Review article

Risk Factors for Pulmonary Thromboembolism Based on a Systematic Review and Meta-analysis

Factores de riesgo de tromboembolismo pulmonar, basado en una revisión sistemática con metaanálisis

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ABSTRACT

Introduction: Pulmonary thromboembolism is a blockage of the pulmonary vasculature caused by blood clots. It is a serious and potentially life-threatening medical condition associated with many factors. However, not all risk factors have the same predictive value.

Objective: To evaluate the ability of a model based on a systematic review and meta-analysis to predict the risk of pulmonary thromboembolism.

Methods: A systematic review with meta-analysis of case-control cohort studies and meta-analysis was carried out. For this purpose, an electronic search of the literature was carried out for the various studies related to the topic from September 10 to December 31, 2024.

Results: The meta-analysis showed that the factors most strongly associated with the risk of pulmonary thromboembolism were, in order of importance: deep vein thrombosis increased the risk more than fourfold (OR: 4.03; 95 % CI: 3.04-5.35); followed by a history of sickle cell disease (OR: 3.09; 95 % CI: 2.05-4.68); active cancer (OR: 2.99; 95 % CI: 2.35-3.80); and finally, triglyceride values greater than or equal to 1,9 mmol/L (OR: 2.38; 95 % CI: 1.08-5.28). An index was obtained with thirteen factors, with item weights based on the OR values and approximated to whole numbers.

Conclusions: A significant association was found between the different risk factors and the likelihood of developing pulmonary thromboembolism. Heterogeneity between studies ranged from low to moderate.
Keywords: risk factors; pulmonary thromboembolism; systematic review; meta-analysis.

RESUMEN

Introducción: La tromboembolia pulmonar es una obstrucción en la vasculatura pulmonar causada por coágulos de sangre. Es una afección médica grave y potencialmente mortal, y está asociada a muchos factores, sin embargo, no todos los factores de riesgo tienen el mismo valor predictivo.
Objetivo: Evaluar la capacidad de predecir el riesgo de tromboembolia pulmonar de un modelo basado en una revisión sistemática y metaanálisis.
Métodos: Se realizó una revisión sistemática y metaanálisis de estudios analíticos de casos y testigos, de cohorte y metaanálisis. Para lo cual se realizó una búsqueda electrónica de la literatura para los diversos estudios relacionados con el tema desde el 10 de septiembre al 31 de diciembre del año 2024.
Resultados: Se demostró en el metaanálisis que los factores con mayor asociación al riesgo de tromboembolia pulmonar fueron en orden de importancia: la trombosis venosa profunda incrementó el riesgo en más de cuatro veces (OR: 4,03; IC al 95 %: 3,04-5,35); seguida del antecedente de sicklemia (OR: 3,09; IC al 95 %: 2,05-4,68); el cáncer activo (OR: 2,99; IC al 95 %: 2,35-3,80); y finalmente valores de triglicéridos mayor o igual a 1,9 mmol/L (OR: 2,38; IC al 95 %: 1,08-5,28). Se obtuvo un índice con trece factores, con ponderaciones de sus ítems según el valor del OR y aproximado a números enteros.
Conclusiones: Se demostró la asociación significativa entre los diferentes factores riesgo y la probabilidad de desarrollar un TEP. La heterogeneidad entre los estudios fue entre baja a modera.
Palabras clave: factores de riesgo; troemboembolismo pulmonar; revisión sistemática; metaanálisis.

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Introduction

Pulmonary thromboembolism (PTE) is an important cause of morbidity and mortality worldwide. It is part of the broader complex of venous thromboembolism (VTE), which is considered a chronic, frequently recurring disease associated with death, anticoagulant-related bleeding, and long-term disability.[1,2]

The yearly incidence of PTE is from 60 to 70 cases per 100 000. In the United States and Europe, PTE is responsible for 100 000 and 300 000 annual deaths, respectively.[3,4,5,6] In Cuba, there is insufficient data to establish an incidence rate. A recent study in that country found an incidence of 16,3 % in patients with a previous diagnosis of deep vein thrombosis.[7]

As a rule, at least one risk factor can be identified in most patients with PTE; however, the predictive value of each varies according to different studies.[2,3,4,5]

These factors have also been used in the design and validation of different risk scales, which, although they have demonstrated their predictive value, still need to be refined and, above all, adapted to the local circumstances.[8,9,19,11,12,13,14]

These aspects could be solved if the present research answered the following clinical question: what factors are associated with the highest risk of developing a PTE?

To answer this question, the present investigation aimed to evaluate the ability of a model based on a systematic review and meta-analysis to predict the risk of pulmonary thromboembolism.

Methods

A systematic review with meta-analysis of case-control, cohort, and meta-analytical studies was done. An electronic literature search of various studies related to the topic was conducted from September 10 to December 31, 2024, using the PUBMED, Google Scholar, MEDLINE, Embase, LILACS, WHO and SciELO search engines.

No limits were set on language, country, or publication date. Reference lists of previous systematic reviews or relevant original research articles were searched to identify studies not found in the initial database search.

The selected studies comprised updated theoretical aspects that should be included in this systematic review, including epidemiological, historical, procedural, evaluative, and conceptual aspects. Non-original studies, studies with descriptive designs, those not directly related to the title of the systematic review, and those without an author's name or Digital Object Identifier System (DOI) were excluded.

Result management. The research results were entered into the Zotero reference manager version 5.0.94. Duplicate articles were identified using this manager and manually by independent reviewers. All duplicate articles were removed.

Study selection. The authors independently examined the titles and abstracts identified by the planned search strategies. Research that was eligible by title or abstract was retrieved in full. Potentially eligible studies were reviewed by at least one author in full-text versions. Articles that met the inclusion criteria were independently assessed by the researchers, and discrepancies were sorted out by discussion of the inclusion and exclusion criteria. In order to increase the reliability and safety of the process, the degree of agreement of the reviewers was measured by calculating the kappa statistic for each of the items on the selection sheet. In cases where there were discrepancies between two reviewers regarding the decision of whether or not to include an article, a third researcher (expert in the subject) was appointed to arbitrate the discrepancies and make the final decision.

