UNIVERSIDAD D CÓRDOBA

TESIS DOCTORAL

- Programa de Doctorado: *Biomedicina* -

Asociación entre el Síndrome Metabólico y variables proinflamatorias. Revisión Sistemática y Meta-Análisis.

Association between the Metabolic Syndrome and proinflammatory variables. Systematic Review and Meta-Analysis.

[Memoria presentada para optar al título de Doctor por la Universidad de Córdoba]

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TITULO: *ASOCIACIÓN ENTRE EL SÍNDROME METABÓLICO Y VARIABLES PROINFLAMATORIAS*

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DOCTORANDA/O

ELENA RAYA CANO

TÍTULO DE LA TESIS:

ASOCIACIÓN ENTRE EL SÍNDROME METABÓLICO Y VARIABLES PROINFLAMATORIAS. REVISIÓN SISTEMÁTICA Y META-ANÁLISIS

INFORME RAZONADO DE LAS/LOS DIRECTORAS/ES DE LA TESIS
(se hará mención a la evolución y desarrollo de la tesis, así como a trabajos y publicaciones derivados de la misma)

La doctoranda ha llevado a cabo su tesis doctoral bajo nuestra supervisión directa, realizando varios estudios de investigación que le han permitido presentar la tesis como compendio de publicaciones, y alcanzar los objetivos específicos propuestos en su plan de investigación:

- Actualizar y revisar la evidencia científica disponible sobre la asociación entre Síndome metabólico (SMet) y variables proinflamatorias; incluyen el ácido úrico, los niveles de transaminasas y el recuento de leucocitos.

- Cuantificar el tamaño del efecto de cada variable proinflamatoria sobre el SMet.

- Identificar qué biomarcadores proinflamatorios presentan una asociación significativa con el SMet.

- Establecer la fuerza de asociación de las distintas variables proinflamatorias y el SMet.

Destacar que la doctoranda muestra en la Introducción un profundo conocimiento y experiencia en el tema de investigación.

Los objetivos planteados están correctamente formulados y han sido alcanzados en la investigación desarrollada.

La metodología es adecuada, empleando revisión sistemática y meta-análisis de los estudios indexados en las bases de datos PubMed y Scopus.

Los resultados son descritos con exhaustividad, claridad y meticulosidad. De la misma manera, la discusión ha sido adecuada y suficientemente respaldada por las referencias bibliográficas más importantes. Las conclusiones son acordes con los objetivos formulados.

Por último, las referencias bibliográficas son amplias y actualizadas.

La Doctoranda ha conseguido publicar los siguientes artículos:

Raya-Cano E, Vaquero-Abellán M, Molina-Luque R, De Pedro-Jiménez D, Molina-Recio G, & Romero-Saldaña M. Association between metabolic syndrome and uric acid: a systematic review and meta-analysis. Scientific reports. 2022; 12(1), 18412. DOI:10.1038/s41598-022-22025-2

Raya-Cano E, Molina-Luque R, Vaquero-Abellán M, Molina-Recio G, Jiménez-Mérida R, & Romero-Saldaña M. Metabolic syndrome and transaminases: systematic review and meta-analysis. Diabetology & metabolic syndrome. 2023; 15(1), 220. DOI: 10.1186/s13098-023-01200-z

Raya-Cano E, Vaquero-Abellán M, Molina-Luque R, Molina-Recio G, Guzmán-García JM, Jiménez-Mérida R, Romero-Saldaña M. Association between Metabolic Syndrome and Leukocytes: Systematic Review and Meta-Analysis. Journal of Clinical Medicine. 2023; 12(22):7044. DOI: 10.3390/jcm12227044)

Gracias a ello, le ha permitido alcanzar los indicios de calidad exigidos en el programa de doctorado en Biomedicina de la Universidad de Córdoba para llevar a cabo una Tesisi Doctoral por compendio de artículos.

Finalmente, es preciso destacar que la doctoranda ha mostrado un alto grado de traslación ya que, derivadas de sus investigaciones, ha presentado comunicaciones científicas en congresos nacionales e internacionales:

Póster "Comparison of anthropometric indices for predicting the risk of metabolic syndrome".
Póster "Association between metabolic syndrome and uric acid: Systematic review and meta-analysis".

Por todo ello, se autoriza la presentación de la tesis doctoral.

Córdoba, a 6 de diciembre de 2023

Las/los directoras/es

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"El éxito es la suma de pequeños esfuerzos repetidos día tras día"

Robert Collier

Tesis Doctoral como Compendio de Publicaciones

1. Raya-Cano E, Vaquero-Abellán M, Molina-Luque R, De Pedro-Jiménez D, Molina-Recio G, & Romero-Saldaña M. Association between metabolic syndrome and uric acid: a systematic review and meta-analysis. Scientific reports. 2022; 12(1), 18412. DOI:10.1038/s41598-022-22025-2

2. Raya-Cano E, Molina-Luque R, Vaquero-Abellán M, Molina-Recio G, Jiménez-Mérida R, & Romero-Saldaña M. Metabolic syndrome and transaminases: systematic review and meta-analysis. Diabetology & metabolic syndrome. 2023; 15(1), 220. DOI: 10.1186/s13098-023-01200-z

3. Raya-Cano E, Vaquero-Abellán M, Molina-Luque R, Molina-Recio G, Guzmán-García JM, Jiménez-Mérida R, Romero-Saldaña M. Association between Metabolic Syndrome and Leukocytes: Systematic Review and Meta-Analysis. Journal of Clinical Medicine. 2023; 12(22):7044. DOI: 10.3390/jcm12227044

Agradecimientos

La culminación de la presenta Tesis Doctoral representa un logro significativo en mi trayectoria académica alcanzada hasta el momento. A todas las personas que han contribuido a la realización de este trabajo, mi más profundo y sincero agradecimiento, muy especialmente:

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A Dr. Rafael Molina Luque, gracias por estar siempre, por tu apoyo constante, por tus palabras de aliento y sobre todo, por tu tiempo. Eres un gran ejemplo de esfuerzo y constancia. A Dr. Guillermo Molina Recio, por su disponibilidad y confianza.

Por último, mi más sincero agradecimiento y eterno cariño a mi familia. Cabe hacer mención especial a mis padres; siento enorme agradecimiento por inculcarme el valor de la constancia, el esfuerzo y la responsabilidad. Su comprensión y apoyo sin límites, así como las oportunidades que me han brindado, han sido esenciales para lograr este objetivo. Gracias de corazón por tanto.

Y a mis hermanos, por apostar siempre por mí sin ninguna condición, por su cariño y amor incondicional.

A todos los que me han acompañado en esta etapa, gracias infinitas por vuestro apoyo.

Índice

Resumen

Introducción: El síndrome metabólico (SMet) es un grupo de anomalías metabólicas caracterizadas por obesidad central, hipertensión, dislipidemia y desregulación de la glucemia, que está asociado con el riesgo de diabetes, enfermedad cardiovascular y mortalidad general. Se ha convertido en una epidemia a nivel mundial, como resultado del incremento de los problemas derivados de la obesidad (estrés oxidativo, inflamación de bajo grado, entre otros). Las alteraciones en la homeostasis del ácido úrico (AU) se han correlacionado con varias enfermedades como gota, SMet, enfermedades cardiovasculares, diabetes, hipertensión y enfermedades renales. A su vez, la presencia de enzimas hepáticas elevadas puede preceder al desarrollo del SMet, observándose alteraciones del hígado que se relacionan directamente con problemas metabólicos. El recuento de leucocitos es un marcador selectivo de infección aguda e inflamación, que podría dar información sobre estado metabólico de los sujetos.

Objetivos: Evaluar y comparar la eficacia diagnóstica de variables proinflamatorias para el SMet. Actualizar y revisar la evidencia científica disponible sobre la asociación entre SMet y variables proinflamatorias; incluyen el ácido úrico, los niveles de transaminasas y el recuento de leucocitos. Cuantificar el tamaño del efecto de cada variable proinflamatoria sobre el SMet. Identificar qué biomarcadores proinflamatorios presentan una asociación significativa con el SMet.

Material y Métodos: Se realizó una revisión sistemática y meta-análisis de los estudios indexados en las bases de datos PubMed y Scopus. Se evaluó la calidad metodológica con la herramienta STROBE, el riesgo general de sesgo con RevMan (Colaboración Cochrane) y la calidad de la evidencia mediante Grade Pro.

Resultados: En la primera revisión sistemática y meta-análisis se incluyeron 43 artículos que compararon las concentraciones de AU entre 91,845 sujetos con SMet y 259,931 controles. Los sujetos que presentaban SMet tuvieron una media superior de AU, de 0,57 mg/dl (IC 95% 0,54-0,61) ($p<0,001$). En la segunda, se incluyeron 17 artículos que compararon las concentraciones de enzimas hepáticas entre 76,686 sujetos SMet+ y 201,855 SMet-. La concentración de ALT, AST y GGT en los sujetos con SMet+ fue significativamente más alta que en el grupo control 7,13 UI/L (CI95% 5,73 – 8,54; $p<0,001$), 2,68 UI/L (CI95% 1,82 – 3,54; $p<0,001$; $I^2= 96\%$) y 11,20 UI/L (CI95% 7,11 – 15,29; $p<0,001$; $I^2= 96\%$), respectivamente. Y en el tercero, se incluyeron 14 artículos

que compararon las concentraciones de leucocitos en 21,005 sujetos con SMet y 66,339 controles. Los sujetos que presentaban SMet tuvieron una media de leucocitos superior, 0,64 cells $x10^9$/L; CI95% 0,55 – 0,72; p<0,001; I^2= 93%.

Conclusiones: Las variables proinflamatorias analizadas presentan una asociación significativa con el SMet. La evaluación en profundidad de la relación del AU, las enzimas hepáticas (ALT, AST, GGT) y los leucocitos en el proceso fisiopatológico del SMet podría conducir a nuevas perspectivas en el diagnóstico temprano.

Palabras clave: ácido úrico, alanina transaminasa, aspartato aminotransferasa, gamma-glutamiltransferasa, leucocitos, marcador biológico, recuento de glóbulos blancos, síndrome metabólico.

Abstract

Introduction: Metabolic syndrome (MetS) is a group of metabolic abnormalities characterized by central obesity, hypertension, dyslipidemia, and dysregulation of blood glucose, associated with the risk of diabetes, cardiovascular disease, and overall mortality. It has become a worldwide epidemic because of the increase in problems derived from obesity (oxidative stress, and low-grade inflammation, among others). Alterations in uric acid (UA) homeostasis have been correlated with several diseases such as gout, MetS, cardiovascular disease, diabetes, hypertension, and kidney disease. In turn, elevated liver enzymes may precede the development of MetS, with liver alterations being observed that are directly related to metabolic problems. The leukocyte count is a selective marker of acute infection and inflammation, which could provide information on the metabolic status of the subjects.

Objectives: To evaluate and compare the diagnostic efficacy of proinflammatory variables for MetS. To update and review the available scientific evidence on the association between MetS and proinflammatory variables, including uric acid, transaminase levels, and leukocyte count. Quantify the size of the effect of each proinflammatory variable on MetS. To identify which proinflammatory biomarkers have a significant association with MetS.

Material and Methods: A systematic review and meta-analysis of the studies indexed in the PubMed and Scopus databases was performed. The methodological quality was assessed with the STROBE tool, the overall risk of bias with RevMan (Cochrane Collaboration) and the quality of evidence with Grade Pro.

Results: The first systematic review and meta-analysis included 43 articles comparing UA concentrations between 91,845 subjects with MetS and 259,931 controls. Subjects with MetS had a higher mean UA of 0,57 mg/dL (95% CI 0,54-0,61) ($p<0,001$). In the second, 17 articles were included that compared liver enzyme concentrations between 76,686 MetS+ and 201,855 MetS- subjects. The concentration of ALT, AST and GGT in MetS+ subjects was significantly higher than in the control group 7,13 IU/L (CI95% 5,73 – 8,54; $p<0,001$), 2,68 IU/L (CI95% 1,82 – 3,54; $p<0,001$; $I^2= 96\%$) and 11,20 IU/L (CI95% 7,11 – 15,29; $p<0,001$; $I^2= 96\%$), respectively. In the third, 14 articles were included that compared leukocyte concentrations in 21,005 subjects with MetS and

66,339 controls. Subjects with MetS had a higher mean leukocyte count, 0,64 cells $x10^9$/L; CI95% 0,55 – 0,72; p<0,001; I^2= 93%.

Conclusions: The proinflammatory variables analyzed show a significant association with MetS. An in-depth evaluation of the relationship of UA, liver enzymes (ALT, AST, GGT) and leukocytes in the pathophysiological process of MetS could lead to new perspectives in early diagnosis.

Keywords: alanine transaminase, aspartate aminotransferase, biologic marker, gamma-glutamiltransferasa, leukocytes, metabolic syndrome, uric acid, white blood cells count.

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Abreviaturas y acrónimos

ALT	Alanina transaminasa
ALP	Fosfatasa alcalina
AST	Aspartato transaminasa
AU	Ácido Úrico
DMT2	Diabetes Mellitus tipo II
ECV	Enfermedades Cardiovasculares
EHGNA	Enfermedad del Hígado graso no alcohólico
GGT	Gamma-glutamiltransferasa
HDL	*High Density Lipoprotein* (Lipoproteína de alta densidad)
IDF	Federación Internacional de Diabetes
IL-6	Interleucina-6
IL-1b	Interleucina-1 beta
MesH	*Medical Subject Headings*
NCEP ATP III	Panel III de tratamiento de adultos del programa Nacional de Educación sobre el colesterol
OMS	Organización Mundial de la Salud
PA	Presión arterial
PCR	Proteína C reactiva
PRISMA	*Preferred Reporting Items for Systematic Reviews and Meta-analysis*
RI	Resistencia a la insulina
RNS	Especies reactivas nitrógeno
ROS	Especies reactivas de oxígeno
SMet	Síndrome Metabólico
STROBE	*Strengthening the Reporting of Observational Studies*
TNF-α	Factor de necrosis tumoral alfa
VSG	Velocidad de sedimentación globular
WBC	White blood cell count (Recuento de glóbulos blancos)

1. Introducción

1.1. Marco teórico y justificación

En la década de 1980, surgió el término "Síndrome X" para describir una serie de anomalías metabólicas que estaban interrelacionadas y aumentaban el riesgo de desarrollar enfermedades cardiovasculares (ECV). Este síndrome englobaba componentes como la obesidad abdominal, la hipertensión, la dislipemia y la resistencia a la insulina (RI). Fue una conceptualización crucial que permitió una comprensión más integrada de las condiciones subyacentes a las ECV y la diabetes mellitus tipo 2 (DMT2). Esta nomenclatura sentó las bases para lo que posteriormente se conocería como el Síndrome Metabólico (SMet)[1].

Paradójicamente, no existe una definición clínica acordada para el SMet a pesar de que las definiciones existentes comparten los mismos criterios diagnósticos. Sin embargo, al tratarse de un síndrome, se acepta que el diagnóstico requiere la asociación de, al menos, dos o más factores de riesgo de ECV. Después de que la Organización Mundial de la Salud (OMS) definiera el SMet en 1998[2], los grupos de estudio y organizaciones acreditadas han continuado los esfuerzos para unificar la definición de SMet. Sin embargo, todavía se utilizan varios criterios de diagnóstico en la investigación. A continuación, se enumeran en orden cronológico, las definiciones más representativas y sus principales diferencias:

1. Criterios de la OMS (1998)[2]

El diagnóstico de SMet se establece con la presencia de RI, definida como DMT2 o alteración de la tolerancia a la glucosa o alteración de la glucosa en ayunas (>100 mg/dl), junto con dos o más de los componentes enumerados a continuación:

- Presión arterial ≥140/90 mmHg o tratamiento con antihipertensivos.
- Triglicéridos ≥ 150 mg/dl.
- Obesidad abdominal (relación cintura-cadera > 0,9 en hombres o > 0,85 en mujeres, o índice de masa corporal > 30 kg/m^2).
- HDL-colesterol < 35 mg/dl hombres, < 39 mg/dl mujeres.
- Microalbuminuria (tasa de secreción de albúmina urinaria ≥ 20 μg/min, o proporción de albúmina a creatinina ≥ 30 mg/dl).

2. **Criterios del Panel III de Tratamiento de Adultos del Programa Nacional de Educación sobre el Colesterol (NCEP ATP III) (2001)[3]**

El diagnóstico de SMet se realiza con la presencia de tres de los siguientes cinco criterios:

- Obesidad abdominal; mujeres > 88 cm, hombres >102 cm.
- Triglicéridos ≥ 150 mg/dl.
- HDL-colesterol; mujeres < 50 mg/dl, hombres < 40 mg/dl.
- Presión arterial ≥ 130/85 mmHg.
- Alteración de la glucosa en ayunas o DMT2 ≥110 mg/dl.

3. **Criterios de la Federación Internacional de Diabetes (2005)**[4]

En este caso, es necesario que la persona presente obesidad central (específica del grupo étnico), más dos de los siguientes criterios:

- Triglicéridos ≥ 150 mg/dl.
- HDL-colesterol; mujeres < 50 mg/dl, hombres < 40 mg/dl.
- Presión arterial ≥ 130/85 mmHg.
- Glucosa en ayunas o DMT2 ≥110 mg/dl.

4. **Harmonizing the Metabolic Syndrome (2009)[5]**

Para el diagnóstico de SMet se requiere la presencia de tres o más de los siguientes componentes:

- Circunferencia de cintura elevada (población y definiciones específicas de cada país).
- Triglicéridos ≥ 150 mg/dl
- HDL-colesterol; mujeres < 50 mg/dl, hombres < 40 mg/dl.
- Presión arterial ≥ 130/85 mmHg
- Glucosa en ayunas ≥100 mg/dl.

A pesar de las diferencias, todas las definiciones se basan sobre un pilar sólido formado por cuatro características principales: obesidad central, hipertensión, dislipemia y RI[6]. La alta prevalencia del SMet parece ser un punto en común entre diferentes definiciones y poblaciones de todo el mundo.

En base a esto, se plantea un ámbito de intervención y medidas preventivas. Cada país debe identificar sus propios factores de riesgo y aplicar estrategias para su prevención y gestión. Se refleja la necesidad de una mayor investigación para esclarecer los mecanismos comunes entre los factores de riesgo de la DMT2 y ECV, incluyendo los presentes en el SMet.

➢ Epidemiología

A nivel mundial, la prevalencia del SMet ha aumentado de manera constante en las últimas décadas, en gran parte debido a factores como el envejecimiento de la población, la urbanización, los cambios en los estilos de vida, entre ellos, la dieta. Según estimaciones de la OMS, alrededor de una cuarta parte de la población adulta mundial se ve afectada por el SMet. En Europa, la prevalencia del SMet varía según los países. Algunos estudios epidemiológicos indican que aproximadamente el 20-30% de la población adulta europea puede cumplir con los criterios diagnósticos para el SMet[7].

Se trata de una alteración no transmisible multifactorial que contribuye de forma importante a la morbimortalidad, por lo que se considera una carga para la salud pública en todo el mundo[8]. Por ello, el diagnóstico precoz y la prevención del SMet son esenciales.

➢ Fisiopatología

De manera similar a su definición, la fisiopatología del SMet no está consensuada; sin embargo, se sostiene de manera sólida que este síndrome surge como resultado de la interacción compleja entre factores genéticos y ambientales. El SMet se distingue por un conjunto de factores de riesgo aterogénicos interconectados que incluyen resistencia a la insulina, estrés oxidativo, dislipidemia, niveles elevados de presión arterial, inflamación crónica, obesidad y factores de estilo de vida como patrones dietéticos e inactividad física[9].

- Resistencia la insulina

En una situación normal, un aumento de la glucosa en sangre estimula la liberación de insulina de las células beta pancreáticas. La insulina, favorece la captación de glucosa de la circulación por las células para la glucólisis o se almacena como glucógeno en el hígado o en el músculo. La insulina no sólo regula el metabolismo de la

glucosa, sino que también modula el metabolismo de los lípidos. La lipogénesis aumenta en respuesta a la insulina, mientras que inhibe la lipólisis[10,11]. La RI es una respuesta fisiológica alterada a la estimulación de los tejidos diana, como el hígado, los músculos y el tejido adiposo, lo que dificulta el metabolismo de la glucosa y resulta en hipertrofia de las células beta, aumento de la producción de insulina en las células beta e hiperinsulinemia[12,13].

Se ha demostrado que la acumulación ectópica de lípidos en el músculo y el hígado predispone a la RI, desempeñando un papel central en el inicio, la progresión y la transición del SMet a ECV y DMT2[14,15].

