

Pulmonary Thromboembolism (PTE) and Nephrotic Syndrome: A Systematic Review and Meta-analysis of Prevalence

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Abstract

Background: The incidence of thromboembolic complications in nephrotic children varies between 2% to 5% with a higher incidence in nephrotic syndrome than steroid responsive NS. Thrombosis is probably less recognized or under-reported in children with nephrotic syndrome. **Aim:** This work aims to determine the prevalence of pulmonary thromboembolism (PTE) in nephrotic syndrome patients. **Materials and Methods:** Careful search was performed over multiple medical databases to locate Internal Medicine studies, which studied the outcome of pulmonary thromboembolism (PTE) in nephrotic syndrome patients. Using the meta-analysis process, either with fixed or random-effects models, we conducted a meta-analysis on PTE prevalence as the main outcome. **Results:** 10 studies were identified involving 9926 patients. The meta-analysis process revealed that pulmonary thromboembolism (PTE prevalence) in nephrotic syndrome patients of 10.6% ($p < 0.0001$). We also found a nonsignificant publication bias (8 studies of 10 under funnel plot), ($p > 0.05$). **Conclusion:** To conclude, pulmonary thromboembolism is considered the third ranking cardiovascular disease. Pulmonary thromboembolism is difficult to detect as it is mainly asymptomatic, detected only as incidentally, and diagnosed only after many visits to physicians; or remain undiagnosed during a person's life. Similarly, the prevalence among young persons is poorly documented.

Keywords: Pulmonary Thromboembolism; Nephrotic Syndrome

Introduction

Nephrotic syndrome (NS) is defined with the aid of the presence of heavy proteinuria (protein excretion greater than 3.5 g/24 h), hypoalbuminemia (much less than three.0 g/dl), hyperlipidemia, and peripheral edema. Thrombotic diseases are also often observed. Arterial and venous thrombosis is the capability of headaches of NS. Arterial thrombosis is less common than venous thrombosis and the maximum common places are femoral arteries, even though other arteries can be involved. Stroke associated with NS has rarely been reported in numerous case reports. We file 10 cases of acute ischemic stroke (AIS) related to NS and the outcomes of a retrospective cohort study evaluating AIS sufferers with and without NS. The study's reason is to outline the incidence of AIS with NS and examine whether NS is associated with atherosclerosis progression. ^[1]

To reduce the morbidity and mortality of VTE in patients with NS, international guidelines advocate consideration of prophylactic anticoagulation for excessive risk patients for the duration of NS. There aren't any prospective randomized scientific trials that examine using prophylactic anticoagulation in sufferers with NS. ^[2]

Pulmonary thromboembolism (PTE) is now the third most common cardiovascular sickness. The epidemiology of PE is difficult to characterize due to the fact PE can be asymptomatic,

detected only as an incidental finding; identified only after many visits to clinical professionals; or remain undiagnosed during a person's life. Further, the prevalence of PE among younger persons is poorly documented. Current guidelines provide little statistics regarding the diagnostic workup for PE in children and young adults. a few of the many risk factors for PE, hypoalbuminemia as a result of nephrotic syndrome is one of the maximum critical in younger patients because of their higher prevalence of this syndrome. ^[3]

The incidence of thromboembolic complications in nephrotic children varies between 2% to 5% with a higher incidence in NS than steroid responsive NS. Thrombosis is probably less recognized or under-reported in children with nephrotic syndrome. The median time to thromboembolic events is about 71 days after the diagnosis of nephrotic syndrome. ^[4]

This work aims to determine the prevalence of pulmonary thromboembolism (PTE) in nephrotic syndrome patients.

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How to Cite this Article: Muammar JM, et al. Pulmonary Thromboembolism (PTE) and Nephrotic Syndrome: A Systematic Review and Meta-analysis of Prevalence. Ann Med Health Sci Res. 2020;10: 1111-1114.

Literature Review

Our review came following the (PRISMA) statement guidelines.^[5]

Study eligibility

The included studies should be in English, a journal published article, and a human study describing nephrotic syndrome patients.

The excluded studies were non-English or animal studies or describing other types of chronic kidney disease patients (e.g. end-stage renal disease).