The standardized extraction form of the Cochrane Collaboration was used to extract the following data independently: name of the study (along with the name of the first author and the year of publication), country where the study was conducted, study design, number of participants, exposure, outcome and reporting of bias.

When data were insufficient or incomplete, this information was obtained from the text, tables, or the use of the data included in the study was calculated.

Bias analysis. Risk of bias assessment was performed on the studies selected by independent, duplicate, blinded, full-text reading. Observational studies were assessed using the Newcastle-Ottawa tool, and randomized clinical trials were evaluated using the Cochrane RoB 2 tool. Methodological limitations described by the authors or according to the authors' analysis, and inconsistencies in the primary studies were also considered.

Information analysis. The meta-analysis was performed using Epidat software version 3.1; R version 4.5.0 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical analyses using the "meta" package and JASP 0.19.3.0.

The dichotomous outcome was determined by calculating the odds ratio (OR).

To estimate heterogeneity, the following were used: the Q statistic, the variance (between studies), the intra-study variance, the coefficient of variation between studies (variance between studies divided by the weighted overall effect measure), and the RI coefficient, which represents the proportion of total variance due to the variance between studies and, therefore, takes the values between 0 and 1.

The I^2 statistic was also determined, which describes the percentage of variability in the effect estimates that is due to heterogeneity rather than sampling error (chance).

The prediction interval (PI) was also determined, it indicates how the actual magnitude of the effect varies between populations, and does so on a scale that allows us to evaluate the usefulness of the intervention.

Ethical considerations

In the present study it was not necessary to take this into account since it is a review of articles, so no contact with the patients was required.

Search strategy for the most relevant articles:

The initial search was carried out in the most relevant databases (PUBMED, Google Scholar, MEDLINE, Embase, LILACS, WHO and SciELO). 1137 references were accepted after excluding the duplicate ones. Finally, the sample was represented by 56 studies fulfilling the purposes of the present investigation (fig. 1).

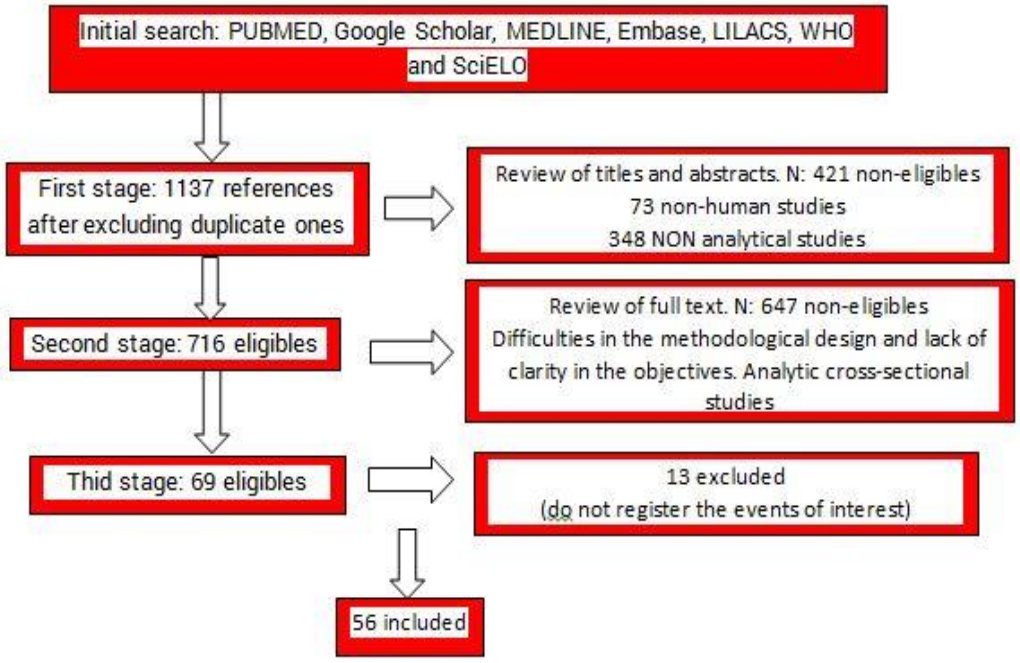

Fig 1- Information search flowchart.

Results

Result of the qualitative analysis of PE risk factors, which includes authors, country, year.

Deep vein thrombosis

- Cui YQ, *et al.*[12] 2021; China. Design: prospective cohort. Population: 100. OR: 11.68; CI: 1.88-7.52; *p*: 0.008.
- Yang C, *et al.*[13] 2024; China. Design: prospective cohort. Population: 636. OR: 11.07; CI: 3.81- 32.16; *p*: <0.001.
- Dentali F, *et al.*[14] 2020; Italy. Design: cohort. Population: 836. OR: 4.43; IC: 2.67-7.37.
- Heijboer RRO, *et al.*[15] 2019; USA. Design: cohort. Population: 20043. OR: 3.9; CI: 3.5-6.7; *p*: 0.001.
- Tang G, *et al.*[16] 2021; China. Design: cohort. Population: 1011. OR: 2.749; CI: 0.92-8.16; *p*: 0.007.

Sickle cell anemia

- Austin H, *et al.*[17] 2007; USA. Design: cases and controls. Population: 1170. OR: 3.9; CI: 2.2-6.9; *p*: 0.026.
- Folsom AR, *et al.*[18] 2007; USA. Design: cohort. Population: 249. HR: 2.05; CI: 1.12-3.76.
- Noubiap JJ, *et al.*[19] 2018; South Africa. Design: meta-analysis. Population: 66139. OR: 3.66; CI: 3.57-3.75; *p*: < 0.0001.
- Bucknor MD, *et al.*[20] 2013; USA. Design: cohort. Population: 2642. RR: 4.37; RR: 2.58-7.42; *p*: 0.0010.
- Lin KH, *et al.*[21] 2024; USA. Design: cohort. Population: 94323. OR: 1.95; CI: 1,72-2,20.

