Review
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Strategies in Management of Pulmonary Embolism With Acute Ischemic Stroke: A Systematic Review

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Abstract

Pulmonary embolism (PE) and acute ischemic stroke (AIS) are serious conditions with high morbidity and mortality. In the USA, PE causes around 100,000 deaths annually, with higher incidence in males. AIS following PE occurs in 1-10% of cases and is a leading cause of death within 2 - 4 weeks post-stroke. Managing concurrent PE and AIS is complex due to the need for anticoagulation, which is contraindicated after thrombolysis for AIS. This review evaluates the impact of various PE treatments - anticoagulation, thrombolysis, and embolectomy - on mortality in patients with both conditions. Following PRISMA 2020 guidelines, a systematic review was conducted across six databases from January 2010 to December 2023. The primary outcome measured was mortality, comparing treated vs. untreated patients for PE. Secondary outcomes included marked symptom improvement, slight improvement or deterioration of symptoms, and the complications. Data were analyzed descriptively, summarizing patient demographics, clinical characteristics, and treatment outcomes. Treatment modalities, such as anticoagulation, thrombolysis, catheter-directed thrombectomy, surgical thrombectomy, and conservative management, were evaluated based on their impact on symptom improvement, survival, and mortality. Initial querying of six databases yielded 1,679 articles, with only 21 remaining after a thorough review. Thrombolysis led to 100% symptom improvement and survival, with 0% mortality. Anticoagulation resulted in symptom improvement and survival in 62.5% of cases, with a 12.5% mortality rate. Catheter-directed and surgical thrombectomy had symptom improvement and survival in 66.7% and 75% of cases, respectively, with no mortality. Conservative management, defined here as management without anticoagulation or thrombolytic therapy, was associated with symptom worsening or no improvement and 50% mortality. This systematic review, based on observational data from case reports, highlights the diverse strategies used by physicians. Proactive and aggressive treatments, especially thrombolysis, show better outcomes and lower mortality rates. However, specific recommendations cannot be made from these results alone, emphasizing the need for well-designed prospective, randomized controlled trials to design structured guidelines for healthcare providers.

Keywords: Pulmonary embolism; Ischemic stroke; Case reports; Anticoagulation; Thrombolysis; Mechanical thrombectomy; Catheter-directed thrombolysis; Patent foramen ovale

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Introduction

Pulmonary embolism (PE) and acute ischemic stroke (AIS) are significant medical conditions associated with significant morbidity and mortality. In the USA, PE is a major cause of death, with around 100,000 fatalities each year [1]. The incidence of PE is higher in males, with 56 cases per 100,000 compared to 48 per 100,000 in females [2]. AIS following PE occurs in 1-10% of cases, and PE is the leading cause of death within the first 2 - 4 weeks post-stroke [3-5]. When PE and AIS occur concurrently, management becomes particularly complex due to the need for anticoagulation in PE, which is contraindicated after pharmacological thrombolysis for ischemic stroke due to the increased risk of cerebral bleeding [6]. The lack of a standardized management protocol for this scenario highlights the urgent need for effective strategies.

The objective of this study is to evaluate the impact of various treatments for PE, including anticoagulation therapy, thrombolysis, and embolectomy, compared to no treatment, on mortality among patients concurrently diagnosed with AIS. Secondary outcomes include assessing improvement and deterioration in symptoms and incidence of complications associated with these interventions.

Methods

The systematic review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines [7] as shown in Figure 1.

