Hospitalization Burden in Pulmonary Arterial Hypertension: Evidence from Systematic Reviews of RCTs and RWS

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Background

Clinical context: Pulmonary arterial hypertension (PAH) is a progressive and chronic disease affecting the pulmonary vasculature and right heart. The most common symptoms are dyspnea on exertion, fatigue and rapid exhaustion, palpitations, hemoptysis, edema, and syncope.[1] Patients with PAH typically face delayed diagnosis,[1,2] which leads to an increased likelihood of being diagnosed at an advanced disease stage, marked by severe symptoms and morbidity events, including hospitalizations.[2,3]

The burden of hospitalization: Evidence from randomized controlled trials (RCTs)[4] and real-world studies (RWS)[5] has shown that, in patients with PAH, high hospitalization rates are associated with worse survival[6] and drive substantial economic costs.[7] Both RCTs and RWS have reported high hospitalization rates among patients with PAH; however, rates have been found to be discrepant, with higher rates found in RWS, and have seldom been systematically evaluated across these study types.

Objective

Using data identified from two systematic literature reviews (SLRs), the objective of this research was to evaluate and compare hospitalization rates in patients with PAH, either all-cause or PAH-related, reported in RCTs against those observed in RWS.

Methods

Scope of evidence review and synthesis: Two SLRs were conducted to identify and synthesize clinical and economic burden data specific to PAH. Table 1 lists the eligibility criteria and the outcomes that were extracted and synthesized; the current analysis focuses specifically on evidence identified for hospitalization rates.

Methodological framework: The SLRs were conducted in strict accordance with international methodological standards and best practices for identifying and synthesizing clinical and economic evidence.[8-10]

Electronic databases: Electronic databases were searched from inception until December 2024 (MEDLINE, Embase; clinical SLR: PsycINFO, CENTRAL, CDSR; economic SLR: Econlit, Tufts, and EQ-5D publications repository). The electronic searches were supplemented by searches of conference abstracts (Conference Proceedings Citation Index-Science, Embase conferences) and health technology assessment agencies' websites (International Network of Agencies for Health Technology Assessment, National Institute for Health and Care Excellence, Canada's Drug Agency, and Scottish Medicines Consortium), and hand searches of specific congresses relevant for PAH (e.g., European Respiratory Society, World Symposia on Pulmonary Hypertension Association), as well as the primary studies included by SLRs retrieved by the electronic searches.

Eligibility criteria: Records retrieved from the aforementioned sources were independently assessed by two reviewers against the eligibility criteria (Table 1), and discrepancies were resolved by consensus or arbitrated by a third reviewer. Data were extracted by one reviewer and validated by a second reviewer.

Table 1. PICOS criteria

Parameter	Criteria	
	Clinical SLR	Economic SLR
Population	Adults (≥ 18 years) with PAH (WHO Group 1) [a]	
Intervention and comparator	Approved targeted PAH therapies vs. any/no comparator [b]	Approved targeted PAH therapies vs. any/no comparator [b, c] Any/no interventions vs. any/no comparator
Outcomes	• Efficacy (e.g., morbidity/mortality, hospitalizations, WHO functional class) • Safety (e.g., adverse events) • Health-related quality of life	• Direct costs (e.g., hospital, outpatient) • Indirect costs (e.g., wages lost) • Cost-effectiveness (e.g., ICERs, QALYs) • Utilities (e.g., EQ-5D)
Study design [d]	RCTs, OLEs, single-arm interventional trials	Economic analyses, observational studies (prospective/retrospective), and utility studies
Limits	English language	

[a] Excludes studies where PAH representation is <20%, patients aged <18 years comprise ≥20% of the sample, or focus is on other PH subtypes.
[b] Excludes intravenous iloprost, which is not approved for PAH therapy.
[c] For economic evaluations only.
[d] Excludes case studies, narrative reviews, and editorials.
Abbreviations: ICER, incremental cost-effectiveness ratio; OLE, open-label extension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PICOS, Population, Intervention, Comparator, Outcomes, Study; QALY, quality-adjusted life-year; RCT, randomized controlled trial; SLR, systematic literature review; WHO, World Health Organization.

