

Review

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Lipid profile and mortality in patients with pulmonary thromboembolism; a systematic review and meta-analysis

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Abstract

Introduction: Acute pulmonary thromboembolism (PTE) is a life-threatening disease. Considering the availability and accessibility of assessing the serum lipids, this study aims to define the predictive value of lipid profile, as well as the history of lipid disorders, for the mortality of PTE patients.

Content: Clinical studies, in which the relation of lipid profile, including triglyceride (TG), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol, as well as history of imbalance of lipids, with mortality of PTE patients was reported, were included. Non-English articles, reviews, letters, editorials, and non-English papers were excluded. A systematic search was conducted in PubMed, Embase, Scopus, and Web of Science databases.

The risk of bias was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal tools and CMA 4 was utilized for the quantitative synthesis. Out of 3,724 records, six studies were included in this systematic review. Lipid profile is suggested as a prognostic marker for survival in patients with PTE so higher initial serum HDL, LDL, and total cholesterol levels were associated with lower mortality rates in PTE patients. In addition, dyslipidemia was found to be associated with mortality of PTE patients. Based on the quantitative synthesis, there was a greater serum level of HDL in the survival group (standardized mean difference: -0.98 ; 95 % CI: -1.22 to -0.75 ; p -value <0.01).

Summary and Outlook: Mortality is lower in PTE patients with greater serum lipid levels; therefore, the early prognosis of PTE may be ascertained by measuring serum lipids within the first 24 h of admission.

Keywords: pulmonary thromboembolism; prognosis; mortality; lipid profile

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Introduction

Pulmonary thromboembolism (PTE) is a serious and fatal disease with increasing prevalence [1, 2]. The annual incidence of PTE is approximately 300,000–600,000 cases in the United States (US) and Europe [3] and 5.7 per 100,000 in Iran [4]. The mortality of PTE can be as high as 30 % [5–7]. Necroscopic examination shows that PTE is the cause of death in about 5–10 % of hospitalized patients [5]. PTE also has a significant economic burden, costing \$2–10 billion annually [6]. PTE has a multifactorial etiology and its risk factors may be genetic or acquired [7].

Dyslipidemia and dyslipoproteinemia are well-known risk factors for arterial thrombosis. In addition, studies suggest that lipids and lipoproteins may affect hemostasis [8]. Triglyceride (TG) elevates the level of plasminogen activator inhibitor (PAI-1) [9] and low-density lipoprotein (LDL) cholesterol can activate platelets and induce tissue factor expression and can impair fibrinolysis [10]. In addition, high-density lipoprotein (HDL) cholesterol inhibits platelet aggregation, decreases viscosity, and suppresses tissue factor activity so it behaves as an anti-atherothrombotic [11, 12].

Because most PTE patients have a high mortality rate within the first hours of presentation, an insight into its possible prognosis is of paramount importance [13]. Recent studies indicate that the current scores used to determine the PTE patients' prognosis like the Geneva risk score and the 2014 European Society of Cardiology (ESC) model are not reliable in identifying high-risk PTE patients. Moreover, clinicians also question the ability of the pulmonary embolism severity index (PESI) score to identify the risk of early mortality in PTE patients [14, 15]. Naples Prognostic Score, which is based on the inflammatory and nutritional status (with an assessment of serum albumin, and total cholesterol, as well as neutrophil-to-lymphocyte ratio, and lymphocyte-to-monocyte ratios), is also recently suggested as a novel, and multidimensional prognostic scoring system for 30-day all-cause mortality in acute PTE [16].

Considering the mentioned mechanistic pathway and availability of lipid profile tests, this systematic review is conducted to determine the prognostic value of lipid profile status in patients with PTE.

Methods

This systematic review was conducted following the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [17] and Joanna Briggs Institute (JBI) methods for conducting systematic reviews [18].

Eligibility criteria

The studies that assess the possible relation between lipid profile, including serum levels of TG, LDL, HDL, and total cholesterol as well as the history of lipid imbalances, and mortality in patients with PTE with both retrospective and prospective designs were included. Animal studies, case reports, reviews, letters, editorials, and studies published in languages other than English were not included.

