Review Article

Prevalence of pulmonary thromboembolism in nephrotic syndrome patients: A systematic review and meta-analysis

Abdullah Nasser Leslom[1], Ziyad Mohammed Saeed Alrawiah[1], Ahmed Mohammed Ahmed Al-Asmari[1], Moneer Dhafer Ali Alqashaneen[1], Abdulaziz Oudah Tami Alahmari[1], Hamuod Oudah Bin Tami Al-Ahmari[1]

[1]Intern, College of Medicine, King Khalid University, Abha, Saudi Arabia

Abstract

This study was aimed to assess the prevalence of pulmonary thromboembolism in patients with nephrotic syndrome. An electronic search was conducted through nine electronic databases for selection of relevant articles reporting the prevalence of pulmonary thromboembolism in patients with nephrotic syndrome. National Institute of Health was used to assess the quality of each study. Meta-analysis was used to pool the results. Of total 2267 reports screened, we finally included 11 studies including five retrospective cohorts, four prospective cohorts, and two case series studies. Out of these, ten articles were eligible for meta-analysis. The overall prevalence was 7.93% with 95% CI of 4.27 to 14.73. However, a significant heterogeneity ($P < 0.001$) was observed with I2= 96% and $\tau 2 = 0.899$. Moreover, Egger's regression test showed a significant risk of bias ($P = 0.006$). Patients with nephrotic syndrome are prone to pulmonary embolism, therefore early management is critical to decreasing mortality burden.

Keywords: Glomerulosclerosis, nephrotic syndrome, proteinuria, pulmonary thromboembolism

Introduction

Nephrotic syndrome (NS) is a well-defined syndrome mainly characterized by the presence of proteinuria which is more than or equal to 3.5 g/24 h, albuminemia less than 3.0 g, hyperlipidemia, lipiduria, peripheral edema, and increased risk of thromboembolic events.[1-3] According to etiological classification, there are primary and secondary NS, with possible further classification of secondary NS into; NS due to systematic diseases and NS due to medication use. The most common causes of primary NS include membranous nephropathy (MN), minimal change disease (MCD), and focal segmental glomerulosclerosis (FSGS).[2,3] Malignancy, infectious diseases, systemic lupus (SLE), multiple myeloma, diabetes mellitus, and systemic lupus erythematosus are common causes of secondary NS.[2,3] In the same context, common medication associated with secondary NS includes penicillamine, pamidronate, gold compounds, and nonsteroidal anti-inflammatory drugs.[2,3] Noteworthy, some cases of membranoproliferative glomerulonephritis and immunoglobulin A nephropathy can be clinically confused with NS.[2,4,5] Therefore, renal biopsy is necessary to make a definitive diagnosis in certain cases, especially with SLE, to guide treatment strategy.[6]

Pulmonary embolism (PE) is considered now as the third most common cardiovascular pathology.[7] PE can be asymptomatic, passing undiagnosed, or detected incidentally during routine investigations making its epidemiology hard to be properly characterized.[8-10] On the other hand, PE may be presented with more

Address for correspondence: Dr. Abdullah Nasser Leslom, College of Medicine, King Khalid University, P.O. Box 641, Abha, Saudi Arabia.
E-mail: Abdullah.leslom@gmail.com

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serious symptoms ranging from tachycardia, tachypnea up to the sudden cardiovascular collapse, and death.[11] It also may result in some serious long-term complications such as chronic thromboembolic pulmonary hypertension. Hence, the clinical suspicion is the main factor in proper and early detection.[12] Clinically, PE is a common complication of deep venous thrombosis (DVT), which has many risk factors including prior history of DVT/PE, recent surgery, prolonged immobilization, cardiac diseases, autoimmune diseases, cancer, and conditions associated with hypercoagulability (such as antiphospholipid antibody syndrome and NS).[13,14]

The goal of this paper is to provide a comprehensive review of the current literature in terms of PE incidence in NS patients. We aim to give a good quantification of the problem, thus better screening programs can be developed towards this aspect. Most of the care was given in a secondary (hospital) setting but long-term secondary prevention was managed by primary care physicians.

