocyte ratio: A potential new peripheral biomarker of suicidal behavior. Eur Psychiatry. 2020;63(1). DOI: 10.1192/j.eurpsy.2019.20

5. Bergmans RS, Kelly KM, Mezuk B. Inflammation as a unique marker of suicide ideation distinct from depression syndrome among U.S. adults. J Affect Disord. 2019 Feb 2;245:1052. DOI: 0.1016/j.jad.2018.11.046

6. Vasupanrajit A, Jirakran K, Tunvirachaisakul C, Solmi M, Maes M. Inflammation and nitro-oxidative stress in current suicidal attempts and current suicidal ideation: a systematic review and meta-analysis. Mol Psychiatry. 2022 Jan 8;27(3):1350–61. DOI: 10.1038/s41380-021-01407-4

7. Courtet P, Giner L, Seneque M, Guillaume S, Olie E, Ducasse D. Neuroinflammation in suicide: Toward a comprehensive model. World J Biol Psychiatry. 2016 Nov 16;17(8):564–86. DOI: 10.3109/15622975.2015.1054879

8. Demirkol ME, Namlı Z, Tamam L. Efficacy of light therapy on non-seasonal depression

and inflammatory markers. Eur J Psychiatry. 2019;33(3):104–11. Available from: https://doi.org/10.1016/j.ejpsy.2019.03.002

9. Puangsri P, Ninla-aesong P. Potential usefulness of complete blood count parameters and inflammatory ratios as simple biomarkers of depression and suicide risk in drug-naive, adolescents with major depressive disorder: Simple peripheral markers for inflammation in drug-naive, adolescents with major depressive disorder. Psychiatry Res. 2021 Nov 1;305:114216. DOI: 10.1016/j.psychres.2021.114216

10. Rungelrath V, Kobayashi SD, DeLeo FR. Neutrophils in innate immunity and systems biology-level approaches. Wiley Interdiscip Rev Syst Biol Med. 2020 Jan 1;12(1). DOI: 10.1002/wsbm.1458

11. Özyurt G, Binici NC. Increased neutrophil-lymphocyte ratios in depressive adolescents is correlated with the severity of depression. Psychiatry Res. 2018;268:426–31. DOI: 10.1016/j.psychres.2018.08.007

12. Chaplin DD. Overview of the immune response. J Allergy Clin Immunol. 2010 Feb;125(2 Suppl 2). DOI: 10.1016/j.jaci.2009.12.980

13. Ivković M, Pantović-Stefanović M, Dunjić-Kostić B, Jurišić V, Lačković M, Totić- Poznanović S, et al. Neutrophil-to-lymphocyte ratio predicting suicide risk in euthymic patients with bipolar disorder: Moderatory effect of family history. Compr Psychiatry. 2016;66:87–95. DOI: 10.1016/j.comppsych.2016.01.005

14. Zheng Q, Liu J, Ji YJ, Zhang Y, Chen XC, Liu BS. Elevated levels of monocyte- lymphocyte ratio and platelet-lymphocyte ratio in adolescents with non-suicidal self- injury. BMC Psychiatry. 2022;22(1):618. DOI: 10.1186/s12888-022-04260-z

15. Kayhan F, Gündüz Ş, Ersoy SA, Kandeğer A, Annagür BB. Relationships of neutrophil–

lymphocyte and platelet–lymphocyte ratios with the severity of major depression. Psychiatry Res. 2017 Jan 1;247:332–5. DOI: 10.1016/j.psychres.2016.11.016

16. Turkmen K, Erdur FM, Ozcicek F, Ozcicek A, Akbas EM, Ozbicer A, et al. Platelet-to- lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in end- stage renal disease patients. Hemodial Int. 2013 Jul;17(3):391–6. DOI: 10.1111/hdi.12040

17. Isaac V, Wu CY, Huang CT, Baune BT, Tseng CL, McLachlan CS. Elevated neutrophil to lymphocyte ratio predicts mortality in medical inpatients with multiple chronic conditions. Medicine (Baltimore). 2016;95(23). DOI: 10.1097/MD.0000000000003832

18. Mazza MG, Lucchi S, Tringali AGM, Rossetti A, Botti ER, Clerici M. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in mood disorders: A meta- analysis. Prog Neuro-Psychopharmacology Biol Psychiatry. 2018 Jun 8;84:229–36. DOI: 10.1016/j.pnpbp.2018.03.012

19. Demir S, Atli A, Bulut M, İbiloğlu AO, Ggüneş M, Kaya MC, et al. Neutrophil- lymphocyte ratio in patients with major depressive disorder undergoing no pharmacological therapy. Neuropsychiatr Dis Treat. 2015 Aug 27;11:2253–8. DOI: 10.2147/NDT.S89470

20. Ekinci O, Ekinci A. The connections among suicidal behavior, lipid profile and low-grade inflammation in patients with major depressive disorder: a specific relationship with the neutrophil-to-lymphocyte ratio. Nord J Psychiatry. 2017 Nov 17;71(8):574–80. DOI: 10.1080/08039488.2017.1363285

21. Orum MH, Kara MZ, Egilmez OB. Mean platelet volume and neutrophil to lymphocyte ratio as parameters to indicate the severity of suicide attempt. J Immunoassay Immunochem. 2018 Nov 2;39(6):647–59. DOI: 10.1080/15321819.2018.1529682

22. Sunbul EA, Sunbul M, Yanartas O, Cengiz F, Bozbay M, Sari I, et al. Increased Neutrophil/Lymphocyte Ratio in Patients with Depression is Correlated with the Severity of Depression and Cardiovascular Risk Factors. Psychiatry Investig. 2016 Jan 1;13(1):121–6. DOI: 10.4306/pi.2016.13.1.121

23. Ucuz İ, Kayhan Tetik B. Can suicide behavior and seasonality of suicide be predicted from inflammatory parameters in adolescents? Med Hypotheses. 2020;143(May). DOI: 10.1016/j.mehy.2020.110061

24. Dickerson F, Adamos M, Katsafanas E, Khushalani S, Origoni A, Savage C, et al. The association between immune markers and recent suicide attempts in patients with serious mental illness: A pilot study. Psychiatry Res. 2017 Sep 1;255:8–12. DOI: 10.1016/j.psychres.2017.05.005

25. Page M, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar;372:n71. DOI: 10.1136/bmj.n71

26. Howick J, Chalmers I, Glasziou P, Greenhalgh T, Heneghan C, Liberati A, et al. Explanation of the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (Background Document). Oxford Centre for Evidence-Based Medicine. 2011. Available from: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/explanation-of- the-2011-ocebm-levels-of-evidence

27. Gundogdu Meydaneri G, Meydaneri S. Can Neutrophil Lymphocyte Ratio Predict the Likelihood of Suicide in Patients with Major Depression? Cureus. 2018;10(4). DOI: 10.7759/cureus.2510

28. Yagci I, Avci S. Biochemical predictors in presentations to the emergency department after a suicide attemp. Bratisl Med J. 2021;122(3):224–9. DOI: 10.4149/BLL_2021_012

29. Önen Ö, Erkuran HÖ, Bağ Ö, Abacıgil F. Blood Count Parameters as Inflammation Indicators in Children and Adolescents Diagnosed with Depressive Disorder. Psychiatry Clin Psychopharmacol. 2021;31(4):425–33. DOI: 10.5152/pcp.2021.21137

30. Adhikari A, Dikshit R, Karia S, Sonavane S, Shah N, De Sousa A. Neutrophil-lymphocyte ratio and c-reactive protein level in patients with major depressive disorder before and after pharmacotherapy. East Asian Arch Psychiatry. 2018 Jun 1;28(2):53–8.

31. Martínez-Botía P, Velasco A, Rolle V, Jiménez-Trevino L, De la Fuente-Tomás L, Bernardo Á, et al. Sex-dependent grades of haematopoietic modulation in patients with major depressive episodes are associated with suicide attempts. Eur Neuropsychopharmacol. 2020 Nov 1;40:17–30. DOI: 10.1016/j.euroneuro.2020.06.006

32. Grudet C, Wolkowitz OM, Mellon SH, Malm J, Reus VI, Brundin L, et al. Vitamin D and inflammation in major depressive disorder. J Affect Disord. 2020;267(January):33–41. DOI: 10.1016/j.jad.2020.01.168

33. Amitai M, Kaffman S, Kroizer E, Lebow M, Magen I, Benaroya-Milshtein N, et al. Neutrophil to-lymphocyte and platelet-to-lymphocyte ratios as biomarkers for suicidal behavior in children and adolescents with depression or anxiety treated with selective serotonin reuptake inhibitors. Brain Behav Immun. 2022 Aug 1;104:31–8. DOI: 10.1016/j.bbi.2022.04.018

34. Klonsky E, May A, Saffer B. Suicide, Suicide Attempts, and Suicidal Ideation. Annu Rev Clin Psychol. 2016 Mar 28;12:307–30. DOI: 10.1146/annurev-clinpsy-021815-093204

35. Mazza MG, De Lorenzo R, Conte C, Poletti S, Vai B, Bollettini I, et al. Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. Brain Behav Immun. 2020;89(July):594–600. DOI: 10.1016/j.bbi.2020.07.037

36. Galfalvy H, Haghighi F, Hodgkinson C, Goldman D, Oquendo MA, Burke A, et al. A genome-wide association study of suicidal behavior. Am J Med Genet B Neuropsychiatr Genet. 2015 Oct 1;168(7):557–63. DOI: 10.1002/ajmg.b.32330

37. Özdin S, Sarisoy G, Böke Ö. A comparison of the neutrophil-lymphocyte, platelet- lymphocyte and monocyte-lymphocyte ratios in schizophrenia and bipolar disorder patients - a retrospective file review. Nord J Psychiatry. 2017 Oct 3;71(7):509–12. DOI: 10.1080/08039488.2017.1340517

38. Russell AE, Mars B, Wen CP, Chang S Sen, Gunnell D. Evidence for an association between inflammatory markers and suicide: a cohort study based on 359,849 to 462,747 Taiwanese adults. J Affect Disord. 2021 Feb 15;281:967-971. DOI: 10.1016/j.jad.2020.10.047

39. Del Giudice M, Gangestad SW. Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers, and why it matters. Brain Behav Immun. 2018 May 1;70:61– 75. DOI: 10.1016/j.bbi.2018.02.013

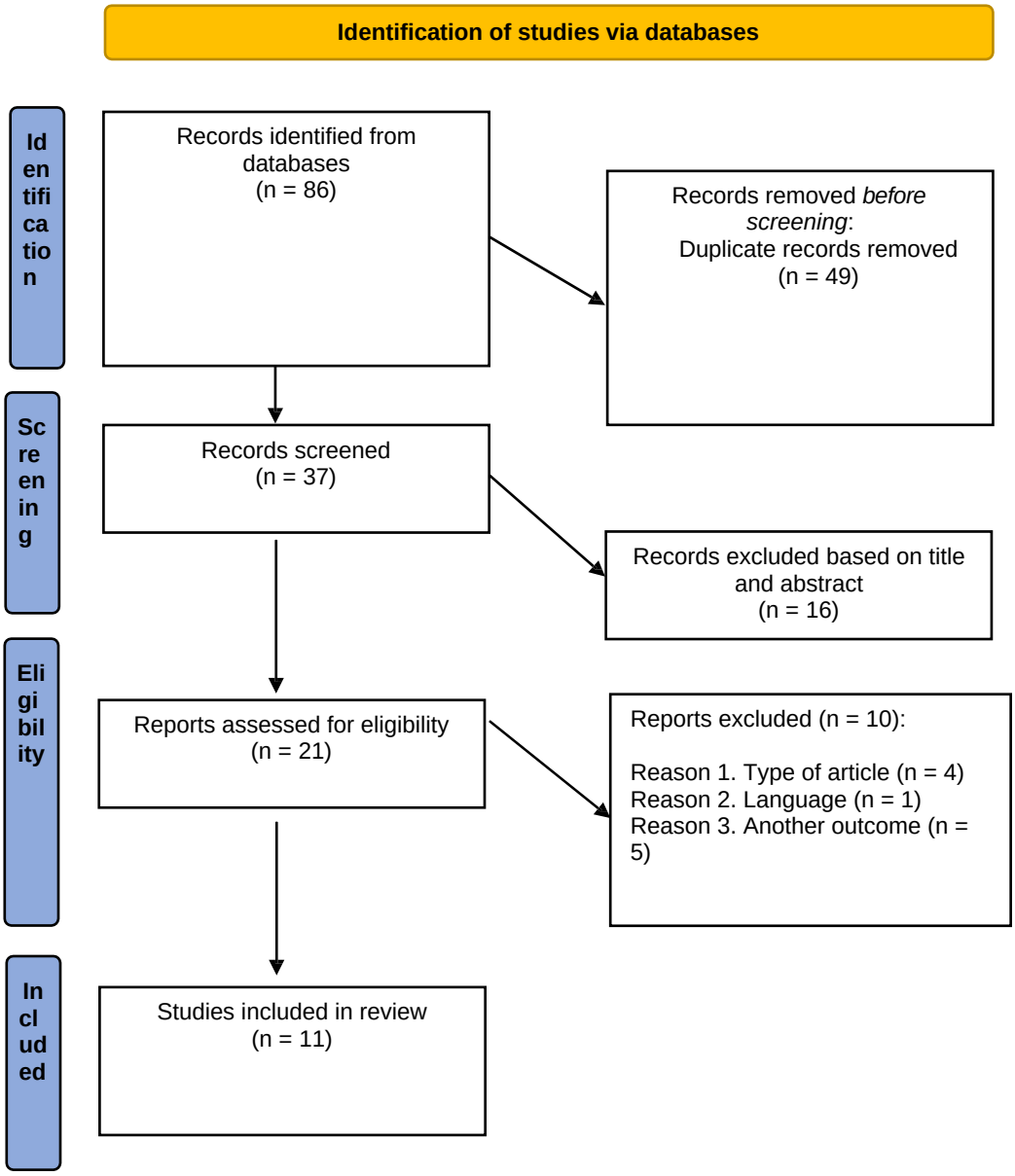


Figure 1. PRISMA 2020 flow diagram for new systematic reviews that included database searches

Table 1. Main characteristics and results of articles included in the review

Author, date Country	Diagnosis	Total sample Mean age (SD) Sex (% females)	Suicidal behavior Mean age (SD) Sex (% females)	Control patients Mean age (SD) Sex (% females)	Healthy controls Mean age (SD) Sex (% females)	Depression and suicidal ideation scales	SI/SA group	Type and quality of study	Outcome
Amitai et al., 2022 *Israel*	Mostly depression + anxiety	N=91 13.9 (2.42) years 56 (62%) females	N=22 15 (65%) females	N=69	Not available	K-SADS-PL CDRS-R C-SSRS	SA	Case-control 2c	NLR and PLR at baseline were higher in SA group than in nSA group. NLR and PLR correlate with SI. NLR was a better predictor of SB than PLR. After eight weeks of fluoxetine treatment, NLR and PLR indexes were higher but not significantly.
Adhikari et al., 2018 *India*	MDD	N=50 39.27 (10.15) years 26 (52%) females	Not available	Not available	Not available	MADRS SIS-MAP	SI	Longitudinal 2c	Baseline: males and females do not differ in any blood parameters, except for a higher total white blood cell count in males. After pharmacotherapy (12 weeks), in females only, neutrophils were increased, lymphocytes decreased and consequently, NLR was increased in response to antidepressant therapy. In males, NLR was associated with decreased depressive symptoms and suicide risk, and higher CRP.
Ekinci and Ekinci, 2017 *Turkey*	MDD	N=189 43 (9.98) years 97 (69.7%) females	N=37 43 (14.15) years 22 (77.3%) females	N=102 41.88 (11.49) years 75 (64.3%) females	N=50 44.12 (4.23) 37 (74%) females	HDRS	SA	Case-control 3b	NLR was higher in patients with SA than in nSA and HC subjects. NLR was a predictor of recent SA in MDD patients. PLR was not significant.
Velasco et al., 2020 *Spain*	MDD	N=538 43.87 (14.36) years 370 (68.8%) females	N=402 41.20 (13.78) years 289 (71.9%) females	N=136 51.77 (13.10) years 81 (59.6%) females	Not available	HDRS	SA	Cross-sectional 2c	NLR was higher in MDD patients with SA vs MDD patients without SA. NLR was a biological marker of SB with a cut-off value of 1.30, 75% sensitivity, and 35% specificity. PLR was higher in MDD patients with SA vs MDD patients without SA. MLR did not show any differences between MDD patients with or without a history of SA.