Information sources and search strategy

An electronic search was conducted in four major databases including Medline via PubMed, Embase, Web of Science, and Scopus in March 2023, with the following keywords: (Lipid OR lipids OR Cholesterol OR Cholesterols OR lipoprotein OR lipoproteins OR triglyceride OR triglycerides OR Triacylglycerol OR Epicholesterol) AND ([“Pulmonary Embolism”] OR [“Pulmonary Thromboembolism”] OR PTE OR PE) AND (Mortal* OR death OR survival OR Fatalit* OR fatal OR outcome OR survivals) and updated via handsearching in March 2024. Two independent authors conducted the electronic searches (A.N. and E.B.). For full coverage of any published studies, after selecting the final articles to be included in this systematic review, the reference lists of these articles and recently published review articles have been checked for possible inclusion in this study by two authors (E.N. and N.R.).

Selection process

Results of the electronic search were imported into EndNote 20 and after removing the duplicated studies, the remaining records were screened in two title/abstract and full-text stages. Two independent authors screened the studies (N.S.G., and E.M., or S.J., and S.M.) and in case of any disagreements, a third author deemed the issue (N.R. or E.J.).

Data collection process and data items

Data extraction was conducted by two authors (N.S.G., and A.N.) with an electronic table in Microsoft Word and disagreements were resolved by another author's opinion (S.G., or E.J.). The following data were extracted from each study: the name of the first author of the study, the year of study publication, the study design, the setting of the study, lipid profile assessments, the sample size, the mean and standard deviation of ages, the number of female and male

cases, and the findings of the studies regarding the association between lipid profiles and mortality.

Study risk of bias assessment

The risk of bias (RoB) in the included studies was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools for cohort or cross-sectional studies based on the study designs [19]. RoB assessments were conducted by two independent authors (E.B. and A.N.) and disagreements were resolved by another author's opinion (S.G., or E.J.).

Effect measures and synthesis methods

Differences between the mortality and survival groups regarding the lipid profile or history of lipid imbalances were utilized for effect measurement. The findings of the studies were narratively synthesized. In addition, meta-analysis was conducted for the studies that reported the means and standard deviations of serum levels of HDL for the mortality and survival groups. The fourth version of Comprehensive Meta-Analysis (CMA 4) was utilized for quantitative synthesis, with 95 % confidence intervals (CIs) and 0.05 level of significance for p-value. I^2 was used to assess the level of heterogeneity between the studies.

Results

Search results

The literature search identified 3,724 potentially relevant studies. After excluding 3,711 of the studies based on title/abstracts, 13 studies were identified for full-text review. Of these, six studies were subsequently excluded because the prognosis was not assessed [20–25], and one study was excluded because the lipid evaluation was not reported [26]. Finally, six studies were included in this systematic review [27–32] (Figure 1).

Study characteristics

The final six studies include one cohort study and five cross-sectional studies. The main characteristics and findings of the enrolled studies are summarized in Table 1. In this study lipid profiles of 1,577 patients diagnosed with PTE in China [27], Romania [28], Turkey [29, 32], Taiwan [30], and Spain [31] were recorded and their relationship with

mortality was evaluated. In three of the studies TG, total cholesterol, LDL, and HDL levels were indicated as lipid assessment factors [27, 28, 32], while in the other three, only serum HDL level, history of hypercholesterolemia, and dyslipidemia were suggested for lipid profile analysis [29–31].

Risk of bias assessments

Table 2 is a summary of the results of RoB assessments. Overall, there was no significant RoB in the included studies. In one study [27], there was a significant concern regarding the RoB, which did not report the characteristics of participants of the study, as well as identifying and dealing with possible cofounders.

Results of individual studies

Four cross-sectional studies found a close relation between serum lipid levels at admission and the prognosis of patients with PTE. In one study done by Chen et al. in China, 142 patients with PTE were selected from 2016 to 2021. This study found HDL cholesterol was significantly higher in the survival group; however, there was no significant difference regarding the LDL, TG, and total cholesterol [27].

In another study done by Souissi et al., 593 patients were analyzed for lipid parameters at admission. All of the included patients were diagnosed with acute PTE, confirmed by computed tomography. This study demonstrated that total cholesterol and LDL levels were significantly associated with mortality risk in univariate analysis; however, in multivariate analysis and ROC curves, only total cholesterol predicted the mortality and LDL level lost significance [28].