- Estrés oxidativo

El estrés oxidativo resulta de la producción desequilibrada de especies reactivas de oxígeno y nitrógeno (ROS y RNS, respectivamente) asociadas con una disminución de la cantidad/expresión y una actividad deteriorada de los sistemas antioxidantes. Cuando están disponibles en cantidades bajas, ROS y RNS actúan como moléculas de transducción de señales que impulsan las actividades celulares y brindan protección celular. Sin embargo, cuando se producen en exceso, como en el caso de los tejidos inflamados, pueden generar otras especies altamente reactivas capaces de oxidar irreversiblemente proteínas, lípidos y ácidos nucleicos. Esta modificación oxidativa desencadena la alteración de la señalización celular y la muerte celular programada[16]. El estrés oxidativo puede ocurrir por múltiples mecanismos, con papeles destacados atribuibles a la disfunción mitocondrial, la activación de la enzima productora de ROS/RNS y al deterioro de la actividad del sistema antioxidante. Varios mediadores proinflamatorios, conocidos por promover el estrés oxidativo, se liberan a los tejidos vasculares, donde estimulan la activación y disfunción endotelial. Las citoquinas inflamatorias (leptina, TNF-α e IL-6), altas cantidades de glucosa, y los ácidos grasos libres desempeñan un papel fundamental en la desregulación y actividad de ROS[17,18].

En el SMet, la producción de ROS podría aumentar mediante la acumulación de ácidos grasos libres plasmáticos que eleva la formación y liberación de ROS y RNS en las células endoteliales y el músculo liso vascular. La exposición del tejido adiposo al estrés oxidativo da como resultado el desarrollo de un estado inflamatorio sistémico, que contribuye a la vasculopatía asociada a la obesidad y al riesgo vascular[19].

- Inflamación crónica

Se ha observado inflamación crónica de bajo grado en la obesidad, la DMT2, las ECV y otras enfermedades crónicas relacionados con el SMet. Está ampliamente establecido que las células inmunitarias desempeñan un papel importante en esta patogénesis. Las alteraciones metabólicas activan el sistema inmunológico y aumentan sistemáticamente los marcadores inflamatorios plasmáticos, como TNF-α, IL-6, IL-1b, etc[20]. Por ello, la inflamación parece ser el vínculo patogénico entre la obesidad y los trastornos metabólicos a través de la activación del sistema inmunológico[21].

Estas alteraciones subyacentes a menudo se presentan como parámetros clínicos del SMet y niveles plasmáticos elevados de citoquinas proinflamatorias y proteínas de fase aguda como la proteína C reactiva. El mantenimiento prolongado o el empeoramiento de este estado metabólicamente disfuncional perpetúa aún más la desregulación del metabolismo de los lípidos y la respuesta inmune, aumentando así el riesgo de que un individuo desarrolle una amplia gama de enfermedades crónicas, entre las que se incluye el SMet[20].

- Factores ambientales

Se han identificado algunos factores ambientales y de estilo de vida (comer en exceso e inactividad física), como principales contribuyentes al desarrollo del SMet. Se puede atribuir un papel causal a la ingesta calórica elevada, ya que se ha demostrado que la adiposidad visceral es un desencadenante importante que activa la mayoría de las vías del SMet[22]. En este sentido, el metaanálisis realizado por Neale et al. sugiere que un alimentación rica en frutas, verduras, cereales integrales y con ingestas reducidas de carne roja resultó en una disminución de los niveles de PCR, lo que sugiere atenuación del estado inflamatorio[23].

Por todo lo comentado anteriormente, la fisiopatología subyacente involucra la RI, la inflamación crónica de bajo grado, la disfunción endotelial y el estrés oxidativo crónico, jugando un papel crucial en la patogenia del SMet[24,25].

- **Variables proinflamatorias**

Los marcadores inflamatorios generalmente aumentan en pacientes con SMet, pero el vínculo entre la inflamación y el desarrollo de SMet no está completamente establecido. Debido a su complejidad y las diversas influencias y consecuencias para otras enfermedades, es difícil hacer una distinción bien definida de la capacidad diagnóstica de los diversos grupos de biomarcadores. La subdivisión tiene limitaciones: la complejidad del síndrome, la interacción de las diversas vías bioquímicas y la superposición de los marcadores[26].

No obstante, existen algunos estudios que han mostrado asociación entre SMet y las siguientes variables indicativas de procesos inflamatorios: ácido úrico (AU), leucocitos, transaminasas hepáticas, proteína C reactiva (PCR), velocidad de sedimentación globular (VSG), entre otras[27,28,29].

En la presente tesis doctoral profundizaremos en tres grupos de biomarcadores inflamatorios: AU, transaminasas y leucocitos.

A. Ácido Úrico

En primer lugar, el AU se define como el producto final del metabolismo de las purinas en los seres humanos[30]. La hiperuricemia es una enfermedad metabólica causada por el aumento de la formación o la reducción de la excreción de ácido úrico sérico (AUS). Desajustes en la homeostasis del SUA se han relacionado con varias enfermedades como gota, SMet, ECV, diabetes, hipertensión y enfermedades renales[31].

A pesar de la frecuente asociación entre los niveles de AUS y el SMet[32,33], la hiperuricemia no figura en los criterios de diagnóstico propuestos para definir esta patología. Sin embargo, la acción prooxidante de la hiperuricemia puede desencadenar inflamación y disfunción endotelial al reducir la disponibilidad de óxido nítrico, promoviendo así el desarrollo de las patologías mencionadas anteriormente[34,35,36].

B. Transaminasas

Además de incrementar el riesgo de padecer una ECV, se ha demostrado que el SMet y sus factores de riesgo, incluyendo la obesidad y la DMT2, están asociados con la patología hepática. En este sentido, el SMet tiene una relación directa con la Enfermedad del hígado graso no alcohólico (EHGNA)[37], siendo ambos predictores del desarrollo de

fibrosis y carcinogénesis hepatocelular[38]. La EHGNA afecta aproximadamente al 25% de la población mundial, y es una de las principales causas de cirrosis, carcinoma hepatocelular y trasplante hepático[39]. Esta alteración, caracterizada por el depósito de lípidos en los hepatocitos, engloba a un grupo de patologías hepáticas que se asemejan a la enfermedad hepática alcohólica, y van desde la esteatosis simple hasta la esteatohepatitis y la cirrosis[40]. Cuando la grasa se deposita en órganos sensibles a la insulina, como el hígado, los músculos y los compartimentos viscerales, aumentan los ácidos grasos libres y las citoquinas inflamatorias, mientras que los niveles de adiponectina disminuyen[15,41]. Esta situación puede desembocar en resistencia a la insulina periférica, aterogénesis temprana, alteraciones en el metabolismo de la glucosa y SMet [42,43].

Estas patologías hepáticas han ganado relevancia como por ser las principales causas de morbilidad y mortalidad relacionadas con el hígado, y por ser un factor de riesgo de la DM, la enfermedad renal crónica, la hipertensión arterial, el SMet y el ECV[44]. En este contexto, la detección precoz de la alteración hepática ayudaría a evitar o diagnosticar otras alteraciones metabólicas. Según estudios recientes, las pruebas de función hepática, incluida la concentración sérica de alanina transaminasa (ALT), aspartato transaminasa (AST), fosfatasa alcalina (ALP) y gamma-glutamiltransferasa (GGT), pueden ser parámetros valiosos en la evaluación del estado metabólico, especialmente en la investigación de trastornos cardio-metabólicos[45]. De manera específica, distintos autores han explorado las asociaciones entre las enzimas hepáticas y SMet y ECV en diferentes poblaciones[46,47]. A este respecto, en estudios prospectivos se ha demostrado que niveles elevados de ALT son predictores de ECV [48,49], así como con el SMet y sus componentes[50]. Por su parte, aunque la GGT se considera un indicador del grado de enfermedad hepática y del consumo de alcohol, varios trabajos revelaron que el nivel de esta enzima también se asocia con diabetes, hipertensión y mortalidad cardiovascular independientemente del daño hepático o el consumo de alcohol[51,52]. Una de las ventajas de estos parámetros es que son medidos de forma común en las pruebas de función hepática y son marcadores bien conocidos de daño hepático[53]. Por lo tanto, esta posible relación entre las enzimas hepáticas séricas y el SMet han llamado mucho la atención en los últimos años.

C. Leucocitos

La evidencia sugiere que los cambios en los parámetros hematológicos relacionados con procesos inflamatorios, como el recuento de glóbulos blancos (WBC) y los marcadores protrombóticos, pueden estar asociados con SMet[54,55]. El WBC, los neutrófilos y los linfocitos son marcadores de inflamación comunes, económicos y ampliamente utilizados en el entorno clínico[56]. Estos marcadores activan los principales tipos de células involucradas en la inflamación aguda y crónica[57].

La serie blanca alterada por los factores de riesgo inflamatorios crónicos mencionados anteriormente, tienen una mayor probabilidad de unirse y adherirse al endotelio vascular, lo que puede causar leucocitosis capilar y, en última instancia, provocar vasoconstricción e hipertensión[58]. Así mismo, el WBC está directamente asociado con la RI e inversamente con la secreción de insulina. En relación con esto, se ha demostrado que el WBC predice tanto el empeoramiento de la sensibilidad a la insulina como la incidencia de DMT2[59]. Además, como consecuencia de la inflamación inducida por la hipertrofia y la infiltración de leucocitos, el tejido adiposo pierde sensibilidad a la insulina, lo que resulta en un aumento de la lipolisis y un deterioro del almacenamiento de lípidos, aumentando su disfuncionalidad. Los ácidos grasos libres y los triglicéridos se movilizan a la circulación, lo que conduce a la acumulación de derivados de lípidos en el músculo esquelético, el hígado y las células B del páncreas, lo que conlleva un deterioro del funcionamiento de los tejidos y una resistencia sistémica a la insulina[20].

El aumento de leucocitos puede estar directamente involucrado en la patogénesis del SMet, al aumentar el desplazamiento de las células inflamatorias al tejido adiposo. El mantenimiento prolongado o el empeoramiento de este estado metabólicamente disfuncional perpetúa aún más la desregulación del metabolismo de los lípidos y las respuestas inmunitarias, lo que aumenta el riesgo de un individuo de desarrollar una amplia gama de enfermedades crónicas[60,61]. Además de asociarse de manera independiente con algunos de los factores que condicionan la aparición del SMet, estudios previos han demostrado una relación significativa entre el WBC y SMet[54,62]. En este sentido, se ha observado que el número de subtipos de células inmunitarias, específicamente, el número total de leucocitos, linfocitos y monocitos es mayor en individuos con SMet[63]. Por lo tanto, ya que la inflamación subclínica crónica está implicada en la génesis del SMet y el WBC puede emplearse como un marcador de

inflamación, la evaluación de la asociación entre el recuento de WBC y el desarrollo de SMet puede generar un nuevo parámetro que ayude en su detección.

Dado que la prevalencia de SMet está aumentando en todo el mundo e incrementa el riesgo de morbimortalidad, la identificación de biomarcadores que permitan detectar de manera precoz el SMet es de gran importancia para su detección precoz, la monitorización de su evolución clínica y la prevención de complicaciones asociadas a este.

2. Hipótesis y objetivos de estudio

2.1. Hipótesis de estudio

El SMet engloba un conjunto de anomalías metabólicas que incluye la obesidad central, la hipertensión, la dislipidemia y la desregulación de la glucemia. Esta alteración está asociada con un incremento del riesgo de desarrollar diabetes, ECV y un aumento de la tasa de mortalidad general. La incidencia y la prevalencia de SMet han aumentado a nivel global, convirtiendo esta enfermedad no transmisible en un importante peligro para la salud pública. Por tanto, la identificación de biomarcadores que permitan detectar de manera precoz el SMet es de gran importancia.

2.2. Objetivos de estudio

2.2.1. Objetivo principal

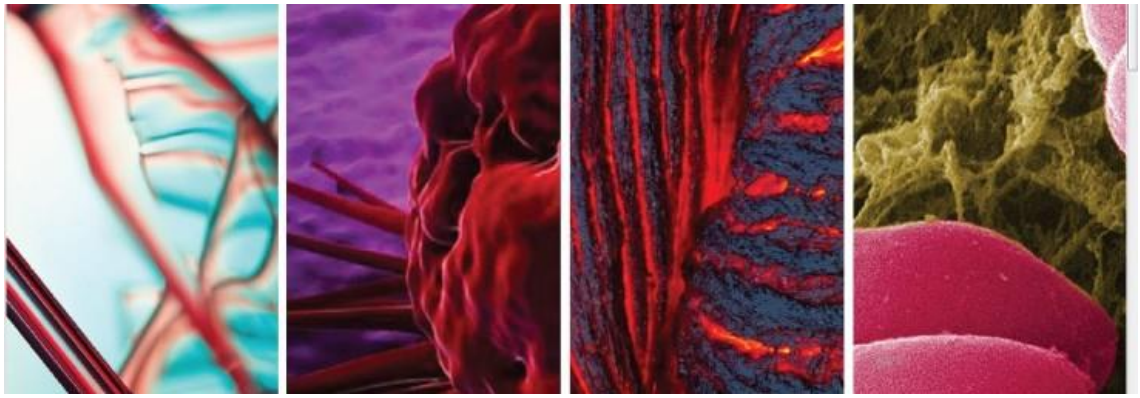
Evaluar y comparar la eficacia diagnóstica de variables proinflamatorias para el SMet.

2.2.2. Objetivos específicos

- Actualizar y revisar la evidencia científica disponible sobre la asociación entre SMet y variables proinflamatorias; incluyen el ácido úrico, los niveles de transaminasas y el recuento de leucocitos.
- Cuantificar el tamaño del efecto de cada variable proinflamatoria sobre el SMet.
- Identificar qué biomarcadores proinflamatorios presentan una asociación significativa con el SMet.
- Establecer la fuerza de asociación de las distintas variables proinflamatorias y el SMet.

3. Resultados

3.1. Capítulo I



Association between metabolic syndrome and uric acid: a systematic review and meta-analysis.

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Association between metabolic syndrome and uric acid: a systematic review and meta-analysis

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This systematic review and meta-analysis aim to provide the best evidence on the association between metabolic syndrome (MetS) and uric acid (UA) by determining the size of the effect of this biomarker on MetS. The review protocol is registered with PROSPERO (CRD42021231124). The search covered the PubMed and Scopus databases. Methodological quality was assessed with the STROBE tool, overall risk of bias with RevMan (Cochrane Collaboration) and quality of evidence with Grade Pro. Initially, 1582 articles were identified. Then, after excluding duplicates and reviewing titles and abstracts, 1529 articles were excluded from applying the eligibility criteria. We included 43 papers (56 groups) comparing UA concentrations between subjects 91,845 with MetS and 259,931 controls. Subjects with MetS had a higher mean UA of 0.57 mg/dl (95% CI 0.54–0.61) ($p < 0.00001$). Given the heterogeneity of the included studies, the researchers decided to perform subgroups analysis. Men with MetS have a higher UA concentration mg/dl 0.53 (95% CI 0.45–0.62, $p < 0.00001$) and women with MetS 0.57 (95% CI 0.48–0.66, $p < 0.00001$) compared to subjects without MetS. Assessment of UA concentration could provide a new avenue for early diagnosis of MetS, as a new biomarker and the possibility of new therapeutic targets.

Metabolic syndrome (MetS) is defined as a set of metabolic abnormalities, including dysglycaemia, central obesity, dyslipidaemia (elevated triglycerides and decreased HDL-cholesterol) and hypertension. These alterations increase the risk of type 2 diabetes mellitus and cardiovascular disease[1]. The pathogenesis of Mets is not well understood but involves complex interactions between genetic background, hormones, and environmental factors such as air pollution, toxins and nutrients[2]. Previous evidence supports that insulin resistance (IR), oxidative stress and low-grade inflammation play a central role[3].

Chronic low-grade systemic inflammation appears to be a central mechanism underlying the pathophysiology of MetS[3,4]. This inflammation is characterised by an increase in pro-inflammatory mediators and the activation of several inflammatory pathways that are significantly associated with cardiovascular events[5]. In addition, the increased concentration of pro-inflammatory substances is primarily related to obesity, especially central obesity, resulting in altered endocrine function of visceral adipose tissue[6].

Due to the increasing prevalence of obesity, the prevalence of MetS has grown worldwide, and it is expected to continue increasing in the coming years[7]. In this respect, the adult population with MetS is estimated between 20 and 30% in most countries[8].Due to the complexity of MetS, with diverse influences and implications for other diseases, it is not easy to make a clear-cut distinction of the diagnostic ability of the various biomarker groups. Moreover, the subdivision has limitations: the complexity of the syndrome, interactions of various biochemical pathways and the overlap of markers[9].

Nevertheless, some studies have shown an association between MetS and the following variables indicative of inflammatory processes: uric acid (UA), C-reactive protein (CRP), liver transaminases (ALT), erythrocyte sedimentation rate (ESR), leukocytes, among others[10–12]. Likewise, through magnetic resonance spectroscopy, different metabolites have been identified in urine, highlighting glucose, lipids, aromatic amino acids, salicylic acid, maltitol, trimethylamine N-oxide and p-cresol sulphate, which have been associated with the progression of MetS[13].

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UA is an enzymatic end product of purine metabolism in humans[14]. Hyperuricaemia is a metabolic disease caused by increased formation or reduced serum uric acid (SUA) excretion. Alterations in SUA homeostasis have been correlated with several diseases such as gout, MetS, cardiovascular disease, diabetes, hypertension and kidney disease[15].

Although SUA levels are often associated with MetS[16,17], hyperuricaemia is not included among the diagnostic criteria that have been proposed internationally for the definition of this pathology. However, the pro-oxidant action of hyperuricaemia may induce inflammation and endothelial dysfunction by decreasing the availability of nitric oxide, thus promoting the development of the pathologies discussed above[18–21].

Given that the prevalence of MetS increases worldwide and raises the risk of morbidity and mortality, identifying biomarkers for the early detection of this pathology is of great importance[22]. Therefore, the main Aim is to provide the best evidence on the association between MetS and UA by determining the effect size of this biomarker.

Methods

Literature search and selection. A systematic review and meta-analysis were carried out, following the criteria established by the PRISMA statement[23]. The search covered the PubMed and Scopus databases. The search strategy was developed by combining the following Medical Subject Headings (MeSH) descriptors: "metabolic syndrome", "uric acid", using the Boolean operator AND. The review was carried out from 2015 to May 2021. In addition, hand searching the reference lists of included studies supplemented the tracking of the available literature. The systematic review was registered in PROSPERO with ID CRD42021231124.

Eligibility criteria. We included longitudinal, cross-sectional, case–control and cohort studies, which investigated the association between MetS and UA. In addition, their results had to include the mean and standard deviation of the study parameters. Furthermore, only papers in English and Spanish and those articles collected data in subjects older than 18 years were considered. Finally, abstracts and unpublished studies comparing subjects with and without MetS were excluded.

Data collection. Two authors (E.R.C. and M.R.S.) separately screened all articles obtained in the search to eliminate duplicates. Then, two other authors (D.P.J. and R.M.L.) independently read the title and abstract and applied the eligibility criteria to select the articles that were finally included in the review. Finally, a fifth authors (M.V.A.) acted as a judge in case of discrepancy. One researcher (E.R.C.) oversaw extracting the data, verified by a second researcher (G.M.R.). A third researcher (M.R.S.) resolved the disagreement in case of a tie.

The extracted articles were drawn up with a table with the main characteristics (author, year, country, study design, reporting guidelines, age of participants, MetS, Aims, conclusions).

The following data were extracted from each study: citation, details of the study population (including age and sex), study design, sample size, study, aims, the mean and standard deviation of UA in those subjects with and without MetS.

Evaluation of the qualitative synthesis. Four authors (R.M.L., D.P.J., G.M.R. and E.R.C.) were responsible for the evaluation of the qualitative synthesis through a triple analysis:

1. Assessment of methodological quality. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement[24] was used for observational studies.
2. Risk of bias assessment. Researchers were using the Cochrane Collaboration[25] tool included in the REVMAN 5.4.2. software, the risks of selection, conduct, detection, attrition, and reporting were analysed.
3. Assessment of the quality of evidence. With the help of the Grade Protool, the evidence profile table was developed, establishing the following levels[26]:

    - High: high confidence in the match between the actual and estimated effect.
    - Moderate: moderate confidence in the effect estimate. There is a possibility that the actual effect is far from the estimated effect.
    - Low: limited confidence in the estimate of the effect. The actual effect may be far from the estimated effect.
    - Very low: low confidence in the estimated effect. The actual effect is very likely to be different from the estimated effect.

Statistical analysis (evaluation of the quantitative synthesis or meta-analysis). For the meta-analysis, the Cochrane Review Manager software (RevMan 5.4.2) was used to perform the statistical calculations and create the forest plots and funnel plots. Due to the difference in effect size of the included studies, a meta-analysis was performed using the Mantel–Haenszel random-effects method according to the DerSimonian and Laird model. The difference between arithmetic means with a 95% confidence interval was used to measure effect size. The risk of publication bias was assessed using the funnel plot. Heterogeneity was analysed using the Chi-square test and the inconsistency index (I^2). According to the Cochrane Collaboration tool, heterogeneity was classified as: unimportant (0–40%), moderate (30–60%), substantial (50–90%) and considerable (75–100%).