Cancer

- Cui YQ, *et al.*[12] 2021; China. Design: prospective cohort. Population: 100. OR: 5.10; CI: 1.58-16.49; *p*: 0,006.
- Jin FY, *et al.*[22] 2022; China. Design: cohort. Population: 160. HR: 5.368. CI: 1.871-18.165; *p*: 0.021.
- Zhu N, *et al.*[23] 2023; China. Design: retrospective cohort. Population: 900. OR: 2.655; CI: 1.449-4.997; *p*: 0.0019.
- Li H, *et al.*[24] 2022; China. Design: cases and controls. Population: 1330. OR: 3.00; CI: 1.88-4.87; *p*: < 0.001.
- Hua X, *et al.*[25] 2022; China. Design: meta-analysis. Population: 815. OR: 2.38; CI: 1.99-2.86; *p*: < 0.001.
- Qdaisat A, *et al.*[26] 2020; USA. Design: cases and controls. Population: 904. OR: 4.50; CI: 3.63-5.61; *p*: < 0.001.

— Maestre A, *et al.*[27] 2015; Spain. Design: cohort. Population: 18707. OR: 3.44; CI: 2.81-4.22; *p*: ≤ 0.0001.

Triglycerides ≥ 1.9 mmol/L

— Huang Y, *et al.*[28] 2022; China. Design: cases and controls. Population: 500. OR: 2.54; CI: 1.251–5.155; *p*: < 0.010.
— Zöller B, *et al.*[29] 2014; Sweden. Design: retrospective cohort. Population: 27042. OR: 1.41; CI: 1.04–1.91; *p*: < 0.026.
— Li H, *et al.*[24] 2023; China. Design: cases and controls. Population: 1330. OR: 1.88; CI: 1.19-2.99; *p*: < 0.007.
— Ageno W, *et al.*[30] 2008; Italy. Design: meta-analysis. Population: 63 552. OR: 17.48; CI: 9.64-25.31; *p*: 0.001.
— Doggen CJM, *et al.*[31] 2004; USA. Design: cases and controls. Population: 477. OR: 2.66; CI: 1.60–4.43.
— Wei J, *et al.*[32] 2024; China. Design: retrospective cohort. Population: 7854. OR: 0.69; CI: 0.54-0.89; *p*: 0.004.

Heart failure

— Zhou J, *et al.*[33] 2020; China. Design: retrospective cohort. Population: 707. OR: 4.38; CI: 2.534-5.507; *p*: 0.018.
— R Charlier SH, *et al.*[34] 2022; Switzerland. Design: cohort. Population: 2653. OR: 1.53; CI: 1.34-1.76.
— Sobiecka M, *et al.*[35] 2021; Poland. Design: retrospective cohort. Population: 411. OR: 2.37; CI: 0.12-17.5; *p*: 0,489.
— Xu T, *et al.*[36] 2021; China. Design: meta-analysis. Population: 530641. RR: 1.57; CI: 1.34-1.84.
— Brown JD, *et al.*[37] 2016; USA. Design: retrospective cohort. Population: 1050. RH: 1.5; CI: 1.4-2.1.
— Fanola CL, *et al.*[38] 2020; USA. Design: cohort. Population: 2696. OR: 1.13; CI: 2.58-3.80.
— Königsbrügge O, *et al.*[39] 2016; Australia. Design: cohort. Population: 1433. OR: 3.07; CI: 1.15-8.20.
— Maestre A, *et al.*[27] 2015; Spain. Design: cohort. Population: 18707. OR: 1.43; CI: 1.12-1.82; *p*: 0.004.

Major surgery

— Qdaisat A, *et al.*[26] 2020; USA. Design: cases and controls. Population: 904. OR: 3.03; CI: 1.33-7.19; *p*: < 0.009.

— Aleidan FAS, *et al.*[40] 2020; Saudi Arabia. Design: cohort. Population: 277. OR: 2.78; CI: 1.36-5.67; *p*: 0.005.
— Neumayer L, *et al.*[41] 2007; USA. Design: cohort. Population: 163624. OR: 1.502, CI: 1.35-1.66; *p*: ≤ 0.0001.
— Groot OQ, *et al.*[42] 2019; USA. Design: cohort. Population: 637. OR: 1.15; CI: 1.04-1.28; *p*: 0.060.
—Ye L, *et al.*[43] 2023; China. Design: retrospective cohort. Population: 292. OR: 6.84; CI: 3.11-15.06; *p*: 0.000.

D-dimer

— Cui LY, *et al.*[44] 2021; China. Design: meta-analysis. Population: 3389. OR: 2.10; CI: 1.10-3.10; *p*: 0.000.
— Shi Y, *et al.*[45] 2022; China. Design: retrospective cohort. Population: 355. OR: 2.32; CI: 1.43-3.77; *p*: < 0.001.
— Yang C, *et al.*[13] 2024; China. Design: prospective cohort. Population: 636. OR: 1.725; CI: 1.10-2.68; *p*: < 0.016.
— Zhou FL, *et al.*[46] 2021; China. Design: prospective cohort. Population: 90. OR: 1.20; CI: 1.03-1.39; *p*: < 0.016.
— Ameri P, *et al.*[47] 2021; Italy. Design: prospective cohort. Population: 90. OR: 1.72; CI: 1.13-2.62; *p*: 0.010.
— Benito N, *et al.*[48] 2020; Spain. Design: cohort. Population: 1275. OR: 4.5; CI: 1.2-17.2; *p*: 0.026.
— Jin FY, *et al.*[22] 2022; China. Design: cohort. Population: 160. HR: 8.44; CI: 4.32-18.53; *p*: 0.004.
— Li H, *et al.*[24] 2023; China. Design: cases and controls. Population: 1330. OR: 5.58; CI: 3.54-8.94; *p*: < 0.007.
— Cui YQ, *et al.*[12] 2021; China. Design: prospective cohort. Population: 100. OR: 10.85; CI: 1.86-63.12; *p*: 0.008.
— Miro O, *et al.*[16]; 2021; Spain. Design: cohort. Population: 368. OR: 2.78; CI: 1.82-4.35.