In the other study conducted by Avci et al. in Turkey, HDL values of 269 patients diagnosed with PTE from 2018 to 2020 were determined. This study found HDL values were significantly lower in the mortality group than in the group without mortality. In multivariate logistic regression and ROC analysis, significant efficacy of HDL value was still observed in predicting mortality [29].

Finally, a cross-sectional study done by Karatas et al. in Turkey showed lower total cholesterol, LDL, HDL, and TG in PTE patients resulting in mortality, even after control for cofounders. In this retrospective study, serum lipid levels of 275 patients who were hospitalized with a diagnosis of acute PTE from 2008 to 2014, were recorded within the first 24 h of admission, and the mortality rate at 30 days was investigated as the clinical outcome. When ROC curves were compared, the area under the curve of total cholesterol level was

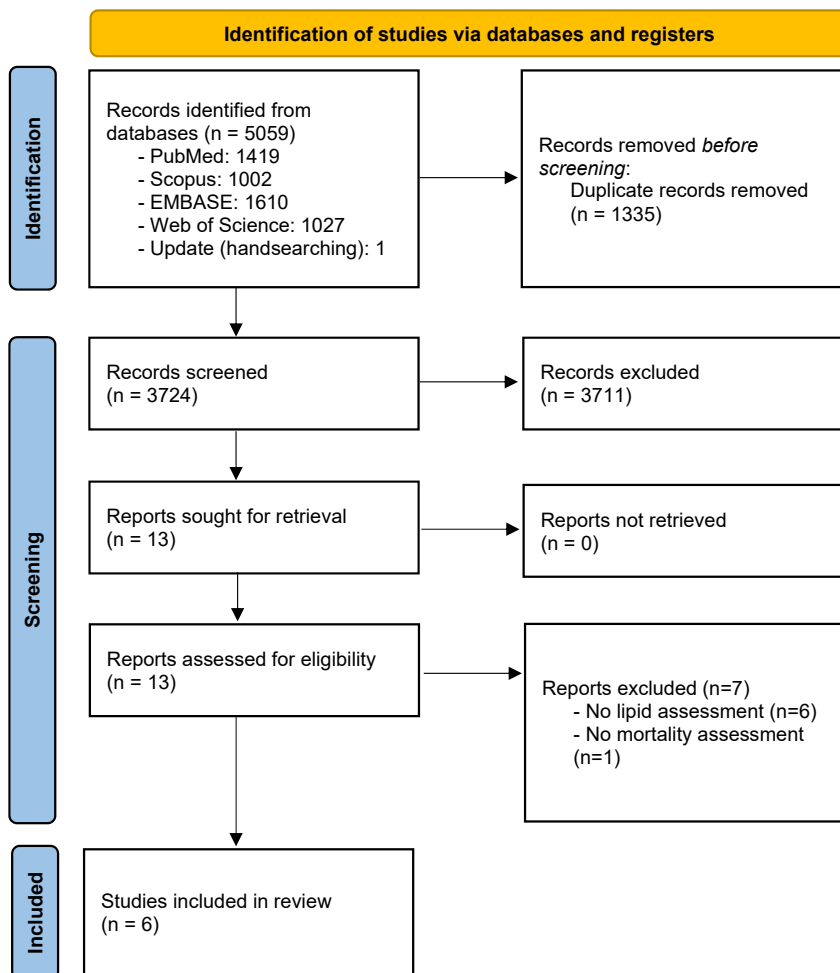


Figure 1: PRISMA flow diagram. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>.

significantly higher compared to TG and LDL levels but was not statistically different from HDL levels [32].

Regarding the association of history of imbalance of lipids and mortality of PTE patients, two studies assessed this relationship. In a retrospective study conducted by Huang et al. in Taiwan, 150 patients hospitalized between 2004 and 2009 were enrolled. In this study history of hypercholesterolemia showed no significant association with 30-day all-cause mortality in Univariate Cox Regression analysis [30]. In a cohort study conducted by Jara-Palomares et al. in Spain, dyslipidemia was shown as a long-term negative prognostic factor for survival in patients with PTE. 148 patients diagnosed with PTE were enrolled in this prospective study and mortality was assessed during a 2-year follow-up period [31].