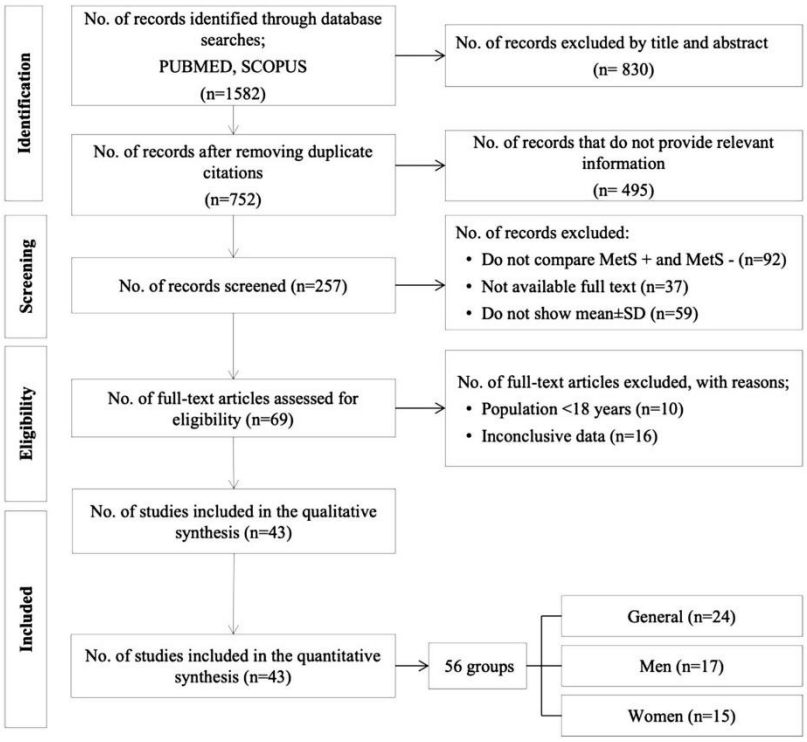

Figure 1. PRISMA flowchart. *MetS:* metabolic syndrome; *SD:* standard deviation.

Results

Characteristics of the studies. Initially, 1582 articles were identified. Then, after excluding duplicates and reviewing titles and abstracts, 1529 articles were excluded from applying the eligibility criteria. Finally, a total of 43 articles were selected for systematic review and meta-analysis (Fig. 1).Given the large number of articles found in the search, it was divided into three subgroups: (i) articles providing UA data globally without distinction of sex (n = 24); (ii) articles with disaggregated data for men (n = 17) and (iii) women (n = 15). The detailed characteristics of the selected studies are shown in Table 1. Regarding research design, all studies were observational. Twenty-seven studies[27–53] defined MetS according to the third report of the National Cholesterol Education Program (NCEP-Adult Treatment Panel (ATP III)[54]. Seven studies[55–61] assessed metabolic syndrome using the International Diabetes Federation (IDF) criteria[62]. Four studies[63–66] used the harmonised criteria[67]. Three studies[68–70] used Chinese Medical Association criteria[71]; Sumiyoshi et al.[72] used the Japanese criteria[73] and, finally, Osadnik[74] used the criteria defined in the study by Buscemi et al.[75].

Concerning the articles' origin, twelve (27.9%) were conducted in China[34,38,39,42,48,50,61,64,66,68–70]. In total, the 43 selected papers compared UA concentrations between 91,845 subjects with MetS and 259931controls. The age of study participants ranged from 18 to 90 years.

Methodological quality assessment. All papers scored 16 points or more out of the 22 items included (highest tercile). No article was excluded for insufficient methodological quality. Table 1 shows a column with the score for each of the reports.

Bias risk analysis. Overall (Fig. 2), the main biases were: random sequential generation, allocation and participant and staff concealment, and blinding of outcome assessment, affecting 72% of the reports. Figure 3 represents the individual assessment of the included studies.

Quantitative analysis. Meta-analysis. *Meta-analysis 1.* This analysis comprises 43 papers, including men and women, together or separately, resulting in 56 groups (Fig. 4). Subjects with MetS had a mean UA 8.2% higher than those without this syndrome (5.89 mg/dl vs. 5.44 mg/dl; $p < 0.00001$). The funnel plot (Fig. 5) shows a low risk of publication bias. The sensitivity analysis performed to assess the pooled estimate's stability concerning each meta-analysis study did not show that any study significantly affected the heterogeneity of the

Author, year, country	Study design	STROBE reporting guidelines[24]	Age of participants	No. of subjects MetS+/ MetS−	MetS criteria	Aims/conclusions
Ahmadnezhad et al., 2018, Iran[55]	Cohort study	19	49.5 ± 8.1 MetS+ 47.1 ± 8.1 MetS−	2481/4727 Total 7208	IDF	Aim: association between serum prooxidant antioxidant balance (PAB), AU and hs-CRP in 7208 participants in the MASHAD study cohort Conclusion: PAB, UA and hs-CRP are independently associated with the presence of MetS
Akboga et al., 2016, Turkey[27]	Cross-sectional study	19	57.2 ± 8.7 MetS+ 55.2 ± 8.9 MetS−	114/63 Total 177	NCEP ATP III	Aim: The aim of the study was to assess the association of serum YKL-40 levels with the presence and severity of MetS Conclusion: Serum levels of YKL-40 are significantly associated with the presence of MetS
Ali et al., 2020, Bangladesh[28]	Cross-sectional study	20	39.5 ± 14.1 MetS+ 27.8 ± 10.4 MetS−	93/327 Total 420	NCEP ATP III	Aim: To assess the relationship of SUA with MetS and its components in Bangladeshi adults Conclusion: Elevated SUA is significantly associated with the prevalence of MetS and its components
Chang et al., 2019, Taiwan[29]	Longitudinal cohort study	20	≥ 30 years	409/2959 Total 3368	NCEP ATP III	Aim: to examine whether the inclusion of additional metabolic components to the current five markers can improve the discriminative validity for MetSdiagnosis Conclusion: The five current metabolic markers used for MetSdiagnosis represent the best combination with the highest discriminative validity
Chen Y et al., 2017,Taiwan[30]	Cross-sectional study	20	33.8 ± 4.8 MetS+ 30.1 ± 5.6 MetS−	2225/20,982 Total 23,207	NCEP ATP III	Aim: to investigate the relationship between UA and the presence of T2DM in the young adult population, and to determine cut-off values for UA to predict the incidence of T2DM, DM and HTN Conclusion: UA is an important predictor of the risk of developing T2DM, HT in adults, especially in the male population
Cheng et al., 2017, Italy[31]	Cross-sectional study	18	56.5 ± 16.2 Men+ 47.8 ± 18.4 Men− 56.6 ± 17.5 Women+ 44.5 ± 18.3 Women−	969/2595 Men Total 3564 1130/2676 Women Total 3806	NCEP ATP III	Aim: To explore gender differences between leukocyte telomere length (LTL) and MetS, 1999–2002 Conclusion: the more MetS components, the greater the shortening of the LTL, especially in women
Continued						

Author, year, country	Study design	STROBE reporting guidelines[24]	Age of participants	No. of subjects MetS+/ MetS−	MetS criteria	Aims/conclusions
Ding et al., 2018, Japan[32]	Retrospective cohort study	20	46.9 ± 9.4 MetS+ 43.5 ± 8.5 MetS−	7835/55,845 Total 63,680	NCEP ATP III	Aim: to estimate future risks of long-term health outcomes related to MetS and its components Conclusion: MetS can help identify individuals with metabolic profiles that confer substantial risk for multiple diseases, providing ancillary value in disease prediction and prevention
Fawzy et al., 2020, Saudi Arabia[33]	Cross-sectional study	20	43.1 ± 12 MetS+ 37.3 ± 16 MetS−	90/90 Total 180	NCEP ATP III	Aim: To investigate possible relationships between UA and MetS and its components in a sample of Saudi adult population Conclusion: Serum UA levels in the Saudi population may be associated with the risk of MetS and its components
He et al., 2021, China[34]	Retrospective cohort study	21	58.3 ± 7.4 Men+ 57.5 ± 7.3 Men− 57.2 ± 7.6 Women+ 53.3 ± 7.9 Women−	1339/1895 Men Total 3234 3032/3694 Women Total 6726	NCEP ATP III	Aim: association between haemoglobin levels and MetS Conclusion: haemoglobin may play an important role in the development of MetS in both men and women
Jeong et al., 2019, Korea[35]	Cross-sectional study	20	49.8 ± 0.5Men+ 43.8 ± 0.4 Men− 58.9 ± 0.6 Women+ 44.4 ± 0.4 Women−	790/1712 Men Total 2502 809/2447 Women Total 3256	NCEP ATP III	Aim: to identify optimal AU level limits for MetS prediction Conclusion: Among Korean adults, SUA levels were found to be strongly associated with the presence of MetS
Kawada et al., 2015, Japan[36]	Cross-sectional study	18	43.7 ± 7.2 MetS+ 42.4 ± 6.8 MetS−	862/4240 Total 5102	NCEP ATP III	Aim: To examine the association between MetS and biomarkers, including CRP, UA and plasma fibrinogen levels, in combination with lifestyle factors Conclusion: CRP, UA, no regular exercise and current smoking are associated with MetS
Klongthlay et al., 2020, Thailand[63]	Cross-sectional study	20	56.2 ± 10.4 MetS+ 51.7 ± 14.2 MetS−	66/136 Total 202	Harmonised criteria	Aim: to assess the prevalence of T2DM and to investigate the relationship between T2DM and risk factors Conclusion: Decreasing SUA, promoting physical activity and smoking cessation may decrease the risk of developing MetS among Thais
Lee et al., 2016, Korea[37]	Retrospective study	21	52.1 ± 8.1 Men+ 52 ± 8.5 Men− 52.6 ± 7.7 Women+ 48.8 ± 7.2 Women−	1695/5195 Men Total 6890 744/3979 Women Total 4723	NCEP-ATP III	Aim: to determine the effect of change in bilirubin concentration on the risk of incident MetS in Korean adults Conclusion: elevated bilirubin values increase the risk of MetS
Li et al., 2016, China[38]	Cross-sectional study	20	18–79 years	691/1452 Men Total 2143 1223/2207 Women Total 3430	NCEP ATP III	Aim: to assess the relationship between SUA and MetS Conclusion: normal SUA level is a contributing clinical predictor of MetS, especially in women
Continued						

Author, year, country	Study design	STROBE reporting guidelines[24]	Age of participants	No. of subjects MetS+/ MetS−	MetS criteria	Aims/conclusions
Liang et al., 2020, China[39]	Prospective cohort study	16	40 ± 8.9 Men+ 37 ± 9.9 Men− 45.1 ± 9.5 Women+ 36.2 ± 10 Women−	576/1949 Male Total 2525 289/1935 Women Total 2224	NCEP ATP III	Aim: to investigate the association of MetS with the incidence of thyroid nodules in Chinese adults Conclusion: nodular thyroid disease is more common in MetS cases
Liu et al., 2018, China[64]	Cross-sectional study	19	69.5 ± 7.0 MetS+ 70.0 ± 7.6 MetS−	524/920 Total 1444	Harmonised criteria	Aim: to explore the associations between liver enzymes and the risk of MetS in older populations Conclusion: elevated liver enzyme levels are positively associated with the prevalence of MetS
Martins et al., 2021, Brazil[56]	Case–control study	17	35–65 years	30/30 Total 60	IDF	Aim: to understand the pathophysiology by assessing the oxidative status associated with inflammatory processes in patients with MetS in comparison to controls Conclusion: AChE, CRP and AU markers can be used as a focus for MetS treatment
Mukhopadhyay et al., 2019, India[40]	Cross-sectional study	18	18–60 years old	113/292 Total 405	NCEP ATP III	Aim: to find out the prevalence of UA problems and their correlation with various anthropometric and metabolic parameters Conclusion: Elevated UA in subjects with MetS
Nardin et al., 2018, Italy[57]	Cross-sectional study	19	68.4 ± 10.4 MetS+ 67 ± 11.9 MetS−	2167/2563 Total 4730	IDF	Aim: to evaluate the relationship between MetS and mean platelet volume in a large cohort of patients undergoing coronary angiography Conclusion: MetS is not an independent predictor of higher mean platelet volume
Nejatinamini et al., 2015, Iran[41]	Case–control study	20	40.6 ± 6 MetS+ 37 ± 5.5 MetS−	41/60 Total 101	NCEP ATP III	Aim: to examine the association of SUA concentrations with MetS components Conclusion: people with MetS have higher levels of UA, the association of UA and MetS components supports that it could be an additional component of MetS
Ni et al., 2020, China[42]	Cross-sectional study	21	45.4 ± 11.7 MetS+ 37.9 ± 10.8 MetS−	100/3049 Total 3149	NCEP ATP III	Aim: to examine the association between SUA and the prevalence of MetS Conclusion: UA levels were associated with MetS and its components
Onat et al., 2016, Turkey[43]	Prospective cohort study	18	48 ± 12 Men+ 48.5 ± 12 Men− 49 ± 12 Women+ 45.8 ± 11.6 Women−	253/615 Men Total 868 293/541 Women Total 834	NCEP ATP III	Aim: to investigate different variables with respect to the independent predictive value of MetS risk Conclusion: elevated UA levels are a strong predictor of MetS in women
Continued						

Author, year, country	Study design	STROBE reporting guidelines[24]	Age of participants	No. of subjects MetS+/ MetS−	MetS criteria	Aims/conclusions
Osadnik et al., 2020, Poland[74]	Cross-sectional study	19	28 ± 4.4 MetS+ 26.8 ± 4.4 MetS−	70/390 Total 460	Buscemi et al. study criteria[75]	Aim: to evaluate the association between calcium, phosphorus and MetS in normal weight individuals Conclusion: calcium and phosphorus levels are significantly associated with MetS
Porchia et al., 2017, Mexico[65]	Cross-sectional study	21	47.2 ± 12.5 MetS+ 37.1 ± 12.8 MetS−	269/164 Total 433	Harmonised criteria	Aim: to determine the interaction of hyperinsulinaemia and hyperuricaemia on the prevalence of MetS Conclusion: UA and insulin increase the prevalence of MetS
Pugliese et al., 2021, Italy[44]	Prospective cohort study	20	62 ± 13 MetS+ 52 ± 16 MetS−	5100/4489 Total 9589	NCEP ATP III	Aim: to evaluate the prognostic role of SUA in patients with MetS Conclusion: SUA levels are associated with an increased risk of cardiovascular mortality independently of the presence of MetS.A threshold of cardiovascular SUA may improve risk stratification
Rhee et al., 2015, Korea[45]	Cross-sectional study	18	24–50 years	90/821 Total 911	NCEP ATP III	Aim: to identify the prevalence of METS and assess the association with clinical markers among male aviators Conclusion: low prevalence of MetS among aviators. Aviators with high ALT, AU, white blood cell counts should be screened for MetS
Sreckovic et al., 2020, Serbia[46]	Cross-sectional study	18	46.7 ± 15 Men+ 47.7 ± 16.7 Men−	21/15 Total 36	ATP III	Aim: to correlate the risk factors for METS and associated factors (HOMA-IR, CRP, AU, ALT, GGT) in patients with and without METS Conclusion: MetS patients had higher values of associated factors HOMA-IR, CRP, AU, ALT, GGT
Sumiyoshi et al., 2019, Japan[72]	Retrospective observational study	20	50.8 ± 9.5 MetS+ 48.8 ± 9.6 MetS−	899/7963 Men Total 8862 132/5799 Women Total 5931	Japan Diagnostic Criteria	Aim: to examine the association between the level of SUA and incident MetS in a Japanese population Conclusion: UA levels were independently associated with MetS
Tabak et al., 2017, Turkey[47]	Case–control study	17	30–65 years	130/50 Total 180	ATP III	Aim: to investigate whether there is a relationship between circulating irisin, RBP-4, PTX-3, IL-33 and adiponectin together with anthropomorphic and biochemical variables involved in the development of insulin resistance in MetS Conclusion: irisin, RBP-4, adiponectin and PTX-3 are characteristic of MetS, which is related to low-grade inflammation

Continued

Author, year, country	Study design	STROBE reporting guidelines[24]	Age of participants	No. of subjects MetS+/ MetS−	MetS criteria	Aims/conclusions
Tao et al., 2020, China[48]	Case–control study	19	62.7 ± 7 MetS+ 62 ± 7.8 MetS−	455/457 Women Total 912	NCEP ATP III	Aim: to investigate the association between UA and creatine ratio and MetS in postmenopausal women Conclusion: the UA/ creatinine ratio was significantly higher in patients with MetS than in controls
Tayefi et al., 2017, Iran[58]	Cross-sectional study	20	50.05 ± 7.9 MetS+ 46.74 ± 8.0 MetS−	3211/3367 Total 6578	IDF	Aim: to determine which of the IDF criteria is suitable for the Iranian population to identify patients with and without MetS Conclusion: suggest that the IDF criteria are adequate to identify individuals within the Iranian population into those with or without MetS
Vigna et al., 2017, Italy[49]	Cohort study	19	16–84 years	154/80 Men Total 234 300/291 Women Total 591	NCEP ATP III	Aim: to assess gender differences in UA, homocysteine and inflammatory biomarkers as determinants of MetS Conclusion: UA is positively related to MetS in both sexes
Wang et al. 2019, China[68]	Cohort study	21	68.9 ± 7.3 MetS+ 69.5 ± 8.3 MetS−	258/999 Total 1257	Chinese Medical Association	Aim: to assess the prevalence of MetS and its association with subclinical carotid atherosclerosis and cardiovascular morbidity and mortality in a Chinese population Conclusion: older adults with Mets have a significantly higher risk of subclinical carotid atherosclerosis, myocardial infarction, stroke and cardiovascular disease (CVD) death than those without MetS
Wang et al.,2020, China[50]	Cross-sectional study	19	68.7 ± 6.5 MetS+ 68.3 ± 6.5MetS−	2207/1791 Total 3998	NCEP ATP III	Aim: to investigate the association between SUA and ALT levels and the risk of MetS Conclusion: a combined increase in SUA and ALT is significantly more associated with MetS than an increase in SUA or ALT alone
Wang et al., 2021, China[69]	Case–control study	20	76.4 ± 6.9 MetS+ 75.3 ± 7.5 MetS−	100/102 Total 202	Chinese Medical Association	Aim: to elucidate the relationships between MetS, Apolipoprotein E (ApoE) and cognitive dysfunction in an elderly Chinese population Conclusion: MetS diagnosis and ApoE are independently associated with cognitive dysfunction
Wang, et al., 2018, China[66]	Cross-sectional study	19	69.34 ± 7.1 MetS+ 70.6 ± 6.7 MetS−	161/307 Total 468	Harmonised criteria	Aim: to investigate the relationship between UA and MetS in elderly women Conclusion: high UA is positively associated with the prevalence of MetS in elderly women
Continued						

Author, year, country	Study design	STROBE reporting guidelines[24]	Age of participants	No. of subjects MetS+/MetS−	MetS criteria	Aims/conclusions
Wu et al., 2018, Taiwan[51]	Cohort study	20	35.7 ± 5.7 Men+ 32.7 ± 5.8 Men− 36.9 ± 5.9 Women+ 32.9 ± 6.4 Women−	2225/20,982 Men Total 23,207 115/3964 Women Total 4079	NCEP ATP III	Aim: to explore the prediction of aerobic exercise and resistance training in MetS and diabetes Conclusion: poor performance in aerobic and endurance exercise tests may be predictive of MetS and diabetes
Yang et al., 2021, China[70]	Case–control study	19	54.8 ± 12.5 MetS+ 45.6 ± 12.7 MetS−	538/5164 Total 5702	Chinese Society of Diabetes	Aim: to explore the association between MetS and biochemical profiles Conclusion: cystatin C levels were significantly associated with the incidence of MetS
Yen et al., 2015, Taiwan[52]	Cohort study	20	76.4 ± 6.7 MetS+ 75.8 ± 7.0 MetS−	31,307/42,240 Total 73,547	ATP III	Aim: to assess the effects of MetS and its components on mortality Conclusion: individual components of MetS are better predictors of all-cause and cause-specific mortality than MetS as a whole
Yu et al., 2015, Korea[59]	Retrospective longitudinal study	20	51.9 ± 8.2 Men+ 51.6 ± 8.3 Men− 52.9 ± 7.6 Women+ 48.6 ± 7.2 Women−	2974/5741 Male Total 8715 1241/4486 Women Total 5727	IDF	Aim: to investigate whether longitudinal effects of baseline SUA levels influence incident MetS while including body composition as a confounder in a large number of subjects Conclusion: elevated SUA levels are strong and independent predictors of MetS
Yu et al., 2018, Korea[60]	Longitudinal study	20	51.8 ± 7.9 Men+ 51.7 ± 8.4 Men− 52.4 ± 7.5 Women+ 48.6 ± 7.2 Women−	2012/5682 Men Total 7694 901/4462 Women Total 5363	IDF	Aim: to investigate the relationship between changes in SUA level and the development of MetS Conclusion: increased SUA independently protects against the development of MetS, suggesting a possible antioxidant role in the pathogenesis of incident MetS
Zhang et al., 2018, China[61]	Cross-sectional study	19	55.1 ± 9.9 Men+ 57.6 ± 9.8 Men− 57.4 ± 8.8 Women+ 54.4 ± 9.9 Women−	1390/4964 Men Total 6354 3998/6225 Women Total 10,223	IDF	Aim: to explore the association between SUA and MetS in rural Chinese adults Conclusion: positive association between SUA and prevalence of MetS in rural Chinese population
Zomorrodian et al., 2015, Iran[53]	Cross-sectional study	20	50.4 ± 7.9 MetS+ 46.8 ± 8.1 MetS−	2175/4317 Total 6492	NCEP ATP III	Aim: to explore the association between Mets and the risk of developing CKD in 6492 participants with and without Mets Conclusion: we demonstrate a significant association between some components of METS and increased prevalence of chronic CKD in the Iranian population

Table 1. Characteristics of included studies (n = 43). *STROBE* Strengthening the Reporting of Observational Studies in Epidemiology, *MetS* metabolic syndrome, *Dx* diagnosis, *IDF* International Diabetes Federation, *UA* uric acid, *hs-CRP* high-sensitivity C-reactive protein, *NCEP ATP III* National Cholesterol Education Program Adult Treatment Panel III, *SUA* serum uric acid, *DM* diabetes mellitus, *T2DM* type 2 diabetes mellitus, *HOMA-IR* Homeostatic Model Assessment of Insulin Resistance, *HT* hypertension, *ALT* alanine aminotransferase, *GGT* gamma glutamyl transferase, *CKD* chronic kidney disease.