Methods

Search strategy and study selection

The study was conducted following the recommendations of the PRISMA checklist for systematic reviews.[15] We conducted a systematic electronic database search for suitable studies till June 2019 in nine databases including Google Scholar, Popline, WHO health library (GHL), System for Information on Grey Literature in Europe (SIGLE), Scopus, Web of Science (ISI), PubMed, Virtual Health Library (VHL), The New York Academy of Medicine (NYAM) using the following search term: (nephrotic syndrome or nephrotic) and (pulmonary embolism or embolism or thrombosis). A manual search was conducted by searching for relevant publications from references of included articles, relevant papers in PubMed and Google Scholar and primary studies that had cited the included papers. Three independent reviewers scanned the titles and abstracts against our inclusion and exclusion criteria to select potential articles. We included all studies reporting the prevalence of PTE in patients with NS. There were no restrictions on country, language, or publication date. Papers were excluded if one of the following exclusion criteria was met: i) *in vitro* or animal studies; ii) data duplication, overlapping, or unreliably extracted or incomplete data; iii) abstract only articles, reviews, thesis, books, conference papers, or articles without available full texts (editorials, author response, letters, and comments) along with any previous systematic reviews, meta-analyses, and literature reviews discussing the topic of interest. Three reviewers independently performed an initial eligibility assessment on the retrieved titles and abstracts. Full texts of eligible articles were then retrieved and reviewed for final inclusion. In both steps of the screening, a decision made by all three reviewers was considered conclusive. Controversies during the process were resolved by discussion and consensus. When necessary, disagreements and discrepancies were resolved by consensus with senior reviewers.

Data extraction

Based on a pilot review and extraction, a data extraction form was developed by two authors, using Microsoft Excel file. Three reviewers independently extracted data from included studies using the excel sheet. Data rechecking was carried out by at least two different authors and rechecked by a third reviewer for accuracy. All the disagreements and discrepancies were resolved by discussion and consensus. Papers published by the same research group were checked for potential duplicate data with reference to the year of patients' recruitment and the hospital where the patients were recruited.

Quality assessment

Three independent reviewers evaluated the risk of bias in included studies. Methodological quality assessment was done using the National Institute of Health (NIH) quality assessment tool.[16] Quality assessment of cohort studies was obtained through a scoring system including 14 questions for cohort studies and nine ones for case series studies. The criterion was judged as follows: a score of 13 to 14 was good, 9 to 12 was fair, and studies scoring below 9 were considered of poor quality for cohort studies; while a score of 8 to 9 was good, 5–8 was fair, and 1 to 4 was poor for case-series studies.[17] Any discrepancy between the reviewers was solved by consensus.

Statistical analysis

R software version 3.4.3 was used to conduct the analyses.[18] To calculate prevalence, a random-effects model was chosen due to the presence of heterogeneity between studies. Heterogeneity was evaluated using the Q statistic and I^2 test.[19,20] To evaluate the presence of publication bias, Egger's regression test was performed and the publication bias was considered significant when the *P* value was <0.1.[21,22] If the publication bias was found, funnel plot with the trim and fill method of Duvall and Tweedie was performed by adding studies that appeared to be missing to enhance the symmetry.[23,24]

Results

Search results

Database search yielded 2267 reports after removal of 389 duplicates via endnote software. Title and abstract screening resulted in the inclusion of 195 and the exclusion of 2072 reports. Out of these, we have included seven studies. Additional 4 studies were found after manual search trials. Finally, we have included 11 studies with a total sample size of 2728 for our systematic review and meta-analysis [Figure 1].

Quality assessment and characteristics of included studies

There were 5 retrospective cohorts, 4 prospective cohorts, and two case series studies. Based on quality assessment, all studies were found to have a fair quality of evidence. The sample size of the included studies was variable starting at 26 patients to as high as 766 included patients. The percentage of included males was variable ranging from 38.46% (10/26) of included patients to reach 80% (80/100) of overall participants. Nearly all the included studies comprised a wide range of ages with high standard deviations (SDs) including infants, children, young