Results

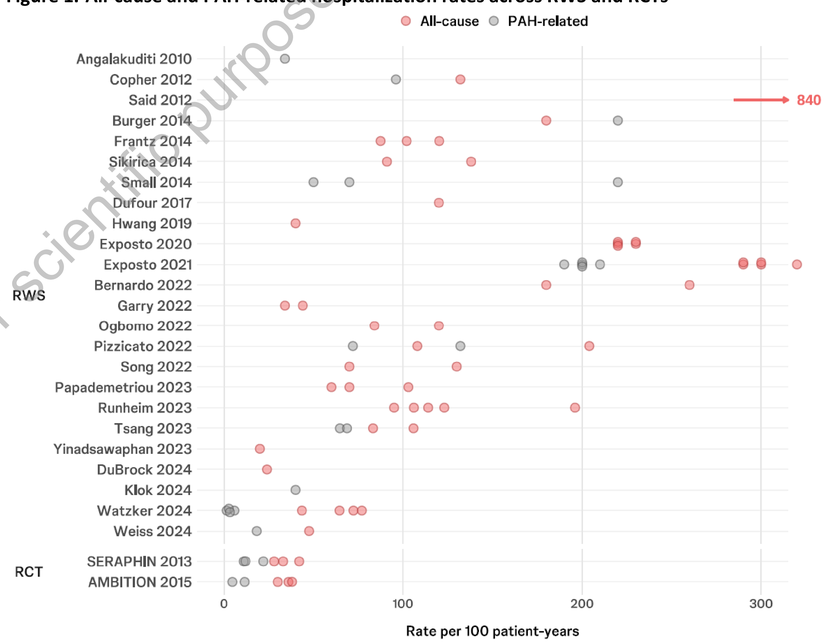
Overall results: The clinical SLR identified 113 eligible interventional trials, 69 of which were single-arm clinical trials or open-label extensions and 44 were RCTs, including 23 Phase 3 RCTs. Of those 23 Phase 3 RCTs, two reported all-cause hospitalization data that could be extracted (AMBITION 2015, SERAPHIN 2013); SERAPHIN reported PAH-related hospitalization for all arms, whereas AMBITION reported pooled data for monotherapy arms.[11,12] The economic SLR synthesized 113 RWS, of which 24 reported hospitalization rates, including 21 studies that reported all-cause hospitalization[13-33] and 10 studies that reported PAH-related hospitalization.[6,7,14,22,27,28,31-34] Publication dates for the 24 RWS that reported hospitalization rates ranged between 2012 and 2024, and study designs were predominantly retrospective chart reviews or insurance claims analyses conducted in the US. Three studies were conducted in Europe,[17,23,31] and one study was conducted in Asia.[19]

RCT hospitalization rates: Both RCTs were large, multicenter, worldwide trials. AMBITION compared combination therapy (ambrisentan plus tadalafil) with single therapy (ambrisentan or tadalafil), whereas SERAPHIN assessed the safety and efficacy of macitentan (3 mg or 10 mg) versus placebo. All-cause hospitalization events per 100 patient-years (PYs) were 30, 36, and 38 (AMBITION; combination therapy, ambrisentan, and tadalafil monotherapy, respectively) and 33, 28, and 42 (SERAPHIN; macitentan 3 mg, 10 mg, and placebo, respectively; Figure 1). SERAPHIN also reported PAH-related hospitalization rates, which were lower at ~11 (macitentan) to 22 (placebo) events per 100 PYs. AMBITION reported PAH-related hospitalizations rates for combination therapy and pooled monotherapy arms. All-cause hospitalization rates were similar in the two trials; however, PAH-related hospitalization accounted for a smaller proportion of all-cause hospitalization in AMBITION than in SERAPHIN.

Several other Phase 3 RCTs reported the proportion of patients who were hospitalized at least once for worsening of PAH during trial duration. There was considerable variation in those data, with proportions for the active arm ranging from 0%[35,36] to 27%.[37]

Real-world hospitalization burden: RWS data were highly variable and hospitalization rates were generally higher than those reported by RCTs, both for all-cause and PAH-related hospitalization (Figure 1). Across the 21 studies reporting all-cause hospitalization (excluding pre-diagnosis and subgroup data when data for the full population were available, as to avoid double counting), the mean rate was 151 events per 100 PYs (median 114; range 20–840). In the 10 studies reporting PAH-related hospitalization (likewise excluding pre-diagnosis and subgroup data, if applicable), the mean rate was 100 events per 100 PYs (median 70; range 1.5–220).