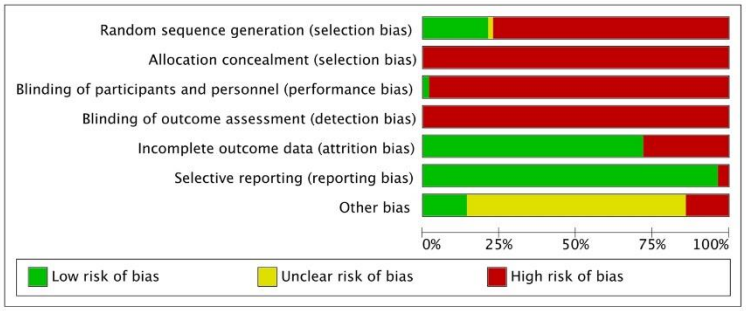

Figure 2. Overall risk of bias of the studies.

meta-analysis; therefore, none was excluded. Given the heterogeneity of the included studies, it was decided to perform subgroup analysis.

Meta-analysis 2. Figure 6, which includes 17 studies, represents the results obtained when analysing the presence of UA in men with and without MetS. In this case, men with MetS showed a higher mean UA, (0.53 mg/dl; 95% CI 0.45 −0.62; $p < 0.00001$; $I^2 = 97\%$). Figure 7 shows that there is a low risk of publication bias.

Meta-analysis 3. Figure 8 compiles the results of 15 studies that examined the association between UA in women and the presence of MetS. The results show that UA level was associated with the diagnosis of METS (0.57 mg/dl; 95% CI 0.48–0.66; $p < 0.00001$; $I^2 = 97\%$). This meta-analysis also observed a low risk of publication bias (Fig. 9).

Quality of evidence. Table 2 shows the evidence profile of the three meta-analyses, providing specific information regarding the overall certainty of the evidence of the studies included in the comparison, the magnitude of the studies examined and the sum of the data available for the outcomes assessed.

Discussion

A systematic review and meta-analysis were conducted to analyse the most recent evidence on the relationship between MetS and UA. Forty-three studies were selected, the effect size and the limitations that have conditioned the results of the different studies were quantified.

Of the included papers, 26 directly associated UA with MetS[28–30,33,35,36,38,40–46,48–50,56,57,59–61,63,65,66,72], and 17 reports collected data indirectly[27,31,32,34,37,39,47,51–53,57,58,64,68–70,74], i.e. they study parameters related to MetS and collect data associated with UA. These studies had limitations, but overall, all demonstrated a sufficient degree of methodological reliability and quality in terms of the association of UA and MetS.

This meta-analysis provides evidence of a relationship between UA level and MetS. The concentration of UA in subjects with MetS was significantly higher than in the control group. The meta-analysis is notable for its large sample size, with 91,845 subjects in the MetS group and 259,931 in the control group. Given the heterogeneity of the included studies, it was decided to perform subgroup analysis. The results obtained show that men with MetS have a higher UA concentration than those without MetS (mean difference (MD): mg/dl 0.53; 95% CI 0.45–0.62; $p < 0.00001$). This was also observed in women (MD 0.57 mg/dl; 95% CI 0.48–0.66, $p < 0.00001$).

Changes in the UA concentrations in human fluids can reflect the metabolic state, immunity, and other human body functions. If the concentration of UA in the blood exceeds normal, the human body fluid becomes acidic, which affects the normal function of human cells, leading to long-term metabolic disease[76]. UA correlates with obesity, diabetes mellitus[76], hypertension[77], cardiovascular disease[78] and chronic kidney disease[79], where UA acts as an oxidant, inducing oxidative stress and endothelial dysfunction[80].

Previous studies have reported significant associations between hyperuricaemia and individual elements of the metabolic syndrome[81,82]. The study by Norvik et al.[83] showed that elevated UA levels are associated with components of the MetS, such as hypertriglyceridaemia, insulin resistance, elevated blood pressure and low high-density lipoprotein cholesterol. Xu et al.[84] concluded that the relationship between SUA and elevated body mass index, hypertension and hyperglycaemia varies by sex. Reducing SUA levels by adopting a healthier lifestyle may be a valuable strategy to reduce the burden of MetS[84].

Overall, the results have shown that people with MetS have 8.2% more UA, so reducing UA could positively impact the development of this syndrome. The results found by several authors[85–87] support this. Yuan et al.[85], in a meta-analysis based on prospective studies of various populations, suggest that for every 1 mg/dl increase in SUA level, the risk of MetS increases by 30% with a linear dose–response relationship. Liu et al.[86] observed a consistent and linear causality of increased UA on the incidence of MetS, concluding that SUA could be an individualised predictor in detecting systemic/hepatic metabolic abnormalities. It is estimated that people with high UA are 1.6 times more likely to develop MetS[87]. Therefore, reducing SUA levels could be a potential treatment to prevent comprehensive metabolic disorders.

Figure 3. Summary of risk of bias by study.

At the methodological level, the assessment of risks of bias in studies is a major issue in this type of research, in line with PRISMA recommendations. Studies with similar methodologies but with discrepancies in quality may have biased results. Among all the papers included in this review, only ten studies[29,35,38,41,42,50,56,63,65,68] had performed this step correctly. The quality of the evidence obtained is "very low" since observational studies have been analysed where there is a high risk of bias and, in addition, they present a very high inconsistency (heterogeneity).

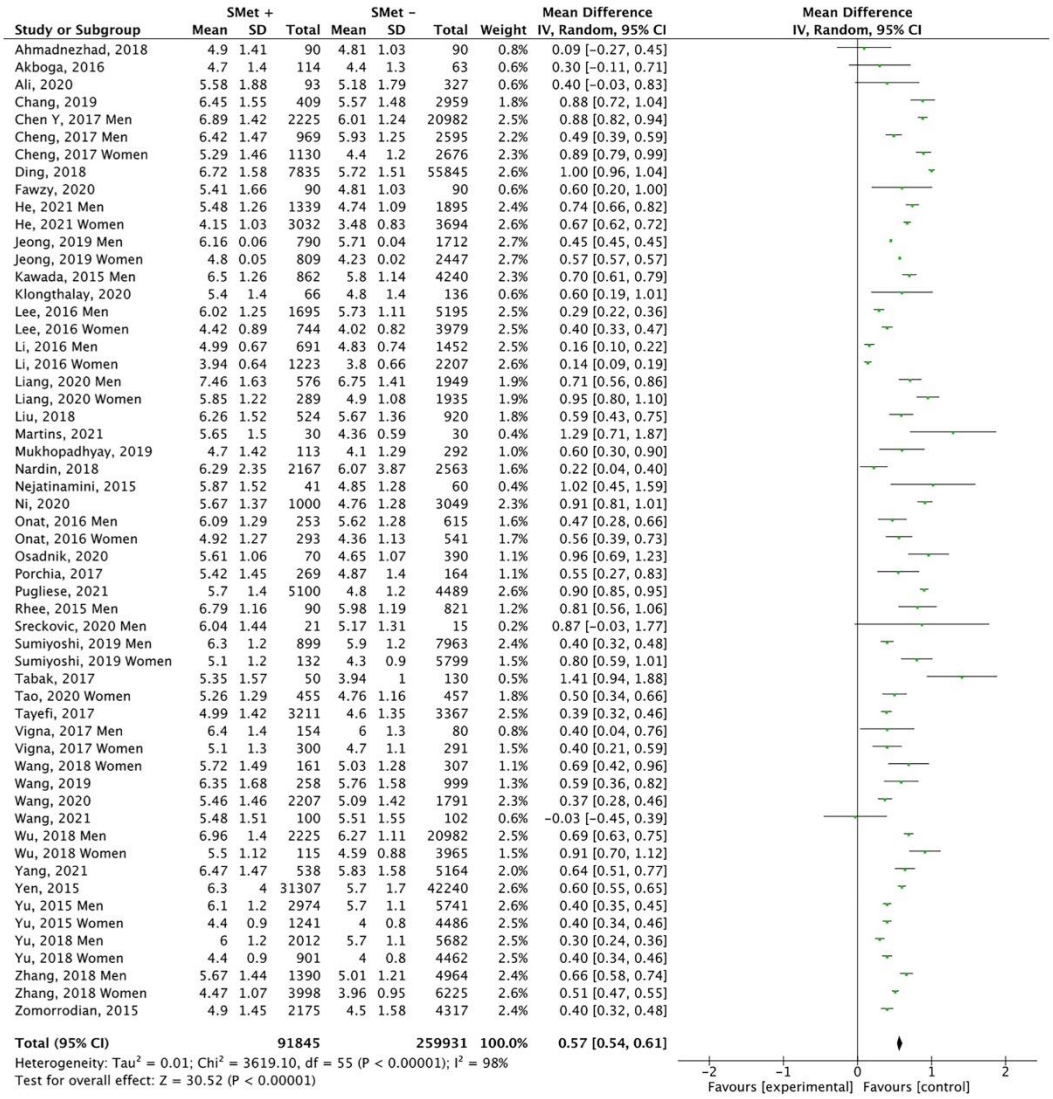

Figure 4. Results and summary statistics of studies analysing uric acid levels in the total population with and without metabolic syndrome (MetS) (meta-analysis 1).

One of the main strengths of this review is the comprehensive search that covered a wide geographical area. In addition, a large sample size of subjects with and without MetS was included, which strengthened the study's statistical power.

The interpretation of the findings in this systematic review and meta-analysis must be made considering some limitations. First, most of the studies are from China, making it difficult to generalise the results to other countries. Author bias should also be a limitation since the same research team wrote several studies. Finally, it should be noted that there is still a lack of uniformly accepted diagnostic criteria for the diagnosis of MetS.

Conclusions

Current diagnostic criteria for MetS vary, although there is a consensus on the main components of the syndrome. None of these criteria includes UA levels in the definition of MetS.

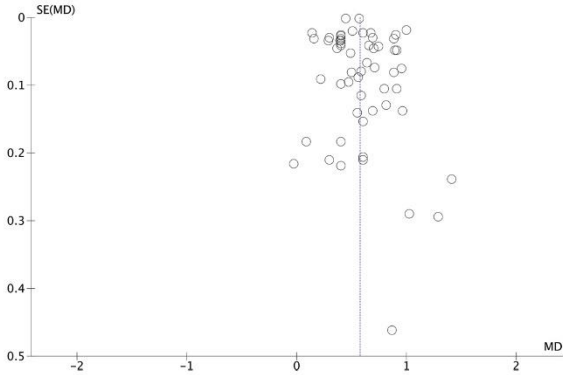

Figure 5. Funnel plot (meta-analysis 1).

Study or Subgroup	SMet + Mean	SD	Total	SMet − Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Chen Y, 2017 Men	6.89	1.42	2225	6.01	1.24	20982	6.8%	0.88 [0.82, 0.94]
Cheng, 2017 Men	6.42	1.47	969	5.93	1.25	2595	6.4%	0.49 [0.39, 0.59]
He, 2021 Men	5.48	1.26	1339	4.74	1.09	1895	6.6%	0.74 [0.66, 0.82]
Jeong, 2019 Men	6.16	0.06	790	5.71	0.04	1712	7.1%	0.45 [0.45, 0.45]
Kawada, 2015 Men	6.5	1.26	862	5.8	1.14	4240	6.5%	0.70 [0.61, 0.79]
Lee, 2016 Men	6.02	1.25	1695	5.73	1.11	5195	6.8%	0.29 [0.22, 0.36]
Li, 2016 Men	4.99	0.67	691	4.83	0.74	1452	6.8%	0.16 [0.10, 0.22]
Liang, 2020 Men	7.46	1.63	576	6.75	1.41	1949	5.8%	0.71 [0.56, 0.86]
Onat, 2016 Men	6.09	1.29	253	5.62	1.28	615	5.2%	0.47 [0.28, 0.66]
Rhee, 2015 Men	6.79	1.16	90	5.98	1.19	821	4.4%	0.81 [0.56, 1.06]
Sreckovic, 2020 Men	6.04	1.44	21	5.17	1.31	15	0.8%	0.87 [−0.03, 1.77]
Sumiyoshi, 2019 Men	6.3	1.2	899	5.9	1.2	7963	6.6%	0.40 [0.32, 0.48]
Vigna, 2017 Men	6.4	1.4	154	6	1.3	80	3.1%	0.40 [0.04, 0.76]
Wu, 2018 Men	6.96	1.4	2225	6.27	1.11	20982	6.8%	0.69 [0.63, 0.75]
Yu, 2015 Men	6.1	1.2	2974	5.7	1.1	5741	6.9%	0.40 [0.35, 0.45]
Yu, 2018 Men	6	1.2	2012	5.7	1.1	5682	6.8%	0.30 [0.24, 0.36]
Zhang, 2018 Men	5.67	1.44	1390	5.01	1.21	4964	6.6%	0.66 [0.58, 0.74]
Total (95% CI)			**19165**			**86883**	**100.0%**	**0.53 [0.45, 0.62]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 503.48$, df = 16 ($P < 0.00001$); $I^2 = 97\%$
Test for overall effect: $Z = 12.25$ ($P < 0.00001$)

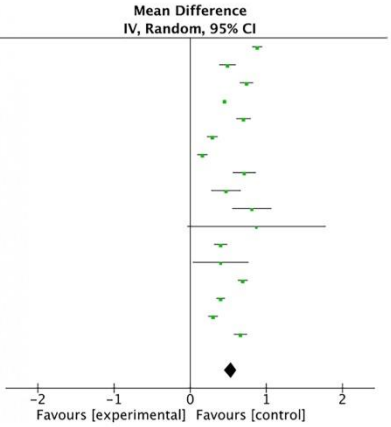

Figure 6. Results and summary statistics of studies analysing uric acid levels in men with and without metabolic syndrome (MetS) (meta-analysis 2).

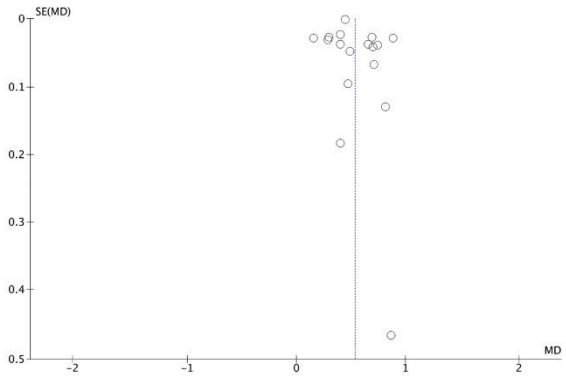

Figure 7. Funnet plot (meta-analysis 2).

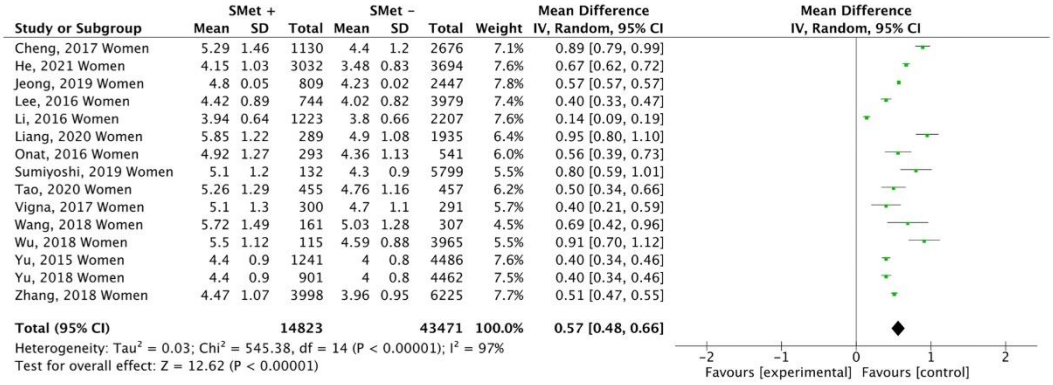

Figure 8. Results and summary statistics of studies analysing uric acid levels in women with and without metabolic syndrome (MetS) (meta-analysis 3).

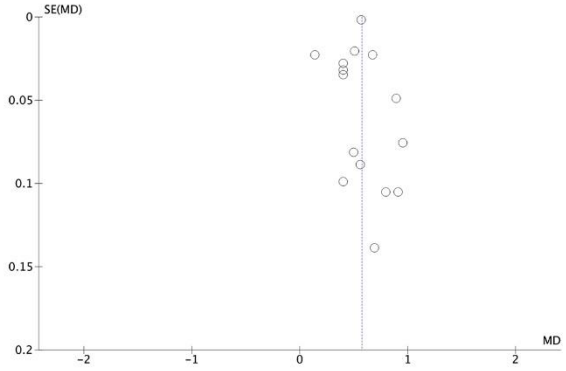

Figure 9. Funnet plot (meta-analysis 3).

Certainty assessment							No. of subjects		Size of the effect	
N of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	MetS+	MetS−	Difference of averages (95% CI)	Quality of evidence
Meta-analysis 1										
n = 56	Observational studies		Very serious	It is not serious	It is not serious	Dose–response gradient	91,845	259,931	0,57 (0.54–0.61)	⊕◯◯◯ Very low
Meta-analysis 2										
n = 17	Observational studies		Very serious	It is not serious	It is not serious	Dose–response gradient	19,165	86,883	0.53 (0.45–0.62)	⊕◯◯◯ Very low
Meta-analysis 3										
n = 15	Observational studies		Very serious	It is not serious	It is not serious	Dose–response gradient	14,823	43,471	0.57 (0.48–0.66)	⊕◯◯◯ Very low

Table 2. Evidence profile with GRADE pro for the three meta-analyses. *MetS* metabolic syndrome, *CI* confidence interval.

The results have shown that UA levels are associated with the presence of MetS. In particular, subjects with MetS have been found to have higher plasma UA. The assessment of UA concentration could provide a new avenue for early diagnosis, identifying new biomarkers, and discovering new therapeutic targets.

A detailed understanding of the components of MetS is essential for the development of effective prevention strategies and appropriate intervention tools, which could curb its increasing prevalence and limit its comorbidity.

However, well-designed, high-quality randomised controlled trials are needed to confirm these findings.

Data availability

All data generated or analysed during this study are included in this published article [and its supplementary information files].

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Author contributions

Two authors (E.R.C. and M.R.S.) separately screened all articles obtained in the search to eliminate duplicates. Then, two other authors (D.P.J. and R.M.L.) independently read the title and abstract and applied the eligibility criteria to select the articles that were finally included in the review. Finally, a fifth authors (M.V.A.) acted as a judge in case of discrepancy. One researcher (E.R.C.) oversaw extracting the data, verified by a second researcher (G.M.R.). A third researcher (M.R.S.) resolved the disagreement in case of a tie. All authors have participated in search of the literature, analysis and evaluation of quality, results and writing. Finally, the authors have approved the final version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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3.2. Capítulo II

Metabolic syndrome and transaminases: systematic review and meta-analysis.