Inclusion and exclusion criteria

Studies included in this review consisted of case reports, case

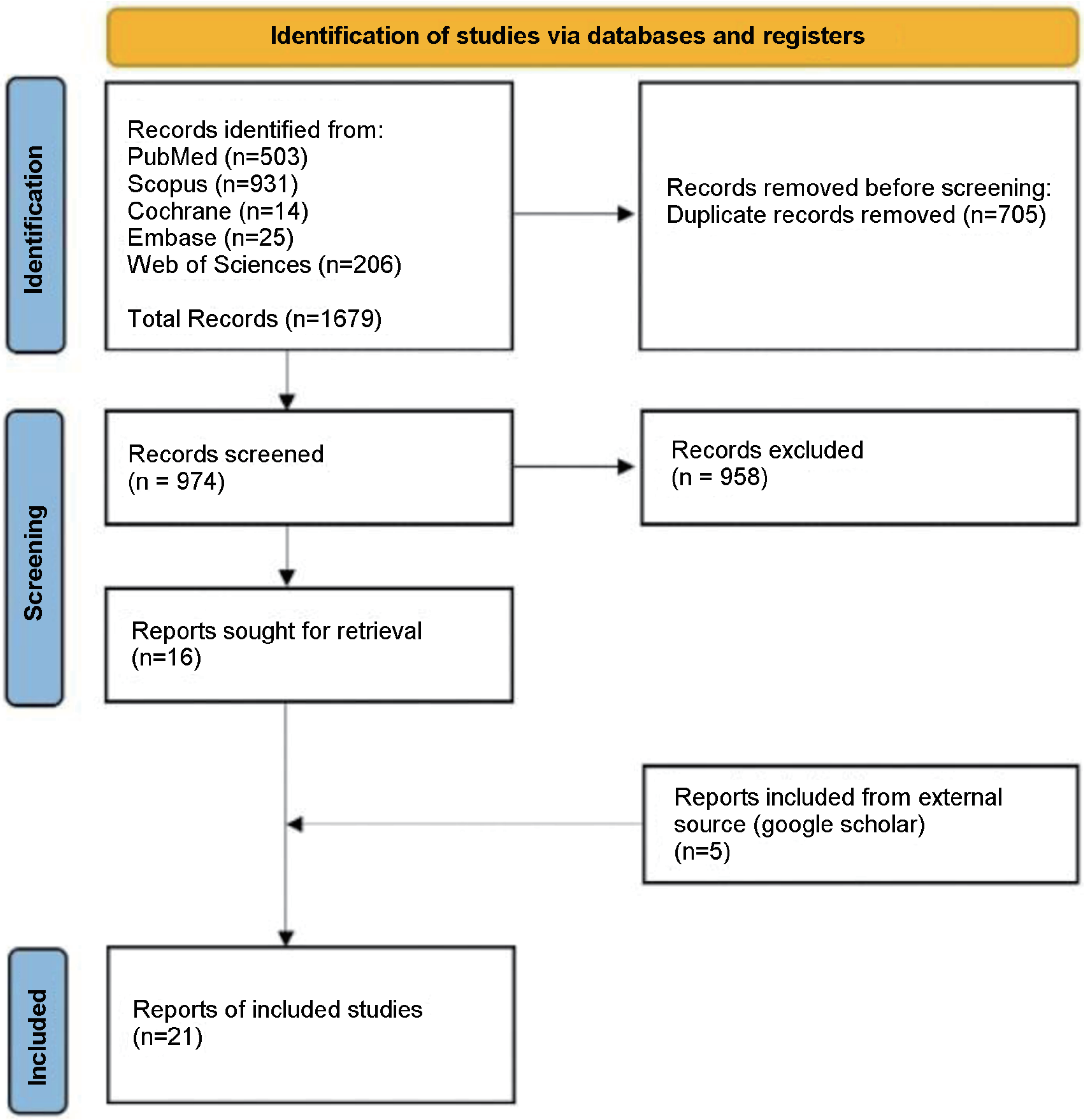

Figure 1. Article selection flow sheet per PRISMA 2020 guidelines [7].

series, and abstracts documenting the concurrent presentation of AIS and PE. Both diagnoses had to be either simultaneous or within 96 h prior or subsequent to each other. Confirmation of PE and ischemic stroke was required through computed tomography pulmonary angiography (CTPA) and brain imaging (computed tomography (CT) and/or magnetic resonance imaging (MRI)). Only studies published between January 2010 and December 2023 were considered. All age groups were included, and only cases documented in English were selected for analysis.

Articles were excluded if they were cohort studies, meta-analyses, review articles, or clinical trials. Additionally, cases where the presentation of PE and AIS occurred more than 96 h apart were not included. Publications from before January 2010, abstracts with limited information, and studies not available in English were also excluded from this review.

Information sources and search strategy

We performed a comprehensive search across six databases - PubMed, Scopus, Cochrane, Embase, Web of Science, and Google Scholar - for case reports, case series, and abstracts documenting the concurrent presentation of PE and AIS from January 2010 to December 2023. The search strategy employed the following search string: ("Pulmonary embolism" OR "lung embolism") AND ("acute ischemic stroke" OR "ischemic stroke" OR "stroke" OR "embolic stroke" OR "cerebral infarct") AND ("case reports" OR "case series"). The initial article search was conducted by SS on May 15, 2024.

Duplicate studies were initially identified and addressed using Rayyan.ai. After duplicates were removed, two reviewers (SS and CV) manually checked the remaining 1,976 articles to ensure all duplicates were eliminated.

Study selection

After duplicates were identified and sorted through, titles and abstracts were screened, leading to a full-text appraisal by SS and CV for inclusion. In the event of any disagreements regarding study inclusion, these were resolved by a third reviewer (JI). Data were extracted from studies deemed eligible for data analysis.

Data collection and analysis

Full-text appraisal involved an initial critical evaluation, followed by data extraction. The extracted data were assessed for relevance, significance, and generalizability. The primary measure extracted by the reviewers was the outcome of patients diagnosed with PE and AIS. Subsequently, the articles were critiqued for their study design.

The analysis in this systematic review of case reports was primarily descriptive, given the nature of the data. Patient demographics (age, sex) and clinical characteristics (risk factors, co-morbidities) were summarized using descriptive statistics. Continuous variables, such as age, were reported as means with standard deviations (SDs) and medians while categorical variables (e.g., sex, presence of risk factors, treatments administered) were presented as frequencies and percentages.