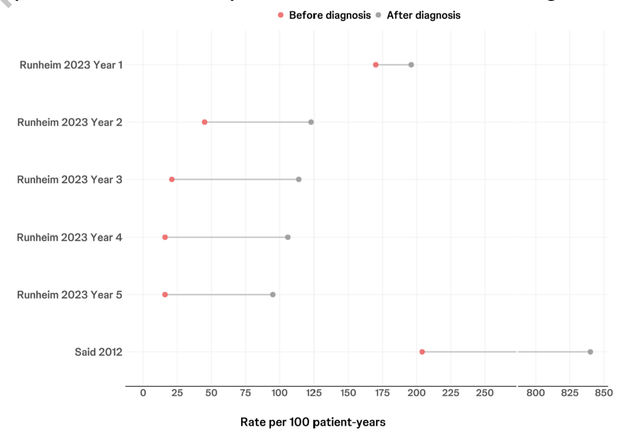
Figure 1. All-cause and PAH-related hospitalization rates across RWS and RCTs



Note: Axis X capped at 350 events per 100 patient-years; Said 2012 reported rate is 840 events per 100 patient-years. Data for the full population, when available, were prioritized; studies with multiple datapoints only reported data for different subgroups. Excludes pre-diagnosis data.
Abbreviations: PAH, pulmonary arterial hypertension; RCT, randomized controlled studies; RWS, real world studies.

Comparative evidence: While comparative evidence was scarce, some RWS provided comparative data for the period before and after diagnosis, and before and after treatment initiation. As expected, hospitalization rates were higher after diagnosis than before diagnosis (Figure 2),[23,24] but substantially lower after treatment initiation compared with the period before initiating treatment (before: 138 to 204; after: 91 to 108).[22,25] Notably, hospitalization rates were particularly high in the year before and the year after diagnosis.[23,24] Two studies reported significantly lower hospitalization rates among a control group of patients who did not have PAH,[23,24] highlighting the elevated burden observed in patients with PAH.

Figure 2. Comparative evidence for hospitalization rates before and after diagnosis



Note: For Said 2012, data are reported for 12 months before and after diagnosis.

Limitations

Scarcity of trial data: As only two RCTs reported all-cause hospitalization rates, the baseline estimates from clinical trials are limited and may not fully represent the broader trial landscape.

Geographic limitation of RWS evidence: Data were mostly generated in the US, which may pose constraints to their generalizability to other contexts and healthcare systems.

Drivers of RCT variance: Trial duration and outcome definition and adjudication were heterogenous across the RCTs eligible for the clinical SLR, which can partially explain the considerable variance observed for hospitalization rates and the proportion of patients hospitalized during the trial duration.

Drivers of RWS variance: The variance observed in RWS hospitalization rates complicates direct comparisons and underscores the influence of diverse study designs, varying regional healthcare practices and administrative coding, and differing baseline patient characteristics and treatment approaches.

Reporting of disease stage and progression: RWS seldom track disease progression in a consistent manner. This makes it difficult to fully isolate the impact of evolving disease severity on hospitalization rates.

Conclusion

Clinical relevance: Hospitalization rates in PAH remain substantial, with RWS frequently reporting rates several-fold higher than those observed in RCTs. Several factors may contribute to the disparity across data sources, including the patient selection that occurs in RCTs, as well as the broader representativeness of RWS, regarding both disease severity and treatment patterns. RWS are essential to capture the clinical burden of PAH.

Persistent high burden: PAH places a sizeable strain on healthcare resources, specifically inpatient services. Evidence consistently showed the persistent high burden of PAH, as hospitalizations rates were consistent in the studies identified by these SLRs, regardless of their publication date.

Unmet need: There is an urgent requirement for optimized treatment combinations that effectively reduce hospitalization rates and their associated clinical and economic impacts.

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