Results of synthesis

Table 3 presents the results of the synthesis of the findings from the studies that reported the association between

serum lipid levels and mortality in PTE patients. Based on the available evidence, higher initial serum HDL, LDL, and total cholesterol levels seem to be associated with a lower rate of mortality in PTE patients. Meta-analysis of two studies that reported HDL levels in mortality and survival groups was associated with statistically significant results (Standard mean difference: -0.98 ; 95 % CIs: -1.22 to -0.75 ; p -value <0.01 ; I^2 : 0.00 %; p -value for heterogeneity: 0.94) (Figure 2).

Discussion

To the best of our knowledge, this study is the first systematic review to summarize the evidence regarding the relationship between lipid profile status and PTE mortality. Available evidence suggests that PTE patients with higher initial serum HDL, LDL, and total cholesterol levels have a lower short-term mortality rate. In addition, dyslipidemia was found to be associated with the mortality of PTE patients.

Table 1: Baseline characteristics of the included studies (TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein).

Study	Setting	Study design	Sample size	Age	Male ratio	Lipid assessments	Prognostic outcomes	Results	Other comments
[27] – conference abstract	Shenyang Medical College, China	Cross-sectional	142	–	–	TG, TC, LDL, HDL at admission	30-day mortality	HDL was lower in the mortality group; no correlation was found between the other assessed lipids.	–
[28] – conference abstract	Spiridon University Hospital, Iasi, Romania	Cross-sectional	593	65.06 ± 14.96	52.6 %	TG, TC, LDL, HDL at admission	In-hospital mortality	TC and LDL were associated with mortality. HDL and TG were not associated.	In multivariate analysis, only total cholesterol was significantly associated.
[29]	Adana City Research and Training Hospital, Adana, Türkiye	Cross-sectional	269	64.51 ± 12.4	45.0 %	HDL at admission	In-hospital mortality	HDL was lower in the mortality group.	The association was still significant in multivariate analyses.
[30]	Taipei Veterans General Hospital, Taiwan	Cross-sectional	150	71.3 ± 14.8	64.0 %	History of hypercholesterolemia	30-day mortality	Hypercholesterolemia was not associated with mortality.	–
[31]	Virgen del Rocío University Hospital, Seville, Spain	Cohort	148	64.2 ± 17.2	50 %	Dyslipidemia (TG>150 mg/dL or HDL<40 mg/dL, in males and <50 mg/dL in females)	2-year mortality	Dyslipidemia shows as a long-term negative prognostic factor for survival	–
[32]	Siyami Ersek Cardiovascular and Thoracic Surgery Center, Istanbul, Türkiye	Cross-sectional	275	65.2 ± 17.4; 66.8 ± 18.2	41.5 %	TG, TC, LDL, HDL	30-day mortality	TC, LDL, HDL, and TG levels were significantly lower in the mortality group	All of the assessed correlations were still significant after adjustment for cofounders.

Table 2: The results of risk of bias assessments.

Cross-sectional studies											
Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	–	–	–
[27] – conference abstract	No	No	Yes	Unclear	No	No	Yes	Unclear	–	–	–
[28] – conference abstract	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–	–	–
[29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–	–	–
[30]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–	–	–
[32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	–	–	–
1. Were the criteria for inclusion in the sample clearly defined?											
2. Were the study subjects and the setting described in detail?											
3. Was the exposure measured in a valid and reliable way?											
4. Were objective, standard criteria used for measurement of the condition?											
5. Were confounding factors identified?											
6. Were strategies to deal with confounding factors stated?											
7. Were the outcomes measured in a valid and reliable way?											
8. Was appropriate statistical analysis used?											
Cohort studies											
Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
[31]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
1. Were the two groups similar and recruited from the same population?											
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?											
3. Was the exposure measured in a valid and reliable way?											
4. Were confounding factors identified?											
5. Were strategies to deal with confounding factors stated?											
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?											
7. Were the outcomes measured in a valid and reliable way?											
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?											
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?											
10. Were strategies to address incomplete follow up utilized?											
11. Was appropriate statistical analysis used?											