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Diabetology & Metabolic Syndrome

REVIEW Open Access

Metabolic syndrome and transaminases: systematic review and meta-analysis

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Abstract

Background Metabolic syndrome (MetS) is a group of metabolic abnormalities characterised by hypertension, central obesity, dyslipidaemia and dysregulation of blood glucose, associated with the risk of diabetes, cardiovascular disease and overall mortality. The presence of elevated liver enzymes may precede the development of MetS, with alterations of the liver being observed that are directly related to metabolic problems. The study aims to provide the best evidence on the association between liver enzymes (ALT, AST, GGT) and MetS by determining the effect size of these biomarkers.

Methods A systematic review and meta-analysis of studies indexed in PubMed and Scopus databases were performed. Study quality was assessed using the STROBE tool. The Grade Pro tool was used to evaluate the evidence, and the quantitative synthesis was performed using RevMan (Cochrane Collaboration).

Results Seventeen articles comparing liver enzyme concentrations between 76,686 with MetS (MetS+) and 201,855 without MetS (MetS-) subjects were included. The concentration of ALT, AST and GGT in the MetS + subjects was significantly higher than in the control group 7.13 IU/L (CI95% 5.73–8.54; $p < 0.00001$; $I^2 = 96\%$), 2.68 IU/L (CI95% 1.82–3.54; $p < 0.00001$; $I^2 = 96\%$) and 11.20 IU/L (CI95% 7.11–15.29; $p < 0.00001$; $I^2 = 96\%$), respectively.

Conclusions The evaluation of the relationship of liver enzymes in the pathophysiological process of MetS could lead to new insights into early diagnosis.

Keywords Metabolic syndrome, Alanine transaminase, Aspartate aminotransferase, Gamma-glutamyltransferase, Biologic marker

Background

Metabolic syndrome (MetS) encompasses several cardiovascular risk factors, including insulin resistance, atherogenic dyslipidaemia, central obesity and hypertension [1]. It is a multifactorial non-communicable disease that significantly contributes to morbidity and mortality and is considered a public health burden worldwide [2].

In addition to increasing the risk of cardiovascular disease (CVD), MetS and its risk factors, including obesity and diabetes mellitus (DM), are associated with liver disease. Liver function is essential for glucose and fatty acid metabolism. Hepatic glucose homeostasis influences

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insulin sensitivity, while peripheral insulin resistance and lipolysis contribute to fat accumulation in the liver (hepatic steatosis) [3].

In this regard, MetS has a direct relationship with non-alcoholic fatty liver disease (NAFLD) [4], both being predictors of the development of fibrosis and hepatocellular carcinogenesis [5].

NAFLD affects approximately 25% of the world's population and is a leading cause of cirrhosis, hepatocellular carcinoma and liver transplantation [6]. This disorder, characterised by lipid deposition in hepatocytes, encompasses a group of liver diseases that resemble alcoholic liver disease, ranging from simple steatosis to steatohepatitis and cirrhosis [7]. These liver diseases have become the leading causes of liver-related morbidity and mortality and a risk factor for DM, chronic kidney disease, hypertension, MetS and CVD [8].

In this context, early liver impairment detection would help prevent or diagnose other metabolic disorders. According to recent studies, liver function tests, including serum alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT), can be valuable parameters in the assessment of metabolic status, especially in the investigation of cardio-metabolic disorders [9]. Specifically, several authors have explored the associations between liver enzymes, MetS, and CVD in different populations [10, 11]. In this regard, elevated ALT levels have been shown to help predict CVD in prospective studies [12, 13], and MetS and its components [14]. Although GGT is considered an indicator of the degree of liver disease and alcohol consumption, several studies have shown that the level of this enzyme is also associated with diabetes, hypertension and cardiovascular mortality independently of liver damage or alcohol consumption [15, 16]. One of the advantages of these parameters is that they are commonly measured in liver function tests and are well-known markers of liver damage [17].

Therefore, this possible relationship between serum liver enzymes and MetS has recently attracted much attention. Therefore, the main objective of the systematic review and meta-analysis is to provide the best degree of evidence on the association between liver enzymes (ALT, AST, GGT) and MetS, determining the effect size of these biomarkers.

Methods

Search strategy and eligibility criteria

This systematic review and meta-analysis were conducted according to the criteria established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [18] (Supplementary file). The search was carried out in the PubMed and Scopus databases. The search strategy was developed by combining the following Medical Subject Headings (MeSH) descriptors: ("aspartate aminotransferase" OR "alanine aminotransferase" OR "gamma-glutamyltransferase") AND ("metabolic syndrome") (Supplementary file). In addition, we included cross-sectional and longitudinal studies published between January 2017 and July 2022 that investigated the association between liver enzymes (ALT, AST, GGT) and MetS. In addition, the results had to include the mean and standard deviation. Only papers written in English and Spanish, and those that collected data from subjects over 18 years of age, were considered. The systematic review was registered in PROSPERO with ID CRD42023366810.

Selection of papers

Two researchers (E.R.C and M.R.S) reviewed titles, abstracts and full texts. In addition, three researchers independently extracted data for studies that met the inclusion criteria (R.J.M, R.M.L. and G.M.R.). Finally, a fourth author (M.V.A.) acted as a judge in case of discrepancy. After sensitivity analysis, two articles [19, 20] were eliminated from the qualitative synthesis due to the heterogeneity of the reported data.

Data extraction

One researcher (E.R.C.) was responsible for extracting the data verified by a second researcher (R.J.M.). A third researcher (M.R.S.) resolved the disagreement in case of a tie. Cohen's Kappa index was used to assess the degree of agreement. The following data were extracted from each study: citation, details of the study population (including age and sex), study design, follow-up period, sample size, and mean and standard deviation of ALT, AST, and GGT in those subjects with Metabolic Syndrome (MetS+) and without Metabolic Syndrome (MetS-). In addition, for articles collecting ALT, AST and GGT data, the mean and standard deviation were extracted.

Evaluation of the qualitative synthesis

The evaluation of the qualitative synthesis was carried out through a triple analysis, and four authors were responsible (R.M.L., R.J.M., E.R.C. and GMR):

a) Assessment of methodological quality. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement [21] was used for observational studies.
b) Risk of bias assessment. Using the Cochrane Collaboration tool [22] included in the REVMAN 5.4.2 software, the risks of selection, conduct, detection, attrition and reporting were analysed.
c) Assessment of the quality of evidence. With the help of the Grade Pro tool, the evidence profile table was developed, establishing the following levels [23]:

- High: high confidence in the match between the actual and estimated effect.
- Moderate: Moderate confidence in the effect estimate. There is a possibility that the actual effect is far from the estimated effect.
- Low: limited confidence in the estimate of the effect. The actual effect may be far from the estimated effect.
- Very low: low confidence in the estimated effect. The actual effect is very likely to be different from the estimated effect.

Statistical analysis (evaluation of quantitative synthesis or meta-analysis)

The Cochrane Review Manager software (RevMan 5.4.2) was used for the meta-analysis to perform the statistical calculation and create the forest and funnel plots. Due to the difference in effect size of the included studies, a meta-analysis was performed using the Mantel-Haenszel random-effects method according to the DerSimonian and Laird model. The difference between arithmetic means with a 95% confidence interval was used to measure effect size. Liver enzyme counts were considered in IU/L. The risk of publication bias was assessed using the funnel plot. Heterogeneity was analysed using the Chi-square test and the inconsistency index (I^2). According to the Cochrane Collaboration tool, heterogeneity was classified as follows: unimportant (0–40%), moderate (30–60%), substantial (50–90%) and considerable (75–100%).

Results

Characteristics of the studies

The search yielded 2,687 records, of which 205 were identified for full-text review (Fig. 1).

Of these, 17 met the inclusion criteria and were selected for systematic review and meta-analysis. Cohen's Kappa clinical concordance index between

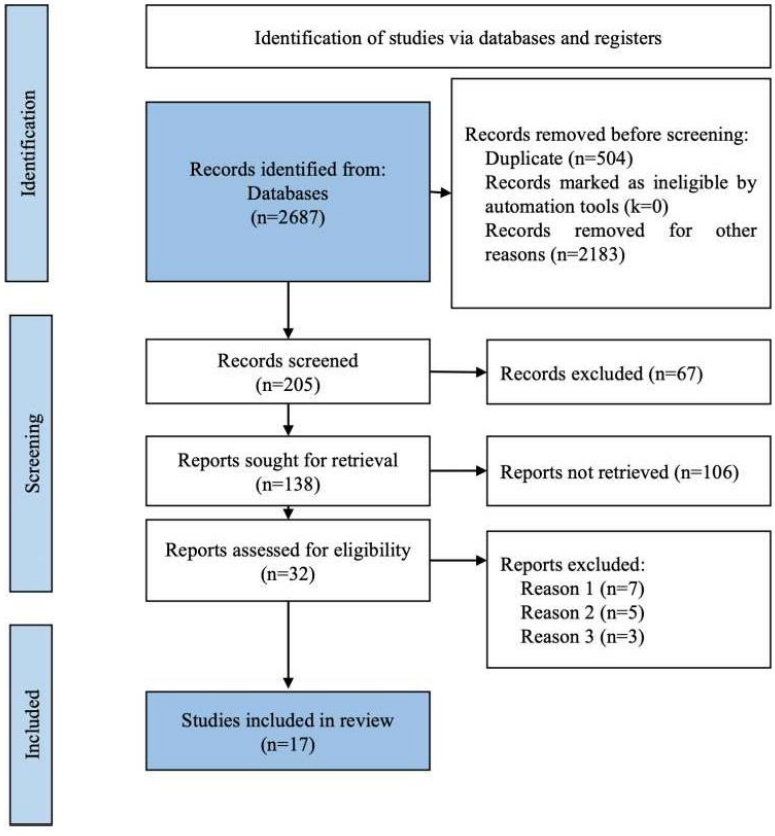

Fig. 1 PRISMA flow chart

the two authors (E.R.C and M.R.S.) who conducted the search was 82.8% (95% CI 70.3–95.3).

The detailed characteristics of the selected studies are shown in Table 1.

In total, 17 articles compared liver enzyme concentrations between 76,686 MetS+and 201,855 MetS- subjects. The age of the participants ranged from 22 to 78 years. Most papers (82.35%) [25, 26, 29–40] included participants of both sexes but analysed the data globally; 3 studies (17.65%) [24, 27, 28] collected data from men and women separately. Concerning origin, 5 articles were developed in China [27, 31, 37, 38, 40], 5 in Japan [26, 32, 34, 35, 37], three articles in Taiwan [25, 30, 39], 1 in Italy [24], 1 in Poland [33], Korea [28] and Iran [29]. Data were extracted from 17 reports from ALT [24–40], 15 studies from AST [25, 26, 28–40], and five from GGT [25, 26, 29, 31, 32].

In seven of the manuscripts [24, 26, 27, 34, 35, 38, 39], MetS was defined according to the criteria of the third report of the National Cholesterol Education Program (NCEP - ATP III) [41]; 5 studies [28–31, 37] assessed MetS using the harmonised criteria [42]; 2 papers [25, 32] using the International Diabetes Federation (IDF) definition [43]; and one article [40] used the Chinese diabetes Society criteria [44]. Finally, Sumiyoshi et al. [36] used the Japanese standards [45] and Osadnik [33], those defined by Buscemi et al. [46].

Methodological quality assessment

According to the STROBE reporting guidelines [21], all reports scored 18 points or more out of the 22 items included (highest tercile). No articles were excluded for poor methodological quality. The score for each of the papers is shown in Table 1.

Bias risk analysis

Overall (Fig. 2), it can be seen that the main biases were: random sequential generation, concealment of allocation and blinding of outcome evaluation (related to participants and staff). Figure 3 represents the individual assessment of the included studies.

Quantitative analysis. Meta-analysis

Figure 4 includes the results for both sexes from the 17 reviewed papers. MetS+subjects showed a higher mean ALT, with the difference reaching 7.13 IU/L (95% CI 5.73–8.54); compared to MetS- subjects. Furthermore, this analysis had a low risk of publication bias (Fig. 5). On the other hand, MetS+subjects showed a higher mean AST, namely, the mean difference was 2.68 IU/L (95% CI 1.82–3.54); compared to MetS- subjects (Fig. 6). Concerning GGT (Fig. 7), the mean difference reached 11.20 IU/L (95% CI 7.11–15.26), being higher among MetS+subjects. All results showed considerable heterogeneity (>95%). Annex I shows a low risk of publication bias in the AST and GGT analysis.

Quality of evidence

Using the Grade Pro tool, the quality of the evidence in this meta-analysis was assessed, and a very low degree of certainty was obtained due to the high inconsistency and risk of bias in the included studies (Table 2).

Discussion

This systematic review with meta-analysis was conducted to analyse the most recent evidence on the relationship between MetS and liver enzymes (ALT, AST and GGT). Seventeen articles were selected in which the effect size was quantified and the limitations that have conditioned the results of the different studies.

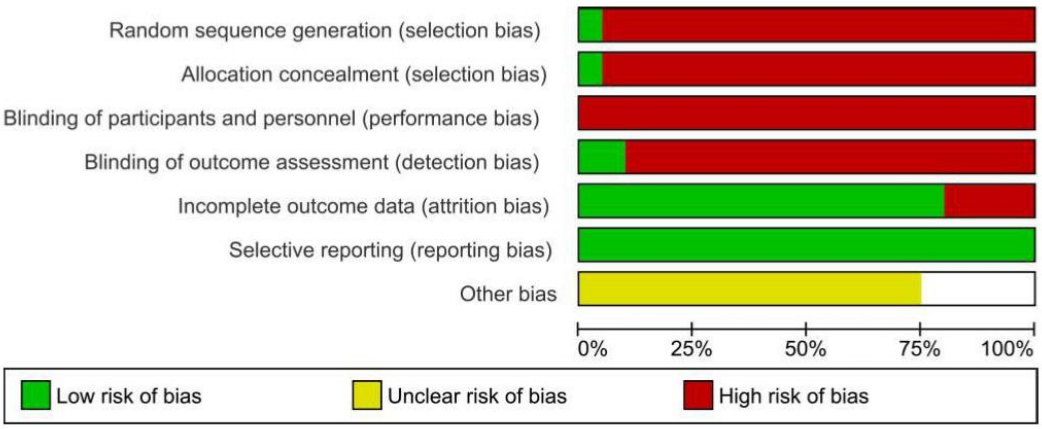

Fig. 2 The overall risk of bias in the studies

Table 1 Characteristics of included studies (n = 17)

Author, year, country	Study design	STROBE(21) Reporting Guidelines	Age of participants	No. Of subjects MetS+/MetS-	MetS criteria	Results
Cheng, et al., 2017, Italy [24].	Cross sectional study	18	**Men** MetS + 56.57 ± 16.25 MetS- 47.88 ± 18.45 **Women** MetS + 56.61 ± 17.58 MetS- 44.57 ± 18.36	**Men** 969/2595 Total 3564 **Women** 1130/2676 Total 3806	NCEP ATP III	ALT values were significantly higher in MetS + participants. **Men** MetS + 33.89 ± 23.55 (ALT) MetS- 29.3 ± 32.27 (ALT) **Women** MetS + 24.92 ± 58.29 (ALT) MetS 20.45 ± 19.43 (ALT)
Cheng YL, et al., 2017. Taiwan [25]	Cohort study	18	MetS + 56.3 ± 12.5 MetS- 50.6 ± 13.2	8564/21,233 Total 29,797	IDF	Subjects with MetS + have higher ALT, AST and GGT levels compared to subjects without MetS-. MetS + 35.1 ± 29.1 (ALT) MetS- 23.8 ± 17.6 (ALT) MetS + 34.2 ± 50.9 (GGT) MetS-21 ± 28.4 (GGT)
Choi, et al., 2017. Japan [26]	Cross sectional study	21	**Men** MetS + 49.5 ± 6.5 MetS- 48.8 ± 6.1	**Men** 251/474 Total 725	NCEP ATP III	ALT, AST, and GGT were significantly higher in middle-aged men with MetS + than in those without MetS-. MetS + 37.5 ± 22.5 (ALT) MetS- 27.6 ± 17.7 (ALT) MetS + 58.3 ± 48.1 (GGT) MetS- 40.8 ± 49.2 (GGT)
Huang, et al., 2018. China [27]	Cross sectional study	18	**Men** MetS + 45.2 ± 9.4 MetS-42.14 ± 11.0 **Women** MetS + 48.5 ± 13.3 MetS- 41.9 ± 10.9	**Men** 43/176 Total 219 **Women** 18/196 Total 214	NCEP ATP III	Subjects with elevated ALT levels are at increased risk of MetS. ALT may be significantly associated with the presence of MetS. **Men** MetS + 27.7 ± 7.5 (ALT) MetS- 24.4 ± 8.9 (ALT) **Women** MetS + 22.3 ± 9.5 (ALT) MetS- 17.4 ± 7.6 (ALT)
Kim, et al., 2022, Korea [28].	Cross sectional study	19	**Men** MetS + 68.5 ± 6.1 MetS- 69.5 ± 6.3 **Women** MetS + 69.3 ± 6.1 MetS- 68.8 ± 6.4	**Men** 583/1106 Total 1689 **Women** 1299/1493 Total 2792	Harmonised criteria	Elevated ALT and AST levels in MetS + subjects. **Men** MetS + 25.8 ± 15.3 (ALT) MetS- 20.1 ± 10.3 (ALT) MetS + 25.2 ± 12.4 (AST) MetS- 23.3 ± 7.7 (AST) **Women** MetS + 21.2 ± 12.3 (ALT) MetS-17.9 ± 11.3 (ALT) MetS + 23.3 ± 9.2 (AST) MetS- 22.5 ± 8.3 (AST)
Kohsari et al., 2021, Iran [29].	Cross sectional study	18	Age of participants 47.3 ± 4.1	Men 1329/3397 Total 4730 Women 1936/3141 Total 5092	Harmonised criteria	Significant association between elevated ALT, AST, GGT and ALP levels and increased risk of MetS. MetS + 27.6 ± 27.1 (ALT) MetS- 23.5 ± 13.9 (ALT) MetS + 21.8 ± 8.5 (AST) MetS- 21.2 ± 8.9 (AST) MetS + 28.9 ± 22.2 (GGT) MetS- 22.4 ± 18.2 (GGT)
Kuo et al., 2018, Taiwan [30].	Cross sectional study	19	MetS + 61.0 ± 11.0 MetS − 57.5 ± 11.6	54,361/125,998 Total 180,359	Harmonised criteria	Subjects with MetS + had higher ALT and AST levels. MetS + 33.1 ± 25.0 (ALT) MetS- 24.6 ± 19.1 (ALT) MetS + 28.6 ± 15.8 (AST) MetS- 25.1 ± 12.1(AST)
Liu, et al., 2018. China [31]	Cross sectional study	19	MetS + 69.58 ± 7.01 MetS- 70.04 ± 7.65	524/920 Total 1444	Harmonised criteria	Elevated ALT, GGT and ALP levels are positively associated with the prevalence of MetS in the elderly population. MetS + 26.98 ± 15.51 (ALT) MetS- 22.01 ± 12.58 (ALT) MetS + 29.80 ± 19.54 (GGT) MetS- 23.42 ± 18.93 (GGT)
Mitsuhashi et al., 2017, Japan [32].	Cohort study	18	MetS + 50.1 ± 9.3 MetS- 44.5 ± 9.4	698/13,266 Total 13,964	IDF	Higher AST, ALT and GGTP values in non-fatty liver MetS subjects. MetS + 23.2 ± 12.7 (ALT) MetS- 17.5 ± 11.4 (ALT) MetS + 34.6 ± 40.0 (GGTP) MetS- 19.3 ± 19.0 (GGTP)

Table 1 (continued)

Author, year, country	Study design	STROBE(21) Reporting Guidelines	Age of participants	No. Of subjects MetS+/MetS-	MetS criteria	Results	
Osadnik et al., 2020, Poland. [33]	Cross sectional study	19	MetS + 28.07 ± 4.48 MetS- 26.86 ± 4.49	70/390 Total 460	Buscemi et al. (46)	MetS + subjects had increased activity of liver enzymes ALT, AST and GGTP. MetS + 30.61 ± 26.97 (ALT) MetS- 18.74 ± 16.01 (ALT)	MetS + 36.27 ± 38.78 (GGTP) MetS- 16.56 ± 9.65 (GGTP)
Sakane et al., 2020, Japan [34].	Cluster randomised controlled trial	20	MetS + 49.4 ± 6.7 MetS- 48.4 ± 7.9	490/844 Total 1334	NCEP ATP III	MetS + group has elevated AST and ALT levels compared to the MetS- group. MetS + 27.9 ± 11.4 (AST) MetS- 23.4 ± 13.8 (AST)	MetS + 37.2 ± 22.0 (ALT) MetS- 25 ± 15.8 (ALT)
Sobage et al., 2020, Japan [35].	Cross sectional study	20	MetS + 51.2 ± 9.7 MetS- 55.4 ± 7.2	418/2246 Total 2664	NCEP ATP III	ALT, AST, GGT and the prevalence of NAFLD were significantly higher in the MetS + group. MetS + 37.0 ± 25.3 (ALT) MetS- 19.3 ± 11.4 (ALT)	MetS + 48.0 ± 37.5 (GGTP) MetS- 26.2 ± 27.0 (GGTP)
Sumiyoshi et al., 2018, Japan [36].	Retrospect. observational study	19	MetS + 50.8 ± 9.5 MetS- 48.8 ± 9.6	1031/13,762 Total 14,793	Japan Diagnostic criteria	Higher ALT and AST levels are observed in the MetS + group. MetS + 32 ± 22 (ALT) MetS- 21 ± 15 (ALT)	MetS + 25 ± 12 (AST) MetS- 21 ± 9 (AST)
Wang, et al., 2018, China [37].	Cross sectional study	19	MetS + 69.34 ± 7.11 MetS- 70.6 ± 6.76	161/307 Total 468	Harmonized criteria	Significantly higher ALT levels in the MetS + group. MetS + 24.77 ± 14.58 (ALT) MetS- 21.64 ± 14.17 (ALT)	MetS + 24.62 ± 14.58 (AST) MetS- 24.19 ± 8.80 (AST)
Wang, et al., 2020, China [38].	Cross sectional study	19	MetS 68.79 ± 6.53 MetS- 68.34 ± 6.58	2207/1791 Total 3998	NCEP ATP III	The combined increase in serum uric acid (SUA) and alanine aminotransferase (ALT) were significantly correlated with MetS and its components. MetS + 22.32 ± 18.39 (ALT) MetS- 18.27 ± 13.52 (ALT)	MetS + 23.18 ± 14.31 (AST) MetS- 22.08 ± 10.98 (AST)
Wu et al., 2021, Taiwan [39].	Prospective Cohort study	20	MetS + 42.88 ± 8.96 MetS- 37.97 ± 9.0	66/680 Total 746	NCEP ATP III	Higher ALT and AST levels are associated with an elevated risk of MetS+. MetS + 31.77 ± 23.77 (ALT) MetS- 20.58 ± 24.07 (ALT)	MetS + 22.92 ± 12.09 (AST) MetS- 19.49 ± 12.52 (AST)
Yang, et al., 2021. China [40]	Case-control study	18	MetS + 54.89 ± 12.53 MetS- 45.67 ± 12.73	538/5164 Total 5702	Chinese society of Diabetes	Higher ALT, AST levels in MetS + subjects. MetS- 30.19 ± 19.87 (ALT) MetS- 25.38 ± 20.74 (ALT)	MetS + 25.65 ± 10.82 (AST) MetS- 23.37 ± 11.42 (AST)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; IDF, International Diabetes Federation; MetS, metabolic syndrome; NAFLD, Non-alcoholic fatty liver disease; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; SUA, serum uric acid

All demonstrated sufficient reliability and methodological quality regarding the association between ALT, AST, GGT and MetS.