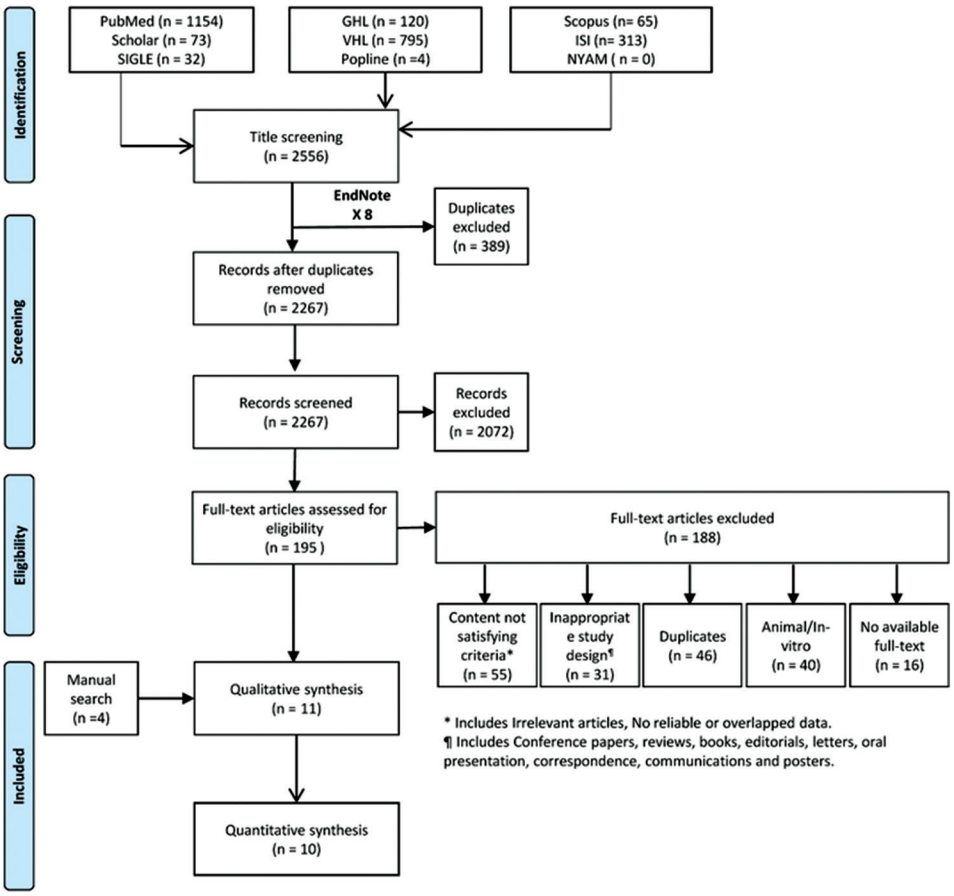

Figure 1: PRISMA flow diagram of the search and review process

adults, and old patients. Mean (SD) ages reported ranged from 7.7 (2.7) to 47.6 (14.8) years old [Table 1].

Prevalence of PTE in NS

Ten studies were finally included in the meta-analysis of PTE prevalence in NS patients. The overall prevalence was 7.93% with 95% CI of 4.27 to 14.73. The reported prevalence rates varied among different studies ranging from 2.09% to 29.88%. However, a significant heterogeneity ($P < 0.001$) was observed with $I^2 = 96\%$ and $\tau^2 = 0.899$. Moreover, Egger's regression test showed a significant risk of bias ($P = 0.006$) [Figure 2]. On using the trim and fill method to enhance funnel plot symmetry, five studies were added on the right side of the plot [Figure 3].

Discussion

The current study founded that NS patients experienced that incidence of PTE estimated by 8%. Moreover, the results are lower than Zhang *et al.*[25] in which the incidence of PTE was 35% of NS patients, out of this 55% of patients were associated with combined renal vein thrombosis and PTE. Moreover, PTE was estimated to affect a quarter of nephrotic syndrome patients.[26] Furthermore, in a large observational cohort of Chinese nephrotic patients, the incidence of arterial thromboembolism and venous thromboembolism was 9% and 8%, respectively. However, pulmonary embolism was the most common venous thromboembolism disorder and accounted for 27%, followed by renal thromboembolism which accounted for 13% of individuals developed venous thromboembolic disorders.[27] In contrast, renal vein thrombosis was the common thromboembolic disorder revealing an incidence of 33%; however, PTE affected only 17% of nephrotic patients as reported by Li *et al.*[28]

Despite being a poorly understood phenomenon, several factors are associated with the development of thromboembolic disorders in NS. The loss of proteins necessary for the regulation of coagulation such as antithrombin and protein S plays a substantial role in the development of thromboembolic diseases in NS.[29] Moreover, genetic predisposition can provide a significant role in the pathogenesis of NS.[30] Indeed, Mehls *et al.*[31] indicated the significant role of age as a significant contributor to the pathophysiology of thrombosis in NS. The risk of thromboembolism is higher in adults compared to children estimating an incidence of 9% and 1% for adults and children, respectively.[31,32] Furthermore, NS type shares in the variety of incidence of thromboembolic disorders among individuals.[25] Harza *et al.*[33] indicated that patients with IgA nephropathy and membranoproliferative glomerulonephritis had a higher risk of pulmonary embolism compared to other types of NS, moreover membranoproliferative glomerulonephritis