Demirkol et al., 2019 *Turkey*	MDD	N=74 Age not available 50 (67.5%) females	Not available	Not available	Not available	HDRS BSSI	SI	Longitudinal 2c	AD + BLT showed significant improvement over AD monotherapy. HDRS scores decreased significantly one day after treatment and continued for two weeks after. SI decreased significantly after treatment. Neutrophils were decreased, lymphocytes were increased and consequently, NLR was decreased significantly in all patients after treatment. PLR index did not differ before or after treatment.
Grudet et al., 2020 *Sweden*	MDD	N=102 38.6 (14.4) years 60 (59%) females	N=17 42.1 (14.3) years 9 (53%) females	N=31 37.7 (15.2) years 18 (58%) females	N=54 37.9 (13.9) 33 (61%) females	HDRS Items SI (HDRS) > 4	SI	Case-control 3b	NLR did not show differences between MDD vs HC or between MDD with SI vs without SI. Lower levels of vitamin D were more associated with a pro-inflammatory status in MDD patients than HC, especially in MDD patients with SI.
Puangsri and Nimla-Aesong, 2021 *Thailand*	MDD	N=193	N=81 MDD SI n=38 MDD SA n=43	MDD nSI n=56	N=56 20 (1.1) years 36 (64.29%) females	PHQ-9 DASS-21 8Q	SA SI	Case-control 3b	NLR was significantly higher in all MDD patients vs HC. PLR was significantly higher in all MDD patients vs HC. PLR was higher in MDD nSI vs HC. MLR in MDD SA was significantly higher than HC and in MDD nSI. MLR tended to be higher in the MDD SI group.
Martínez-Botía, Velasco and Rolle et al., 2020 *Spain*	MDD	N=172 50.08 (11.19) years 86 (50%) females	N=48 50.94 (9.71) years 30 (62.5%) females	N=31 54.35 (11.61) years 16 (51.6%) females	N=93 48.22 (11.44) years 40 (43.0%) females	HDRS	SA	Case-control 3b	NLR was not statistically significant where found between groups. PLR was not statistically significant where found between groups. MLR was more significantly decreased with SA than MDD nSA and HC.
Yagci and Avci, 2021 *Turkey*	Mostly depression + anxiety	N=91 32.53 (10.39) years 57 (62.6%) females	N=46 33 (71.7%) females	Not available	N=45 24 (53.3.%) females	BDI BAI BSSI	SA	Case-control 3b	NLR was higher in SA than in HC. NLR positively correlated between BDI, BAI, and BSSI. However, this correlation was not statistically significant.
Önen et al., 2021 *Turkey*	MDD	N=148; N=58 MDD patients 13.97 (1.98) years 44 (75.9%) females	N=15	N=43	N=90 14.29 (1.67) years 60 (66.7%) females	CDI	SB (not specified if SA or SI)	Case-control 3b	NLR did not show any differences between groups. PLR was higher in the MDD group than in HC. PLR was a biological marker of MDD in children and adolescents with a cut-off value of 112.5, 70% sensitivity,

									and 65% specificity.
Meydaneri and Meydaneri, 2018 *Turkey*	MDD	N=53 33 (12) years 40 (75%) females	N=27 32 (13) years 20 (74%) females	N=26 35 (11) years 20 (77%) females	Not available	None	SA	Cross-sectional 2c	NLR tended to be higher in the SA group. However, this difference was not statically significant. PLR tended to be higher in the SA group. However, this difference was not statically significant.

AD: Antidepressant; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; BLT: Bright Light Therapy; BSSI: Beck Scale for Suicide Ideation; CDI: Children's Depression Inventory; CDRS-R: Children's Depression Rating Scale- revised; CRP: C-Reactive Protein; C-SSRS: Columbia-Suicide Severity Rating Scale; DASS-21: Depression Anxiety Stress scale; HC: Healthy Control; HDRS: Hamilton Depression Rating Scale; K-SADS-PL: Kiddie-Schedule for Affective Disorders & Schizophrenia – Present and Lifetime version; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: Major Depressive Disorder; MLR: Monocyte/lymphocyte ratio; NLR: Neutrophil/lymphocyte ratio; nSA: Non-Suicide Attempt; nSI: Non-Suicidal Ideation; PHQ-9: Patient Health Questionnaire; PLR: Platelet/lymphocyte ratio; SA: Suicide Attempt; SB: Suicidal Behavior; SI: Suicidal Ideation; SD: Standard Deviation; SIS-MAP: Scale for Impact of Suicidality Management and Assessment and Planning of Care; 8Q: 8 Questionnaire (Thai-version of a suicidality module of Mini International Neuropsychiatric Interview).

Table 2. Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, and Monocyte-to-lymphocyte ratio in Major Depressive Disorder with Suicidal Behavior *versus* non-Suicidal Behavior patients

Author, date	*Type of SB*	*MDD with SB*	*MDD without SB*	
NLR		**Mean (SD)**	**Mean (SD)**	***p-value***
Velasco et al., 2020	Recent SA Past SA	2.37 (2.36) 2.22 (2.17)	1.68 (0.80)	**0.001**
Amitai et al., 2022	SA	2.16 (0.78)	1.64 (0.96)	**0.019**
Ekinci and Ekinci, 2017	Recent SA	2.840 (0.162)	1.858 (0.98)	**0.001**
Meydaneri and Meydaneri, 2018	SA	2.04 (0.89)	1.85 (0.81)	0.054
Martínez-Botía, Velasco and Rolle et al., 2020	SA	2.17 (1.66)	1.68 (0.57)	0.291
Grudet et al., 2020	SI	2.3 (1.0)	2.2 (0.8)	0.81
PLR		**Mean (SD)**	**Mean (SD)**	***p-value***
Velasco et al., 2020	Recent SA Past SA	128.20 (61.65) 127.76 (58.91)	109.97 (38.75)	**0.024**
Amitai et al., 2022	SA	159.31 (53.98)	133.56 (58.18)	**0.044**
Ekinci and Ekinci, 2017	Recent SA	141.4 (83.25)	128.11 (48.76)	0.248
Meydaneri and Meydaneri, 2018	SA	120.81 (39.34)	118.55 (42.39)	0.73
Martínez-Botía, Velasco and Rolle et al., 2020	SA	122.39 (64.51)	109.30 (28.50)	0.416
MLR		**Mean (SD)**	**Mean (SD)**	***p-value***
Velasco et al., 2020	Recent SA Past SA	0.28 (0.16) 0.27 (0.15)	0.25 (0.10)	0.573
Martínez-Botía, Velasco and Rolle et al., 2020	SA	0.26 (0.12)	0.25 (0.08)	0.851

MDD: Major Depressive Disorder; MLR: Monocyte/lymphocyte ratio; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; SA: Suicide Attempt; SB: Suicidal Behavior; SI: Suicidal Ideation; SD: Standard Deviation.

Table 3. Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, and Monocyte-to-lymphocyte ratio in Major Depressive Disorder with Suicidal Behavior *versus* Healthy Controls

Author, date	*MDD with SB*	*Healthy Controls*	
NLR	**Mean (SD)**	**Mean (SD)**	***p-value***
Ekinci and Ekinci, 2017	2.840 (0.162)	1.81 (0.33)	**0.001**
Puangsri and Ninla-Aesong, 2021	2.01 (0.07)	1.49 (0.04)	**0.001**
Yagci and Avci, 2021	2.77 (1.6)	2.05 (0.59)	**0.009**
Martínez-Botía, Velasco and Rolle et al., 2020	1.97 (1.35)	1.87 (0.80)	0.510
Grudet et al., 2020	2.3 (1.0)	2.3 (1.2)	0.81
Önen et al., 2021	1.94 (1.11)	1.65 (0.66)	0.780
PLR	**Mean (SD)**	**Mean (SD)**	***p-value***
Puangsri and Ninla-Aesong, 2021	123.18 (3.35)	105.80 (3.11)	**0.024**
Önen et al., 2021	133.95 (41.65)	114.44 (40.53)	**0.005**
Ekinci and Ekinci, 2017	141.4 (83.25)	134.3 (61.4)	0.248
Martínez-Botía, Velasco and Rolle et al., 2020	117.26 (53.49)	117.99 (54.77)	0.952
MLR	**Mean (SD)**	**Mean (SD)**	***p-value***
Puangsri and Ninla-Aesong, 2021	0.21 (0.02)	0.15 (0.01)	**0.027**
Martínez-Botía, Velasco and Rolle et al., 2020	0.26 (0.11)	0.30 (0.13)	**0.017**

MDD: Major Depressive Disorder; MLR: Monocyte/lymphocyte ratio; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; SA: Suicide Attempt; SB: Suicidal Behavior; SI: Suicidal Ideation; SD: Standard Deviation.

Discusión

5. Discusión

El suicidio es un problema de salud pública mundial, ya que, a pesar de ser una muerte evitable, una persona muere por suicidio cada 40 segundos en el mundo. La propia complejidad del comportamiento suicida, la falta de uniformidad en su definición, la heterogeneidad en su evaluación, así como la falta de especificidad en los factores asociados a dicho comportamiento, pone de relieve la inmensa problemática a la hora de buscar marcadores útiles que permitan identificar, clasificar, predecir y evaluar, el riesgo inminente de suicidio con el fin de disminuir, indirectamente, el número de suicidios en el mundo.

La presente Tesis Doctoral tiene como objetivo la formulación del riesgo de suicidio en pacientes con depresión a través del uso de los marcadores periféricos inflamatorios accesibles y coste-efectivos.

Con la finalidad de facilitar al lector la lectura y comprensión de la discusión de los diferentes resultados obtenidos, se procederá a exponer dichos resultados agrupados de acuerdo con los objetivos planteados en la presente Tesis Doctoral.

5.1. Discusión por objetivos

Objetivo 1

Determinar la utilidad de determinados marcadores periféricos de inflamación Indice Neutrófilo/Linfocito (INL), Indice Plaqueta/Linfocito (IPL), e Indice Monocito/Linfocito (IML) en la predicción del comportamiento suicida en pacientes con diagnóstico de depresión mayor.

El primer objetivo de la presente Tesis Doctoral es abordado en el primer artículo, en dónde se comparan pacientes con TDM y TS reciente (en la última semana); pacientes con TDM y antecedentes de TS a lo largo de la vida; y pacientes con TDM sin antecedentes de TS, con el fin de determinar si los índices periféricos de inflamación, INL, IPL e IML, son útiles para diferenciar dichas poblaciones.

Señalar que, los índices periféricos de inflamación, INL, IPL e IML, emergen como posibles indicadores de inflamación sistémica, coste-efectivos y fácilmente accesibles, capaces de predecir, ante situaciones de emergencia o en la práctica clínica habitual, de forma rápida la presencia de vulnerabilidad suicida.

Los neutrófilos constituyen la primera línea de defensa del sistema inmune innato, por tanto, ante una amenaza desencadena una respuesta inflamatoria inespecífica que provoca a nivel celular apoptosis o fagocitosis (Rungelrath et al., 2020). Por otro lado, los linfocitos son quienes regular la respuesta de defensa del sistema inmune adaptativo (Chaplin, 2010). De este modo, el INL, es la ratio que se obtiene al combinar ambas vías de respuesta inmunitaria, proporcionando menos variabilidad y siendo más informativo que otros marcadores inflamatorios como pueden ser la Proteína C Reactiva (PCR) o el perfil lipídico (Ekinci & Ekinci, 2017).

El IPL está relacionado con el estrés. La presencia de estrés activa el sistema nervioso simpático, las plaquetas aumentan y se produce permeabilidad endotelial. Cuando la fuga de los vasos sanguíneos a los tejidos ocurre, los neutrófilos y los macrófagos aparecen, generando así inflamación periférica (Zheng et al., 2022).

El IML se ha asociado a la sobreexpresión genética que influye en la activación y diferenciación de las células inmunitarias, generando citoquinas, relacionadas con los monocitos, y consecuentemente, microglía, encargada de causar neuroinflamación (Zheng et al., 2022).

El principal hallazgo de este estudio es que los pacientes con depresión mayor y antecedentes de tentativa suicida presentan un incremento en el INL en comparación con sus iguales sin dichos antecedentes. De este modo, el INL podría establecerse como marcador de riesgo de la conducta suicida en pacientes con depresión mayor.