Study identification

Basic searching was done over the PubMed, Cochrane library, and Google scholar using the following keywords: Pulmonary Thromboembolism, Nephrotic Syndrome.

Data extraction and synthesis

RCTs, clinical trials, and comparative studies, which studied the outcome of pulmonary thromboembolism (PTE) in nephrotic syndrome patients, will be reviewed.

Outcome measures included PTE prevalence (the main outcome).

Study selection

We found 346 records, 234 excluded based on title and abstract

review; 112 articles are searched for eligibility by full-text review; 62 articles cannot be accessed; 23 studies were reviews and case reports; 17 were not describing the desired outcome; leaving 10 studies that met all inclusion criteria.

Statistical methodology

After the pooling of data, Odds ratios (OR), Standard Mean Differences (SMDs), Proportions (%), with 95% confidence intervals (CI) were calculated, using MedCalc statistical software (Belgium). After the Q test of heterogeneity, the I²-statistics (either the fixed-effects model or the random-effects model) were done within the meta-analysis process.

Results

Our studies were published between 2012 and 2020. Regarding the type of included studies, 6 studies (out of 10 studies) were retrospective, while 3 studies were prospective, and 1 study was a case series study [Table 1].^[6-15]

Regarding patients' characteristics, the total number of patients in all the included studies was 9926 patients [Table 1]. The mean age of all patients was (34.5 years), with 5839 (58.8%) male patients [Table 1].^[6-15]

A meta-analysis study was done on 10 studies that described pulmonary thromboembolism (PTE prevalence) in nephrotic syndrome patients; with an overall number of patients (N=9926) [Table 2].^[6-15]

Each outcome was measured by:

Table 1: Patients and study characteristics.

N	Author	Type of study	Number of patients		Age (average years)	Male patients
			Total			
1	Li et al. ^[6]	Prospective	100		--	80
2	Harza et al. ^[7]	Prospective	191		47.2	102
3	Suri et al. ^[8]	Retrospective	34		7.7	22
4	Yang et al. ^[9]	Retrospective	312		42.2	213
5	Zhang et al. ^[10]	Prospective	512		37	331
6	Maas et al. ^[11]	Case series	125		46	52
7	Zou et al. ^[12]	Retrospective	766		47.6	449
8	Carpenter et al. ^[13]	Retrospective	370		6.3	277
9	Hoseiny Nejad et al. ^[14]	Retrospective	43		7.31	22
10	Shinkawa et al. ^[15]	Retrospective	7473		69	4291

#Studies arranged via publication year.

Table 2: Summary of outcome measures in all studies.

N	Author	Main outcome PTE prevalence	
		Total	PTE event
1	Li et al. ^[6]	100	17
2	Harza et al. ^[7]	191	6
3	Suri et al. ^[8]	34	9
4	Yang et al. ^[9]	312	65
5	Zhang et al. ^[10]	512	153
6	Maas et al. ^[11]	125	5
7	Zou et al. ^[12]	766	16
8	Carpenter et al. ^[13]	370	11
9	Hoseiny Nejad et al. ^[14]	43	8
10	Shinkawa et al. ^[15]	7473	221

Proportion (%)

- For PTE prevalence

Concerning the main outcome measure, we found 10 studies reported pulmonary thromboembolism (PTE prevalence) in nephrotic syndrome patients with a total number of patients (N=9926).

I^2 (inconsistency) was 98% with a highly significant Q test for heterogeneity ($p < 0.0001$), so random-effects model was carried out to assess prevalence; with overall PTE prevalence=10.6% (95% CI=5.006 to 17.96).

Using the random-effects model, the meta-analysis process revealed pulmonary thromboembolism (PTE prevalence) in nephrotic syndrome patients of 10.6% ($p < 0.0001$) [Figure 1].

We also found a nonsignificant publication bias (8 studies of 10 under funnel plot), ($p > 0.05$) [Figure 2].

Discussion

This work aims to determine the prevalence of pulmonary thromboembolism (PTE) in nephrotic syndrome patients.