For treatment outcomes, we evaluated the frequency of symptom improvement, survival, and mortality rates based on different treatment strategies, including anticoagulation, thrombolysis, catheter-directed thrombectomy, surgical thrombectomy, and conservative management. Treatment outcomes were reported as percentages of cases showing symptom improvement, survival, or mortality, and a comparative summary of outcomes was made across treatment groups. The data were presented as a narrative synthesis, summarizing the main findings and identifying potential trends or gaps in the literature related to the concurrent presentation and treatment of AIS and PE.

Certainty of evidence and risk of bias assessment

The included articles were evaluated for the certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria by two reviewers (SS and CV) and assessed for bias based on study design.

The methodological quality was evaluated using a modified Newcastle-Ottawa Scale (NOS) for case series, case reports, and case-control studies, following Murad et al's approach [8]. Reviewers used a standardized procedure to reach consensus on risk of bias. The summarized results are in Tables 1 and 2 [9-29].

Results

Querying the six databases yielded 1,679 articles. After using Rayyan.ai to remove duplicates, 974 original articles remained. Following abstract and title appraisal, 20 case reports and one case series (two cases) met the inclusion criteria, resulting in 22 cases for analysis. Patient data from the included articles (Table 3 [9-29]) were then extracted and analyzed (Table 4).

Table 3 summarizes symptoms of patients with concurrent PE and AIS. Table 4 shows patient demographics: 15 (68.18%) females and seven (31.82%) males. The mean age was 56.68 years (SD: 16.8), with a median age of 59.5 years (Table 4).

In our cohort (Table 5), the prevalent risk factors for PE include oral contraceptive pill (OCP) use and post-major surgical interventions (18.18% each). Other common factors are immobility and varicose veins (9.09% each), and prior lower extremity deep vein thrombosis (DVT) (4.55%). Hypertension is the primary risk factor for ischemic stroke (22.73%), followed by dyslipidemia (13.64%), type 2 diabetes, and prior thromboembolic strokes (9.09% each). Tobacco abuse is a shared risk factor for both conditions (4.55%).

Table 6 details the locations of PE and acute stroke, the various treatment approaches for PE and stroke and the associated outcomes in each study. Table 7 details various treatment approaches for PE and their frequencies. Heparin was used in six cases [9-14]. Thrombolysis was used in five cases [15-19]. Low molecular weight heparin (LMWH) was used in two cases [20, 21]. One case was managed with medical therapy alone [19] and another with an inferior vena cava (IVC) filter alone [22]. Catheter-directed thrombectomy was performed in three cases [23-25], including one mechanical thrombectomy (MT) [24] and two percutaneous thrombectomies with heparin [23, 25]. Surgical approaches were utilized in four cases [26-29].

Of our patients, 72.72% had a patent foramen ovale (PFO), with 37.5% of those having a biatrial thrombus straddling the PFO (Table 8). Among cases mentioning DVT, 31.81% of patients had DVT.

A detailed breakdown of outcomes by different treatment modalities is presented in Table 9. Anticoagulation encompasses treatments like heparin infusion and LMWH, while thrombolysis involves therapies such as recombinant tissue plasminogen activator (rt-PA), urokinase, and streptokinase. Cases categorized as no treatment involve PE being managed conservatively. Among the 22 cases analyzed (Table 9), anticoagulation led to symptom improvement and survival in 62.5% of cases, with a 12.5% mortality rate. Thrombolysis achieved symptom improvement and survival in 100% of cases. Catheter-directed thrombectomy had a 66.7% symptom improvement and survival while surgical thrombectomy had a 75%. Conservative management without anticoagulation or thrombolytic therapy resulted in 50% mortality.

Discussion

In our analysis, females predominated (68.18%) over males (31.82%), with other demographic details such as race or occupation infrequently reported, except for Saleh Velez and Ortiz Garcia [19], which included two African American pa-

Table 1. Risk of Bias

Questions	Dada et al, 2018 [28]	Barros-Gomes et al, 2018 [24]	Delgado et al, 2012 [10]	Hattori et al, 2019 [29]	Christiansen et al, 2017 [17]	De Oliveira et al, 2016 [27]	Gunta and Kamath, 2012 [11]	Konala et al, 2019 [18]	Lio et al, 2019 [13]	Bagate et al, 2018 [12]	Pan et al, 2019 [20]	Pelletier et al, 2010 [9]	Saleh Velez and Ortiz Garcia, 2021 [19]	Duy et al, 2019 [25]	Ozsancak Ugurlu et al, 2015 [23]	Xie et al, 2014 [16]	Chakir et al, 2021 [21]	Naidoo and Hift, 2011 [15]	Nam et al, 2015 [26]	Omar et al, 2013 [22]	Jayalakshmi et al, 2021 [14]
Selection 1. Does the patient(s) represent(s) the whole experience of the investigator (center) or is the selection method unclear to the extent that other patients with similar presentation may not have been reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ascertainment 2. Was the exposure adequately ascertained?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ascertainment 3. Was the outcome adequately ascertained?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Causality 4. Were other alternative causes that may explain the observation ruled out?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Causality 5. Was there a challenge/rechallenge phenomenon?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Causality 6. Was there a dose response effect?	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Causality 7. Was follow-up long enough for outcomes to occur?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Reporting 8. Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners make inferences related to their own practice?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Table 2. GRADE Analysis for Included Studies