IPL e IML no resultan significativos en nuestro trabajo de investigación. La relación entre IPL y suicidio aún no está esclarecida ya que encontramos resultados contradictorios. Por un lado, se considera que IPL es mejor marcador de la gravedad de la depresión, por ejemplo, en presencia de síntomas psicóticos (Kayhan et al., 2017), mientras que otros señalan que, en otras áreas médicas, IPL es mejor predictor de inflamación que INL (Turkmen et al., 2013), lo que encaja con su propia definición, ya que IPL se relaciona con el estrés, causando inflamación, pero no parece ser una respuesta específica de comportamiento suicida. Del mismo modo sucede con el IML, donde no existen hasta la fecha resultados concluyentes. Si bien es cierto, en jóvenes con autolesiones no suicidas, se ha descrito que existe un incremento en IML y en IPL, pero no en INL (Zheng et al., 2022), lo que nos hace pensar que INL podría ser un marcador útil de tentativa suicida, mientras que IPL e IML serían señal de inflamación sistémica sin necesidad del desenlace hacia una conducta suicida, entendiendo dicho comportamiento como un continuum, es decir, como diferentes fenómenos con diferentes explicaciones y predictores (Galfalvy et al., 2015).

Por lo tanto, tal y como se hipotetizó, parece ser que la neuroinflamación tiene un papel determinante en la conducta suicida. Concretamente, son los pacientes con depresión mayor e historia previa de tentativa suicida quienes muestran un incremento en los neutrófilos y una disminución en los niveles de linfocitos.

Estudios previos confirman los resultados obtenidos en nuestro trabajo de investigación, ya que anteriormente, el INL ya se había sugerido como marcador de

vulnerabilidad suicida en quienes presentan antecedentes de tentativa suicida y depresión (Ekinci & Ekinci, 2017). Además, estos hallazgos no sólo se encuentran en población adulta, si no que ya en niños y adolescentes, con depresión y ansiedad, también aparece como biomarcador útil de tendencias suicidas, siendo mejor predictor de intento de suicidio que IPL (Amitai et al., 2022).

Cabe señalar también que, en una muestra de pacientes que intento quitarse la vida mediante intoxicación medicamentosa, los valores de INL e IPL fueron significativamente más elevados en el ingreso hospitalario que al alta médica (Mustafa et al., 2022). Todo ello nos hace pensar, que el estado inflamatorio podría subyacer al incremento de la respuesta inmune que observamos en el sistema nervioso central, contribuyendo así, junto con más variables, a la vulnerabilidad de la conducta suicida en pacientes con depresión mayor.

Finalmente, y recordando la utilidad clínica de estos índices en situaciones de rápido abordaje, nuestro trabajo de investigación es el primero que establece un punto de corte óptimo para INL, priorizando la sensibilidad (75%), frente a la especificidad (35%), ya que ante esa situación resulta imprescindible ser sensible, estableciendo el punto de corte en 1,30. Hasta la fecha, el único punto de corte propuesto para INL fue descrito en el 2018 (Orum et al., 2018), con el fin de diferenciar la tentativa suicida violenta *versus* no violenta, situándose en 2,22.

Objetivo 2

Determinar la existencia de posibles diferencias en los parámetros hematopoyéticos de pacientes con depresión mayor, con y sin antecedentes de tentativa suicida, en comparación con personas sanas.

Objetivos secundarios

a. Analizar la posible existencia de estrés hematopoyético asociado a los antecedentes de tentativa suicida en pacientes con depresión mayor.
b. Establecer si existen diferencias en la respuesta de estrés hematopoyético en función del sexo.
c. Examinar la relación entre la exposición a acontecimientos vitales estresantes proximales y distales y el estrés hematopoyético.

El segundo objetivo se ha abordado en el segundo artículo de la presente Tesis Doctoral. En él, se estudia si existe estrés hematopoyético, subyacente a los procesos inflamatorios en una muestra de pacientes con TDM (con/sin antecedentes de TS) y controles sanos, de forma que posibiliten establecer patrones clínicos y biológicos en dicha población.

Se entiende por hematopoyesis al proceso por el cual todas las células de la sangre e inmunes, residentes de tejido, son producidas a partir de células madre hematopoyéticas de la médula ósea. Esta producción es regulada de forma que se garantice una producción homeostática, que se traduce en un hemograma normal. Sin embargo, las líneas de producción hematopoyética se interrelacionan entre sí, de modo que, si la producción de una de ellas se ve alterada, como por ejemplo por un estresor como podría ser una infección, las otras también lo harían. Esto es lo que conocemos

como estrés hematopoyético. Es decir, que el balance de producción normal se ve alterado debido a la demanda fisiológica subyacente.

El principal hallazgo de este estudio es que, en comparación con los participantes sanos, los pacientes con depresión mayor (con/sin TS), muestran alteraciones en los parámetros hematológicos que confirman la presencia de inflamación y, por tanto, de estrés hematopoyético. Los cambios encontrados entre ambas muestras sugieren un cambio incipiente que favorece el linaje de glóbulos blancos a expensas de la producción del linaje de glóbulos rojos. Además, el equilibro de producción hematopoyética mostró la desaparición de muchas correlaciones y la aparición de correlaciones *de novo*. De este modo, el estrés hematopoyético observado en pacientes con depresión mayor, con/sin TS, va más allá del estado inflamatorio previamente descrito (Courtet et al., 2016; Orum et al., 2018; Velasco et al., 2020). Todos estos cambios fueron más pronunciados en pacientes con TDM y TS, y más pronunciados en el sexo femenino en comparación los hombres.

Las diferencias, en función del sexo, en los marcadores de inflamación ya se han descrito previamente (Majd et al., 2018). En las mujeres, los cambios sugieren la presencia de inflamación sistémica, con un incremento en el IML y una reducción del linaje de glóbulos rojos, de forma que, la producción hematopoyética se ve desregulada debido a una respuesta inmune consolidada. Esto resuelta de especial interés, ya que en ocasiones los síntomas asociados a los trastornos del humor sugieren un antecedente autoinmune y las mujeres, tienen una mayor prevalencia de trastornos autoinmunes (Rainville & Hodes, 2019).

Finalmente, la relevancia de los factores estresantes en la infancia, pero no en la edad adulta, parece ser un factor importante que contribuye a la gravedad del estrés hematopoyético observado en pacientes con DM y TS. La exposición a acontecimientos

vitales estresantes distales es ya un hecho ampliamente aceptado (Serafini et al., 2015). La edad de inicio del abuso, el tiempo de duración de este y el tipo de abuso sufrido durante la infancia (Zatti et al., 2017) se ha asociado previamente, no sólo a un mayor riesgo de padecer depresión (Ono et al., 2017), sino también a la gravedad de esta, así como al riesgo de suicidio (Dal Santo et al., 2020; Liu et al., 2017).

Objetivo 3

Revisar de modo sistemático si los marcadores periféricos de inflamación previamente mencionados, Indice Neutrófilo/Linfocito, Indice Plaqueta/Linfocito, e Indice Monocito/Linfocito, son útiles para diferenciar: i) pacientes con depresión mayor con / sin historia de TS; ii) pacientes con depresión mayor con historia de TS versus controles sanos; y, iii) pacientes con depresión mayor con ideación suicida antes y después de su tratamiento.

El tercer objetivo de la presente Tesis Doctoral es abordado en el tercer artículo. La detección e identificación de marcadores periféricos inflamatorios, como son el INL, IPL e IML, permitirían métodos más personalizados que facilitasen la evaluación, el tratamiento, y en este caso, un incremento en la capacidad predictiva de conducta suicida.

El principal hallazgo de esta revisión es que el INL aparece como un marcador específico de vulnerabilidad suicida en pacientes con depresión, lo cual confirma que los procesos inflamatorios podrían ser relevantes en la patofisiología de dicho comportamiento en pacientes con depresión. Este hallazgo solo se asocia a la historia de tentativa suicida previa, y no, a la ideación suicida (Grudet et al., 2020). Todo ello sostiene la hipótesis de que la conducta suicida es un fenómeno diferente, a la ideación

suicida (Galfalvy et al., 2015), y que, por tanto, el comportamiento suicida ha de entenderse como un continuum con diferentes explicaciones y diferentes factores de riesgo en cada uno de sus estadios. Previamente se ha descrito que la depresión, el dolor, la desesperanza y la impulsividad son factores que predicen la ideación. Sin embargo, estos tres rasgos no son específicos para diferenciar a quienes han intentado quitarse la vida de quienes solo lo han considerado como una opción de alivio del malestar (Klonsky et al., 2016, 2018). Por el contrario, el acceso a los medios de suicidio, la ausencia de miedo a la muerte, una mayor tolerancia al dolor físico o la exposición al comportamiento suicida, son factores de riesgo que gobiernan la transición de la ideación a la conducta suicida (O'Connor & Kirtley, 2018).

En el caso de IPL los resultados no parecen estar del todo claros en el grupo de pacientes con depresión mayor y comportamiento suicida. Sin embargo, IPL sí aparece incrementado al comparar el grupo de depresión mayor (con/sin TS) con los controles sanos. Ello sugiere que, los pacientes con depresión tienen un desbalance en la producción hematopoyética resultado de un estresor que dispara la respuesta de las plaquetas como primera línea de defensa del sistema inmunitario, provocando una respuesta inflamatoria donde se liberan citoquinas, y que finalmente, afecta a la vía de la serotonina (Courtet et al., 2016; Martínez-Botía et al., 2020). Por eso mismo, IPL es considerado, en la literatura científica, un parámetro de gravedad de la inflamación (Kayhan et al., 2017; Turkmen et al., 2013) y no parece ser, un marcador específico de comportamiento suicida.

Finalmente, no se ha encontrado evidencia de que IML este asociado a los pacientes con depresión y comportamiento suicida. Únicamente se ha descrito una reducción en el conteo y en el porcentaje de monocitos en sangre periférica en pacientes con depresión mayor, al compararse con controles sanos (Martínez-Botía et al., 2020).

De modo que, si los monocitos, que influyen en la activación y diferenciación de las células inmunitarias, se movilizan hacia SNC, pueden contribuir de un modo activo a la neuroinflamación descrita previamente en los trastornos del humor (Weber et al., 2017; Zheng et al., 2022). Además, sólo en dos investigaciones se relata que dicho índice se encuentra elevado en jóvenes con trastornos del estado de ánimo que han intentado realizar una conducta autolesiva, diferente del suicidio, frente a quienes no se autolesionan (Zheng et al., 2022) y entre quienes presentan un episodio maniaco, al compararse con pacientes eutímicos (Özdin et al., 2017).

Atendiendo a la respuesta del tratamiento antidepresivo, en pacientes con depresión e ideación suicida, los resultados son limitados y no concluyentes. En primer lugar, es bien conocida la asociación entre depresión, conducta suicida y neuroinflamación, pero sigue sin determinarse si la neuroinflamación es una factor causal o consecuente de la depresión y/o de la conducta suicida (Özyurt & Binici, 2018; Russell et al., 2021). Además, no todos los pacientes con depresión muestran cambios en su respuesta inflamatoria (Adhikari et al., 2018). Por otro lado, no se debe de olvidar que, la respuesta inflamatoria es inespecífica y que se ve influenciada por otros múltiples factores, como el índice de masa corporal, el consumo de tabaco u otras sustancias psicoactivas, dieta desequilibrada, alteraciones en el sueño, ausencia de ejercicio físico, otras enfermedades comórbidas, así como, la duración, el tratamiento y el inicio de la enfermedad psiquiátrica (Adhikari et al., 2018; Del Giudice & Gangestad, 2018; Martínez-Botía et al., 2020; Velasco et al., 2020).

5.2. Limitaciones y Fortalezas

El presente trabajo estima una serie de limitaciones y fortalezas que defino a continuación:

En el primer artículo, se reúne una gran cohorte de participantes procedente de dos centros independientes y de dos países diferentes, pudiendo contribuir los resultados a la generalización en poblaciones caucásicas. Además, cuenta con un grupo control, sin antecedentes de TS, con las mismas características clínicas que el grupo experimental, lo que facilita la determinación de parámetros específicos de comportamiento suicida en dicha población.

Los resultados obtenidos han sido controlados por la edad, el sexo y la gravedad de la depresión, definiendo un punto de corte con valor pronóstico para el comportamiento suicida. No obstante, cabe necesario señalar que se trata de un estudio transversal con resultados preliminares, haciendo necesaria a su vez, la realización de estudios prospectivos que evalúen y monitoricen dichos resultados a lo largo del tiempo. Además, dadas las características de los participantes, la recogida de la muestra ha sido no probabilística. Por otro lado, otras variables de confusión como son el consumo de tabaco, los episodios depresivos previos, el tratamiento antidepresivo (incluyendo dosis y tiempo de este) no se han tenido en cuenta para el presente trabajo.

Respecto del segundo trabajo, la cohorte de pacientes con depresión mayor excluyó a aquellos con enfermedades crónicas graves y los tratados con antinflamatorios, a fin de evitar factores de confusión en el estrés hematopoyético. Además, al disponer de un grupo de donantes sanos, los resultados obtenidos agregan poder al significado clínico de los cambios y las correlaciones en los parámetros

hematológicos encontrados. No obstante, se trata de un estudio transversal con resultados preliminares, y de nuevo, la recogida de la muestra ha sido no probabilística.

Finalmente, en el tercer trabajo de investigación correspondiente a la revisión sistemática, los resultados obtenidos han de tomarse con cautela, ya que se basan en estudios transversales tremendamente heterogéneos, tanto en las características de la muestra como en la evaluación de la depresión y del comportamiento suicida. Además, dado que el número de estudios incluidos es pequeño, no podemos excluir el sesgo de publicación de los estudios y, por tanto, no se puede inferir una relación causal entre los índices Neutrófilo/Linfocito, Plaqueta/Linfocito y Monocito/Linfocito y tentativas o ideaciones suicidas en pacientes con trastorno depresivo mayor. Tampoco han sido tenidos en cuenta otros parámetros inflamatorios o inmunológicos que podrían estar afectando a dicha relación.

5.3. Futuras líneas de investigación

Dada la heterogeneidad de la conducta suicida, su estudio ha de ser multidisciplinar e integrativo con el fin de poder diseñar programas de intervención y prevención eficaces.

Por otra parte, sería interesante que las futuras investigaciones fueran encaminadas a profundizar la relación entre neuroinflamación y la conducta suicida, a través de los marcadores de inflamación periférica, así como la producción hematopoyética. Lo que permitiría una pronta detección de riesgo suicida, así como su tratamiento, al considerase una posible diana terapéutica.

Podría ser interesante también, profundizar en el estudio de los informes clínicos y en la autopsia psicológica como métodos reconocidos y fiables que recogen datos

clínicos y en donde se registran variables de riesgo suicida, dado que la mayor parte de los datos en los que se basan los factores de riesgo proceden de poblaciones con intentos de suicidio previos. De este modo, se nos permitiría extraer un protocolo de gestión de la conducta suicida fiable y homogéneo.