Immobility

— Aleidan FAS, *et al.*[49] 2022; Saudi Arabia. Design: cohort. Population: 1265. HR: 2.97; CI: 1.87–3.95; *p* < 0.001.
— Johannesen CDL, *et al.*[50] 2019; Denmark. Design: cohort. Population: 78936. HR: 1.11; CI: 0.92-1.34.
— Aleidan FAS, *et al.*[40] 2020; Saudi Arabia. Design: cohort. Population: 277. OR: 1.36; CI: 0.66-2.84; *p*: 0.408.

— Tang G, *et al.*[17] 2021; China. Design: cohort. Population: 1011. OR: 2.48; CI: 1.44-4.28; *p*: 0.006.
— Beam DM, *et al.*[51] 2009; USA. Design: cohort. Population: 7940. OR: 1.76; CI: 1.27-2.44; *p*: 0,006.
— McKerrow JI, *et al.*[52] 2022; USA. Design: meta-analysis. Population: 4000. OR: 2.0; CI: 1.5-2.7.
— Jiménez D, *et al.*[53] 2023; Spain. Design: cohort. Population: 3117. OR: 2.34; CI: 1.63-3.36; *p*: ≤ 0.0001.
— Maestre A, *et al.*[27] 2015; Spain. Design: cohort. Population: 18707. OR: 1.60; CI: 1.35-1.90; *p*: ≤ 0.0001.

Obesity

— Heit JA, *et al.*[54] 2016; USA. Design: retrospective cohort. Population: 260 000. OR: 1.08; CI: 1.05-1.11; *p*: < 0.001.
— Hwang HG, *et al.*[55] 2019; South Korea. Design: cohort. Population: 662. OR: 2.02; CI: 1.17-3.46; *p*: 0.010.
— Brink A, *et al.*[56] 2023; Germany. Design: cohort. Population: 15807. OR: 1.33; CI: 1.19-1.48; *p*: < 0.001.
— Zöller B, *et al.*[29] 2014; Sweden. Design: retrospective cohort. Population: 27042. OR: 1.08; CI: 1.06-1.09; *p*: < 0.001.
— Cui LY, *et al.*[44] 2021; China. Design: meta-analysis. Population: 3389. OR: 1.37; CI: 1.03-1.82; *p*: 0.033.
— Johannesen CDL, *et al.*[50] 2019; Denmark. Design: cohort. Population: 78936. HR: 1.4; CI: 1.2-1,7.
— Ageno W, *et al.*[30] 2008; Italy. Design: meta-analysis. Population: 63 552. OR: 2.33; CI: 1.68-3.24; *p*: 0.000.
— R Charlier SH, *et al.*[34] 2022; Switzerland. Design: cohort. Population: 2653. OR: 2.65; CI: 2.24-3.15.

Age ≥ 65 years

— Brink A, *et al.*[56] 2023; Germany. Design: cohort. Population: 15807. OR: 1,70; CI: 1,47-1,96; *p*: < 0,001.
— Dentali F, *et al.*[14] 2020; Italy. Design: cohort. Population: 836. OR: 1,03; CI: 1,01-1,06); *p*: 0,005.
— Zöller B, *et al.*[29] 2014; Sweden. Design: retrospective cohort. Population: 27042. OR: 1,06; CI: 1,04-1,07; *p*: < 0,001.
— Johannesen CDL, *et al.*[51] 2019; Denmark. Design: cohort. Population: 78936. HR: 4,6; CI: 2,6-8,3.

— Avnery O, *et al.*[58] 2019; Spain. Design: cohort. Population: 1655. HR: 1,97; CI: 1,15-3,37.
— Heijboer RRO, *et al.*[15] 2019; USA. Design: cohort. Population: 20043. OR: 1.4; CI: 1.1-1.9; *p*: 0.013.
— Gregson J, *et al.*[59] 2019; United Kingdom. Design: cohort. Population: 731 728. HR: 1.91; CI: 1.76-2.06; *p*: 0.05.
— Nguyen HT, *et al.*[60] 2024; Vietnam. Design: analytic cross-sectional. Population: 585. OR: 1.74; CI: 1.21-2.50; *p*: 0.002.

Cholesterol ≥ 4,8 mmol/L

— Alsulami SS, *et al.*[61] 2023; Saudi Arabia. Design: meta-analysis. Population: 6684. OR: 0.676; CI: 0.04-11.25.
— Guo H, *et al.*[62] 2024; China. Design: cases and controls. Population: 1293. OR: 1.45; CI: 1.01-2.08; *p*: 0.045.
— Huang Y, *et al.*[28] 2022; China. Design: cases and controls. Population: 500. OR: 0.635; CI: 0.316-1.275; *p*: 0.202.
— Doggen CJM, *et al.*[31] 2004; USA. Design: cases and controls. Population: 477. OR: 1.59; CI: 1.00-2.52.
— Wei J, *et al.*[32] 2024; China. Design: retrospective cohort. Population: 7854. OR: 1.51; CI: 1.16-1.97; *p*: 0.002.
— Wu J, *et al.*[63] 2024; China. Design: retrospective cohort. Population: 222. OR: 6.81; CI: 1.86-24.88; *p*: 0.004.

Diabetes *mellitus*

— Ageno W, *et al.*[30] 2008; Italy. Design: meta-analysis. Population: 63 552. OR: 1.41; CI: 1.12-1.77; *p*: 0.003.
— Gregson J, *et al.*[59] 2019; United Kingdom. Design: cohort. Population: 731 728. HR: 0.74; CI: 0.57-0,95; *p*: 0.05.
— Alsulami SS, *et al.*[61] 2023; Saudi Arabia. Design: meta-analysis. Population: 6684. OR: 1.15; CI: 0.75-1.75.
— Deischinger C, *et al.*[64] 2022; Australia. Design: retrospective cohort. Population: 540102. OR: 1.40; CI: 1.36-1.43.
— Ding C, *et al.*[65] 2023; China. Design: meta-analysis. Population: 1404195. OR: 1.20; CI: 1.07-1.35.
— Heit JA, *et al.*[54] 2009; USA. Design: cases and controls. Population: 2367. OR: 1.47; CI: 1.18-1.84; *p*: 0.0001.
— Guo H, *et al.*[62] 2024; China. Design: cases and controls. Population: 1293. OR: 1.05; CI: 0.28-3.61; *p*: 0.037.