The present meta-analysis has shown the relationship between the levels of different liver enzymes studied and MetS. The concentration of the liver enzymes studied in the 76,686 MetS + subjects was significantly higher than in the group of 201,855 controls (MetS-).

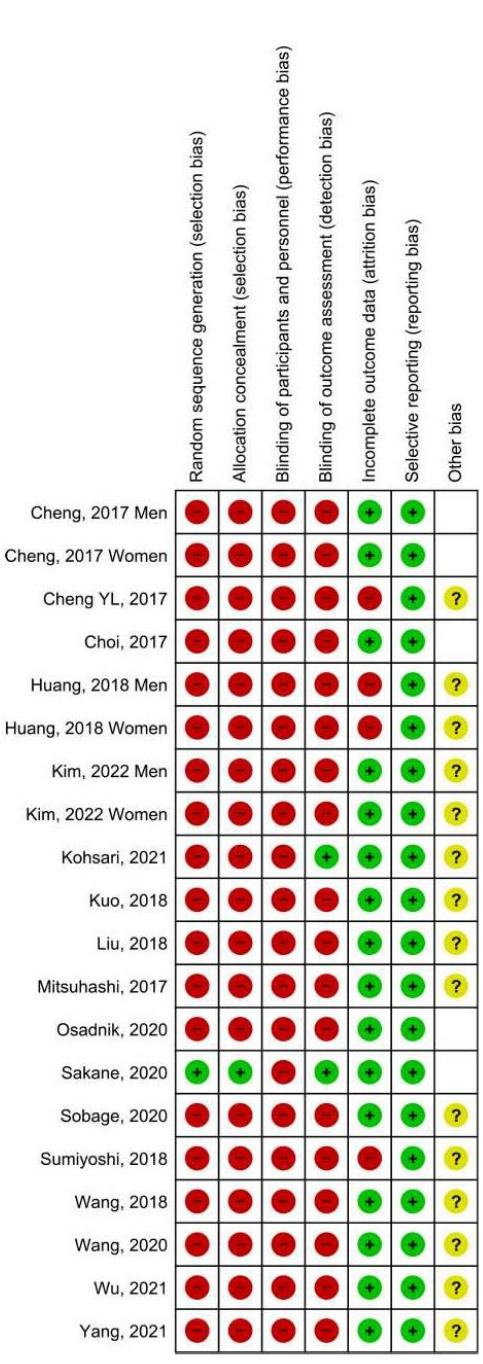

Fig. 3 Summary of risk of bias by study

Table 2 Evidence profile with GRADE pro for the meta-analyses

Certainty assessment							No. of subjects		Size of the effect	Quality of evidence
No. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	MetS+	MetS-	Mean difference (95% CI)	
ALT Meta-analysis										
n = 17	Observational studies	serious	Very serious	It is not serious	It is not serious	dose-response gradient	76.686	201.855	7.13 (5.73–8.54)	⨁◯◯◯ Very low
AST Meta-analysis										
n = 15	Observational studies	serious	Very serious	It is not serious	It is not serious	dose-response gradient	74.526	196.212	2.68 (1.82–3.54)	⨁◯◯◯ Very low
GGT Meta-analysis										
n = 5	Observational studies	serious	Very serious	It is not serious	It is not serious	dose-response gradient	13.302	42.431	11.2 (7.11–15.29)	⨁◯◯◯ Very low

Abbreviations; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; MetS, metabolic syndrome; CI, confidence interval

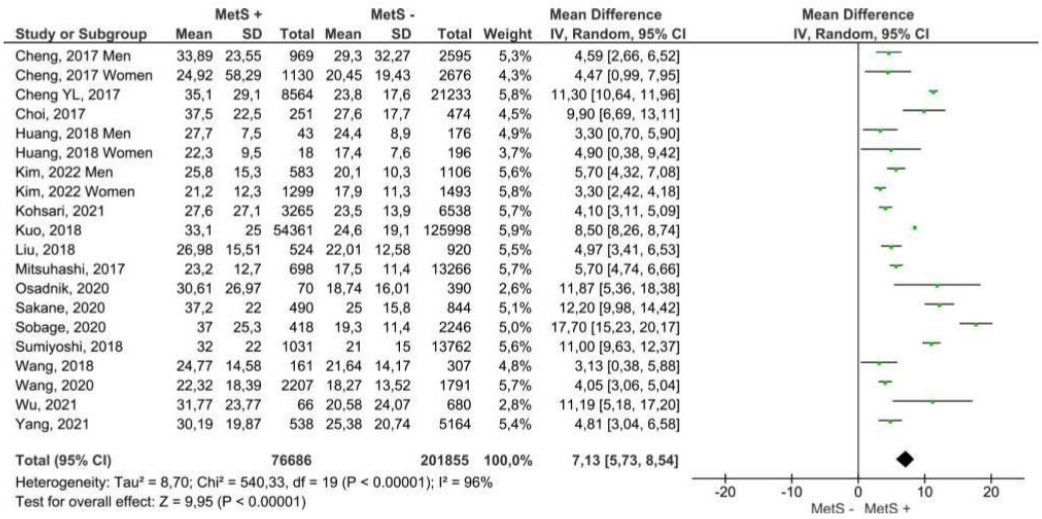

Fig. 4 Results and summary statistics of studies analysing ALT levels in the total population with and without metabolic syndrome (MetS)

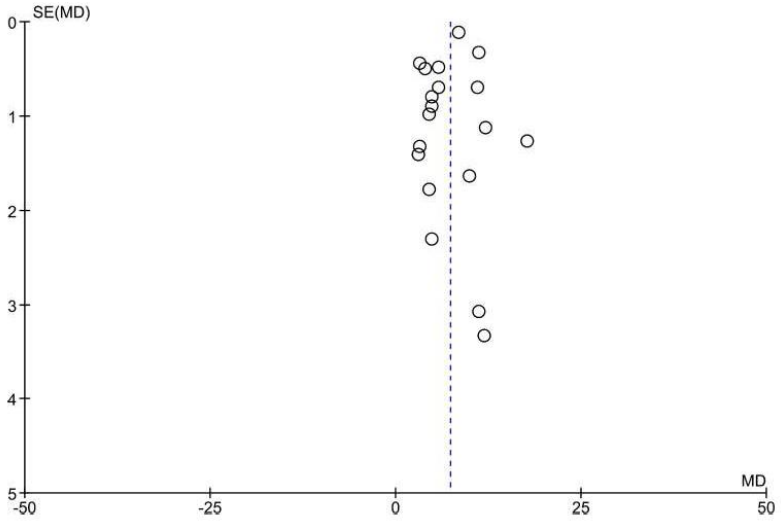

Fig. 5 Publication bias ALT (Funnel plot)

The presence of elevated liver enzymes may precede the development of MetS, with alterations of the liver being observed that are directly related to metabolic problems, such as NAFLD. Recently, it was considered a manifestation of metabolic diseases. However, it has been suggested that NAFLD temporarily precedes DM and that hepatic steatosis may cause insulin resistance [47] and may be an early sign of the development of metabolic diseases [48]. In addition, when fat is deposited in insulin-sensitive organs such as the liver, muscle and visceral compartments, free fatty acids and inflammatory cytokines increase while adiponectin levels decrease [49, 50]. These changes can lead to peripheral insulin resistance, early atherogenesis, impaired glucose metabolism and MetS [51, 52].

Previous studies have reported that NAFLD predates MetS components such as impaired fasting glucose and hypertension [53–55]. The study in young

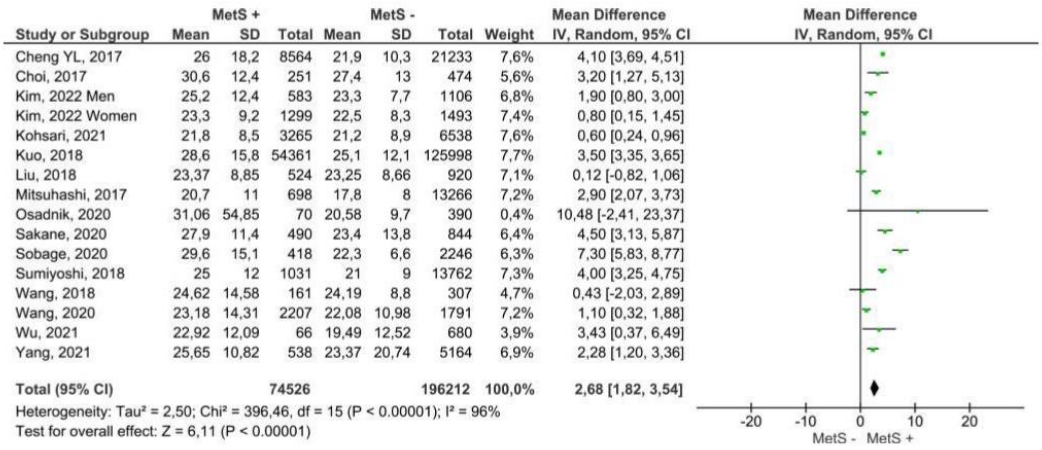

Fig. 6 Results and summary statistics of studies analysing AST levels in the total population with and without metabolic syndrome (MetS)

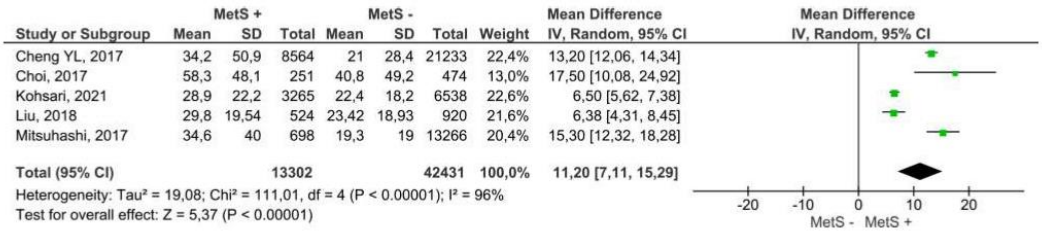

Fig. 7 Results and summary statistics of studies analysing GGT levels in the total population with and without metabolic syndrome (MetS)

adults by Yoo et al. [56] concludes that the degree of hepatic steatosis can predict the future occurrence of MetS. Several studies have reported that NAFLD contributes to the development of DM2 and is associated with increased cardiovascular risk [57, 58]. The meta-analysis of prospective studies by Ballestri et al. [59] concluded that NAFLD significantly increases the incident risk of DM2 and MetS. This fact is highly relevant given that NAFLD is associated with elevated liver enzymes, such as ALT, AST and GGT, so early detection can help in interventions to prevent metabolic diseases such as MetS.

Concerning MetS, studies have shown that liver enzymes could be new candidate biomarkers for its early diagnosis. Our results are consistent with the associations reported between liver enzymes and MetS by other authors. The cross-sectional study by Chen et al. [17] concludes that serum ALT levels, even within the reference range, are significantly associated with MetS. The study by Sattar et al. [60] informs that serum ALT levels, but not AST levels, increased progressively as the number of MetS components increased. The meta-analysis of 10 prospective cohort studies by Kunutsor et al. [61] reported a dose-response relationship between GGT level and the risk of MetS. The meta-analysis by Liu et al. [62], involving 9 cohort studies, evidenced a positive association between GGT levels and the risk of MetS independent of alcohol intake.

In addition, there are significant gender differences, with males having higher levels than females, and the reference ranges established by the laboratories also vary. The study by Cheng et al. [24] reveals that male subjects had a higher prevalence of MetS and higher ALT levels; these results are in line with studies by Huang et al. [27] and Kim et al. [28].

However, further epidemiological investigations using longitudinal designs are needed to understand the associations between serum ALT, AST, and GGT levels and MetS.

These findings have important clinical implications regarding the optimal strategies to be adopted to prevent the development of MetS. In addition, monitoring liver enzyme values to detect their gradual elevation could alert to future metabolic problems.

Limitations and strengths

At the methodological level, the assessment of risks of bias in studies is a major issue in this type of research, in line with PRISMA recommendations. Studies with similar methodologies but with discrepancies in quality may have biased results. The quality of the evidence obtained is "very low" because observational studies have been analysed where there is a high risk of bias and, in addition, present a very high inconsistency (heterogeneity).

The authors were unable to fully examine the impact of adjustment for all known and potential risk factors, due to the varying degree of adjustment for confounding factors across individual studies.

One of the main strengths of this review is the comprehensive search covering a wide geographical area. In addition, a large sample size of subjects with and without MetS was included, which increased the study's statistical power. However, considering some limitations, interpreting the findings in this systematic review and meta-analysis should be done cautiously. Firstly, non-randomised comparisons in observational studies may suffer from bias, which could affect the findings and thus weaken the strength of the evidence. Secondly, the included studies used different definitions to diagnose MetS, which may alter the findings. Also, the heterogeneity of the analyses was very high, which makes the results less robust. Finally, another limitation was that no additional strategies were used in the current search to locate unpublished reviews (grey literature).

Conclusions

The results have shown that MetS+subjects have higher levels of all liver enzymes tested than MetS- subjects. These findings provide a rationale for further evaluation of the relationship of liver enzymes in the pathophysiological process of MetS and could lead to new perspectives in early diagnosis.

The relevance of these findings has several implications for clinical practice, such as early diagnosis of MetS, early prevention of associated liver damage, better understanding of the pathophysiology, as well as the management and direction of effective care strategies for these patients.

However, primary studies with higher methodological quality should be performed to provide more robustness to the collected findings. Also, regarding this severe health problem, more research is needed in different populations to identify the importance of liver enzymes in MetS or other cardiovascular diseases.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-023-01200-z.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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None.

Authors' contributions
Selection of papers. Two researchers (E.R.C and M.R.S) reviewed titles, abstracts and full texts. In addition, three researchers independently extracted data for studies that met the inclusion criteria (R.J.M, R.M.L. and G.M.R.). Finally, a fourth author (M.V.A.) acted as a judge in case of discrepancy. Data extractionOne researcher (E.R.C.) was responsible for extracting the data verified by a second researcher (R.J.M.). A third researcher (M.R.S.) resolved the disagreement in case of a tie. Cohen's Kappa index was used to assess the degree of agreement. The following data were extracted from each study: citation, details of the study population (including age and sex), study design, follow-up period, sample size, and mean and standard deviation of ALT, AST, and GGT in those subjects with Metabolic Syndrome (MetS+) and without Metabolic Syndrome (MetS-). In addition, for articles collecting ALT, AST and GGT data, the mean and standard deviation were extracted.

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Data Availability
All data generated or analysed during this study are included in this published article [and its supplementary information files].

Declarations

Ethics approval and consent to participate
Not applicable.

Competing interests
The authors declare no competing interests.

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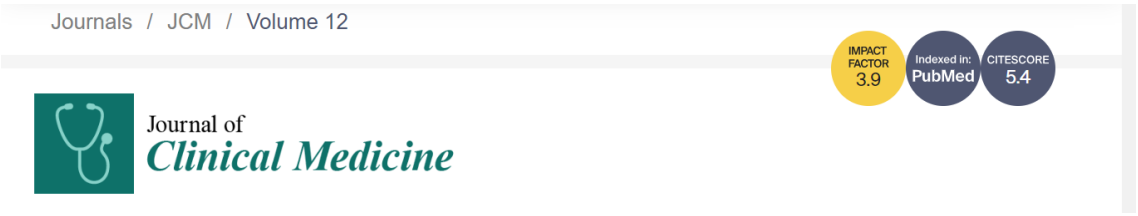
Publisher's Note

3.3. Capítulo III



Association between Metabolic Syndrome and Leukocytes: Systematic Review and Meta-Analysis.

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Systematic Review

Association between Metabolic Syndrome and Leukocytes: Systematic Review and Meta-Analysis

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Abstract: Background: Metabolic syndrome (MetS) is a group of metabolic abnormalities characterised by central obesity, hypertension, dyslipidaemia, and dysregulation of blood glucose, which is associated with the risk of diabetes, cardiovascular disease, and overall mortality. White blood cell count is a selective marker of acute infection and inflammation, which could provide information on the metabolic status of subjects. This study aims to provide the best evidence on the association between MetS and white blood cell count by determining the effect size of this biomarker. **Methods:** A systematic review and meta-analysis of studies indexed in the PubMed and Scopus databases were performed. Methodological quality was assessed using the STROBE tool, overall risk of bias using RevMan (Cochrane Collaboration), and quality of evidence using Grade Pro. **Results:** We included 14 articles comparing leukocyte concentrations in 21,005 subjects with MetS and 66,339 controls. Subjects with MetS had a higher mean leukocyte count, 0.64 cells $\times 10^9$/L; CI95% 0.55–0.72; $p < 0.00001$; $I^2 = 93\%$. **Conclusions:** An in-depth evaluation of the relationship of leukocytes in the pathophysiological process of MetS could lead to new insights into early diagnosis.

Keywords: metabolic syndrome; leukocytes; white blood cells; biologic marker

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1. Introduction

Metabolic syndrome (MetS) is a group of metabolic abnormalities that includes central obesity, hypertension, dyslipidaemia, and blood glucose disorders. This condition is associated with an increased risk of developing diabetes, cardiovascular disease, and a raised overall mortality rate [1]. In addition, the incidence and prevalence of MetS have increased globally, making this non-communicable disease a major public health hazard [2,3]. Therefore, early diagnosis and prevention of MetS are essential. The underlying pathophysiology involves insulin resistance (IR), chronic low-grade inflammation, and oxidative stress, playing a crucial role in the pathogenesis of MetS [4,5].

Inflammatory markers are generally increased in patients with MetS, but the link between inflammation and the development of MetS is less well established. However, evidence suggests that changes in haematological parameters related to inflammatory processes, such as white blood cell count (WBC) and prothrombotic markers, may be associated with MetS [6,7]. WBC, neutrophils, and lymphocytes are common, inexpensive, and widely used markers of inflammation in the clinical setting [8]. These markers activate the main cell types involved in acute and chronic inflammation [9]. Additionally, white blood cells altered by chronic inflammatory risk factors are more likely to bind and adhere to vascular endothelium, which can cause capillary leukocytosis and eventually lead to vasoconstriction and hypertension [10].