Conclusiones

6. Conclusiones

1. La neuroinflamación es un mecanismo esencial en la etiopatogenia de la conducta suicida en personas con trastorno depresivo mayor.

2. La formulación del riesgo de suicidio a través de los marcadores periféricos de inflamación es una herramienta válida y aplicable para establecer patrones diferenciales en personas con trastorno depresivo mayor.

3. El Indice Neutrófilo-Linfocito es un marcador periférico de inflamación útil y diferencial de tentativa suicida en personas con trastorno depresivo mayor con un punto de corte establecido en 1.30.

4. Las personas con trastorno depresivo mayor muestran un patrón hematopoyético diferencial que confirma la presencia de inflamación al compararse con población sana. Dichas alteraciones muestran cambios que favorecen el linaje de glóbulos blancos a expensas de producción del linaje de glóbulos rojos. Estas diferencias son más pronunciadas en mujeres, en quienes han estado expuestos a experiencias adversas en la edad temprana y quienes presentan antecedentes de comportamiento suicida.

5. El Indice Plaqueta-Linfocito y el Indice Monocito-Linfocito son marcadores útiles de inflamación sistémica, pero no son diferenciales de conducta suicida en personas con trastorno depresivo mayor.

Referencias

7. **Referencias**

Adhikari, A., Dikshit, R., Karia, S., Sonavane, S., Shah, N., & De Sousa, A. (2018). Neutrophil-lymphocyte Ratio and C-reactive Protein Level in Patients with Major Depressive Disorder Before and After Pharmacotherapy. *East Asian Archives of Psychiatry : Official Journal of the Hong Kong College of Psychiatrists*, *28*(2), 53–58. https://doi.org/10.12809/eaap181746

Allan, N. P., Gorka, S. M., Saulnier, K. G., & Bryan, C. J. (2023). Anxiety Sensitivity and Intolerance of Uncertainty: Transdiagnostic Risk Factors for Anxiety as Targets to Reduce Risk of Suicide. *Current Psychiatry Reports*, *25*(4). https://doi.org/10.1007/S11920-023-01413-Z

Amitai, M., Kaffman, S., Kroizer, E., Lebow, M., Magen, I., Benaroya-Milshtein, N., Fennig, S., Weizman, A., Apter, A., & Chen, A. (2022). Neutrophil to-lymphocyte and platelet-to-lymphocyte ratios as biomarkers for suicidal behavior in children and adolescents with depression or anxiety treated with selective serotonin reuptake inhibitors. *Brain, Behavior, and Immunity*, *104*, 31–38. https://doi.org/10.1016/j.bbi.2022.04.018

Anestis, M. D., Soberay, K. A., Gutierrez, P. M., Hernández, T. D., & Joiner, T. E. (2014). Reconsidering the link between impulsivity and suicidal behavior. *Personality and Social Psychology Review : An Official Journal of the Society for Personality and Social Psychology, Inc*, *18*(4), 366–386. https://doi.org/10.1177/1088868314535988

Angst, J., Hengartner, M. P., Rogers, J., Schnyder, U., Steinhausen, H. C., Ajdacic-Gross, V., & Rössler, W. (2014). Suicidality in the prospective Zurich study: prevalence, risk factors and gender. *European Archives of Psychiatry and Clinical*

Neuroscience, *264*(7), 557–565. https://doi.org/10.1007/S00406-014-0500-1

Ayuso-Mateos, J. L., Baca-García, E., Bobes, J., Giner, J., Giner, L., Pérez, V., Sáiz, P. A., & Saiz Ruiz, J. (2012). Recommendations for the prevention and management of suicidal behaviour. *Revista de Psiquiatria y Salud Mental*, *5*(1), 8–23. https://doi.org/10.1016/J.RPSM.2012.01.001

Barbeito, S., Vega, P., Sánchez-Gutiérrez, T., Becerra, J. A., González-Pinto, A., & Calvo, A. (2021). A systematic review of suicide and suicide attempts in adolescents with psychotic disorders. *Schizophrenia Research*, *235*, 80–90. https://doi.org/10.1016/J.SCHRES.2021.07.029

Beautrais, A. L., & N Zealand M of H. (2005). *Suicide Prevention: A review of evidence of risk and protective factors, and points of effective intervention. Ministry of Health.*

Bergen, H., Hawton, K., Waters, K., Ness, J., Cooper, J., Steeg, S., & Kapur, N. (2012). Premature death after self-harm: a multicentre cohort study. *Lancet (London, England)*, *380*(9853), 1568–1574. https://doi.org/10.1016/S0140-6736(12)61141-6

Bobes García, J., Ubago, J. G., & Saiz Ruiz, J. (2011). *Suicidio y psiquiatría Recomendaciones preventivas y de manejo del comportamiento suicida.* Triacastela, Madrid.

Borges, G., Benjet, C., Orozco, R., Medina-Mora, M. E., & Menendez, D. (2017). Alcohol, cannabis and other drugs and subsequent suicide ideation and attempt among young Mexicans. *Journal of Psychiatric Research*, *91*, 74–82. https://doi.org/10.1016/J.JPSYCHIRES.2017.02.025

Bostwick, J. M., Pabbati, C., Geske, J. R., & McKean, A. J. (2016). Suicide Attempt as a Risk Factor for Completed Suicide: Even More Lethal Than We Knew. *The American Journal of Psychiatry*, *173*(11), 1094–1100.

https://doi.org/10.1176/APPI.AJP.2016.15070854

Brezo, J., Paris, J., & Turecki, G. (2006). Personality traits as correlates of suicidal ideation, suicide attempts, and suicide completions: a systematic review. *Acta Psychiatrica Scandinavica*, *113*(3), 180–206. https://doi.org/10.1111/J.1600-0447.2005.00702.X

Brundin, L., Bryleva, E. Y., & Thirtamara Rajamani, K. (2017). Role of Inflammation in Suicide: From Mechanisms to Treatment. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *42*(1), 271–283. https://doi.org/10.1038/NPP.2016.116

Bryan, C. J., May, A. M., & Harris, J. (2019). Examining emotion relief motives as a facilitator of the transition from suicidal thought to first suicide attempt among active duty soldiers. *Psychological Services*, *16*(2), 293–301. https://doi.org/10.1037/SER0000234

Burón, P., Jimenez-Trevino, L., Saiz, P. A., García-Portilla, M. P., Corcoran, P., Carli, V., Fekete, S., Hadlaczky, G., Hegerl, U., Michel, K., Sarchiapone, M., Temnik, S., Värnick, A., Verbanck, P., Wasserman, D., Schmidtke, A., & Bobes, J. (2016). Reasons for Attempted Suicide in Europe: Prevalence, Associated Factors, and Risk of Repetition. *Archives of Suicide Research : Official Journal of the International Academy for Suicide Research*, *20*(1), 45–58. https://doi.org/10.1080/13811118.2015.1004481

Canon, M. E., & Crimmins, E. M. (2011). Sex differences in the association between muscle quality, inflammatory markers, and cognitive decline. *The Journal of Nutrition, Health & Aging*, *15*(8), 695–698. https://doi.org/10.1007/S12603-011-0340-X

Cao, J., Chen, X., Chen, J., Ai, M., Gan, Y., He, J., & Kuang, L. (2021). The

Association Between Resting State Functional Connectivity and the Trait of Impulsivity and Suicidal Ideation in Young Depressed Patients With Suicide Attempts. *Frontiers in Psychiatry*, *12*. https://doi.org/10.3389/FPSYT.2021.567976

Carballo, J. J., Currier, D., Figueroa, A. E., Giner, L., Kelly, S. A., Sublette, M. E., & Oquendo, M. A. (2009). Neurobiological underpinnings of suicidal behavior: Integrating data from clinical and biological studies. *European Journal of Psychiatry*, *23*, 243–259.

Chang, B. P., Franklin, J. C., Ribeiro, J. D., Fox, K. R., Bentley, K. H., Kleiman, E. M., & Nock, M. K. (2016). Biological risk factors for suicidal behaviors: a meta-analysis. *Translational Psychiatry*, *6*(9). https://doi.org/10.1038/TP.2016.165

Chaplin, D. D. (2010). Overview of the immune response. *The Journal of Allergy and Clinical Immunology*, *125*(2 Suppl 2). https://doi.org/10.1016/J.JACI.2009.12.980

Conejero, I., Olié, E., Courtet, P., & Calati, R. (2018). Suicide in older adults: current perspectives. *Clinical Interventions in Aging*, *13*, 701–712. https://doi.org/10.2147/CIA.S130670

Courtet, P., Jaussent, I., Genty, C., Dupuy, A. M., Guillaume, S., Ducasse, D., & Olié, E. (2015). Increased CRP levels may be a trait marker of suicidal attempt. *European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology*, *25*(10), 1824–1831. https://doi.org/10.1016/J.EURONEURO.2015.05.003

Courtet, P., Giner, L., Seneque, M., Guillaume, S., Olie, E., & Ducasse, D. (2016). Neuroinflammation in suicide: Toward a comprehensive model. *The World Journal of Biological Psychiatry : The Official Journal of the World Federation of Societies of Biological Psychiatry*, *17*(8), 564–586.

https://doi.org/10.3109/15622975.2015.1054879

Da Matta, A., Gonçalves, F. L., Bizarro, L., & De, L. (2012). Delay discounting: concepts and measures Decision-making and delay discounting. *Psychology & Neuroscience*, *5*, 135–146. https://doi.org/10.3922/j.psns.2012.2.03

Dal Santo, F., Carballo, J. J., Velasco, A., Jiménez-Treviño, L., Rodríguez-Revuelta, J., Martínez-Cao, C., Caro-Cañizares, I., de la Fuente-Tomás, L., Menéndez-Miranda, I., González-Blanco, L., García-Portilla, M. P., Bobes, J., & Sáiz, P. A. (2020). The Mediating Role of Impulsivity in the Relationship Between Suicidal Behavior and Early Traumatic Experiences in Depressed Subjects. *Frontiers in Psychiatry*, *11*. https://doi.org/10.3389/FPSYT.2020.538172

De Araújo, R. M. F., & Lara, D. R. (2016). More than words: The association of childhood emotional abuse and suicidal behavior. *European Psychiatry : The Journal of the Association of European Psychiatrists*, *37*, 14–21. https://doi.org/10.1016/J.EURPSY.2016.04.002

Del Giudice, M., & Gangestad, S. W. (2018). Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers, and why it matters. *Brain, Behavior, and Immunity*, *70*, 61–75. https://doi.org/10.1016/J.BBI.2018.02.013

Diaz-Olivan, I., Porras-Segovia, A., Barrigon, M. L., Cruz, M. de la, & Baca-Garcia, E. (2021). Stressful life events as proximal risk factors for a suicide crisis: Case-control study. *Actas Española Psiquiatria*, *49*(3), 88–95.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctôt, K. L. (2010). A meta-analysis of cytokines in major depression. *Biological Psychiatry*, *67*(5), 446–457. https://doi.org/10.1016/J.BIOPSYCH.2009.09.033

Ducasse, D., Holden, R. R., Boyer, L., Artéro, S., Raffaella, Guillaume, S., Courtet, P., & Olié, E. (2018). Psychological Pain in Suicidality: A Meta-Analysis. *The*

Journal of Clinical Psychiatry, *79*(3). https://doi.org/10.4088/JCP.16R10732

Ekinci, O., & Ekinci, A. (2017). The connections among suicidal behavior, lipid profile and low-grade inflammation in patients with major depressive disorder: a specific relationship with the neutrophil-to-lymphocyte ratio. *Nordic Journal of Psychiatry*, *71*(8), 574–580. https://doi.org/10.1080/08039488.2017.1363285

Espandian, A., González, M., Reijas, T., Florez, G., Ferrer, E., Saiz, P. A., Salgado-Barreira, A., González, A., Brenlla, J., Docasar, L., & Bobes, J. (2020). Relevant risk factors of repeated suicidal attempts in a sample of outpatients. *Revista de Psiquiatria y Salud Mental*, *13*(1), 11–21. https://doi.org/10.1016/J.RPSM.2019.03.003

Fonseca-Pedrero, E., Díez-Gómez, A., de la Barrera, U., Sebastian-Enesco, C., Ortuño-Sierra, J., Montoya-Castilla, I., Lucas-Molina, B., Inchausti, F., & Pérez-Albéniz, A. (2020). Suicidal behaviour in adolescents: A network analysis. *Revista de Psiquiatria y Salud Mental*. https://doi.org/10.1016/J.RPSM.2020.04.007

Fragoso, Y. D., Frota, E. R. C., Lopes, J. S., Noal, J. S., Giacomo, M. C., Gomes, S., Gonçalves, M. V. M., Da Gama, P. D., & Finkelsztejn, A. (2010). Severe depression, suicide attempts, and ideation during the use of interferon beta by patients with multiple sclerosis. *Clinical Neuropharmacology*, *33*(6), 312–316. https://doi.org/10.1097/WNF.0B013E3181F8D513

Franklin, J. C., Ribeiro, J. D., Fox, K. R., Bentley, K. H., Kleiman, E. M., Huang, X., Musacchio, K. M., Jaroszewski, A. C., Chang, B. P., & Nock, M. K. (2017). Risk factors for suicidal thoughts and behaviors: A meta-analysis of 50 years of research. *Psychological Bulletin*, *143*(2), 187–232. https://doi.org/10.1037/BUL0000084

Galfalvy, H., Haghighi, F., Hodgkinson, C., Goldman, D., Oquendo, M. A., Burke, A.,

Huang, Y. yu, Giegling, I., Rujescu, D., Bureau, A., Turecki, G., & Mann, J. J. (2015). A genome-wide association study of suicidal behavior. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics : The Official Publication of the International Society of Psychiatric Genetics*, *168*(7), 557–563. https://doi.org/10.1002/AJMG.B.32330

Giner, L., & Guija, J. A. (2014). Number of suicides in Spain: differences between data from the Spanish Statistical Office and the Institutes of Legal Medicine. *Revista de Psiquiatria y Salud Mental*, *7*(3), 139–146. https://doi.org/10.1016/J.RPSM.2014.01.002

Gobbi, G., Atkin, T., Zytynski, T., Wang, S., Askari, S., Boruff, J., Ware, M., Marmorstein, N., Cipriani, A., Dendukuri, N., & Mayo, N. (2019). Association of Cannabis Use in Adolescence and Risk of Depression, Anxiety, and Suicidality in Young Adulthood: A Systematic Review and Meta-analysis. *JAMA Psychiatry*, *76*(4). https://doi.org/10.1001/JAMAPSYCHIATRY.2018.4500

González-Castro, T. B., Tovilla-Zárate, C. A., Juárez-Rojop, I. E., López-Narváez, M. L., Pérez-Hernández, N., Rodríguez-Pérez, J. M., & Genis-Mendoza, A. D. (2021). The role of gene polymorphisms, and analysis of peripheral and central levels of interleukins in suicidal behavior: A systematic review. *Journal of Affective Disorders*, *279*, 398–411. https://doi.org/10.1016/J.JAD.2020.10.024

Grudet, C., Wolkowitz, O. M., Mellon, S. H., Malm, J., Reus, V. I., Brundin, L., Nier, B. M., Dhabhar, F. S., Hough, C. M., Westrin, Å., & Lindqvist, D. (2020). Vitamin D and inflammation in major depressive disorder. *Journal of Affective Disorders*, *267*, 33–41. https://doi.org/10.1016/J.JAD.2020.01.168

Guía de Práctica Clínica de Prevención y Tratamiento de la Conducta Suicida. (2020). *Plan de calidad para el Sistema Nacional de Salud del Ministerio de Sanidad*,

Política Social e Igualdad. Agencia de Evaluación de Tecnologías Sanitarias de Galicia: Avalia-t.