The included studies were published between 2012 and 2020. Regarding the type of included studies, 6 studies (out of 10 studies) were retrospective, while 3 studies were prospective, and 1 study was a case series study.

Regarding patients' characteristics, the total number of patients in all the included studies was 9926 patients. The mean age of all patients was (34.5 years), with 5839 (58.8%) male patients.

Concerning the main outcome measure, we found 10 studies reported pulmonary thromboembolism (PTE prevalence) in nephrotic syndrome patients with a total number of patients (N=9926).

Using the random-effects model, the meta-analysis process revealed pulmonary thromboembolism (PTE prevalence) in nephrotic syndrome patients of 10.6% ($p < 0.0001$). Which came in agreement with Leslom et al.,^[16] Al-Azzawi et al.,^[17] Artoni et al.,^[18] Guenther & Kemp,^[19] Iwaki et al.,^[1] Li et al.,^[20] Shinkawa et al.,^[15] Kumar et al.,^[4] and Song et al.^[3]

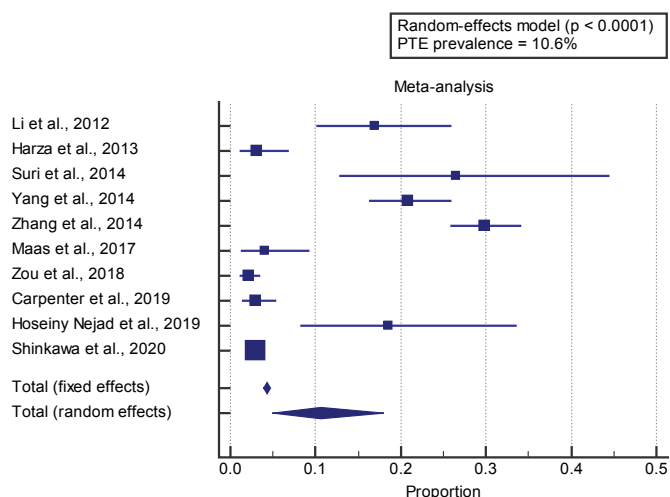


Figure 1: Forest plot demonstrating PTE prevalence.

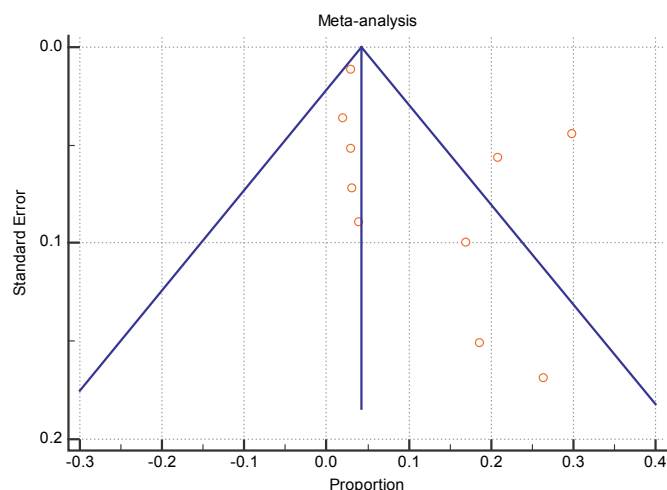


Figure 2: Funnel plot demonstrating PTE prevalence.

Leslom et al., reported that this study became aimed to evaluate the prevalence of pulmonary thromboembolism in patients with nephrotic syndrome. An electronic search was carried out via nine digital databases for the selection of relevant articles reporting the prevalence of pulmonary thromboembolism in patients with nephrotic syndrome. The National Institute of Health was used to evaluate the high-quality of each study. Meta-analysis becomes used to pool the results. Of general 2267 reviews screened, we ultimately included 11 researches together with five retrospective cohorts, 4 potential cohorts, and case series studies. Out of those, ten articles have been eligible for meta-analysis. The overall prevalence was 7.93%. However, a significant heterogeneity ($P < 0.001$) was observed with $I^2 = 96\%$ and $\tau^2 = 0.899$.^[16]