Table 1: Characteristics of included studies

Author ID	Study design	Sample size	Age (mean (SD))	Male (event/total)	Quality rating
Zou/2018/China	Retrospective cohort	766	47.6 (14.8)	449/766	Fair
Chugh/1981/India	Retrospective cohort	44	29.7	32/44	Fair
Li/2012/China	Prospective cohort	100	18-73#	80/100	Fair
Mehls/1986/Germany	Retrospective cohort	320	1-62#	121/204	Fair
Harza/2013/Romania	Prospective cohort	191	47.2 (14.6)	102/191	Fair
Maas/2017/Netherlands	Case series	125	46	52/125	Fair
Zhang/2014/USA	Prospective cohort	512	37 (17)	331/512	Fair
Suri/2014/India	Retrospective cohort	34	7.7 (2.7)	22/34	Fair
Yang/2014/China	Retrospective cohort	312	42.2 (1.4)	213/312	Fair
Mahmoodi/2013/Netherlands	Prospective cohort	298	42 (18)	177/298	Fair
Hoyer/1986/Germany	Case series	26	NR	10/26	Fair

NR=not reported, # range

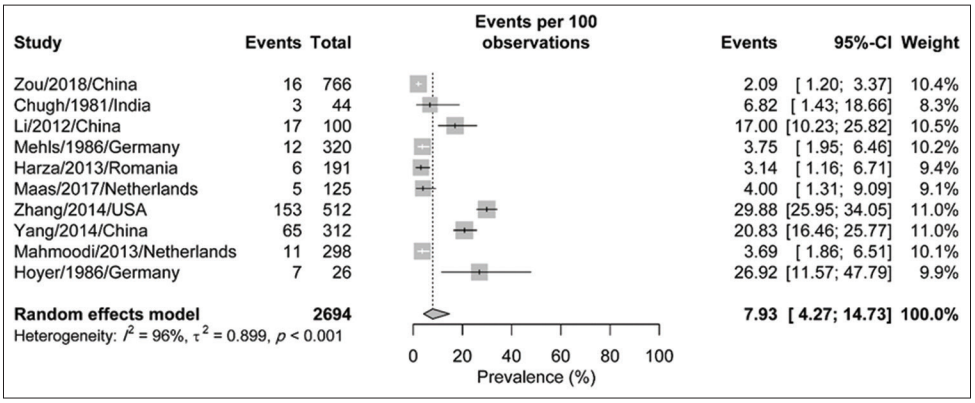

Figure 2: Forest plot of PTE prevalence in NS

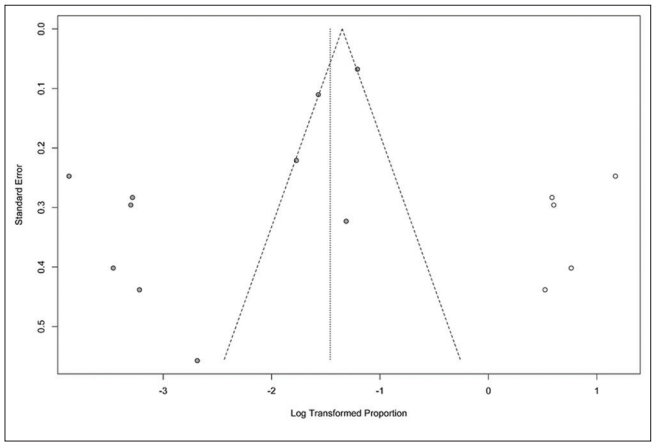

Figure 3: Funnel plot with trim and fill methods

possessed the highest risk of pulmonary embolism and deep venous thrombosis.

Thromboembolic disorders in NS is dangerous and can progress to mortality if not medically controlled.[28] The scarcity of studies that report the management of thromboembolic disorders in NS can be explained through the low incidence of thromboembolic disorders affecting those patients. However, usage of low-molecular-weight heparin in high-risk patients of nephrotic is associated with good efficacy in reduction of thromboembolic disorders and low reported side effects.[34] Moreover, urokinase is effective in the management of urgent cases associated with pulmonary embolism in nephrotic syndrome.[35]

Our study was interpreted with several limitations. Firstly, the inclusion of retrospective studies, therefore selection bias could not be avoided. Secondly, significant heterogeneity was found that can be explained by the difference in age, sex, and type of NS in the included studies.

Conclusion

Pulmonary embolism is a common complication of nephrotic syndrome that needs special care from physicians. Our study highlights the need for good therapeutic approaches for the prevention of pulmonary embolism in individuals affected with nephrotic syndrome. Moreover, the awareness of Primary Care Physicians, which long-term secondary prevention is also managed by them.[36]

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Conflicts of interest

There are no conflicts of interest.

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