Study	Year	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence	GRADE
Dada et al [28]	2018	Case report	High	None	Direct	None	Not significant	Low	Low
Barros-Gomes et al [24]	2018	Case report	High	None	Direct	None	Not significant	Low	Low
Delgado et al [10]	2012	Case report	High	None	Direct	None	Not significant	Low	Low
Hattori et al [29]	2019	Case report	High	None	Direct	None	Not significant	Low	Low
Christiansen et al [17]	2017	Case report	High	None	Direct	None	Not significant	Low	Low
De Oliveira et al [27]	2016	Case report	High	None	Direct	None	Not significant	Low	Low
Gunta and Kamath [11]	2012	Case report	High	None	Direct	None	Not significant	Low	Low
Konala et al [18]	2019	Case report	High	None	Direct	None	Not significant	Low	Low
Lio et al [13]	2019	Case report	High	None	Direct	None	Not significant	Low	Low
Bagate et al [12]	2018	Case report	High	None	Direct	None	Not significant	Low	Low
Pan et al [20]	2019	Case report	High	None	Direct	None	Not significant	Low	Low
Pelletier et al [9]	2010	Case report	High	None	Direct	None	Not significant	Low	Low
Saleh Velez and Ortiz Garcia [19]	2021	Case report	High	None	Direct	None	Not significant	Low	Low
Duy et al [25]	2019	Case report	High	None	Direct	None	Not significant	Low	Low
Ozsancak Ugurlu et al [23]	2015	Case report	High	None	Direct	None	Not significant	Low	Low
Xie et al [16]	2014	Case report	High	None	Direct	None	Not significant	Low	Low
Chakir et al [21]	2021	Case report	High	None	Direct	None	Not significant	Low	Low
Naidoo et al [15]	2011	Case report	High	None	Direct	None	Not significant	Low	Low
Nam et al [26]	2015	Case report	High	None	Direct	None	Not significant	Low	Low
Omar et al [22]	2013	Case report	High	None	Direct	None	Not significant	Low	Low
Jayalakshmi et al [14]	2021	Case report	High	None	Direct	None	Not significant	Low	Low

tients, and Pelletier et al [9], identifying a patient as a general surgeon. Most PEs are located in lobar, segmental, or subsegmental branches of the pulmonary artery with saddle PE, occurring in 3-6% of cases [30, 31]. In our study, 72.7% of cases involved bilateral PE.

Research indicates that 50% of individuals with proximal vein DVT also have concurrent PE. PE is linked to an elevated risk of ischemic stroke, potentially through paradoxical embolism (PDE) via a PFO. The prevalence of PFO in the general population is around 25%, and those with a PFO have a stroke risk four times higher than those without [3, 32]. In our study, 72.7% of patients with ischemic stroke had a PFO, and 27.3% had both DVT and PFO. PDE may occur when a clot from DVT passes through a PFO, causing cerebral ischemia. Additionally, in cases of acute PE, elevated right atrial pressure can lead to a right-to-left shunt through the PFO, resulting in systemic embolization [33, 34].

Management Strategies and Outcomes

Anticoagulation

PE left untreated has a mortality rate of up to 30% [35]. Anticoagulation with unfractionated heparin significantly reduces mortality in confirmed PE cases [1], but managing PE concurrent with AIS is challenging. It is recommended to defer initiating anticoagulation for PE until 24 h after administering rt-PA after the stroke, due to the risk of hemorrhagic conversion of stroke [6]. However, delaying anticoagulation initiation for more than 24 h in PE leads to a threefold increase in mortality [36], creating a dilemma in deciding when to start anticoagulation in PE patients with concurrent AIS. In our reviewed cases, anticoagulation led to symptom improvement and survival in 62.5% of cases, while 25% had worsening or no improvement in symptoms, and 12.5% resulted in mortality. Two cases demonstrated marked improvements when heparin was administered within 24 h of rt-PA for ischemic stroke [9, 10]. Jayalakshmi et al [14] reported a patient who underwent decompression craniotomy followed by full-dose heparin, achieving a positive outcome under close monitoring. Similarly, Pan et al [20] preferred LMWH due to its lower bleeding risk postoperatively, also resulting in a positive outcome.