— Wu J, *et al.*[63] 2024; China. Design: retrospective cohort. Population: 222. OR: 4.21; CI: 0.29-60.28; *p*: 0.289.

Smoking

— Brink A, *et al.*[56] 2023; Germany. Design: cohort. Population: 15807. OR: 1.40; CI: 1.05–1.87; *p*: < 0.021.

— Zhou J, *et al.*[33] 2020; China. Design: retrospective cohort. Population: 707. OR: 1.25; CI: 1.09-1.52; *p*: 0.003.

— Zhou FL, *et al.*[46] 2021; China. Design: retrospective cohort. Population: 90. OR: 48.74; CI: 4.15-571.78; *p*: 0.002.

— Johannesen CDL, *et al.*[50] 2019; Denmark. Design: cohort. Population: 78936. HR: 1.4; CI: 1.2-1.6.

— R Charlier SH, *et al.*[34] 2022; Switzerland. Design: cohort. Population: 2653. OR: 1.00; CI: 0.87-1.14.

Arterial hypertension

— Althunayan TA, *et al.*[66] 2019; Saudi Arabia. Design: cases and controls. Population: 304. OR: 2.23; CI: 0.58-8.60; *p*: 0.245.

—Alsulami SS, *et al.*[61] 2023; Saudi Arabia. Design: meta-analysis. Population: 6684. OR: 0.88; CI: 0.55-1.41.

— Zhou FL, *et al.*[46] 2021; China. Design: retrospective cohort. Population: 90. OR: 10.04; CI: 1.12-90.33; *p*: 0.002.

— Dentali F, *et al.*[14] 2020; Italy. Design: cohort. Population: 836. OR: 1.53; CI: 1.01-2.32.

— Gregson J, *et al.*[59] 2019; United Kingdom. Design: cohort. Population: 731 728. HR: 0.81; CI: 0.64-1.02; *p*: 0.890.

— Badr OI, *et al.*[67] 2021; Saudi Arabia. Design: cohort. Population: 159. OR: 1.29; CI: 0.65-2.55; *p*: 0.466.

— Guo H, *et al.*[62] 2024; China. Design: cases and controls. Population: 1293. OR: 1.793; CI: 1.13-2.82; *p*: 0.028.

— Wu J, *et al.*[63] 2024; China. Design: retrospective cohort. Population: 222. OR: 0.39; CI: 0.08-2.05; *p*: 0.267

Meta-analysis

Deep vein thrombosis was the factor with the greatest increase in PTE risk. OR: 4.03; 95 % CI: 3.04-5.35. The coefficient of variation between studies was of 0.142 and the RI coefficient: 0.693 and I^2: 31.36 %; PI: 1,231 – 11,293 (fig. 2).

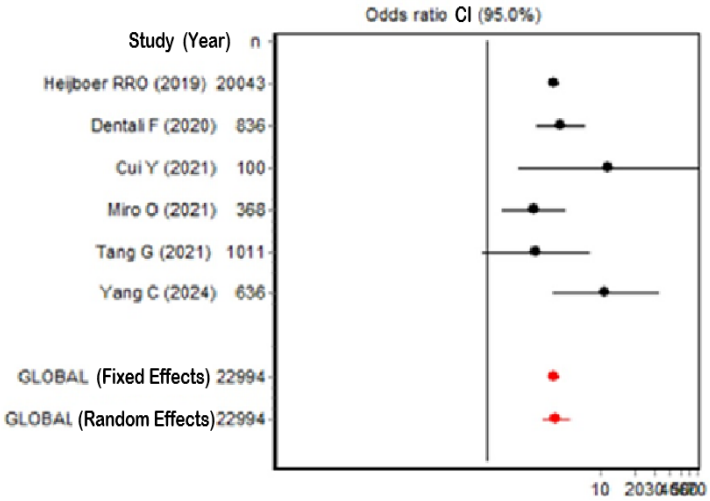

Fig. 2- Deep vein thrombosis. Forest plot.

There is an association between sickle cell anemia and PTE risk. OR: 3.09; 95% CI: 2.05-4.68. The coefficient of variation between studies was of 0.3243 and the RI coefficient: 0.9955 and I^2: 45.76 %. PI: 1.006 – 9.619 (fig. 3).

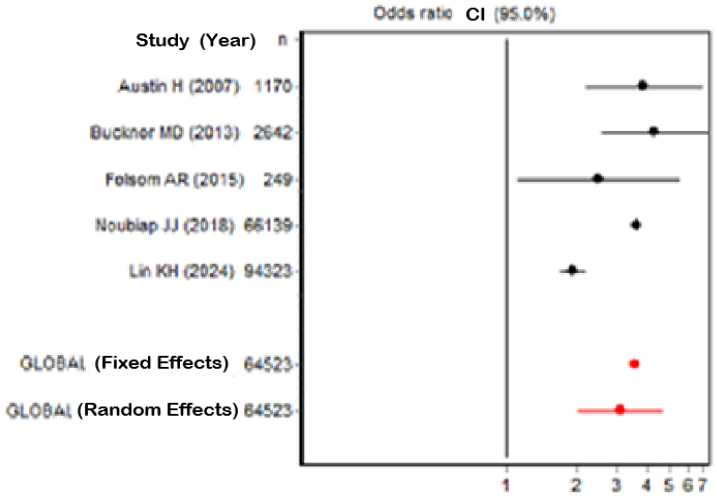

Fig. 3- Sickle cell anemia. Forest plot.

There is an association between history of active cancer and PTE. OR: 3.11; 95 % CI: 2.40-4.03. The coefficient of variation between studies was of 0.2158 and the RI coefficient: 0.6550 and I^2: 48.32 % PI: 1.6091 – 5.918 (fig. 4).