Hawton, K., Bergen, H., Cooper, J., Turnbull, P., Waters, K., Ness, J., & Kapur, N. (2015). Suicide following self-harm: findings from the Multicentre Study of self-harm in England, 2000-2012. *Journal of Affective Disorders*, *175*, 147–151. https://doi.org/10.1016/J.JAD.2014.12.062

Hawton, K., Casañas I Comabella, C., Haw, C., & Saunders, K. (2013). Risk factors for suicide in individuals with depression: a systematic review. *Journal of Affective Disorders*, *147*(1–3), 17–28. https://doi.org/10.1016/J.JAD.2013.01.004

Instituto Nacional de Estadística. (2021). *Defunciones según causa de muerte. Tasas de mortalidad por causas*. https://www.ine.es/prensa/edcm_2021.pdf

Ivković, M., Pantović-Stefanović, M., Dunjić-Kostić, B., Jurišić, V., Lačković, M., Totić-Poznanović, S., Jovanović, A. A., & Damjanović, A. (2016). Neutrophil-to-lymphocyte ratio predicting suicide risk in euthymic patients with bipolar disorder: Moderatory effect of family history. *Comprehensive Psychiatry*, *66*, 87–95. https://doi.org/10.1016/J.COMPPSYCH.2016.01.005

Jiménez-Treviño, L., Saiz, P. A., García-Portilla, M. P., Blasco-Fontecilla, H., Carli, V., Iosue, M., Jaussent, I., López-Castroman, J., Vaquero-Lorenzo, C., Sarchiapone, M., Baca-García, E., Courtet, P., & Bobes, J. (2019). 5-HTTLPR-brain-derived neurotrophic factor (BDNF) gene interactions and early adverse life events effect on impulsivity in suicide attempters. *The World Journal of Biological Psychiatry : The Official Journal of the World Federation of Societies of Biological Psychiatry*, *20*(2), 137–149. https://doi.org/10.1080/15622975.2017.1376112

Kayhan, F., Gündüz, Ş., Ersoy, S. A., Kandeğer, A., & Annagür, B. B. (2017). Relationships of neutrophil-lymphocyte and platelet-lymphocyte ratios with the

severity of major depression. *Psychiatry Research*, *247*, 332–335. https://doi.org/10.1016/J.PSYCHRES.2016.11.016

Klonsky, E. D., May, A. M., & Saffer, B. Y. (2016). Suicide, Suicide Attempts, and Suicidal Ideation. *Annual Review of Clinical Psychology*, *12*, 307–330. https://doi.org/10.1146/ANNUREV-CLINPSY-021815-093204

Klonsky, E. D., Saffer, B. Y., & Bryan, C. J. (2018). Ideation-to-action theories of suicide: a conceptual and empirical update. *Current Opinion in Psychology*, *22*, 38–43. https://doi.org/10.1016/j.copsyc.2017.07.020

Koo, Y. W., Kõlves, K., & De Leo, D. (2017). Suicide in older adults: differences between the young-old, middle-old, and oldest old. *International Psychogeriatrics*, *29*(8), 1297–1306. https://doi.org/10.1017/S1041610217000618

Larkin, C., Di Blasi, Z., & Arensman, E. (2014). Risk factors for repetition of self-harm: a systematic review of prospective hospital-based studies. *PloS One*, *9*(1). https://doi.org/10.1371/JOURNAL.PONE.0084282

Leiva-Murillo, J. M., López-Castromán, J., Baca-García, E., & Consortium, E. (2013). Characterization of suicidal behaviour with self-organizing maps. *Computational and Mathematical Methods in Medicine*, *2013*. https://doi.org/10.1155/2013/136743

Liu, J., Fang, Y., Gong, J., Cui, X., Meng, T., Xiao, B., He, Y., Shen, Y., & Luo, X. (2017). Associations between suicidal behavior and childhood abuse and neglect: A meta-analysis. *Journal of Affective Disorders*, *220*, 147–155. https://doi.org/10.1016/J.JAD.2017.03.060

Majd, M., Graham-Engeland, J. E., Smyth, J. M., Sliwinski, M. J., Lipton, R. B., Katz, M. J., & Engeland, C. G. (2018). Distinct inflammatory response patterns are evident among men and women with higher depressive symptoms. *Physiology &*

Behavior, *184*, 108–115. https://doi.org/10.1016/J.PHYSBEH.2017.11.009

Mann, J. J., Waternaux, C., Haas, G. L., & Malone, K. M. (1999). Toward a clinical model of suicidal behavior in psychiatric patients. *The American Journal of Psychiatry*, *156*(2), 181–189. https://doi.org/10.1176/AJP.156.2.181

Martínez-Botía, P., Velasco, A., Rolle, V., Jiménez-Trevino, L., De la Fuente-Tomás, L., Bernardo, Á., Arias, T., Muñoz-Turrillas, M. del C., García-Alvarez, L., González-Blanco, L., Rodríguez-Revuelta, J., Garcia-Portilla, M. P., Courtet, P., Bobes, J., Gutiérrez, L., & Sáiz, P. A. (2020). Sex-dependent grades of haematopoietic modulation in patients with major depressive episodes are associated with suicide attempts. *European Neuropsychopharmacology : The Journal of the European College of Neuropsychopharmacology*, *40*, 17–30. https://doi.org/10.1016/J.EURONEURO.2020.06.006

Martins-Monteverde, C. M. S., Von Werne Baes, C., Reisdorfer, E., Padovan, T., De Carvalho Tofoli, S. M., & Juruena, M. F. (2019). Relationship Between Depression and Subtypes of Early Life Stress in Adult Psychiatric Patients. *Frontiers in Psychiatry*, *10*(FEB). https://doi.org/10.3389/FPSYT.2019.00019

McGirr, A., & Turecki, G. (2007). The relationship of impulsive aggressiveness to suicidality and other depression-linked behaviors. *Current Psychiatry Reports*, *9*(6), 460–466. https://doi.org/10.1007/S11920-007-0062-2

Miranda-Mendizabal, A., Castellví, P., Parés-Badell, O., Alayo, I., Almenara, J., Alonso, I., Blasco, M. J., Cebrià, A., Gabilondo, A., Gili, M., Lagares, C., Piqueras, J. A., Rodríguez-Jiménez, T., Rodríguez-Marín, J., Roca, M., Soto-Sanz, V., Vilagut, G., & Alonso, J. (2019). Gender differences in suicidal behavior in adolescents and young adults: systematic review and meta-analysis of longitudinal studies. *International Journal of Public Health*, *64*(2), 265–283.

https://doi.org/10.1007/S00038-018-1196-1

Mirkovic, B., Delvenne, V., Robin, M., Pham-Scottez, A., Corcos, M., & Speranza, M. (2021). Borderline personality disorder and adolescent suicide attempt: the mediating role of emotional dysregulation. *BMC Psychiatry*, *21*(1). https://doi.org/10.1186/S12888-021-03377-X

Misumida, N., Kobayashi, A., & Kanei, Y. (2015). Racial differences in the neutrophil-to-lymphocyte ratio in patients with non-ST-segment elevation myocardial infarction. *Coronary Artery Disease*, *26*(5), 381–385. https://doi.org/10.1097/MCA.0000000000000237

Modabbernia, A., Taslimi, S., Brietzke, E., & Ashrafi, M. (2013). Cytokine alterations in bipolar disorder: a meta-analysis of 30 studies. *Biological Psychiatry*, *74*(1), 15–25. https://doi.org/10.1016/J.BIOPSYCH.2013.01.007

Mustafa, A., Zehra, D. P., Süleyman, B., Hulya, O., & Miray, A. (2022). Evaluation of inflammatory parameters in patients who attempted suicide by taking drugs. *Bratislavske Lekarske Listy*, *123*(6), 435–439. https://doi.org/10.4149/BLL_2022_067

Nanni, V., Uher, R., & Danese, A. (2012). Childhood maltreatment predicts unfavorable course of illness and treatment outcome in depression: a meta-analysis. *The American Journal of Psychiatry*, *169*(2), 141–151. https://doi.org/10.1176/APPI.AJP.2011.11020335

O'Connor, R. C., & Kirtley, O. J. (2018). The integrated motivational-volitional model of suicidal behaviour. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *373*(1754). https://doi.org/10.1098/RSTB.2017.0268

Onaemo, V. N., Fawehinmi, T. O., & D'Arcy, C. (2022). Risk of suicide ideation in comorbid substance use disorder and major depression. *PloS One*, *17*(12).

https://doi.org/10.1371/JOURNAL.PONE.0265287

Ono, K., Takaesu, Y., Nakai, Y., Shimura, A., Ono, Y., Murakoshi, A., Matsumoto, Y., Tanabe, H., Kusumi, I., & Inoue, T. (2017). Associations among depressive symptoms, childhood abuse, neuroticism, and adult stressful life events in the general adult population. *Neuropsychiatric Disease and Treatment*, *13*, 477–482. https://doi.org/10.2147/NDT.S128557

Orum, M. H., Kara, M. Z., & Egilmez, O. B. (2018). Mean platelet volume and neutrophil to lymphocyte ratio as parameters to indicate the severity of suicide attempt. *Journal of Immunoassay & Immunochemistry*, *39*(6), 647–659. https://doi.org/10.1080/15321819.2018.1529682

Özdin, S., Sarisoy, G., & Böke, Ö. (2017). A comparison of the neutrophil-lymphocyte, platelet-lymphocyte and monocyte-lymphocyte ratios in schizophrenia and bipolar disorder patients - a retrospective file review. *Nordic Journal of Psychiatry*, *71*(7), 509–512. https://doi.org/10.1080/08039488.2017.1340517

Özyurt, G., & Binici, N. C. (2018). Increased neutrophil-lymphocyte ratios in depressive adolescents is correlated with the severity of depression. *Psychiatry Research*, *268*, 426–431. https://doi.org/10.1016/J.PSYCHRES.2018.08.007

Pandey, G. N., Rizavi, H. S., Zhang, H., Bhaumik, R., & Ren, X. (2018). Abnormal protein and mRNA expression of inflammatory cytokines in the prefrontal cortex of depressed individuals who died by suicide. *Journal of Psychiatry & Neuroscience : JPN*, *43*(6), 376–385. https://doi.org/10.1503/JPN.170192

Postolache, T. T., Komarow, H., & Tonelli, L. H. (2008). Allergy: a risk factor for suicide? *Current Treatment Options in Neurology*, *10*(5), 363–376. https://doi.org/10.1007/S11940-008-0039-4

Potvin, S., Stip, E., Sepehry, A. A., Gendron, A., Bah, R., & Kouassi, E. (2008).

Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. *Biological Psychiatry*, *63*(8), 801–808. https://doi.org/10.1016/J.BIOPSYCH.2007.09.024

Powell, K. E., Kresnow, M., Mercy, J. A., Potter, L. B., Swann, A. C., Frankowski, R. F., Lee, R. K., & Bayer, T. L. (2001). Alcohol consumption and nearly lethal suicide attempts. *Suicide & Life-Threatening Behavior*, *32*(1 Suppl), 30–41. https://doi.org/10.1521/SULI.32.1.5.30.24208

Quinlivan, L., Cooper, J., Davies, L., Hawton, K., Gunnell, D., & Kapur, N. (2016). Which are the most useful scales for predicting repeat self-harm? A systematic review evaluating risk scales using measures of diagnostic accuracy. *BMJ Open*, *6*(2). https://doi.org/10.1136/BMJOPEN-2015-009297

Rainville, J. R., & Hodes, G. E. (2019). Inflaming sex differences in mood disorders. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *44*(1), 184–199. https://doi.org/10.1038/S41386-018-0124-7

Ribeiro, J. D., Huang, X., Fox, K. R., & Franklin, J. C. (2018). Depression and hopelessness as risk factors for suicide ideation, attempts and death: meta-analysis of longitudinal studies. *The British Journal of Psychiatry : The Journal of Mental Science*, *212*(5), 279–286. https://doi.org/10.1192/BJP.2018.27

Rungelrath, V., Kobayashi, S. D., & DeLeo, F. R. (2020). Neutrophils in innate immunity and systems biology-level approaches. *Wiley Interdisciplinary Reviews. Systems Biology and Medicine*, *12*(1). https://doi.org/10.1002/WSBM.1458

Russell, A. E., Hemani, G., Jones, H. J., Ford, T., Gunnell, D., Heron, J., Joinson, C., Moran, P., Relton, C., Suderman, M., Watkins, S., & Mars, B. (2021). An exploration of the genetic epidemiology of non-suicidal self-harm and suicide

attempt. *BMC Psychiatry*, *21*(1), 207. https://doi.org/10.1186/S12888-021-03216-Z

Sáiz, P. A., & Bobes, J. (2014). Suicide prevention in Spain: an uncovered clinical need. *Revista de Psiquiatria y Salud Mental*, *7*(1), 1–4. https://doi.org/10.1016/J.RPSM.2014.01.003

Sanchez-Teruel, D., & Robles-Bello, M. A. (2014). Factores protectores que promueven la resiliencia ante el suicidio en adolescentes y jóvenes. *Papeles Del Psicologo*, *35*(3), 181–192. http://www.papelesdelpsicologo.es