Conversely, anticoagulation led to deterioration in functional status in some cases. Bagate et al [12] reported a case where heparin caused hemorrhagic transformation of the ischemic stroke, resulting in the patient's brain death. In Chakir et al's COVID-19 case [21], the patient was treated with aspirin for ischemic stroke and LMWH for PE, leading to only slight neurological improvement. Lio et al [13] described a patient who, treated with unfractionated heparin for bilateral lobar

Table 3. Patient Information, Risk Factors and Presenting Symptoms

Study	Age/sex	Risk factors	Presenting symptoms
Pelletier et al, 2010 [9]	35/F	Recent leg varicosal stripping, one spontaneous abortion, OCP use	Collapsed, altered consciousness, expressive aphasia, subtle facial asymmetry
Delgado et al, 2012 [10]	76/F	Hypertension, dyslipidemia	Sudden right leg paresis and hypoesthesia
Gunta and Kamath, 2012 [11]	16/F	Long car ride, OCP, family history of venous thromboses and PE, MTHFR mutation, antithrombin III deficiency	Unresponsive, labored respirations, shortness of breath, cough, leg pain for 2 days
Bagate et al, 2018 [12]	44/M	Psychiatric disorder	Non-shockable cardiac arrest, impaired consciousness
Lio et al, 2019 [13]	69/M	Testicular carcinoma	Signs of cardiogenic shock, questionable GI bleeding
Jayalakshmi et al, 2021 [14]	52/M	Not mentioned	Not mentioned
Naidoo and Hift, 2011 [15]	38/F	Immobility, dilated cardiomyopathy, HIV on antiretroviral therapy	Dyspnea, pleuritic chest pain, right-sided hemiplegia
Xie et al, 2014 [16]	55/F	History of varicose veins of lower extremities	Chest distress, dyspnea, loss of consciousness, sudden non-fluent language, dyskinesis of right extremities
Christiansen et al, 2017 [17]	59/F	Post-operative day 2 abdominoplasty and liposuction, OCP	Left-sided weakness, dysarthria, acute respiratory distress
Konala et al, 2019 [18]	82/M	Type 2 diabetes mellitus, previous lower extremity DVT	Loss of consciousness while urinating, mild dyspnea before syncope
Saleh Velez and Ortiz Garcia, 2021 [19]	72/F	Not mentioned	Collapsed, comatose state, flaccid quadriplegia, cardiac arrest
Saleh Velez and Ortiz Garcia, 2021 [19]	75/F	Hypertension	Mild dysarthria, right arm paresis, severe pleuritic pain, shortness of breath
Pan et al, 2019 [20]	27/F	Post-operative day 7 C-section, Glenn anastomosis 7 years prior for cor biloculare	Dizziness, chest tightness, dysarthria, facial asymmetry, right hemiparesis
Chakir et al, 2021 [21]	60/M	Type II diabetes, COVID-19 infection	Left hemiplegia, typical anginal chest pain, hypotonia, left sensory deficit
Omar et al, 2013 [22]	69/M	Post-operative day 1 right total hip replacement, hypertension, dyslipidemia, prior surgical repair of iliac artery aneurysm	Shortness of breath, wheezing, confusion, aphasia, right-sided weakness
Ozsancak Ugurlu et al, 2015 [23]	64/F	Not mentioned	Shortness of breath, chest pain, recurrent syncope, convulsion
Barros-Gomes et al, 2018 [24]	68/F	Hypertension, tobacco abuse, COPD	Facial droop, right arm weakness, aphasia
Duy et al, 2019 [25]	53/F	Three prior ischemic strokes	Unconsciousness, dyspnea, right hemiplegia
Nam et al, 2015 [26]	69/F	Not significant	Dyspnea, drowsy mental status, right-sided hemiplegia after surgery
De Oliveira et al, 2016 [27]	41/F	Post-operative day 10 lap cholecystectomy	Dysarthria, acute respiratory distress, left calf tenderness
Dada et al, 2018 [28]	55/M	Not mentioned	Left facial droop, left-sided weakness, garbled speech
Hattori et al, 2020 [29]	68/F	History of multiple cerebral emboli, SLE on prednisolone	Dysarthria, dysphagia, left facial paralysis

COPD: chronic obstructive pulmonary disease; DVT: deep vein thrombosis; GI: gastrointestinal; HIV: human immunodeficiency virus; OCP: oral contraceptive pill; PE: pulmonary embolism; SLE: systemic lupus erythematosus.

PE and later undergoing emergent thrombectomy for basilar occlusion, deteriorated and died from progressive obstructive shock and renal failure. In contrast, Gunta and Kamath [11] reported a pediatric case where unfractionated heparin for PE followed by mechanical clot retrieval and aspirin for stroke led to long-term favorable functional improvement.

Table 4. Descriptive Analysis of the Extracted Data From Included Studies

Patients, N	22
Case reports, N	20
Case series, N	1
Female, N (%)	15 (68.18%)
Male, N (%)	7 (31.82%)
Mean patient age, years	56.68 (SD: 16.8)
Median patient age, years	59.5

SD: standard deviation.

Thrombolysis

Thrombolytic therapy, available as systemic or catheter-directed, is an alternative treatment for PE. Systemic thrombolysis is typically reserved for hemodynamically unstable patients, with an absolute contraindication being a non-hemorrhagic stroke within the previous 3 months. Despite this, we identified five cases [15-19] using thrombolysis, all of which resulted in symptom improvement and survival. For instance, Naidoo and Hift [15] observed rapid neurological improvement, likely due to reperfusion of critical cerebral ischemia. Christiansen et al [17] treated a post-surgical patient with intravenous (IV) alteplase for ischemic stroke and PE, along with MT. Although thrombolysis is contraindicated within 14 days of major surgery, they argued that the intracerebral hemorrhage risk with anticoagulation was too high, and thrombolysis would address both PE and stroke. With optimal surgical control of the resulting abdominal hematoma, complete neurological and respiratory recovery was observed.