Likewise, WBC count is directly associated with insulin resistance and, inversely, with insulin secretion. Concerning this, WBC count has been shown to predict both worsening insulin sensitivity and the incidence of type 2 diabetes [11]. Furthermore, due to hypertrophy-induced inflammation and leukocyte infiltration, adipose tissue loses sensitivity to insulin, resulting in increased lipolysis and impaired lipid storage, augmenting its dysfunctionality. As a result, free fatty acids and triglycerides are mobilised into the circulation, accumulating lipid derivatives in skeletal muscle, liver, and pancreatic B-cells, leading to impaired tissue function and systemic insulin resistance [12].

Thus, increased WBC may be directly involved in the pathogenesis of MetS by increasing the movement of inflammatory cells into adipose tissue. Prolonged maintenance or worsening of this metabolically dysfunctional state further perpetuates dysregulation of lipid metabolism and immune responses, increasing the individual's risk of developing a wide range of chronic diseases [13,14].

In addition, previous studies have shown a significant relationship between WBC and MetS [6,15]. In this regard, it has been observed that the number of immune cell subtypes, specifically, the total number of leukocytes, lymphocytes, and monocytes, is higher in individuals with MetS [16]. Therefore, since chronic subclinical inflammation is implicated in the genesis of MetS and WBC can be used as a marker of inflammation, assessing the association between WBC count and the development of MetS may generate a new parameter to aid in its detection.

The primary aim of this systematic review and meta-analysis is to offer the most robust evidence regarding the correlation between Metabolic Syndrome (MetS) and leukocyte levels, ascertaining the magnitude of this biomarker's impact.

2. Materials and Methods

2.1. Search Strategy and Eligibility Criteria

This systematic review and meta-analysis were conducted according to the criteria established by the PRISMA statement [17] (Supplementary Materials). The search was performed in the PubMed and Scopus databases, covering January 2017 to January 2022. The search methodology was formulated by amalgamating the following Medical Subject Headings (MeSH) descriptors: "metabolic syndrome", "leukocytes", and "white blood cells" with the Boolean operator AND. Cross-sectional and longitudinal studies investigating the association between MetS and leukocytes or articles collecting data related to both parameters were included. In addition, the results had to include the mean and standard deviation. Only manuscripts in English and Spanish and those collecting data on subjects older than 18 years were considered. Papers from subjects previously diagnosed with diabetes, obesity or active infections that could increase the level of leukocytes in their study groups were excluded. The systematic review was registered in PROSPERO with ID CRD42022228327.

2.2. Selection of Papers

E.R.C. and M.R.S. conducted independent reviews of all the articles retrieved in the search to remove duplicates. Subsequently, R.J.M., R.M.L., J.M.G.G., and G.M.R., four other authors, individually examined the titles and abstracts, applying eligibility criteria to select the articles that ultimately made it into the review. Lastly, M.V.A., the fifth author, served as a judge in the event of any discrepancies.

2.3. Data Extraction

One researcher (E.R.C) extracted the data, verified by a second investigator (R.J.M). A third researcher (M.R.S) decided in case of disagreement between them. Cohen's Kappa index was used to assess the degree of agreement. We collected the following information from each study: citation, characteristics of the study population (including age and gender), study methodology, duration of follow-up, sample size, as well as the average and standard deviation of leukocyte levels in individuals with Metabolic Syndrome (MetS+)

and those without Metabolic Syndrome (MetS−). In addition, the mean and standard deviation were extracted for reports collecting neutrophil, lymphocyte, and monocyte data.

2.4. Evaluation of the Qualitative Synthesis

A team of four authors (R.M.L, R.J.M, E.R.C, and G.M.R) conducted a thorough qualitative synthesis assessment through a triple analysis:

(a) Methodological quality evaluation was performed using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement [18] for observational studies.

(b) Risk of bias evaluation was conducted using the Cochrane Collaboration tool [19] integrated into the REVMAN 5.4.2 software (Cochrane Collaboration, Copenhagen, Denmark). This analysis assessed risks related to selection, conduct, detection, attrition, and reporting.

(c) Evaluating the evidence quality. Utilizing the Grade Pro tool (McMaster University and Evidence Prime), we constructed the evidence profile table, assigning specific levels as outlined [20]:

- High: Strong assurance in aligning the actual and estimated effect;
- Moderate: Reasonable confidence in the estimated effect. The actual effect may differ significantly;
- Low: Restricted confidence in the estimated effect. The actual effect may deviate substantially from the estimate;
- Very Low: Minimal confidence in the estimated effect. The actual effect is highly likely to vary extensively from the estimate.

2.5. Statistical Analysis (Evaluation of Quantitative Synthesis or Meta-Analysis)

The statistical computations and generation of forest and funnel plots for the meta-analysis were conducted using the Cochrane Review Manager software (RevMan 5.4.2). Given the variation in effect sizes among the included studies, a meta-analysis was executed utilizing the Mantel–Haenszel random-effects approach, following the DerSimonian and Laird model. The difference between arithmetic means with a 95% confidence interval was used to measure effect size. Leukocyte count was measured in cells $\times 10^9$/L. Publication bias risk was evaluated through an examination of the funnel plot. Heterogeneity was assessed by computing the Chi-square test and the inconsistency index (I^2). Following the Cochrane Collaboration tool, heterogeneity was categorized as follows: unimportant (0–40%), moderate (30–60%), substantial (50–90%), and considerable (75–100%).

3. Results

3.1. Characteristics of the Studies

The search yielded 89 records, of which 25 were identified for full-text review (Figure 1). Of these, 14 met the inclusion criteria and were therefore selected for systematic review and meta-analysis.

Regarding the research design, all studies were observational: 10 cross-sectional studies [10,21–29], 3 cohort studies [9,30,31], and 1 case–control study [32]. In total, the 14 papers compared leukocyte concentrations between 21,005 MetS+ and 66,339 MetS− subjects. The ages of the participants ranged from 18 to 85 years. Most of the papers (57.14%) [9,22,24,26–28,30,32] included participants of both sexes, but analysed the data globally; 3 studies (21.4%) included only men [21,23,25], and 3 others collected data from men and women separately [10,29,31]. In relation to provenance, half of the articles found were developed in the Chinese population [9,10,22,26,28–31]. In addition, neutrophil data were extracted from 7 articles [9,22,26–30], lymphocyte data from 6 studies [9,22,24,27,31,32], monocyte data from 4 papers [28–30,32], and eosinophil and basophil data from 2 manuscripts [28,29].

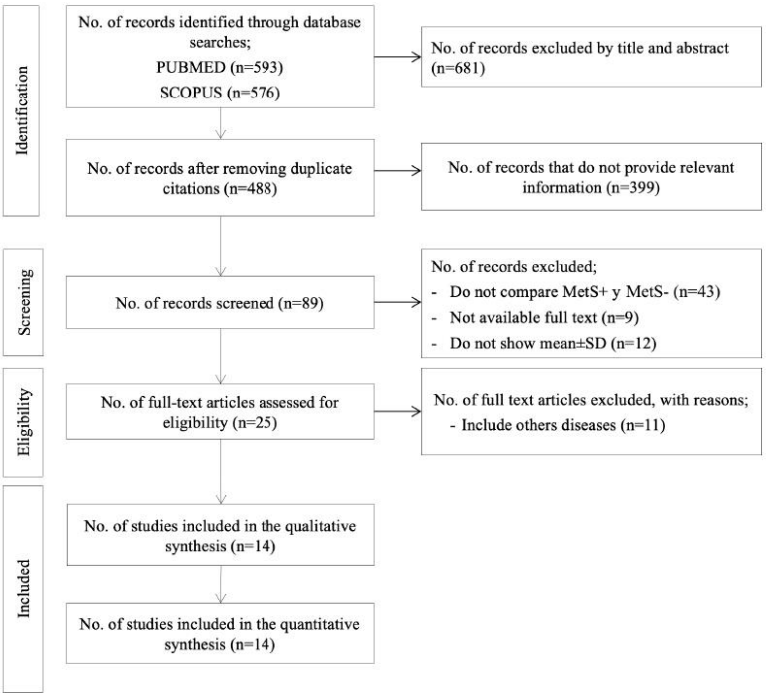

Figure 1. PRISMA flow chart. MetS, metabolic syndrome; SD, standard deviation.

MetS was defined according to the National Cholesterol Education Program (NCEP-ATP III) third report criteria [33] in 7 research studies [22–24,27,29,31,32]; 3 studies [10,21,28] assessed MetS using the International Diabetes Federation (IDF) definition [34]; 2 studies [25,26] used harmonised criteria [35]; and 2 articles [9,30] as defined by the Chinese Diabetes Society [36].

The in-depth features of the chosen studies can be found in Table 1.

Table 1. Characteristics of included studies (n = 14).

Author, Year, Country	Study Design	STROBE[18] Reporting Guidelines	Age of Participants	No. of Subjects MetS+/MetS−	MetS Criteria	Results
Ahmadzadeh et al., 2017, Iran [21]	Cross-sectional study	19	Men MetS+ 41.4 ± 9.9 MetS− 36.4 ± 9.6	Men 3203/7911 Total 11,114	IDF	Increased WBC ($p < 0.001$) is related to a higher number of MetS criteria. Men MetS+ 7.2 ± 1.7 (WBC) MetS− 6.7 ± 1.7 (WBC)
Chen et al., 2019, China [22]	Cross-sectional study	20	MetS+ 56.5 ± 0.5 MetS− 47.6 ± 0.4	254/598 Total 852	NCEP ATP III	Elevated WBC levels in MetS+ subjects. MetS+ 7.03 ± 0.1 (WBC) MetS− 6.4 ± 0.06 (WBC)
Chen et al., 2020, China [10]	Cross-sectional study	19	Women MetS+ 60.7 ± 10.0 MetS− 52.6 ± 12.7 Men MetS+ 57.2 ± 10.5 MetS− 54.8 ± 13.5	Women 277/641 Total 918 Men 140/343 Total 483	IDF	Haematological parameters, including WBC and subtypes, correlate with the occurrence of MetS. Women MetS+ 6.69 ± 1.67 (WBC) MetS− 6.1 ± 1.53 (WBC) Men MetS+ 7.24 ± 1.66 (WBC) MetS− 6.87 ± 1.59 (WBC)
Hoi et al., 2017, Japan [23]	Cross-sectional study	21	Men MetS+ 49.5 ± 6.5 MetS− 48.8 ± 6.1	Men 251/474 Total 725	NCEP ATP III	Significantly higher white blood cell count in MetS+ subjects. Men MetS+ 6.57 ± 1.55 (WBC) MetS− 5.95 ± 1.44 (WBC)
Li et al., 2019, China [30]	Retrospective cohort study	19	MetS+ 52.5 ± 13.6 MetS− 41.1 ± 13.3	120/1948 Total 2068	Chinese Diabetes Society	The MetS+ group had higher TSH and inflammation levels, indicated by higher WBC, LY, and Mo/HDL. MetS+ 7.1 ± 2.11 (WBC) MetS− 6.4 ± 1.6 (WBC) MetS+ 2.57 ± 0.79 (Lymphocyte) MetS− 2.25 ± 0.61 (Lymphocyte) MetS+ 3.89 ± 1.52 (Neutrophil) MetS− 3.57 ± 1.2 (Neutrophil) MetS+ 0.43 ± 0.15 (Monocyte) MetS− 0.39 ± 0.13 (Monocyte)
Lin et al., 2021, China [9]	Cohort study	20	MetS+ 45 ± 11.6 MetS− 44.9 ± 13.18	179/1363 Total 1542	Chinese Diabetes Society	Subjects with MetS+ have higher levels of leukocytes, neutrophils, and total lymphocytes. Elevated levels of leukocytes, neutrophils, and lymphocytes increased the incidence of MetS. MetS+ 6.6 ± 1.4 (WBC) MetS− 6.21 ± 1.3 (WBC) MetS+ 3.6 ± 1.03 (Neutrophil) MetS− 3.39 ± 0.94 (Neutrophil) MetS+ 2.39 ± 0.68 (Lymphocyte) MetS− 2.25 ± 0.56 (Lymphocyte)
Liu C et al., 2019, Taiwan [24]	Cross-sectional study.	19	MetS+ 50.4 ± 11.1 MetS− 45.6 ± 11.1	10,475/23,538 Total 34,013	NCEP ATP III	Inflammatory biomarkers (WBC, CRP, and Hs-CRP), lipid markers (total cholesterol, triglycerides, and LDL-cholesterol), and glycaemic markers (fasting glucose, HbA1c, insulin, HOMA-IR, and SUA) were on average higher in the MetS+ group than in MetS− ($p < 0.001$). MetS+ 6.83 ± 1.72 (WBC) MetS− 6.05 ± 1.45 (WBC)

Table 1. *Cont.*

Author, Year, Country	Study Design	STROBE[18] Reporting Guidelines	Age of Participants	No. of Subjects MetS+/MetS−	MetS Criteria	Results
Mauss et al., 2020, Germany [25]	Cross-sectional study	19	Men MetS+ 49.5 ± 8.1 MetS− 44.5 ± 9.9	Men 137/552 Total 689	Harmonised criteria	Total leukocyte count and CRP were higher in the MetS+ group, while leukocyte ratios showed no significant differences. Men MetS+ 7.1 ± 1.81 (WBC) MetS− 6.44 ± 1.68 (WBC)
Meng et al., 2017, China [26]	Cross-sectional study	21	MetS+ 52.7 ± 9.7 MetS− 48.9 ± 9.7	2292/4020 Total 6312	Harmonised criteria	They observe that leukocyte, neutrophil, and lymphocyte concentrations are associated with MetS. MetS+ 5.84 ± 1.46 (WBC) MetS− 5.32 ± 1.29 (WBC) MetS+ 3.29 ± 0.97 (Neutrophil) MetS− 2.98 ± 0.97 (Neutrophil) MetS+ 1.98 ± 0.49 (Lymphocyte) MetS− 1.77 ± 0.65 (Lymphocyte)
Tanaka et al., 2020, China [31]	Cohort study	19	Women MetS+ 55.2 ± 10.4 MetS− 44.8 ± 9.8 Men MetS+ 50.3 ± 9.4 MetS− 44.8 ± 9.7	Women 401/8035 Total 8436 Men 1184/10,542 Total 11,726	NCEP ATP III	Higher levels of WBC are observed in the MetS group. **Women** MetS+ 6.0 ± 1.5 (WBC) MetS− 5.3 ± 1.4 (WBC) **Men** MetS+ 6.6 ± 1.7 (WBC) MetS− 5.7 ± 1.5 (WBC)
Uslu et al., 2018, Turkey [32]	Case–control study	19	MetS+ 47 ± 13.5 MetS− 44 ± 15.2	147/134 Total 281	NCEP ATP III	MHR is a useful inflammatory marker to assess MetS and disease severity. MetS+ 7.96 ± 2.63 (WBC) MetS− 6.69 ± 1.58 (WBC) MetS+ 0.59 ± 0.26 (Monocyte) MetS− 0.48 ± 0.16 (Monocyte)
Vahit et al., 2017, Turkey [27]	Cross-sectional study	20	MetS + 57.4 ± 8.8 MetS− 56.3 ± 9.1	371/391 Total 762	NCEP ATP III	MRLs such as MHR may be novel and valuable indicators in MetS. MetS+ 7.55 ± 1.66 (WBC) MetS− 7.49 ± 1.69 (WBC) MetS + 4.32 ± 1.34 (Neutrophil) MetS− 4.51± 1.36 (Neutrophil)
Xie et al., 2021, China. [28]	Cross-sectional study	19	MetS+ 26.1 MetS− 25.7	655/2189 Total 2844	IDF	Lasso's logistic regression algorithm helped to identify MetS with high accuracy in an occupational population. MetS+ 7.37 ± 1.79 (WBC) MetS− 6.68 ± 1.65 (WBC) MetS+ 0.42 ± 0.15 (Monocyte) MetS− 0.39 ± 0.13 (Monocyte) MetS+ 0.17 ± 0.13 (Eosinophil) MetS− 0.18 ± 0.18 (Eosinophil) MetS+ 2.45 ± 0.69 (Lymphocytes) MetS− 2.39 ± 0.71 (Lymphocytes) MetS+ 4.32 ± 1.42 (Neutrophil) MetS− 3.71 ± 1.25 (Neutrophil) MetS+ 0.07 ± 0.16 (Basophil) MetS− 0.05 ± 0.11 (Basophil)

Table 1. *Cont.*

Author, Year, Country	Study Design	STROBE[18] Reporting Guidelines	Age of Participants	No. of Subjects MetS+/MetS−	MetS Criteria	Results
Yang et al., 2020, China. [29]	Cross-sectional study	19	≥60 years	Women 608/1771 Total 2379 Men 311/1889 Total 2200	NCEP ATP III	They observe interactions between leukocytes, monocytes, neutrophils, and sex in MetS. **Women** MetS+ 5.68 ± 1.31 (WBC) MetS− 5.15 ± 1.28 (WBC) MetS+ 1.8 ± 0.57 (Lymphocytes) MetS− 1.61 ± 0.51 (Lymphocytes) MetS+ 0.3 ± 0.1 (Monocyte) MetS− 0.28 ± 0.1 (Monocyte) MetS+ 3.41 ± 0.99 (Neutrophil) MetS− 3.1 ± 1.01 (Neutrophil) MetS+ 0.13 ± 0.11 (Eosinophil) MetS− 0.13 ± 0.13 (Eosinophil) MetS+ 0.03 ± 0.02 (Basophil) MetS− 0.03 ± 0.02 (Basophil) **Men** MetS+ 5.87 ± 1.43 (WBC) MetS− 5.48 ± 1.53 (WBC) MetS+ 1.75 ± 0.53 (Lymphocytes) MetS− 1.56 ± 0.62 (Lymphocytes) MetS+ 0.35 ± 0.16 (Monocyte) MetS− 0.34 ± 0.13 (Monocyte) MetS+ 3.56 ± 1.14 (Neutrophil) MetS− 3.4 ± 1.21 (Neutrophil) MetS+ 0.16 ± 0.15 (Eosinophil) MetS− 0.14 ± 0.14 (Eosinophil) MetS+ 0.04 ± 0.02 (Basophil) MetS− 0.03 ± 0.02 (Basophil)

CRP, C-reactive protein; HbA1c, haemoglobin A1c; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; hsCRP, high-sensitivity C-reactive protein; IDF, International Diabetes Federation; LY, lymphocytes; LMR, lymphocyte-to-monocyte ratio, MetS, metabolic syndrome; MHR, monocyte to high-density lipoprotein cholesterol ratio; Mo/HDL, monocyte/high-density lipoprotein; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; SUA, serum uric acid; TSH, thyroid-stimulating hormone; WBC, white blood cells.

3.2. Methodological Quality Assessment

Every report scored 19 or higher out of the 22 items outlined in the STROBE reporting guidelines [18], placing them in the highest tercile. No articles were excluded for poor methodological quality. In Table 1, you can observe the individual scores assigned to each paper.

3.3. Bias Risk Analysis

Overall (Figure 2), it can be seen that the main biases were random sequential generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment. Only one of the included articles collected data randomly with allocation concealment [30]. Figure 3 represents the individual assessment of the included studies.

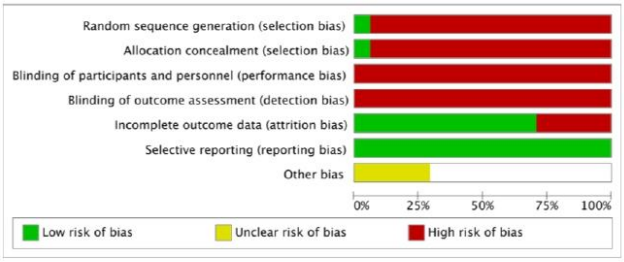

Figure 2. Overall risk of bias observed in the studies.

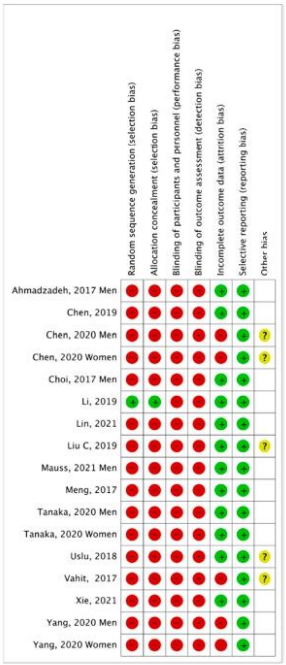

Figure 3. Summary of risk of bias by study [9,10,21–32].

3.4. Quantitative Analysis and Meta-Analysis

Figure 4 shows the Forest Plot, including the results for both sexes from the 14 review articles. MetS+ subjects showed a higher mean leukocyte count, namely the mean difference was 0.64 cells $\times 10^9$/L (CI95% 0.55–0.72; $p < 0.00001$; $I^2 = 93\%$), compared to MetS− subjects.