Schneider, B. (2009). Substance use disorders and risk for completed suicide. *Archives of Suicide Research : Official Journal of the International Academy for Suicide Research*, *13*(4), 303–316. https://doi.org/10.1080/13811110903263191

Serafini, G., Muzio, C., Piccinini, G., Flouri, E., Ferrigno, G., Pompili, M., Girardi, P., & Amore, M. (2015). Life adversities and suicidal behavior in young individuals: a systematic review. *European Child & Adolescent Psychiatry*, *24*(12), 1423–1446. https://doi.org/10.1007/S00787-015-0760-Y

Serafini, G., Parisi, V. M., Aguglia, A., Amerio, A., Sampogna, G., Fiorillo, A., Pompili, M., & Amore, M. (2020). A Specific Inflammatory Profile Underlying Suicide Risk? Systematic Review of the Main Literature Findings. *International Journal of Environmental Research and Public Health*, *17*(7). https://doi.org/10.3390/IJERPH17072393

Shalit, N., Shoval, G., Shlosberg, D., Feingold, D., & Lev-Ran, S. (2016). The association between cannabis use and suicidality among men and women: A population-based longitudinal study. *Journal of Affective Disorders*, *205*, 216–224. https://doi.org/10.1016/J.JAD.2016.07.010

Sunbul, E. A., Sunbul, M., Yanartas, O., Cengiz, F., Bozbay, M., Sari, I., & Gulec, H. (2016). Increased Neutrophil/Lymphocyte Ratio in Patients with Depression is

Correlated with the Severity of Depression and Cardiovascular Risk Factors. *Psychiatry Investigation*, *13*(1), 121–126. https://doi.org/10.4306/PI.2016.13.1.121

Turkmen, K., Erdur, F. M., Ozcicek, F., Ozcicek, A., Akbas, E. M., Ozbicer, A., Demirtas, L., Turk, S., & Tonbul, H. Z. (2013). Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in end-stage renal disease patients. *Hemodialysis International. International Symposium on Home Hemodialysis*, *17*(3), 391–396. https://doi.org/10.1111/HDI.12040

Ucuz, İ., & Kayhan Tetik, B. (2020). Can suicide behavior and seasonality of suicide be predicted from inflammatory parameters in adolescents? *Medical Hypotheses*, *143*. https://doi.org/10.1016/J.MEHY.2020.110061

Valkanova, V., Ebmeier, K. P., & Allan, C. L. (2013). CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. *Journal of Affective Disorders*, *150*(3), 736–744. https://doi.org/10.1016/J.JAD.2013.06.004

Velasco, A., Lengvenyte, A., Rodriguez-Revuelta, J., Jimenez-Treviño, L., Courtet, P., García-Portilla, M.P., Bobes, J., & Sáiz, P.A. (2023). Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-lymphocyte ratio in depressed patients with suicidal behavior: A systematic review. *European Psychiatry : The Journal of the Association of European Psychiatrists*, 1–25. https://doi.org/10.1192/J.EURPSY.2023.18

Velasco, Á., Rodríguez-Revuelta, J., Olié, E., Abad, I., Fernández-Peláez, A., Cazals, A., Guillaume, S., de la Fuente-Tomás, L., Jiménez-Treviño, L., Gutiérrez, L., García-Portilla, P., Bobes, J., Courtet, P., & Sáiz, P. A. (2020). Neutrophil-to-lymphocyte ratio: A potential new peripheral biomarker of suicidal behavior. *European Psychiatry : The Journal of the Association of European Psychiatrists*, *63*(1). https://doi.org/10.1192/J.EURPSY.2019.20

Wang, Q., Liu, Y., & Zhou, J. (2015). Neuroinflammation in Parkinson's disease and its potential as therapeutic target. *Translational Neurodegeneration*, *4*(1). https://doi.org/10.1186/S40035-015-0042-0

Weber, M. D., Godbout, J. P., & Sheridan, J. F. (2017). Repeated Social Defeat, Neuroinflammation, and Behavior: Monocytes Carry the Signal. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *42*(1), 46–61. https://doi.org/10.1038/NPP.2016.102

Wirth, M., Villeneuve, S., Haase, C. M., Madison, C. M., Oh, H., Landau, S. M., Rabinovici, G. D., & Jagust, W. J. (2013). Associations between Alzheimer disease biomarkers, neurodegeneration, and cognition in cognitively normal older people. *JAMA Neurology*, *70*(12), 1512–1519. https://doi.org/10.1001/JAMANEUROL.2013.4013

World Health Organization. (2021). *World Health Organization. Suicide worldwide in 2019: global health estimates*. Licence: CC BY-NC-SA 3.0 IGO.

World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (2013). *JAMA*, *310*(20), 2191–2194. https://doi.org/10.1001/JAMA.2013.281053

Yuodelis-Flores, C., & Ries, R. K. (2015). Addiction and suicide: A review. *The American Journal on Addictions*, *24*(2), 98–104. https://doi.org/10.1111/AJAD.12185

Zatti, C., Rosa, V., Barros, A., Valdivia, L., Calegaro, V. C., Freitas, L. H., Ceresér, K. M. M., Rocha, N. S. da, Bastos, A. G., & Schuch, F. B. (2017). Childhood trauma and suicide attempt: A meta-analysis of longitudinal studies from the last decade. *Psychiatry Research*, *256*, 353–358. https://doi.org/10.1016/J.PSYCHRES.2017.06.082

Zhang, Q., Zhu, B., & Li, Y. (2017). Resolution of Cancer-Promoting Inflammation: A New Approach for Anticancer Therapy. *Frontiers in Immunology*, *8*. https://doi.org/10.3389/FIMMU.2017.00071

Zhang, Y., Träskman-Bendz, L., Janelidze, S., Langenberg, P., Saleh, A., Constantine, N., Okusaga, O., Bay-Richter, C., Brundin, L., & Postolache, T. T. (2012). Toxoplasma gondii immunoglobulin G antibodies and nonfatal suicidal self-directed violence. *The Journal of Clinical Psychiatry*, *73*(8), 1069–1076. https://doi.org/10.4088/JCP.11M07532

Zheng, Q., Liu, J., Ji, Y. J., Zhang, Y., Chen, X. C., & Liu, B. S. (2022). Elevated levels of monocyte-lymphocyte ratio and platelet-lymphocyte ratio in adolescents with non-suicidal self-injury. *BMC Psychiatry*, *22*(1). https://doi.org/10.1186/s12888-022-04260-z

Otras aportaciones científicas

8. Otras aportaciones científicas

8.1. Artículos científicos

- Fernández-Sevillano J, González-Pinto A, Rodríguez-Revuelta J, Alberich S, Gónzalez-Blanco L, Zorrilla I, **Velasco Á**, López MP, Abad I, Sáiz PA. Suicidal behaviour and cognition: A systematic review with special focus on prefrontal déficits. J Affect Disord. 2021 Jan 1;278:488-496. doi: 10.1016/j.jad.2020.09.044.
- Dal Santo F, Carballo JJ, **Velasco A**, Jiménez-Treviño L, Rodríguez-Revuelta J, Martínez-Cao C, Caro-Cañizares I, de la Fuente-Tomás L, Menéndez-Miranda I, González-Blanco L, García-Portilla MP, Bobes J, Sáiz PA. The mediating role of Impulsivity in the relationship between suicidal behavior and early traumatic experiencies in depressed subjects. Front Psychiatry. 2020 Nov 10;11:538172. doi: 10.3389/fpsyt.2020.538172.
- Jiménez-Treviño L, **Velasco Á**, Rodriguez-Revuelta J, Abad I, De la Fuente-Tomás L, González-Blanco L, García-Álvarez L, Fernández-Peláez A, Menéndez-Miranda I, Flórez G, García-Portilla P, Bobes J, Sáiz PA. Factors associated with tobacco consumption in depression. Adicciones. 2019 Sep 1;31(4):298-308. doi: 10.20882/adicciones.1191.
- Bousoño M, Al-Halabí S, Burón P, Garrido M, Díaz-Mesa EM, Galván G, García-Álvarez L, **Velasco Á**, Rodríguez-Revuelta J, Wasserman C, Carli V, Hoven C, Sarchiapone M, Wasserman D, Bousoño M, García-Portilla MP, Iglesias C, Sáiz PA, Bobes J. Alcohol use and risk factors for self-harm behavior in Spanish adolescents. Adicciones. 2021 Jan 15;33(1):53-62. doi: 10.20882/adicciones.1239.

- De la Fuente-Tomas L, Sánchez-Autet M, García-Álvarez L, González-Blanco L, **Velasco Á**, Sáiz Martínez PA, Garcia-Portilla MP, Bobes J. Clinical staging in severe mental disorders: bipolar disorder, depression and schizophrenia. Rev Psiquiatr Salud Ment (Engl Ed). 2019 Apr-Jun;12(2):106-115. doi: 10.1016/j.rpsm.2018.08.002.
- García-Portilla MP, García-Álvarez L, de la Fuente-Tomás L, **Velasco-Iglesias Á**, Sáiz PA, González-Blanco L, Bobes Bascarán MT, Baamonde B, Alcalde I, Merayo-Lloves J, Bobes J. Could structural changes in the retinal layers be a new biomarker of mental disorders? A systematic review and thematic synthesis. Rev Psiquiatr Salud Ment (Engl Ed). 2019 Apr-Jun;12(2):116-129. doi: 10.1016/j.rpsm.2018.12.001.
- **Velasco Á**, Rodríguez-Revuelta J, de la Fuente-Tomás L, Fernández-Peláez AD, Dal Santo F, Jiménez-Treviño L, Abad I, González-Blanco L, García-Portilla MP, Saiz PA. Is the alteration in emotional recognition a specific risk factor of suicide attempt?. Rev Psiquiatr Salud Ment (Engl Ed). 2019 Jul-Sep;12(3):196-198. doi: 10.1016/j.rpsm.2018.06.002.
- Fernández-Peláez AD, Rodriguez-Revuelta J, Abad I, **Velasco A**, García-Portilla MP, Sáiz PA. Usefulness of Short Persnality and Life Event Scale (S-PLE) for detection of suicide attempters. Rev Psiquiatr Salud Ment. 2017.Oct-Dec;10(4):218-219. doi: 10.1016/j.rpsm.2017.07.002.

8.2. Ponencias en congresos y reuniones científicas

- **Ángela Velasco Iglesias.** Importancia de las experiencias adversas tempranas en el comportamiento suicida. Simposio: El estudio de la conducta suicida desde una perspectiva integrador: Estrés y vulnerabilidad para predecir el riesgo de suicidio. Congreso Nacional Psicología, 22 de julio de 2019, Vitoria, España.

8.3. Comunicaciones científicas presentadas en congresos

8.3.1. Internacionales

- Sáiz PA, **Velasco A**, Abad I, Fernández-Peláez A, Rodríguez-Revuelta J, Courtet P, Cazals A, Olié E, García-Portilla MP, Guillaume S, Bobes J. Neutrophil to Lymphocyte ratio: useful peripheral biomarker of suicidal behavior? 26th European Congress of Psychiatry, 3-6 march 2018, Nice, France.
- Abad I, **Velasco A**, De la Fuente-Tomás L, Sáiz PA, Bobes J, García-Portilla MP, García-Álvarez L, González-Blanco L, Rodríguez-Revuelta J. Relation between cognition and suicidality in patients with early stage schizophrenia. 26th European Congress of Psychiatry, 3-6 march 2018, Nice, France.
- **Velasco A**, Rodríguez-Revuelta J, Martínez-Cengotitabengoa M, Abad I, De la Fuente-Tomás L, Fernández Sevillano J, García-Álvarez L, González-Blanco L, Fernández-Peláez A, García-Portilla MP, Bobes J, Saiz PA. Cognitive performance in patients with major depression and suicide ideation. 17th European Symposium on Suicide & Suicidal Behaviour, 5-8 September 2018, Ghent, Belgium.
- De la Fuente-Tomás L, Sánchez-Autet M, **Velasco A**, Arranz B, Sierra P, Safont G, González-Blanco L, García-álvarez L, Rodriguez-Revuelta J, Fernández-Peláez A, Sáiz PA, García-Portilla MP. Lifetime history of suicide atempt: A

severity marker in initial phases of bipolar disorder. 17th European Symposium on Suicide & Suicidal Behabiour, 5-8 September 2018, Ghent, Belgium.

- **Velasco A**, Martínez-Botía P, Rodriguez-Revuelta J, Abad I, De la Fuente-Tomás L, Arias T, Muñoz-Turrillas MC, Gutiérrez L, García-Portilla MP, Bobes J, Sáiz PA. Grades of hematopoietic distress in major depressive disorder patients associated with suicidal attempt. European Psychiatric Association, 6-9 April 2019, Varsovia, Polonia.
- Martínez-Botía P, **Velasco A**, Rodriguez-Revuelta J, Abad I, Arias T, De la Fuente-Tomás L, Muñoz-Turrillas MC, García-Álvarez L, González-Blanco L, Jiménez-Treviño L, Gutiérrez L, García-Portilla MP, Bobes J, Sáiz PA. Hematopoietic distress in patients with major depressive disorder and suicidal behavior: gender related differences. Annual Meeting American Psychiatric Association (APA), 18-22 May 2019, San Francisco, Estados Unidos.

8.3.2. Nacionales

- Rodríguez-Revuelta J, **Velasco A**, González-Blanco L, Sáiz PA, Fernández-Peláez A, Abad I, De la Fuente-Tomás L, García-Álvarez L, García-Portilla MP, Bobes J. Utilidad de la Escala Abreviada de Personalidad y Acontecimientos Vitales (S-PLE) en la detección de las tentativas de suicidio. XX Congreso Nacional de Psiquiatría, 16-11 de noviembre de 2017, Barcelona, España.
- González-Blanco L, **Velasco A**, Abad I, Fernández-Peláez A, García-Álvarez L, Villa R, De la Fuente-Tomás L, Menéndez-Miranda I, Rodríguez-Revuelta J. Factores asociados al consumo de tabaco en pacientes con depresión mayor. XLV Jornadas Nacionales Socidrogalcohol, 8-10 de marzo de 2018, Toledo, España.