For PE complicated by right heart thrombus, thrombolysis and surgical thrombectomy are treatment options. Konala et al [18], referencing the pulmonary embolism-3 trial results [37], chose thrombolysis with alteplase followed by IV heparin, resulting in a post-thrombolysis ischemic stroke. This underscores the risk of PDE in PE with PFO post-thrombolysis. Management of such cases may involve catheter-directed thrombolysis (CDT) with percutaneous PFO closure or surgical embolectomy with PFO closure.

Evidence from the ULTIMA and SEATTLE-II trials provides insights into the effectiveness of CDT in PE management. The ULTIMA trial, though limited by a small sample size and design constraints, suggests potential benefits of CDT in reducing right ventricular dilation, pulmonary hypertension, and thrombus burden compared to anticoagulation alone. SE-

Table 5. Prevalence of Main Predisposing Factors

Predisposing factors	N	%
PE		
OCP use	4	18.18
Post major surgical interventions	4	18.18
Immobility	2	9.09
Varicose veins	2	9.09
Prior lower extremity DVT	1	4.55
Family history of venous thromboses and PE	1	4.55
Homozygous for MTHFR mutation/ATIII deficiency	1	4.55
Tobacco abuse	1	4.55
COPD	1	4.55
HIV on ART	1	4.55
SLE	1	4.55
Pregnancy, especially first 6 weeks postpartum	1	4.55
Compression by mass (testicular carcinoma)	1	4.55
History of Glenn anastomosis	1	4.55
COVID-19 infection	1	4.55
Ischemic stroke		
Hypertension	5	22.73
Dyslipidemia	3	13.64
Type 2 diabetes mellitus	2	9.09
Prior thromboembolic strokes	2	9.09
Tobacco abuse	1	4.55

ART: antiretroviral therapy; AT: antithrombin; COPD: chronic obstructive pulmonary disease; DVT: deep vein thrombosis; HIV: human immunodeficiency virus; OCP: oral contraceptive pill; PE: pulmonary embolism; SLE: systemic lupus erythematosus.

Table 6. Case Reports Describing Multiple Permutations of Treatment Combinations and Their Outcomes

Study	Location of PE	Treatment of PE	Location of stroke	Treatment of stroke	PFO and treatment	DVT	PFO with thrombus	Outcome
Pelletier et al, 2010 [9]	Bilateral	Heparin infusion	Left tempoparietal	rt-PA, IVC filter	Present, closed	Negative		Marked improvement
Naidoo and Hift, 2011 [15]	Bilateral	Streptokinase	Left frontoparietal	Not treated, since neuro improved	Absent	Positive, right		Marked improvement
Delgado et al, 2012 [10]	Bilateral segmental, subsegmental	Heparin infusion	Left ACA	rt-PA	Present, not closed	Not mentioned		Marked improvement
Gunta and Kamath, 2012 [11]	Bilateral main	Heparin infusion, LMWH IVC filter	Left striatocapsular and internal capsule	MT followed by aspirin	Present, planned closure at later date	positive		Marked improvement
Omar et al, 2013 [22]	Descending trunk, right main segmental/ subsegmental	IVC filter	Left MCA	MT	Present, not a candidate for PFO closure	Not mentioned		Bed-ridden and non-verbal
Ozsancak Ugurlu et al, 2015 [23]	Bilateral main into lobar branches	Percutaneous embolectomy (MT), heparin infusion	Left occipital and bilateral cerebellar lobes	Not treated	Not mentioned	Not mentioned		Marked improvement
Xie et al, 2014 [16]	Bilateral	Urokinase, LMWH, aspirin and clopidogrel	Left temporal, parietal, insular lobes and basal ganglia	Increased aspirin and clopidogrel dose	Absent	Negative		Marked improvement, recurrence of PE 10 months later
Nam et al, 2015 [26]	Bilateral	Surgical embolectomy	Left MCA and multifocal, embolic infarctions in right cerebrum	Decompressive craniectomy	Present, closed	Not mentioned	Biatrial thrombus across PFO	Long-term ventilatory support, no neuro improvement
De Oliveira et al, 2016 [27]	Not mentioned	Surgical thrombectomy	Not mentioned	Not mentioned	Present, closed	Present, left	Right atrial thrombus straddling PFO	Marked improvement
Christiansen et al, 2017 [17]	Bilateral lobar and segmental	rt-PA, LMWH, aspirin	Right MCA	rt-PA, MT	Present, not closed	Negative		Abdominal hematoma post thrombolysis, marked improvement

Table 6. Case Reports Describing Multiple Permutations of Treatment Combinations and Their Outcomes - *(continued)*