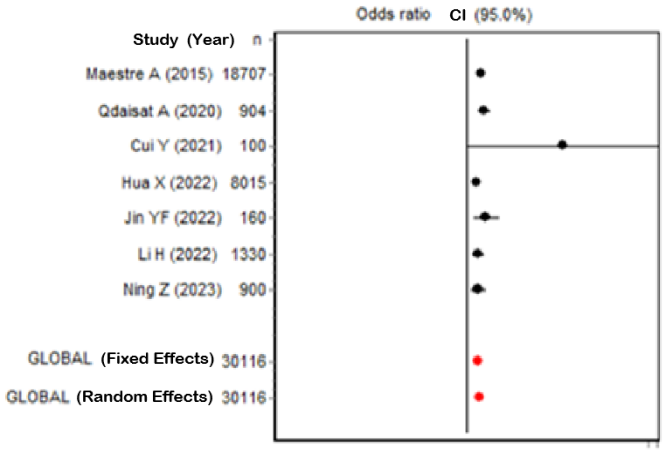

Fig.4- Active cancer. Forest plot.

There is an association between triglycerides greater or equal to 1.9 mmol/L and PTE risk. OR: 2.38; 95 % CI: 1.08-5.28. The coefficient of variation between studies was of 2.7530 and the RI coefficient: 0.9603 and I^2: 48.51 % PI: 0.997 – 15.975 (fig. 5).

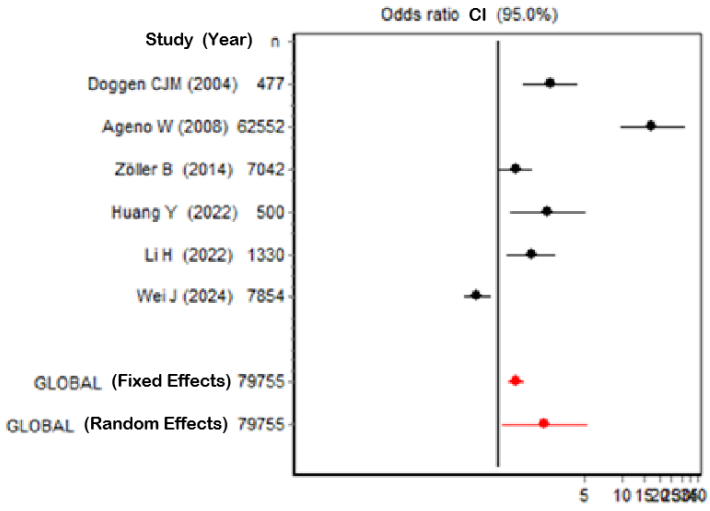

Fig.5- Triglycerides. Forest plot.

The history of cardiac failure increased the risk of PTE. OR: 2.01; 95 % CI: 1.55-2.60. The coefficient of variation between studies was of 0.5306 and the RI coefficient: 0.8854 and I^2: 37.28 % PI: 0.904 – 6.262 (fig.6).

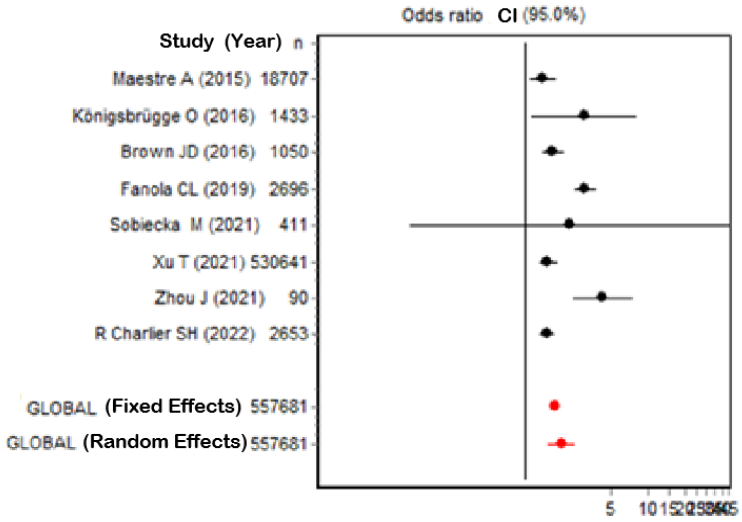

Fig. 6- Cardiac failure. Forest plot.

The relationship between a history of major surgery and PTE risk was also demonstrated. OR: 1.91; 95 % CI: 1.37-2.62. The coefficient of variation between studies was of 0.595 and the RI coefficient: 0,571 and I^2: 33.31 % PI: 0.652 – 11.097 (fig.7).

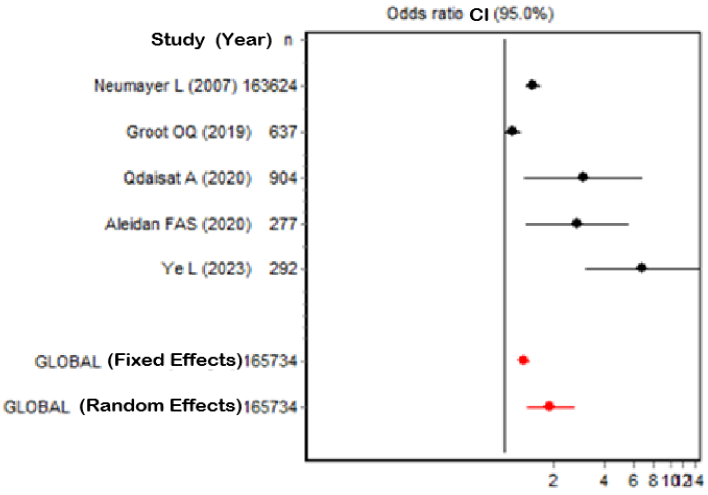

Fig. 7- Major surgery. Forest plot.

In the first group, serum values of D-dimer and the likelihood of developing PTE were evaluated. The results showed that there is an association between the values of D-dimer and PTE. OR: 1.85;95 % CI: 1.828-1.872. The coefficient of variation between studies was 0.799 and the RI coefficient: 0.475 and I^2: 49.67 %; PI: 0.873-5.966 (fig. 8).