- Abad I, **Velasco A**, De la Fuente-Tomás L, Alacrau-Crespo A, González-Blanco L, Guillaume S, Dubois J, Rodriguez-Revuelta J, García-Portilla MP, Sáiz PA, Séneque M, Olié E, Couret P. Toma de decisiones e inflamación periférica en el comportamiento suicida. XI Encuentros en Psiquiatría: Conducta Suicida. 6-7 Abril 2018, Sevilla, España.
- **Velasco A**, Dal Santo F, Rodriguez-Revuelta J, Abad I, De la Fuente-Tomás L, González-Blanco L, García-Álvarez L, Fernández-Peláez A, García-Portilla MP, Bobes J, Sáiz PA. Emotion recognition in major depressed patients: evidence of lack of relationship with suicidal behavior. 31st ECNP Congress, 6-9 octubre 2018, Barcelona, España.
- **Velasco A**, Rodriguez-Revuelta J, De la Fuente-Tomás L, Abad I, Dal Santo F, Fernández-Peláez A, González-Blanco L, Jimenez-Treviño L, García-Portilla MP, Sáiz PA. Testosterona y comportamiento suicida en pacientes con depresión mayor. XXI Congreso Nacional de Psiquiatría, 18-20 octubre 2018, Granada, España.
- **Velasco A**, De la Fuente-Tomás L, Dal Santo F, Martínez-Cao C, García-Álvarez L, Sáiz PA. Grades of hemaopoietic distress in major depressive disorder patients associates with suicide attempts. VII Laboratorio de ideas CIBERSAM, 13 de junio de 2019, Oviedo, España.

8.4. Capítulos de libro

- Menéndez-Miranda I, Rodriguez-Revuelta J, García-Portilla MP, Sáiz PA, García-Álvarez L, Burón P, Fernández-Peláez AD, **Velasco A**, Bobes J. La respuesta electrodermal en la prevención del suicidio. VIII Encuentros en Psiquiatría. 2018; pp. 63-75. Enfoque Editorial S.C., ISBN 978-84-16813-73-5.
- García-Portilla MP, García-Álvarez L, Bobes-Bascarán T, Díaz-Mesa E, GalvánPatrignani G, Prieto ML, Paredes MA, Suárez M, Cuervo L, De la Fuente-Tomás L, **Velasco A**, Sáiz PA, Bobes J. Programa de cesación tabáquica multicomponente para personas con trastorno mental grave (esquizofrenia y trastorno bipolar). 2018. Gofer. ISBN: 978-84-09-01951-9.
- Sáiz PA, Rodríguez-Revuelta J, **Velasco A,** De la Fuente-Tomás L, González-Blanco L, García-Álvarez L, Jiménez-Treviño L, Menéndez-Miranda I, García-Portilla MP, Bobes J. La conducta suicida como complicación de la depresión resistente. IX Encuentros en Psiquiatría: De la antropología a la investigación y clínica de la conducta suicida. 2019; pp. 51-56. Canal Editorial, ISBN: 978-84-17524-23-4.
- Rodríguez-Revuelta J, Abad I, **Velasco A,** De la Fuente-Tomás L, González-Blanco L, Dal Santo F, Menéndez-Miranda I, García-Álvarez L, García-Portilla MP, Sáiz PA, Bobes J. ¿Son útiles los marcadores de inflamación periférica en la prevención del comportamiento suicida? IX Encuentros en Psiquiatría: De la antropología a la investigación y clínica de la conducta suicida. 2019; pp. 141-148. Canal Editorial, ISBN: 978-84-17524-23-4.
- Valtueña M, **Velasco A**, Irene A, García-Álvarez L. Nuevas adicciones comportamentales. Manual de Trastornos Adictivos 3Ed. 2020; pp. 453-460. ISBN: 978-84-09-25077-6.

8.5. Co-tutorización Trabajos Fin de Grado

- Título del trabajo: ¿Es útil la proteína c-reactiva como marcador de riesgo del comportamiento suicida en pacientes con depresión?
  Alumno: Carmen Fernandez Maseda
  Fecha de defensa: 12/06/2019
  Tutor: Pilar Alejandra Sáiz Martínez
  Co-tutor: **Ángela Velasco Iglesias**
  Entidad de realización: Grado en Enfermería, Universidad de Oviedo.

- Título del trabajo: Factores asociados a un modelo de estrés hematopoyético en pacientes con depresión y comportamiento suicida.
  Alumno: Belén Mayo Francos
  Fecha de defensa: 18/06/2020
  Tutor: Pilar Alejandra Sáiz Martínez
  Co-tutor: **Ángela Velasco Iglesias**
  Entidad de realización: Grado en Enfermería, Universidad de Oviedo.

Anexos

9. Anexos

9.1. Anexo I

SERVICIO DE SALUD
DEL PRINCIPADO DE ASTURIAS

HOSPITAL UNIVERSITARIO CENTRAL DE ASTURIAS

Comité de Ética de la Investigación del
Principado de Asturias
C/ Celestino Villamil s/n
33006.-Oviedo
Tfno: 985.10.79.27/985.10.80.28
e-mail: ceicr_asturias@hca.es

Área Sanitaria

Oviedo, 15 de Julio de 2014

El Comité de Ética de la Investigación del Principado de Asturias, ha revisado el Proyecto nº 61/14, titulado: "FUNCIONAMIENTO NEUROPSICOLÓGICO Y PERFIL INFLAMATORIO EN EL COMPORTAMIENTO SUICIDA". Investigadora Principal Dra. (Área de Universidad de Oviedo)

El Comité ha tomado el acuerdo de considerar que el citado proyecto reúne las condiciones éticas necesarias para poder realizarse y en consecuencia emite su autorización.

Le recuerdo que deberá guardarse la máxima confidencialidad de los datos utilizados en este proyecto.

9.2. Anexo II

CONSENTIMIENTO INFORMADO

Hoja de Información al paciente

Funcionamiento neuropsicológico y perfil inflamatorio en el comportamiento suicida

Investigador principal: _____

Nombre de la Organización: _____

Propósito de este estudio

La conducta suicida es una de las complicaciones más graves asociadas al trastorno depresivo uni y bipolar. Diversos estudios indican que la conducta suicida está determinada por múltiples factores, entre ellos, variables de índole neuropsicológica, social y genética. A pesar de los esfuerzos de muchos investigadores este tipo de conductas es todavía muy difícil de predecir dada su compleja naturaleza. Por ello hemos iniciado esta investigación que pretende estudiar algunas de las características neuropsicológicas de los pacientes que realizan comportamientos suicidas y los que estarían en riesgo de su comisión con la esperanza de que nuestros hallazgos, junto a los de otros equipos de investigación que están trabajando en el mismo sentido, ayuden a diseñar herramientas que permitan detectar lo más precozmente posible pacientes con un riesgo elevado de presentar conductas suicidas.

Mediante este documento lo que solicitamos es su colaboración en esta investigación, y para ello debemos realizar una serie de pruebas, que en ningún momento suponen riesgo para su salud:

- Una entrevista clínica para determinar su estado de salud.
- Una evaluación neuropsicológica para determinar su funcionamiento cognitivo.
- Una extracción de sangre para valoración de parámetros inflamatorios

Los datos que se obtengan de las evaluaciones realizadas serán archivados en bases de datos anónimas y el tratamiento de los datos de carácter personal se ajustará a lo dispuesto en la Ley Orgánica 15/1999, de 13 de diciembre de protección de datos de carácter personal. Su intimidad quedará salvaguardada en todo momento, y su nombre o el de sus familiares no aparecerán en ningún tipo de comunicación. Por otro lado, los resultados de esta investigación únicamente serán utilizados para el mejor conocimiento del comportamiento suicida.

La información que se obtenga de los análisis realizados le será comunicada cuando sea importante para su salud. Si se tratase de información no relevante para su salud, usted decidirá si quiere o no que se le comunique. En todo momento, usted tendrá derecho al acceso a los datos que se obtengan de las evaluaciones realizadas. Para ejercer dicho derecho deberá solicitarlo al médico responsable de su tratamiento.

Su colaboración es totalmente voluntaria, pudiendo abandonar el estudio en cualquier momento o decidiendo no participar en él.

Su colaboración es totalmente voluntaria. Si tiene alguna duda sobre lo que acaba de leer o sobre cualquier otro aspecto de esta investigación antes de firmar esta hoja de consentimiento informado, puede preguntársela en cualquier momento a su médico:

Nombre:

Dirección / señas:

Teléfono contacto:

e-mail:

Hoja de Consentimiento Informado

Entiendo que el estudio "Funcionamiento neuropsicológico y perfil inflamatorio periférico en el comportamiento suicida" en el que participo es una investigación para mejorar el estado actual del conocimiento sobre las bases clínicas y neuropsicológicas subyacentes al comportamiento suicida y que implicará mi participación en evaluaciones en las cuales se me preguntará sobre mi salud y funcionamiento, así como se evaluará mi funcionamiento neurocognitivo. Entiendo que no hay riesgos implicados y que puedo beneficiarme de participar en este estudio y que no afectará a mi salud de ningún modo.

He leído la información anterior. He tenido la oportunidad de hacer preguntas sobre ella y me han contestado satisfactoriamente las preguntas que he realizado. Doy mi consentimiento voluntario para participar como sujeto en este estudio, y entiendo que tengo el derecho de retirarme del mismo en cualquier momento sin que ello pueda afectar de ninguna manera mi asistencia médica posterior.

Nombre del paciente Firma del paciente

_____ _____

____/____/____ (dd/mm/aa)

Nombre del investigador Firma del investigador

_____ _____

____/____/___ (dd/mm/aa)

9.3. Anexo III

PROTOCOLO BREVE CONDUCTA SUICIDA

Código de centro: ..... **Código de paciente en PI14/02029:** ..... **Incidencias (extraccion/procesamiento):**	1	**Sexo:** Hombre ☐ Mujer ☐	2	**Fecha nacimiento:** ...../...../..... **Fecha valoración:** ...../...../..... **Fecha extracción:** ...../...../.....	3	4 **Año de llegada:** ..... 5 **País de origen:**	

6	**ETNIA PADRE** ○ Caucásica ○ Gitana ○ Negro ○ Asiática ○ Magrebí ○ Hispano	7	**ETNIA MADRE** ○ Caucásica ○ Gitana ○ Negro ○ Asiática ○ Magrebi ○ Hispana	8	**CONVIVENCIA** ○ Padre ○ Madre ○ Hijos ○ Hermanos ○ Familiares ○ Conyuge/pareja ○ Amigos ○ Solo ○ Institución
9	**ESTADO CIVIL** ○ Soltero ○ Casado/conviv + 6 meses ○ Separado/divorciado ○ Viudo	10	**AÑOS ESTUDIOS** ..... **NIVEL** ○ Primarios ○ Secundarios ○ Bachiller ○ Universitario	11	**SITUACION LABORAL** ○ Paro sin subsidio ○ Paro con subsidio ○ Invalidez permanente ○ Incapacidad temporal ○ Activo ○ Jubilado
12	**NIVEL ECONOMICO** ○ <500 ○ Entre 500-1500 ○ Entre 1500-2000 ○ Entre 2000- 2500 ○ + de 2500 ○ NS / NC	13	**ORIENTACION SEXUAL** ○ Heterosexual ○ Bisexual ○ Homosexual	14	**CREENCIAS RELIGIOSAS** SI ☐ NO ☐ (saltar pregunta) ○ Católico ○ Judío ○ Musulmán ○ Protestantes ○ Otros Practicante SI ☐ NO ☐

15 **ANTECEDENTES FAMILIARES**

	SI	NO	NS/NC	ENF. PSIQUIATRICA		SI	NO	NS/NC	ENF. PSIQUIATRICA
Abuelo materno	☐	☐	☐	.....	Hermano 4	☐	☐	☐	.....
Abuela materna	☐	☐	☐	.....	Hermano 5	☐	☐	☐	.....
Abuelo paterno	☐	☐	☐	.....	Pareja	☐	☐	☐	.....
Abuela paterna	☐	☐	☐	.....	Hijo 1	☐	☐	☐	.....
Madre	☐	☐	☐	.....	Hijo 2	☐	☐	☐	.....
Padre	☐	☐	☐	.....	Hijo 3	☐	☐	☐	.....
Hermano 1	☐	☐	☐	.....	Hijo 4	☐	☐	☐	.....
Hermano 2	☐	☐	☐	.....	Hijo 5	☐	☐	☐	.....
Hermano 3	☐	☐	☐	.....	Hijo 6	☐	☐	☐	.....

16	**Nº HERMANOS**	17	**Nº HIJOS** .....

18 ACONTECIMIENTOS VITALES BRUGHA (últimos 6 meses)

1. Ha sufrido usted una enfermedad, lesión o agresión grave	Si	No
2. Algún familiar cercano ha sufrido una enfermedad, lesión o agresión grave	Si	No
3. Ha muerto uno de sus padres, hijos o su pareja/conyuge	Si	No
4.Ha muerto un amigo cercano a la familia algún otro familiar (tíos, prmos, abuelos).....	Si	No
5. Se ha separado a causa de problemas en su matrimonio	Si	No
6. Ha roto una relación estable	Si	No
7. Ha tenido un problema grave con algún amigo cercano, vecino o familiar	Si	No
8. Se ha quedado sin empleo o ha buscado empleo durante más de un mes sin éxito	Si	No
9. Le han despedido de su trabajo	Si	No
10. Ha tenido una crisis económica grave	Si	No
11. Ha tenido problemas con la policía o ha comparecido ante un tribunal	Si	No
12. Le han robado o ha perdido algún objeto de valor	Si	No

19	**PROBLEMAS PSICOSOCIALES**	20	**ABUSO EN LA INFANCIA**	21	**ABUSO ADOLESCENCIA/ EDAD ADULTA**
	○ Grupo de apoyo primario ○ Medio social ○ Escuela ○ Trabajo ○ Vivienda ○ Finanzas ○ Acceso a SS salud ○ Sistema legal ○ Otros problemas psicosociales		○ Físico ○ Sexual ○ Abandono ○ Emocional ○ Pérdida padre ○ Pérdida madre		○ Físico ○ Sexual ○ Emocional

22 ESCALA EVALUACIÓN ACTIVIDAD GLOBAL PREVIO EEAG

- ○ 100-91: Actividad satisfactoria en una amplia gama de actividades, nunca parece superado por los problemas de su vida, es valorado por los demás a causa de sus abundantes cualidades positivas. Sin síntomas.
- ○ 90-81: Síntomas ausentes o mínimos, buena actividad en todas las áreas, interesado e implicado en una amplia gama de actividades, socialmente eficaz, generalmente satisfecho de su vida, sin más preocupaciones o problemas que los cotidianos.
- ○ 80-71: Si existen síntomas, son transitorios y constituyen reacciones esperables ante agentes estresantes psicosociales; sólo existe una ligera alteración de la actividad social, laboral o escolar.
- ○ 70-61: Algunos síntomas leves o alguna dificultad en la actividad social, laboral o escolar, pero en general funciona bastante bien, tiene buenas relaciones interpersonales.
- ○ 60-51: Síntomas moderados o dificultades moderadas en la actividad social, laboral o escolar.
- ○ 50-41: Síntomas graves o cualquier alteración grave de la actividad social, laboral o escolar.
- ○ 40-31: Una alteración de la verificación de la realidad o de la comunicación o alteración importante en varias áreas, como el trabajo escolar, las relaciones familiares, el juicio, el pensamiento o el estado de ánimo.
- ○ 30-21: La conducta está considerablemente influida por ideas delirantes o alucinaciones, o existe una alteración grave de la comunicación o el juicio o incapacidad para funcionar en casi todas las áreas.
- ○ 20-11: Algún peligro de causar lesiones a otros o a sí mismo u ocasionalmente deja de mantener la higiene personal mínima o alteración importante de la comunicación.
- ○ 10-1: Peligro persistente de lesiones graves a otros o a sí mismo o incapacidad persistente para mantener una higiene personal mínima o acto suicida grave con expectativa manifiesta de muerte.
- ○ 0: información inadecuada.