Study	Location of PE	Treatment of PE	Location of stroke	Treatment of stroke	PFO and treatment	DVT	PFO with thrombus	Outcome
Barros-Gomes et al, 2018 [24]	Bilateral	MT	Left ICA	Not treated	Present, not closed	Not mentioned	Thrombus in PFO	Not reported
Bagate et al, 2018 [12]	Bilateral	Heparin infusion	Left parietal lobe	Not treated	Present, not closed	Not mentioned		Brain death
Dada et al, 2018 [28]	Main	Surgical clot removal, heparin infusion	Left temporal occipital lobe	rt-PA not given, outside window	Present, closed	Positive, right	Biatrial thrombus straddling PFO	Marked improvement
Duy et al, 2019 [25]	Bilateral	Percutaneous thrombectomy (MT), heparin infusion	Left MCA	MT	Present, anticoagulant therapy only	Negative		Marked improvement
Konala et al, 2019 [18]	Bilateral main	rt-PA, heparin infusion, IVC filter	Left caudate/ putamen area	Not treated	Present, patient refused closure	Positive, bilateral	Biatrial thrombus straddling PFO	Marked improvement
Hattori et al, 2020 [29]	Bilateral main	Surg pulmonary embolectomy, IVC filter	Brain stem and left occipital lobe	Not treated	Present, closed	Positive	Thrombus straddling PFO	Marked improvement
Lio et al, 2019 [13]	Bilateral lobar	Heparin infusion	Basilar artery occlusion	MT	Present, not closed	Not mentioned		Dead
Pan et al, 2019 [20]	Left inferior and right lobar	LMWH	Left basal ganglia	Not treated	Absent	Negative		Marked improvement
Saleh Velez and Ortiz Garcia, 2021 [19]	Bilateral	Medical therapy	Right ICA	Medical therapy	Present	Negative		Dead
Saleh Velez and Ortiz Garcia, 2021 [19]	Bilateral main	Catheter-directed thrombolysis, IV heparin	Left MCA	rt-PA deferred, unknown, last time well	Present	Positive, left		Marked improvement
Jayalakshmi et al, 2021 [14]	Not mentioned	Heparin	Right MCA	Decompressive craniotomy	Not mentioned	Not mentioned		Marked improvement
Chakir et al, 2021 [21]	Bilateral	LMWH	Right MCA	Aspirin	Absent	Negative		Slight improvement in neuro

ACA: anterior cerebral artery; DVT: deep vein thrombosis; LMWH: low molecular weight heparin; ICA: internal carotid artery; IV: intravenous; IVC: inferior vena cava; MCA: middle cerebral artery; MT: mechanical thrombectomy; PE: pulmonary embolism; PFO: patent foramen ovale; rt-PA: recombinant tissue plasminogen activator.

Table 7. Frequencies of Treatment Approaches for PE

Treatment approach for PE	Number of cases
Thrombolysis	5
rt-PA + AC	2
Streptokinase alone	1
Urokinase + AC	1
Catheter thrombolysis + AC	1
Heparin	6
Post rt-PA	2
Post MT	2
With craniotomy	1
Only	1
LMWH	2
Only	1
Aspirin	1
IVC filter only	1
Medical therapy only	1
Catheter-directed thrombectomy	3
MT	1
Percutaneous thrombectomy + heparin	2
Surgical approach	4
Surgical embolectomy/thrombectomy	2
Surgical pulmonary embolectomy + IVC	1
Surgical clot removal + heparin	1

AC: anticoagulation; LMWH: low molecular weight heparin; IVC: inferior vena cava; MT: mechanical thrombectomy; PE: pulmonary embolism; rt-PA: recombinant tissue plasminogen activator.

ATTLE-II, a single-arm study without a heparin-only comparison, further supports CDT's potential advantages, though the lack of a control group means that results should be cautiously interpreted given the study's inherent limitations [38-40].

Embolectomy

Embolectomy is a viable alternative when thrombolysis is contraindicated, with options for surgical or catheter-directed procedures. In our study, percutaneous thrombectomy using unfractionated heparin yielded symptomatic improvement in two cases [23, 25], though Barros-Gomes et al [24] did not report outcomes. Surgical embolectomy is recommended when an embolus is trapped within a PFO, right atrium, or right ventricle [41]. In cases where a thrombus is identified within a PFO, closure of the PFO is sometimes considered to prevent further embolic events. However, closing the PFO during the acute phase might increase the risk of right-sided heart failure, as the PFO can function as a pressure-release mechanism to relieve elevated right atrial pressure. Consequently, some clinicians may delay closure until the patient is stable, typically several months after the acute event [3]. However, mortality rates for pulmonary embolectomy range from 27% to 41% [42, 43]. In our cohort, surgical thrombectomy resulted in symptom improvement and survival in 75.0% cases, with no reported mortality and 25.0% having functional status deterioration.

Table 8. Prevalence of PFO, PFO With Thrombus, and DVT in Patients With Concurrent PE and AIS

Findings	Present	Absent	Not mentioned
PFO	16 (72.72%)	4 (18.18%)	2
PFO with thrombus	6/16 (37.5%)		
DVT	7 (31.81%)	7 (31.81%)	8

AIS: acute ischemic stroke; DVT: deep vein thrombosis; PE: pulmonary embolism; PFO: patent foramen ovale.