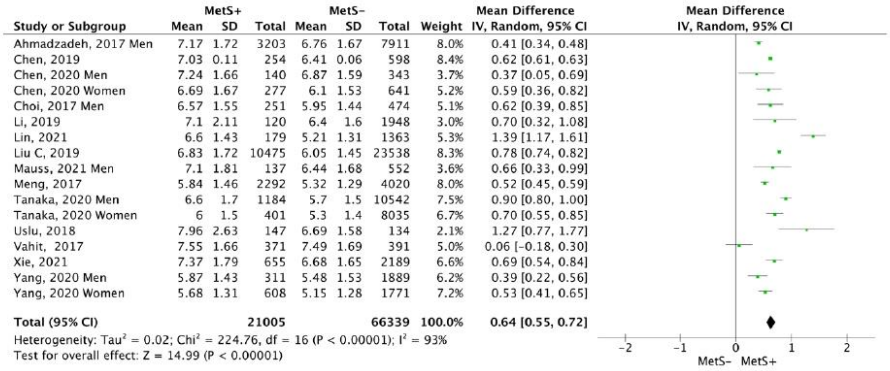

Figure 4. Results and summary statistics of studies analysing leukocyte levels in the total population with and without metabolic syndrome (MetS) [9,10,21–32].

The Funnel Plot (Figure 5) shows a low risk of publication bias. The sensitivity analysis did not show that any study significantly affected the heterogeneity of the meta-analysis; therefore, no articles were excluded.

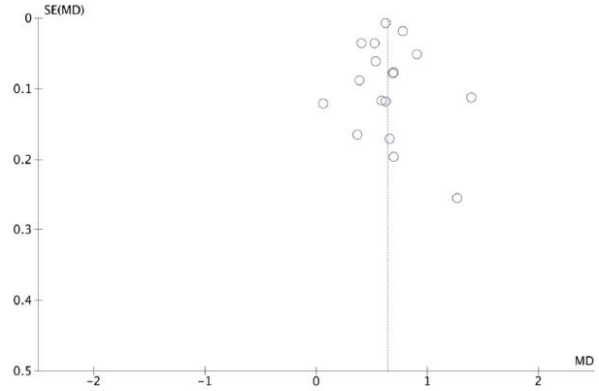

Figure 5. Funnel plot.

MetS+ subjects showed a higher mean number of neutrophils, specifically, the mean difference was 0.28 cells $\times 10^9$/L (CI95% 0.2–0.36; $p < 0.00001$; $I^2 = 88\%$), compared to MetS− subjects (Figure 6).

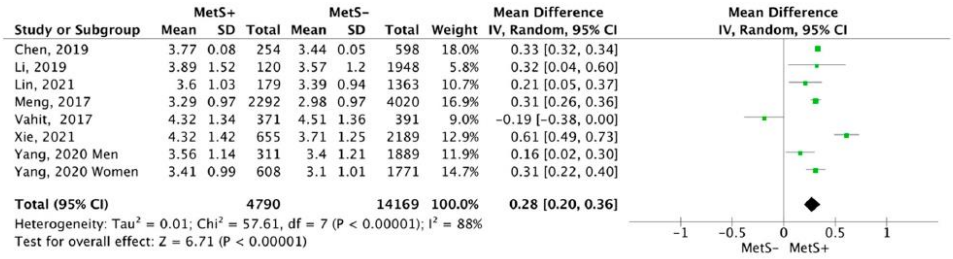

Figure 6. Results and summary statistics of studies analysing neutrophil levels in the total population with and without metabolic syndrome (MetS) [9,22,26–30].

In relation to lymphocytes (Figure 7), MetS+ subjects showed a higher mean, the mean difference was 0.19 cells $\times 10^9$/L (CI95% 0.14–0.23; $p < 0.00001$; $I^2 = 87\%$), compared to MetS− subjects.

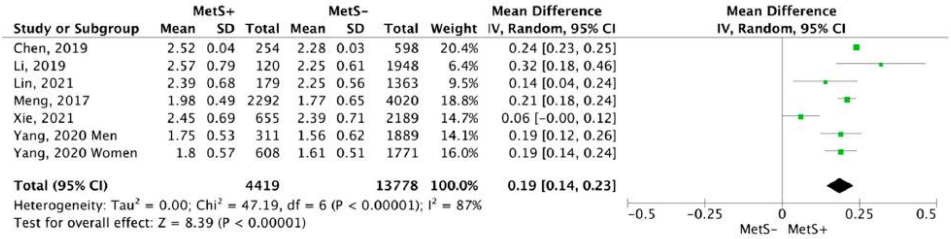

Figure 7. Results and summary statistics of studies analysing lymphocyte levels in the total population with and without metabolic syndrome (MetS) [9,22,26,28–30].

3.5. Quality of Evidence

Table 2 shows the evidence profile of the meta-analysis, providing specific information regarding the overall certainty of the evidence of the studies included in the comparison, the magnitude of the studies examined, and the sum of the data available for the outcomes assessed.

Table 2. Evidence profile with GRADE pro for the meta-analyses.

Certainty Assessment							No. of Subjects		Size of the Effect	Quality of Evidence
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirect Evidence	Imprecision	Other Considerations	MetS+	MetS−	Mean Difference (95% CI)	
Meta-analysis White blood cells										
$n = 14$	Observational studies	serious	Very serious	It is not serious	It is not serious	dose-response gradient	21,005	66,339	0.64 (0.55–0.72)	⊕○○○ Very low
Meta-analysis Neutrophils										
$n = 7$	Observational studies	serious	Very serious	It is not serious	It is not serious	dose-response gradient	4790	14,169	0.28 (0.2–0.36)	⊕○○○ Very low
Meta-analysis Lymphocytes										
$n = 6$	Observational studies	serious	Very serious	It is not serious	It is not serious	dose-response gradient	4419	13,778	0.19 (0.14–0.23)	⊕○○○ Very low

MetS, metabolic syndrome; CI, confidence interval.

4. Discussion

A comprehensive review and meta-analysis were performed to examine the latest evidence regarding the association between Metabolic Syndrome (MetS) and leukocyte levels. Fourteen articles were selected to quantify the size effect and the limitations that have conditioned their results. All demonstrated sufficient reliability and methodological quality regarding the association between leukocytes and MetS.

The present meta-analysis shows the relationship between the level of leukocytes and MetS. The leucocyte concentration in the 21,005 MetS+ subjects was significantly higher than in the group of 66,339 controls (mean difference (MD): 0.64 cells $\times 10^9$/L; CI95% 0.55–0.72; $p < 0.00001$).

The results of this review support how elevated white blood cell count is closely related to MetS. The mechanisms that explain this association are not entirely clear, but some possibilities have been suggested. On the one hand, IR, defined as the decreased capability of insulin to stimulate glucose uptake by muscle and adipose tissues and to suppress hepatic glucose production [37], may contribute to metabolic disturbances and accumulation of inflammatory markers, such as total leukocytes and other inflammatory factors [29].

On the other hand, MetS indicates metabolic dysregulation or dysfunction, strongly associated with atherosclerotic cardiovascular disease and often accompanied by chronic low-grade inflammation [4,38]. This inflammation can induce the synthesis of several groups of cytokines and proteolytic enzymes and decrease the formation of prostacyclin and nitric oxide, which can cause impaired endothelial integrity and functional impairment, leading to an increase in white blood cells and their subtypes [9,11,13]. Furthermore, TNF-a has been shown to be consistently expressed in adipose tissue, and these proinflammatory cytokines lead to elevated leukocyte levels [39]. This increase may lead to hypertension and loss of vasodilatory capacity [40]. The study by Marques P et al. [41] reports that neutralising chemokine axes partially inhibit leukocyte adhesion through altered adhesiveness of proinflammatory monocytes to dysfunctional endothelium, suggesting a potential link between the systemic inflammatory response and the development of CVD in MetS.

In addition, Lorenzo et al. note that elevated total white blood cell, neutrophil, and lymphocyte counts can be detected in people at increased risk of diabetes due to insulin sensitivity and low-grade inflammation [14]. Metabolic alterations and inflammation enter a vicious cycle of T-cell activation, senescence, and proinflammatory cytokine production that worsens pathological conditions [42].

Our results are consistent with reported associations between leukocytes and MetS. Previous longitudinal and cross-sectional studies have associated WBC with the incidence and prevalence of MetS [6,43]. The cross-sectional study by Babio et al. [44] demonstrates that WBC count was associated with increased risk and prevalence of MetS and concluded that WBC count is positively associated with three parameters used as defining criteria for MetS: hyperglycaemia, HDL-cholesterol, and hypertriglyceridaemia. Therefore, circulating white blood cells could represent a critical factor in the study of obesity and its associated comorbidities, such as MetS and CVD [45]. In addition, the study by Wang et al. [46] confirms that monitoring longitudinal changes in leukocyte markers may help provide a strategy for primary prevention of future cardiovascular events. Thus, cardiometabolic risk factors contribute to developing and worsening this proinflammatory and prothrombotic state associated with MetS, leading to detrimental metabolic conditions. Many of these conditions are acquired through lifestyle and are modifiable, indicating the importance of prevention and treatment methods to improve cardiometabolic risk factors to reduce their impact on MetS [47,48].

5. Limitations and Strengths

In this kind of research, evaluating the potential biases in study methodologies is a crucial concern under PRISMA guidelines. Studies with similar methodologies but discrepancies in quality may have biased results. The quality of the evidence obtained is

"very low" because observational studies have been analysed. These study designs pose a high bias risk and show a very high inconsistency (heterogeneity). The authors were unable to thoroughly examine the impact of adjustment for all known and potential risk factors due to the varying degrees of adjustment for confounding factors across individual studies. One of the main strengths of this review is a large sample size of subjects with and without MetS was included, which increased the study's statistical power. However, analysing the findings in this systematic review and meta-analysis should be conducted with caution, considering some limitations. Firstly, non-randomised comparisons in observational studies may suffer from biases, which could affect the results and thus weaken the strength of the evidence. Secondly, the different criteria or definitions used to diagnose MetS in the included studies may influence the determination and identification of affected individuals. Also, the treatment approach and health objectives may change depending on the definition. Third, with increasing age, there is decreased adaptive immunity and increased inflammation or immunoaging, which affects the levels of proinflammatory cytokines that can alter the leukocyte profile [49]. Fourth, most studies come from the Far East region, making it difficult to generalize the results to other countries. Fifth, further research is required to identify the importance of increased neutrophils and lymphocytes in MetS and other cardiovascular diseases. Finally, another limitation was that no additional strategies were used in the current search to locate unpublished reviews (grey literature).

6. Conclusions

The results have shown that subjects with MetS have higher levels of leukocytes (0.64 cells $\times 10^9$/L; CI95% 0.55–0.72; $p < 0.00001$), neutrophils (0.28 cells $\times 10^9$/L; CI95% 0.2–0.36; $p < 0.00001$), and lymphocytes (0.19 cells $\times 10^9$/L; CI95% 0.14–0.23; $p < 0.00001$). These results provide a rationale for further evaluation of the relationship of leukocytes in the pathophysiological process of MetS. They could lead to new insights in early diagnosis, identification of new biomarkers, and discovery of new therapeutic targets for pharmacological interventions. Further research is therefore required to identify the importance of white blood cell counts in MetS or other cardiovascular diseases.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/jcm12227044/s1, PRISMA 2020 Checklist [50].

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4. Conclusiones

Derivadas del objetivo principal

Evaluar y comparar la eficacia diagnóstica de variables proinflamatorias para el SMet.

- **Primera publicación** (Capítulo I; *"Association between metabolic syndrome and uric acid: a systematic review and meta-analysis"*): Los resultados han evidenciado que los niveles de AU se asocian con la presencia de SMet. En concreto, se ha observado que los sujetos que presentan SMet tienen mayor AU plasmático.
- **Segunda publicación** (Capítulo II;*"Metabolic syndrome and transaminases: systematic review and meta-analysis*"): Los sujetos con SMet tienen mayores niveles de todas las enzimas hepáticas analizadas con respecto a los sujetos sin SMet.
- **Tercera publicación** (Capítulo III;*"Association between Metabolic Syndrome and Leukocytes: Systematic Review and Meta-Analysis"*): Los sujetos que presentan SMet tienen mayores niveles de leucocitos, neutrófilos y linfocitos.

Derivadas de los objetivos específicos

1. Actualizar y revisar la evidencia científica disponible sobre la asociación entre SMet y variables proinflamatorias; incluyen el ácido úrico, los niveles de transaminasas y el recuento de leucocitos.
    - **Primera publicación** (Capítulo I; *"Association between metabolic syndrome and uric acid: a systematic review and meta-analysis"*): Se incluyeron 43 artículos (56 grupos) que compararon las concentraciones de AU entre 91,845 sujetos con SMet y 259,931 controles.
    - **Segunda publicación** (Capítulo II;*"Metabolic syndrome and transaminases: systematic review and meta-analysis*"): Se incluyeron 17 artículos que compararon las concentraciones de enzimas hepáticas entre 76,686 sujetos SMet+ y 201,855 SMet-.
    - **Tercera publicación** (Capítulo III;*"Association between Metabolic Syndrome and Leukocytes: Systematic Review and Meta-Analysis"*): Se

incluyeron 14 artículos que compararon las concentraciones de leucocitos en 21,005 sujetos con SMet y 66,339 controles.

2. Cuantificar el tamaño del efecto de cada variable proinflamatoria sobre el SMet.
    - ❖ **Primera publicación** (Capítulo I; *"Association between metabolic syndrome and uric acid: a systematic review and meta-analysis"*): Los sujetos que presentaban SMet tuvieron una media superior de AU, de 0,57 mg/dl (IC 95% 0,54-0,61) (p<0,00001). Dada la heterogeneidad de los estudios incluidos, se decidió realizar un análisis de subgrupos. Los hombres con SMet tienen una concentración 0,53 mg/dl (IC 95%: 0,45-0,62, p<0,00001) más alta de AU y las mujeres con SMet 0,57 mg/dl (IC 95%: 0,48-0,66, p <0,00001), en comparación con los sujetos sin SMet.
    - ❖ **Segunda publicación** (Capítulo II;*"Metabolic syndrome and transaminases: systematic review and meta-analysis*"): La concentración de ALT, AST y GGT en los sujetos con SMet+ fue significativamente más alta que en el grupo control 7,13 UI/L (CI95% 5,73 – 8,54; p<0,00001), 2,68 UI/L (CI95% 1,82 – 3,54; p<0.00001; I^2= 96%) y 11,20 UI/L (CI95% 7,11 – 15,29; p<0,00001; I^2= 96%), respectivamente.
    - ❖ **Tercera publicación** (Capítulo III;*"Association between Metabolic Syndrome and Leukocytes: Systematic Review and Meta-Analysis"*): Los sujetos que presentaban SMet tuvieron una media de leucocitos superior, 0,64 cells x10^9/L; CI95% 0,55 – 0,72; p<0,00001; I^2= 93%.
3. Identificar qué biomarcadores proinflamatorios presentan una asociación significativa con el SMet.
    - ❖ Los biomarcadores analizados presentan una asociación significativa con el SMet. Por ello, la evaluación en profundidad de la relación AU, enzimas hepáticas y leucocitos en el proceso fisiopatológico del SMet podría conducir a nuevas perspectivas en el diagnóstico temprano.
4. Establecer la fuerza de asociación de las distintas variables proinflamatorias y el SMet.
    - ❖ Para conocer la variable que tiene mayor relevancia, hemos comparado los valores predictivos, es decir, se ha recurrido a calcular la ratio entre el valor obtenido en el metaanalisis y el valor medio normal. Los valores normales de las variables se describen a continuación; AU: 2,5-6,2 mg/dl, ALT: 14-36 UI/L, AST: 35 UI/L, GGT: 5-40 UI/L, leucocitos: 4,000-

11,000 cells $x10^9$/L. Por tanto, los sujetos con SMet han mostrado un incremento, con respecto a los sujetos sin SMet de un 9,1% más de AU, 19,8% de ALT, 7,6% de AST, 28% de GGT y 5,8% de leucocitos. Con los datos obtenidos, podríamos deducir que la variable que representa mayor relevancia es GGT. Señalar, que se requiere mayor investigación para poder corroborar estos resultados.

5. Indicios de calidad

PRIMERA PUBLICACIÓN	
Título	Association between metabolic syndrome and uric acid: a systematic review and meta-analysis
Autores (p.o. de firma)	Elena Raya-Cano, Manuel Vaquero-Abellán, Rafael Molina-Luque, Domingo de Pedro-Jiménez, Guillermo Molina-Recio, Manuel Romero-Saldaña.
Revista (año, vol., pág.)	Scientific Reports. 2022; 12(1), 18412.
Base de datos de indexación (año)	Journal of Citation Reports (JCR). 2022
Categoría	Multidisciplinary Sciences
Factor de impacto	4.6
Lugar que ocupa/Nº de revistas del Área temática	22/73 (Q2)

SEGUNDA PUBLICACIÓN	
Título	Metabolic syndrome and transaminases: systematic review and meta-analysis.
Autores (p.o. de firma)	Elena Raya-Cano, Rafael Molina-Luque, Manuel Vaquero-Abellán, Guillermo Molina-Recio, Rocío Jiménez-Mérida, Manuel Romero-Saldaña.
Revista (año, vol., pág.)	Diabetology & Metabolic Syndrome. 2023; 15(1), 220.
Base de datos de indexación (año)	Journal of Citation Reports (JCR). 2023
Categoría	Endocrinology & metabolism
Factor de impacto	4.8 (2022)
Lugar que ocupa/Nº de revistas del Área temática	41/145 (Q2)

TERCERA PUBLICACIÓN	
Título	Association between Metabolic syndrome and leukocytes: systematic review and meta-analysis.
Autores (p.o. de firma)	Elena Raya-Cano, Manuel Vaquero-Abellan, Rafael Molina-Luque, Guillermo Molina-Recio, Jose Miguel Guzmán-García, Rocío Jiménez-Mérida, Manuel Romero-Saldaña.
Revista (año, vol., pág.)	Journal of Clinical Medicine 2023, 12, 7044.
Base de datos de indexación (año)	Journal of Citation Reports (JCR). 2023
Categoría	Medicine, General & Internal - Scie
Factor de impacto	3.9 (2022)
Lugar que ocupa/Nº de revistas del Área temática	58/169 (Q2)

6. Plan de Formación e Investigación Doctorado

A continuación, más allá de las publicaciones de alto impacto presentadas en el documento, se detallan las numerosas aportaciones científicas derivadas directamente del desarrollo de la tesis doctoral, destacando:

- Asistencia a seminarios del Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), curso 2020/2021, 2021/2022, 2022/2023.
- Realización de cursos de formación complementaria de carácter transversal y/o especializados:
    - Formación doctoral en Investigación: bases teóricas. Universidad de Córdoba. 75h, 3 ECTS.
    - Buenas prácticas en el laboratorio. IAVANTE. 29h, 6.09 créditos CFC.
    - Aplicaciones de la Inmunohistoquímica para la investigación. Universidad de Córdoba. 12h.
    - Curso Meta-analisis y Revisiones sistemáticas: Toma de decisiones basadas en la evidencia. Servicio Andaluz de Salud. 50h, 8.78 CFC.
- Asistencia al Congreso Internacional de Investigación en salud y envejecimiento.
    - Póster "Comparison of anthropometric indices for predicting the risk of metabolic syndrome".
    - Póster "Association between metabolic syndrome and uric acid: Systematic review and meta-analysis".
- Jornada Formativa sobre el Doctorado en la Universidad de Córdoba.
- I Jornada para el Fomento de la Internacionalización del Programa de Doctorado en Biomedicina.
- XI Lección Conmemorativa Maimónides y premios IMIBIC 2021.
- IX Congreso Científico de Investigadores en Formación. Nuevos desafíos, nuevas oportunidades.
- Sesión "Estudios estructura-función en proteínas clave en Enfermedad Cardiovascular". 0,2 créditos CFC.
- Actividad de movilidad complementaria para la formación específica. Realizada del 25 al 28 de abril de 2022 con una duración de 30h en la Facultad de Enfermería, Universidad Islas Baleares (UIB);
    - Colaboración en la realización del trabajo de campo del proyecto de

investigación del Fondo de Investigación Sanitaria (FIS) PI13/01477 titulado "Evaluación de la eficacia de una intervención multifactorial breve en el aumento de la adherencia a la prescripción de ejercicio físico en pacientes con riesgo cardiovascular moderado o alto".

  - Asistencia a los seminarios de investigación del Instituto de Investigación Sanitaria de les Illes Balears (IdISBa).
  - Impartición de la sesión científica "Asociación entre síndrome metabólico y variables proinflamatorias".

- Asistencia a las Jornadas de Jóvenes Investigadores del IMIBIC, curso 2022/2023.
- Jornada "Oligospain: un nuevo camino frente al oligodendroglioma". 5h, 0.4 créditos.
- Apoyo en Actividades Docentes
  - Departamento de Enfermería de la Facultad de Medicina y Enfermería de la Universidad de Córdoba. Asignaturas: Enfermería Clínica y Cuidados Críticos. 20h.

7. Bibliografía

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3. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001; 285(19): 2486-97. PMID: 1136870
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