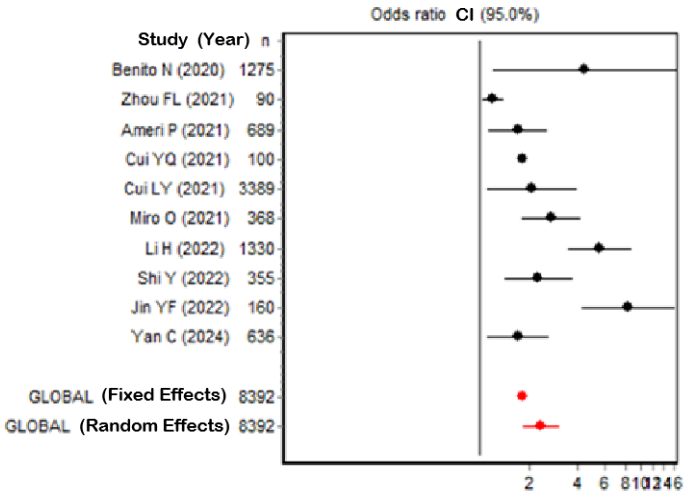

Fig.8- D-dimer. Forest plot.

There is an association between immobilization and PTE risk. OR: 1.80; IC to 95 %: 1.43-2.26. The coefficient of variation between studies was of 0.3671 and the RI coefficient: 0.4912 and I^2: 41.32 %; PI: 0.908-3.542.

Obesity was associated with the risk of developing PTE. OR: 1,53; 95 % CI: 1,16-2,01. The coefficient of variation between studies was of 2.6191 and the RI coefficient: 0,9899 and I^2: 46,16 %; PI: 0.643- 3.636.

Age greater or equal to 65 years was associated with PTE risk. OR: 1.15; 95 % CI: 1.06-1.25. The coefficient of variation between studies was 1.35; and the RI coefficient: 0.92 and I^2: 88.21 %; PI: 0.756 – 4.223.

There is an association between cholesterol and PTE values. OR: 1.44; 95 % CI: 1.02-2.03. The coefficient of variation between studies was 0.768 and the RI coefficient: 0.612 and I^2: 45.70 %; PI: 1.032- 2.046.

There is an association between a history of diabetes *mellitus* and PTE. OR: 1.29; 95 % CI: 1.08-1.55. The coefficient of variation between studies was of 0.958 and the RI coefficient: 0.590 and I^2: 52.60 %; PI: 0.871-3.045.

There is an association between smoking and PTE risk. OR: 1,27; 95 % CI: 1,03-1,57. The coefficient of variation between studies was of 1.0103 and the RI coefficient: 0.8233 and I^2: 50.47 %; PI: 0.723-2.118.

There was no association between the history of HTN and PTE risk. OR: 1.28; 95 % CI: 0.89-1.85. The coefficient of variation between studies was of 5.7339 and the RI coefficient: 0.7056 and I^2: 45.32 %; PI: 0.521-2.683.

In the present research, we can assume, considering the precision interval value, that the average effect size in the universe of comparable populations is within acceptable intervals, and that there is no evidence that the effect size varies between studies. Likewise, the I^2 values allowed the heterogeneity to be classified as low to moderate (table 1).

Table 1- Risk factors for pulmonary thromboembolism. Logistic regression analysis

Factor	Population	OR	95 % Confidence Interval	
			Inferior	Superior
Deep vein thrombosis	22994	4,03	3,04	5,35
Cancer	30116	3,11	2,40	4,03
Sickle cell anemia	164523	3,09	2,05	4,68
Triglycerides	79755	2,38	1,08	5,28
Cardiac failure	557681	2,01	1,55	2,60
Major surgery	165734	1,91	1,37	2,62
D-Dimer	8392	1,85	1,82	1,87
Immobility	115253	1,80	1,43	2,26
Obesity	361447	1,53	1,16	2,01
Cholesterol	17030	1,44	1,02	2,04
Diabetes *mellitus*	2750143	1,29	1,08	1,55
Smoking	98193	1,27	1,03	1,57
Age ≥ 65 years	144904	1,15	1,06	1,25
Arterial hypertension	430785	1,28	0,89	1,85

Discussion of results

The present systematic review was supported by the presence of a group of risk factors associated with the likelihood of developing PTE.

In the present study, deep vein thrombosis was the factor with greater association to PTE risk. It is explained by the fact that they are different manifestations of the same pathogenic process, and the fact that PTE occurs by the fragmentation of a thrombus in a deep vein; on the other hand, there are the conditions in the lung for the thrombotic process. So much so that several complex mechanisms participate in the pathogeny, including endothelial damage and macrophage activation, as well as the participation of red blood cells and platelets, as part of the beginning of the thromboembolic process.[68]

The aforementioned endothelial damage has an essential pathogenic action, since physiological mechanisms such as the actions of thrombomodulin, endothelial protein C receptor, tissue factor pathway inhibitor and proteoglycans with effects similar to heparin that explain an anticoagulant effect, are not present due to local and systemic inflammation, as well as blood hypoxemia. In addition to this, there is a reduction of nitric oxide and prostacyclin actions and increased platelet aggregation, which increases the thrombotic events.[69]

Both sickle cell anemia and sickle cell traits manifest themselves in the laboratory with a chronically activated coagulation system, which could be associated with a greater risk of PTE. In these patients, coagulation activation occurs because the amplification phase of coagulation is increased on the surface irreversibly sickled erythrocytes; they also have significantly increased levels of D-dimer, thrombin-antithrombin III, and prothrombin 1 þ 2 fragments. This chronic activation is an attractive explanation for the risk of thrombotic events. Besides, alterations in the structure of red blood cells lead to hemolysis, release of prothrombotic substances such as phosphatydilserines and depletion of nitric oxide, which causes activation of platelets and the coagulation cascade, impaired fibrinolysis, vasoconstriction, reduced blood flow and ischemic vascular injury.[70,71,72,73]

On the other hand, some hypotheses have been raised about the physiopathologic mechanisms underlying the increased thrombotic risk due to asplenia.[70,71,72,73]

Cancer represents an important risk factor for the development of thrombosis in general and PTE in particular, with an estimated risk for PTE between 4 and 6,5 times higher than in people without cancer.[74]