Al-Azzawi et al., reported that 512 patients with NS underwent CT pulmonary angiography for PE and renal CT venography for RVT. One hundred and 80 of the 512 patients (35%) had PE and/or RVT. Of those, 153 patients had PE and 85 of the 153 (56%) patients had related RVT with PE. They found PE to be more common than RVT in nephrotic patients and most patients had been asymptomatic (84%).^[17]

Artoni et al., reported that the latest large case management study accomplished in adults with nephrotic syndrome showed an about 3-fold increased chance of venous thromboembolism. In youngsters, the occurrence of venous thromboembolic events has been reported in numerous case collections of sufferers with active disease and found a 19% the incidence of pulmonary embolism and/or renal vein thrombosis in 80 youngsters with a nephrotic syndrome that underwent total-body CT scan.^[18]

Guenther & Kemp, reported that pulmonary thromboembolism as a cause of death in children with nephrotic syndrome is uncommon. They said 34 children with 35 thromboembolic events; nine had pulmonary thromboembolism, and 2 of those youngsters have been diagnosed at autopsy. "PTE [pulmonary thromboembolism] was usually visible 1 to 9 days after hospitalization in children who had presented with relapse of NS [nephrotic syndrome], or with edema and heavy proteinuria" and that 77% of kids with pulmonary thromboembolism had breathing difficulties. Wright and Watts^[16] indicated the

incidence of venous thrombosis in children becomes 21.9 according to 10,000 admissions, with 21% of those being pulmonary thromboemboli.^[19]

Iwaki et al. reported that sufferers with NS have a high prevalence (21% to 51% of patients) of venous thrombosis, especially deep vein and renal vein thrombosis, and pulmonary emboli, specifically in younger sufferers under 20, and CVT has also been rarely reported. Alternatively, the relative chance of arterial thrombosis was low (1.0 to 5.5%), compared to that of venous thrombosis. In, Sasaki et al. reported an additional case of ischemic stroke with NS and reviewed 21 earlier cases stated in 19 literatures. However, the incidence and the clinical characteristics of AIS sufferers have remained unclear.^[1]

Li et al., reported that they found that the prevalence of venous thromboembolism is about 10% in FSGS patients with nephrotic syndrome. The maximum of the sufferers had a PE. Hemoconcentration and relapse of the nephrotic syndrome had been risk factors for the development of VTE in FSGS. Negative D-dimer may exclude venous thromboembolism in patients with nephrotic syndrome.^[20]

Shinkawa et al., reported that of the 7473 hospitalized patients with a nephrotic syndrome without VTE, 221 (3.0%) developed VTE. In the VTE group, 14 (6.3%), 11 (5.0%), and 198 (89.6%) patients developed pulmonary embolism, renal vein thrombosis, and deep vein thrombosis, respectively.^[15]

Kumar et al., reported that Nephrotic syndrome is associated with hypercoagulable states and a subsequent high hazard of venous and rarely arterial thromboembolism. Although venous thromboembolism has been a known hazard, the occurrence of pulmonary embolism in sufferers with nephrotic syndrome is primarily based on information from different case series. Here we file a 5-year-old child with nephrotic syndrome who developed life-threatening cerebral dural venous sinus thrombosis and pulmonary embolism within a month of disorder onset. Pulmonary embolism (PE) has been reported in 15% of cases with the advent of more sensitive methods. The incidence of thromboembolic complications in nephrotic children varies between 2% to 5% with a higher incidence in SRNS than steroid responsive NS. Sino-venous thrombosis is probably less recognized or under-reported in children with nephrotic syndrome. The median time to thromboembolic events is about 71 days after the diagnosis of nephrotic syndrome.^[4]

Conclusion

To conclude, pulmonary thromboembolism is considered the third ranking cardiovascular disease. Pulmonary thromboembolism is difficult to detect as it is mainly asymptomatic, detected only as incidentally, and diagnosed only after many visits to physicians; or remain undiagnosed during a person's life. Similarly, the prevalence among young persons is poorly documented.

Competing Interests

The authors declare that they have no competing interests. All the listed authors contributed significantly to the conception and design of study, acquisition, analysis, and interpretation of data and drafting of the manuscript, to justify authorship.

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