PSICOPATOLOGÍA

23	**HISTORIA PREVIA**	24	**DIAGNÓTICO ACTUAL**	26	**TRATAMIENTO ACTUAL**
	○ Tratamiento ○ Hospitalización		**CIE-10**		○ Psiquiatra ○ Fármacos ○ Psicólogo ○ Otro ○ Ninguno
		25	**COMORBILIDAD:**		
			CIE-10		

27	**TRATAMIENTO PSIQUIATRICO ACTUAL** ..... dosis .... dosis .... dosis .... dosis			..... dosis .... dosis .... dosis .... dosis			
28	**Nº EPISODIOS DEPRESIVOS PREVIOS**		29	**EDAD DIAGNOSTICO PRIMER EPISODIO DEPRESIVO**			
	ENFERMEDAD SOMÁTICA						
30	**DIAGNOSTICO** ☐ Crónico ☐ Último año		31	**TRATAMIENTO SOMATICO ACTUAL** ☐ Si ☐ No			
	ANTECEDENTES SUICIDIO						
32	**INTENTO SUICIDIO FAMILIA** ○ Padre ○ Madre ○ Hermanos ○ Abuelos ○ Otros.....		33	**SUICIDIO CONSUMADO FAMILIA** ○ Padre ○ Madre ○ Hermanos ○ Abuelos ○ Otros.....	34	**SUICIDIO CONSUMADO MEDIO (ULTIMOS 6 MESES)** ○ Escuela ○ Trabajo ○ Familia ○ Amigos ○ Proximidad geográfica ○ Medios de comunicación	
	HISTORIA SUICIDIO						
35	**NUMERO DE INTENTOS PREVIOS**.....		36	**EDAD DEL 1º**	37	**INTENTOS ULTIMO AÑO**	

CONSUMO DE TÓXICOS							
	CONSUMO ACTUAL		**Cantidad**	**Edad inicio consumo**	**CONSUMO PASADO**		**Edad cese consumo**
	si	**no**			**si**	**no**	
Tabaco			Cigarrillos/día:				
Alcohol			UBEs/ semana:				
Cannabis							
Benzodiacepinas							
Cocaína							
Deriv. anfetamínicos							
Alucinógenos							
Ketamina							
Inhalantes							
Opiáceos							
Otros							

5.1.1. Escala de Hamilton para la Depresión (Hamilton Depression Rating Scale, HDRS)

Ítems	*Criterios operativos de valoración*
1. Humor deprimido (tristeza, depresión, desamparo, inutilidad)	0. Ausente 1. Estas sensaciones se indican solamente al ser preguntado 2. Estas sensaciones se relatan oral y espontáneamente 3. Sensaciones no comunicadas verbalmente, es decir, por la expresión facial, la postura, la voz y la tendencia al llanto 4. El paciente manifiesta estas sensaciones en su comunicación verbal y no verbal de forma espontánea
2. Sensación de culpabilidad	0. Ausente 1. Se culpa a sí mismo, cree haber decepcionado a la gente 2. Ideas de culpabilidad, o meditación sobre errores pasados o malas acciones 3. La enfermedad actual es un castigo. Ideas delirantes de culpabilidad 4. Oye voces acusatorias o de denuncia y/o experimenta alucinaciones visuales amenazadoras
3. Suicidio	0. Ausente 1. Le parece que la vida no merece la pena ser vivida 2. Desearía estar muerto o tiene pensamientos sobre la posibilidad de morirse 3. Ideas de suicidio o amenazas 4. Intentos de suicidio (cualquier intento serio se califica 4)
4. Insomnio precoz	0. Ausente 1. Dificultades ocasionales para dormirse, por ejemplo, más de media hora 2. Dificultades para dormirse cada noche
5. Insomnio medio	0. Ausente 1. El paciente se queja de estar inquieto durante la noche 2. Está despierto durante la noche; cualquier ocasión de levantarse de la cama se califica 2 (excepto si está justificada: orinar, tomar o dar medicación, etc.)
6. Insomnio tardio	0. Ausente 1. Se despierta a primeras horas de la madrugada pero vuelve a dormirse 2. No puede volver a dormirse si se levanta de la cama
7. Trabajo y actividades	0. Ausente 1. Ideas y sentimientos de incapacidad. Fatiga o debilidad relacionadas con su actividad, trabajo o aficiones 2. Pérdida de interés en su actividad, aficiones o trabajo, manifestado directamente por el enfermo o indirectamente por desatención, indecisión y vacilación 3. Disminución del tiempo dedicado a actividades o descenso en la productividad 4. Dejó de trabajar por la presente enfermedad
8. Inhibición (lentitud de pensamiento y de palabra, empeoramiento de la concentración, actividad motora disminuida)	0. Palabra y pensamiento normales 1. Ligero retraso en el diálogo 2. Evidente retraso en el diálogo 3. Diálogo difícil 4. Torpeza absoluta
9. Agitación	0. Ninguna 1. «Juega» con sus manos, cabellos, etc. 2. Se retuerce las manos, se muerde las uñas, los labios, se tira de los cabellos, etc.
10. Ansiedad psíquica	0. No hay dificultad 1. Tensión subjetiva e irritabilidad 2. Preocupación por pequeñas cosas 3. Actitud aprensiva aparente en la expresión o en el habla 4. Terrores expresados sin preguntarle

5.1.1. Escala de Hamilton para la Depresión
(Hamilton Depression Rating Scale, HDRS)

11. Ansiedad somática	0. Ausente 1. Ligera 2. Moderada 3. Grave 4. Incapacitante Signos fisiológicos concomitantes de la ansiedad, como: • Gastrointestinales: boca seca, flatulencia, diarrea, eructos, retortijones • Cardiovasculares: palpitaciones, cefalalgias • Respiratorios: hiperventilación, suspiros • Frecuencia urinaria • Sudoración
12. Síntomas somáticos gastrointestinales	0. Ninguno 1. Pérdida del apetito, pero come sin necesidad de que lo estimulen. Sensación de pesadez en el abdomen 2. Dificultad en comer si no se le insiste. Solicita o necesita laxantes o medicación intestinal para sus síntomas gastrointestinales
13. Síntomas somáticos generales	0. Ninguno 1. Pesadez en las extremidades, espalda o cabeza. Dorsalgias, cefalalgias, algias musculares. Pérdida de energía y fatigabilidad 2. Cualquier síntoma bien definido se califica 2
14. Síntomas genitales	0. Ausente 1. Débil 2. Grave 3. Incapacitante Síntomas como • Pérdida de la libido • Trastornos menstruales
15. Hipocondría	0. No la hay 1. Preocupado de sí mismo (corporalmente) 2. Preocupado por su salud 3. Se lamenta constantemente, solicita ayudas, etc. 4. Ideas delirantes hipocondríacas
16. Pérdida de peso (completar A o B)	A. Según manifestaciones del paciente (primera evaluación) 0. No hay pérdida de peso 1. Probable pérdida de peso asociada con la enfermedad actual 2. Pérdida de peso definida (según el enfermo) B. Según peso evaluado por el psiquiatra (evaluaciones siguientes) 0. Pérdida de peso inferior a 500 g en una semana 1. Pérdida de peso de más de 500 g en una semana 2. Pérdida de peso de más de 1 kg en una semana (por término medio)
17. *Insight* (conciencia de enfermedad)	0. Se da cuenta de que está deprimido y enfermo 1. Se da cuenta de su enfermedad pero atribuye la causa a la mala alimentación, clima, exceso de trabajo, virus, etc. 2. Niega que esté enfermo

6.2.2. Gravedad Médica de la Tentativa Suicida (Medical Damage Scale, MDS)

Totalmente alerta / consciente. Ninguna o mínimas consecuencias. Cortes superficiales, sin ninguna o pequeña hemorragia, requiere mínimo o ningún tratamiento. Defenestración con sólo pequeñas magulladuras	**0**
Consciente pero adormilado	**1**
Letárgico con disminución de las facultades mentales. Alguna lesión y tratamiento en cuarto de urgencias o extrahospitalario. Cortes con hemorragia moderada con coagulación antes de pérdida significativa de sangre; requiere cuidados mínimos. Defenestración con torceduras o pequeñas lesiones, no afectación de tendones, ligamentos, huesos, ni hemorragia interna, ni lesión tisular o cerebral. Ahorcamiento con quemaduras por la cuerda	**2**
Adormilado pero fácilmente despertable. Cortes con hemorragia de venas mayores, peligro de pérdida considerable de sangre si no se interviene quirúrgicamente; necesita suturas pero no transfusión, áreas vitales intactas, sin cambios en signos vitales. Defenestración con fracturas de extremidades, necesita tratamiento pero no reparación mayor de tendones. Se espera recuperación completa. Ahorcamiento con lesiones más importantes pero que sólo requieren tratamiento ambulatorio	**3**
Comatoso: retirada con estímulos dolorosos, reflejos intactos, lesión suficiente para hospitalización	**4**
Comatoso: no retirada con estímulos dolorosos, mayoría de reflejos intactos, no depresión respiratoria ni circulatoria, daño suficiente para monitorización en UCI. Cortes con pérdida grave de sangre; requiere sutura, transfusión y reparación de tendones. Cortes en tórax, abdomen o cabeza pero los órganos vitales están indemnes. Defenestración con lesiones graves de huesos y/o tendones en múltiples áreas, hemorragias internas. Ahorcamiento con secuelas pero no en áreas vitales. Se requiere reanimación y hospitalización	**5**
Comatoso: mayoría de reflejos ausentes, depresión respiratoria y circulatoria, UCI y actitud terapéutica agresiva. Lesiones sistémicas graves	**6**
Comatoso: reflejos ausentes, depresión respiratoria con cianosis y/o fallo circulatorio y shock. Cortes con pérdidas mayores de sangre con shock, lesiones en áreas vitales con afectación de constantes vitales. Recuperación con tratamiento hospitalario dudosa. Defenestración con lesión grave en áreas vitales y parálisis. Ahorcamiento con lesiones de la médula espinal	**7**
Muerte	**8**

6.3.6. Escala de Acontecimientos Traumáticos en la Infancia (Childhood Trauma Questionnaire, CTQ)

1

Instrucciones: Este cuestionario aborda experiencias que pudo tener durante su infancia o adolescencia. Para cada cuestión, marque la casilla que mejor le convenga. Aunque algunas preguntas se refieren a temas íntimos y personales, es importante responder honestamente.

Cuando era pequeño y/o adolescente:	Nunca	Raramente	A veces	A menudo	Casi siempre
1. No tenía suficiente para comer	☐	☐	☐	☐	☐
2. Me sentía cuidado y protegido	☐	☐	☐	☐	☐
3. Algunos miembros de mi familia me llamaban "tonto", "vago" o "feo"	☐	☐	☐	☐	☐
4. Mis padres estaban demasiado borrachos o "colocados" para ocuparse de la familia	☐	☐	☐	☐	☐
5. Alguien de mi familia me hacía sentir importante o especial	☐	☐	☐	☐	☐
6. Tenía que vestirme con ropa sucia	☐	☐	☐	☐	☐
7. Me sentía querido	☐	☐	☐	☐	☐
8. Pensaba que mis padres no querían que hubiera nacido	☐	☐	☐	☐	☐
9. Me golpeaban tan fuerte que tuve que ir al médico o al hospital	☐	☐	☐	☐	☐
10. No he querido cambiar de familia	☐	☐	☐	☐	☐
11. Algún miembro de mi familia me pegaba tan fuerte que me dejaba marcas o moratones	☐	☐	☐	☐	☐
12. Me castigaban con un cinturón, un palo, una cuerda u otro objeto contundente	☐	☐	☐	☐	☐
13. Los miembros de mi familia cuidaban unos de otros	☐	☐	☐	☐	☐
14. Miembros de mi familia me insultaban o decían cosas que me hacían daño	☐	☐	☐	☐	☐
15. Creo que he sido maltratado físicamente	☐	☐	☐	☐	☐
16. He tenido una infancia perfecta	☐	☐	☐	☐	☐
17. Me golpeaban tan fuerte que alguien llegó a notar las marcas (ej. un profesor, un vecino o un médico)	☐	☐	☐	☐	☐
18. Sentía que alguien de mi familia me odiaba	☐	☐	☐	☐	☐
19. Los miembros de mi familia se sentían próximos entre sí	☐	☐	☐	☐	☐
20. Alguien intentó tocarme o me hizo hacer tocamientos sexuales	☐	☐	☐	☐	☐
21. Alguien me amenazó con hacerme daño si no hacía algún acto sexual con él	☐	☐	☐	☐	☐
22. Tenía la mejor familia del mundo	☐	☐	☐	☐	☐
23. Alguien me obligó a hacer actos sexuales o me hizo ver tales actos	☐	☐	☐	☐	☐

6.3.6. Escala de Acontecimientos Traumáticos en la Infancia (Childhood Trauma Questionnaire, CTQ)

2

Cuando era pequeño y/o adolescente:	Nunca	Raramente	A veces	A menudo	Casi siempre
24. He sido víctima de propósitos sexuales deshonestos	☐	☐	☐	☐	☐
25. Creo que sufrí maltrato psicológico	☐	☐	☐	☐	☐
26. Había alguien que me llevaba al médico si lo necesitaba	☐	☐	☐	☐	☐
27. Pienso que han abusado de mi sexualmente	☐	☐	☐	☐	☐
28. Mi familia era una fuente seguridad y apoyo	☐	☐	☐	☐	☐