Conservative management

When management without anticoagulation or thrombolytic therapy was utilized, outcomes were poor: 50% of cases resulted in functional status deterioration (bed-bound and non-verbal), and 50% ended in mortality, highlighting the crucial role of treatment strategies. In Omar et al's case [22], where anticoagulation and thrombolysis were withheld due to hemorrhagic transformation on follow-up brain imaging, an endovascular approach was employed for the stroke, and an IVC filter was placed. Despite this approach aiming to mitigate bleeding risks, the patient remained bed-ridden and non-verbal. Similarly, the first case reported by Saleh Velez and Ortiz Garcia [19] relied solely on

Table 9. Outcomes by Treatment Modality in Patients With PE and AIS

Treatment modality	Symptom improvement and survival	Deterioration in functional status	Mortality	Not reported	Total cases
Anticoagulation	5 (62.5%)	2 25.0%)	1 (12.5%)	0 (0.0%)	8
Thrombolysis	5 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	5
Catheter-directed thrombectomy	2 (66.7%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	3
Surgical thrombectomy	3 (75.0%)	1 (25.0%)	0 (0.0%)	0 (0.0%)	4
Treatment without anticoagulation or thrombolytic therapy	0 (0.0%)	1 (50.0%)	1 (50.0%)	0 (0.0%)	2
Total	15 (68.2%)	4 (18.2%)	2 (9.1%)	1 (4.5%)	22

AIS: acute ischemic stroke; PE: pulmonary embolism.

medical therapy for both PE and stroke, which tragically resulted in the patient's death. The decision to avoid aggressive treatments like thrombolysis and thrombectomy, in this case, appears to have contributed to impairment in functional status.

Strengths

This systematic review boasts a comprehensive search strategy, adherence to PRISMA guidelines, and stringent inclusion criteria, ensuring high-quality studies. Detailed data extraction, GRADE scoring for quality assessment, and Rayyan.ai for duplicate identification enhance accuracy. The review provides valuable insights into clinical characteristics, management strategies, and outcomes, highlighting the lack of established protocols and the need for further research. By documenting diverse treatment approaches and offering a balanced discussion of outcomes, the review contributes to the robustness and clinical relevance of potential management strategies.

Limitations

The review's limitations include a small sample size, with only 22 patients, which restricts the generalizability of the findings to a broader population. The lack of complete demographic data, such as information on race and occupation, further limits the ability to fully characterize the patient population. The heterogeneity in the quality and completeness of reporting across case reports may affect the reliability and consistency of the results. Several case reports did not account for multiple comorbidities, which could confound the relationships between treatment modalities and outcomes. Furthermore, the absence of control groups in this study of case reports and case series limits the ability to make causal inferences. The inherent biases of the study, particularly selection bias, also affect the validity of the conclusions drawn from these findings. The influence of age and sex on survival prognosis in this complex presentation remains unclear.

Gaps in the existing literature

Several gaps require further research and clarification.

Optimal treatment strategies for combined PE and AIS

The effectiveness and safety of thrombolytic therapy, MT, and anticoagulation in managing both PE and AIS need further study [19]. The efficacy of combining treatments, such as rt-PA with MT, remains unclear and requires more clinical evidence. The role of CDT alone or with mechanical methods in high-risk PE patients unable to receive thrombolysis or those who are unstable post-thrombolysis also needs investigation [44].

Safety and timing of anticoagulation post-rt-PA

There is no consensus on the optimal timing for initiating anticoagulation after rt-PA administration for AIS. Literature shows delay up to 24 h post-rt-PA, highlighting the need to balance bleeding risks with early anticoagulation in patients with both AIS and PE [19].

Over-treatment and management of subsegmental PE (SSPE)

Current approaches often lead to over-treatment of SSPE, in asymptomatic or low-risk patients. Research is needed to identify which patients can safely forgo anticoagulation without increasing recurrent event risks [45].

Conclusion

The findings from this systematic review, primarily based on observational data from case reports, illustrate the diverse strategies employed by physicians in the management of combined PE and AIS. While proactive treatments, such as thrombolysis and thrombectomy, tend to yield better outcomes, the lack of robust clinical evidence and the reliance on case reports limit the ability to draw definitive conclusions and specific treatment recommendations. Therefore, this comprehensive overview underscores the importance of well-designed prospective, randomized controlled trials to confirm the efficacy and safety of various treatments. Such trials would investigate standardized treatment protocols, to guide structured clinical guidelines to manage this complex presentation.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

SS designed the research, performed the research, analyzed data, and wrote the paper. CV performed the research, analyzed data, and contributed to writing the paper. JI reviewed the paper.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

AC: anticoagulation; AIS: acute ischemic stroke; DVT: deep vein thrombosis; L: left; LMWH: low molecular weight heparin; MCA: middle cerebral artery; MT: mechanical thrombectomy; PE: pulmonary embolism; R: right

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