Table 3: Meta-synthesis of the results of the study, based on the association between serum levels of the lipids with in-hospital mortality.

Study	TG	Total cholesterol	HDL	LDL
[27] – conference abstract	No relation.	No relation.	Lower	No relation.
[28] – conference abstract	No relation.	Lower	No relation.	Associated ^a
[29]	–	–	Lower	–
[32]	Lower	Lower	Lower	Lower

^aDid not mention if it is a positive or negative association.

Few studies have investigated the correlation between serum lipid profile and thrombosis. In the most recent one, Wei et al. claimed that low serum TG levels as well as high serum LDL levels are significantly associated with an increased risk of venous thromboembolism (VTE) in acute stroke patients [33]. One of the pathophysiological reasons can be the basis of the thrombotic process which is

inflammation that can lead to oxidative changes and decrease cholesterol synthesis [34, 35]. A study on mice has shown that HDL and cholesterol regulate the pulmonary inflammatory response after tissue injury [36]. On the other hand, HDL can prevent monocyte flow to the arterial wall and this protects endothelial cells against inflammation and oxidative stress [37, 38]. Finally, the function of lipoprotein lipase increases in acute phase reactions breaks down circulating TGs, and results in lower TG levels [39]. Although we found a relationship between serum lipid levels and mortality in PTE patients; however, the limitations of the evidence, suggested caution in the clinical translation of the findings of this study and there is still a need for future studies, with a larger sample size on this topic.

Systematic and predefined approach of the review and a comprehensive database search as well as hand searching for full coverage of the published evidence were the main strengths of this study. The exclusion of non-English papers was the main limitation of this study. In addition, only two

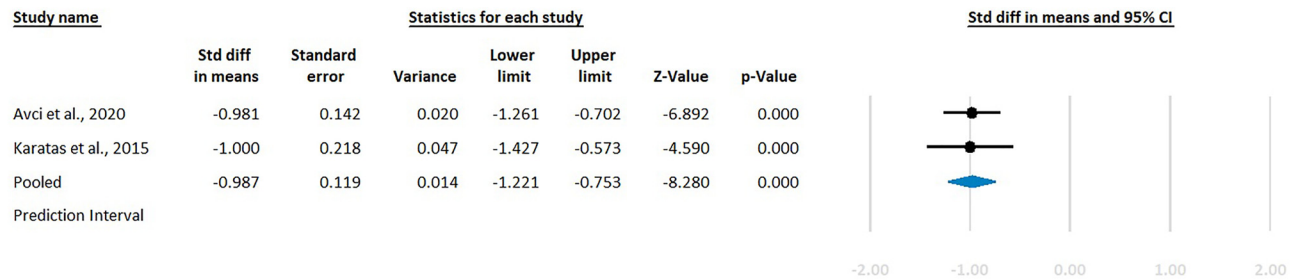


Figure 2: Forest plot of the evidence regarding the difference in HDL levels between mortality and survival groups.

studies that reported enough information to conduct the meta-analysis were utilized for quantitative synthesis. Future multi-center studies and comprehensive reports of the characteristics of the disease can strengthen the evidence in this regard and help appropriate management in PTE patients.

Conclusions

Measurement of serum lipids in the first 24 h of hospitalization may be a valuable marker for determining the early prognosis of PTE. PTE patients with a higher rate of serum lipids have a lower rate of mortality. PTE patients with higher HDL levels have a better prognosis, suggesting that assessing the serum levels of this lipid is an available prognostic factor for predicting short-term mortality in PTE patients.

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Research ethics: The ethics committee of the Tabriz University of Medical Science reviewed and approved the study protocol (Ethical Code: IR.TBZMED.VCR.REC.1402.039).

Informed consent: Not applicable.

Author contributions: E.B, E.N, N.S, S.H, S.S, A.G, and E.M: systematic search; study selection, data extraction, risk of bias assessment; S.G and A.N: meta-analysis, preparing the figures and writing the manuscript; N.R, S.G and E.J: supervision and critically editing the manuscript. All authors approved the final version for submission.

Competing interests: The authors report no relationships that could be construed as a conflict of interest.

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Data availability: All data generated or analyzed during this study are included in this published article.

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