The risk varies depending on tumor-related factors, such as the site and stage of the cancer, treatment of the malignancy, patient-related factors and biomarkers. In short, the association between cancer and PTE is based on complex mechanisms that give rise to a state of hypercoagulation, determined by the massive release of inflammatory cytokines, by the expression of hemostatic proteins in tumor cells and by the activation of the coagulation system, among other mechanisms.[74,75,76,77]

Elevated triglyceride levels were associated with an increased risk of PTE. Current research suggests a high risk of thrombosis based on several mechanisms, including increased platelet sensitivity to aggregation and a weakened activation of the coagulation cascade. Elevated triglycerides may decrease endothelial production of nitric oxide and prostacyclin, potent inhibitors of platelet activation, as well as increase vascular expression of tissue factors and activate coagulation factors by reducing the action of activated protein C .[78,79,80]

Patients with chronic heart failure have a higher risk of PTE, independent of other factors. In fact, they have lower pulmonary reserve, greater venous stasis, liver

dysfunction, as well as activation of the inflammatory cascade and impaired plasma fibrinolytic activity. These factors may explain their increased susceptibility to deep venous thrombus formation and the subsequent development of PTE.[39,81,82,83]

Although most surgical procedures increase the risk of PTE, the risk varies considerably between operations and between individual patients undergoing surgery. Furthermore, independent patient risk factors affect the cumulative risk of deep vein thrombosis and PTE.[84,85]

Surgical intervention is a transient condition associated with an increased risk of PTE due to some mechanisms such as venous stasis, endothelial activation and local accumulation of tissue factors, among others. Venous stasis occurs both during and after surgery and it is responsible for increased hemostasis, cellular marginalization and local hypoxia, which amplifies endothelial activation; and with it the greater predisposition to thrombotic phenomena.[84,85,86,87]

D-dimer is the end product of fibrin degradation and serves as a serological indicator of coagulation and fibrinolytic activation. There is undoubtedly a pathophysiological basis for the interrelationship with the various mechanisms of coagulation and inflammation, with D-dimer being a measurable marker of this entire phenomenon, and in turn, serves as an explanation for its predictive utility.[88,89,91]

However, the authors of this study believe that the D-dimer cut-off points and PE risk require careful interpretation and individual assessment of each patient, where the presence of other relevant risk factors, particularly DVT, should be considered.

During immobilization, the risk of venous thromboembolism in general, and PTE in particular, increases due to different mechanisms such as compression of the popliteal veins, blood stasis, and activation of the coagulation cascade.[92,93]

The possible relationship between blood stasis, endothelial damage and hypercoagulability can be explained by the fact that stasis leads to several changes, including hypoxia and inflammation of endothelial cells, as well as leukocyte activation. The coagulation system can subsequently be activated; these aspects explain the higher incidence of PTE in these patients.[92,93,94]

Obesity is considered a weak risk factor for thromboembolic disease. It can cause thrombosis due to the activity of adipocytokines, which increases coagulation and inflammation and decreases the fibrinolytic cascade.[95,96,97]

The risk of venous thromboembolism increases exponentially with age, partly because clotting factor concentrations typically increase with age. Likewise, there is a higher prevalence of risk factors for venous thromboembolism in the elderly.[98,99,100,101]

On the other hand, it remains to be seen whether dyslipidemia is related to DVT. Some studies have found that hyperlipidemia may increase the risk of DVT,[102,103] while other studies have found that the association between blood lipid levels and DVT risk were uncertain or even irrelevant.[104,105]

The strong correlation between lipids and protein C reflects a certain association between lipids and coagulation. While high HDL-cholesterol levels reduce the risk of PTE, total cholesterol may increase it.[102,103]

While some studies question the association with the risk of PTE in diabetic patients; others find that this disease contributes to the increased risk of PTE.

The increased risk of PTE could be associated with the presence of factors such as comorbidities and concomitant cardiometabolic disorders that may contribute to the hypercoagulability and endothelial dysfunction described in diabetic patients, such as decreased levels of protein C and increased levels of tissue factor, fibrinogen, and coagulation factors VII, VIII and XIII, and not necessarily to diabetes *mellitus*.[59,106]

However, a recent study detected an increase in thrombin generation, along with a higher number of circulating microparticles carrying endogenous procoagulant triggers in plasma samples from type 2 diabetic patients.[34]

New prospective studies will be necessary to clarify the association of diabetes *mellitus* with an increased risk of PTE. The present authors' judgment and clinical experience support the association of diabetes *mellitus* with an increased risk of PTE.

Smoking was also found to be another factor associated with an increased risk of PTE. Although it is a proven risk factor for atherosclerotic disease, its association with PTE is not well established.[59] However, a meta-analysis showed that smoking was significantly associated with the prevalence of VTE.[107]

This association may be dose dependent. A large meta-analysis showed that, compared with those who never smoked, the relative risks were significantly higher.[108]

Finally, it has been shown that nicotine and other addictive substances present in cigarettes increase the percentage of reactive oxygen substances, which determines a lower availability of nitric oxide and generates an inflammatory and prothrombic microenvironment and, consequently, increases platelet reactivity and lipid peroxidation.[109]

Finally, the association between HTN and the risk of PTE is not well established. Although this entity is recognized as the most relevant and prevalent modifiable risk factor for the development of cardiovascular diseases, its contribution to the risk of PTE is divergent; for example, some authors cite an association with such

risk,[14,46,62] other studies do not demonstrate this.[59,61,63,66] In fact, a recent meta-analysis found that higher systolic blood pressure showed an inverse association with venous thromboembolism.[110]

These results may be due to the competing risk of other comorbidities such as atrial fibrillation (usually treated with anticoagulants), which is associated with HTN. Similarly, some antithrombotic effects of antihypertensive drugs, such as angiotensin-converting enzyme inhibitors, have been described [110]. In fact, the profibrinolytic activity of the angiotensin-converting enzyme inhibitors is demonstrated.[111] Our study found inconsistent associations between HTN and PTE risk.

The present study showed a significant association between different risk factors and the risk for pulmonary thromboembolism. Deep vein thrombosis, a history of sickle cell anemia and active cancer stood out among them. It was also proven that there is no evidence that the effect size varies between studies.

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Interest conflict statement

The authors deny any conflict of interest.