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SYSTEMATIC REVIEW

Exploring the Economic Burden of Pulmonary Arterial Hypertension and Its Relation to Disease Severity and Treatment Escalation: A Systematic Literature Review

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Abstract

Background Pulmonary arterial hypertension (PAH) is a highly progressive disease characterized by luminal narrowing of the pulmonary arteries, leading to progressive dyspnoea and restricted functional capacity, which can ultimately result in right ventricular failure and death. Treatment goals include improving functional class and walk distance, recovering right ventricular function, halting disease progression, and improving survival. PAH carries a high mortality rate, and treatment escalation is a common feature of disease management. Due to the substantial impact of PAH, a high economic burden has been observed. A systematic literature review (SLR) was carried out to assess the contemporary economic burden of PAH, including the impact of disease severity and treatment escalation.

Methods An electronic database search was conducted and supplemented with a hand search of health technology assessments and conference materials. Studies were included from 2012 to 2024, with no restrictions on geographical location. The inclusion criteria specified that adult patients with PAH (≥ 18 years) and only English language studies were captured.

Results The review included 148 studies and evaluations, 110 of which were observational studies, 14 were economic evaluations, and 24 were health technology assessments. The studies identified reported on several healthcare resource utilization (HCRU) outcomes including hospitalization, PAH-related hospitalization, inpatient visits, emergency department (ED) visits, intensive care unit (ICU) visits, and outpatient visits. Cost data were also reported, including total costs and costs for each of the above-mentioned types of HCRU, as well as specific costs such as pharmacy and drug costs. The results provide an overview of the high economic burden caused by PAH, indicating that the economic burden increases with increasing severity; reported mean monthly costs were as high as US $14,614 (cost converted to USD 2024) for the highest severity group. These data also demonstrated the impact of PAH-specific therapies in reducing HCRU, with efficacious treatment shifting management from an inpatient to outpatient setting (i.e., reduced inpatient admissions and length of stay). Further, while treatment escalation resulted in increased pharmacy costs, this was offset by a reduction in HCRU, including hospitalizations and ED visits. Timely diagnosis was also associated with reduced economic burden, as patients with a longer delay prior to diagnosis reported a higher mean number of monthly hospitalizations, ICU stays, and ED visits. Functional limitation is a common feature of PAH disease progression and can severely impact a patient's ability to work. This SLR identified few studies that investigated such outcomes as well as broader indirect costs, such as out-of-pocket costs and productivity loss.

Discussion This study highlights the considerable economic burden associated with PAH, which is particularly evident for HCRU, and the importance of effective disease management in reducing this burden. Additionally, these findings demonstrate the economic value of treatment escalation and suggest higher drug costs can potentially be offset through improved patient outcomes and associated reductions in HCRU.

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1 Introduction

Pulmonary arterial hypertension (PAH) is a highly progressive, life-threatening condition characterized by progressive narrowing of the pulmonary arteries, leading to increased pulmonary vascular resistance, restricted functional capacity, right ventricular failure, and ultimately, death [1]. PAH

Key Points for Decision Makers

Patients with poorly managed PAH incur higher economic burden owing to faster disease progression and worse disease severity, with hospitalization a key driver of high costs.

Appropriate disease management, i.e., timely diagnosis, monitoring, and escalation of treatment leads to reduced healthcare resource use and consequent lowering of costs and holistic economic burden.

To reduce the overall burden on the healthcare system and improve PAH care, there is a need for earlier diagnosis, improved risk assessment, and guideline-directed treatment strategies.

is a subgroup of pulmonary hypertension (PH) and is designated as group 1 PH by the World Health Organization (WHO) [2]. The pathology of PAH puts excessive burden on the right ventricle and impacts blood flow between the heart and the lungs [3], causing a multitude of symptoms, including fatigue, dyspnea, edema, and chest pain, which adversely affect quality of life (QoL) [4].

Pharmacologic therapy for PAH includes conventional therapies and treatments with regulatory approval for PAH (PAH-specific treatments) [5, 6]. Conventional therapies include oxygen diuretics, anticoagulants, and digoxin [7]. PAH-specific treatments can be split into four major categories: endothelin receptor antagonists (ERAs) targeting the endothelin pathway; phosphodiesterase type-5 inhibitors (PDE5is) and guanylate cyclase stimulators (sGCs) targeting the nitric oxide pathway; prostacyclin analogs and prostacyclin receptor agonists targeting the prostacyclin pathway [7–10]; and the recently approved activin signaling inhibitor (ASI) sotatercept [11].

PAH management and treatment strategy are largely determined by disease severity [7], as evaluated through regular assessment of the risk of death [7]. Assessment tools focus primarily on three parameters: WHO functional class (WHO FC), serum levels of the biomarker N-terminal pro-B-type natriuretic peptide (NT-proBNP) N-terminal pro-B-type natriuretic peptide, and the 6-min walk test, i.e., the distance a patient can walk in 6 min [7, 12].

Following diagnosis, patients are recommended to initiate disease-specific treatment, most often with combination therapy in accordance to published guidelines, and undergo an assessment for the risk of death every 3–6 months to refine the disease management strategy [7]. The main treatment goal is to achieve and maintain a low risk status. Patients at a higher risk status require treatment escalation and additional therapies [7].

The management of PAH creates a considerable economic burden on patients and healthcare services, driven by the high rates of healthcare resource utilization (HCRU) owing to hospitalizations, outpatient visits, and emergency department (ED)/intensive care unit (ICU) visits [13–15], as well as high pharmacologic treatment costs [16, 17]. Additionally, substantial indirect costs have been linked to PAH, including productivity losses due to the impact of PAH on function, as well as absenteeism, due to missed work days for clinic visits and hospitalizations.

This systematic literature review (SLR) aimed to provide an up-to-date understanding of the global economic burden of PAH through exploring published articles of economic models, cost, and HCRU data, including general and PAH-related hospitalization, ICU admissions, and outpatient and ED visits. Given the highly progressive nature of PAH and the requirement for treatment escalation, this SLR also aimed to assess the economic impact of increased disease severity and different treatments, with a particular focus on treatment escalation.

2 Methods

The review was conducted according to the updated 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Guidelines [18].

2.1 Search Strategy

To capture up-to-date published evidence on the contemporary economic burden of PAH, including direct costs, indirect costs, and HCRU data, a literature search was designed and conducted across Embase, Medline and Medline In-Process, EconLit, and the Cochrane Library via the OVID® platform.

An electronic database search was completed on 17 January 2024, with a time horizon of approximately 12 years (searches dated back to 1 January 2012). No geographical restrictions were applied to the searches as the aim was to understand the global economic burden of PAH; however, only English-language studies were included in the review. SLRs and meta-analyses were initially included, with the ten most relevant according to the inclusion criteria being selected for a complete review of the bibliography. This was to ensure all studies fulfilling the inclusion criteria were captured; however, the identified SLRs were not extracted or included in the results. Database search strategies are presented in Supplementary Table 1 through Table 8.

In addition to the database searches, a gray literature search was completed, in which conference materials from

the following congresses, not indexed in Embase, were reviewed: ERS, ESC, the World Conference on Lung and Respiratory Disease, and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Conference abstracts published from 1 January 2020 to 17 January 2024 were included, as it was assumed that studies of a reasonable quality published prior to this date would have been published in a peer-reviewed journal by the time the search was completed. In addition, a search of the following health technology assessment (HTA) websites was completed to identify any relevant economic evaluations for interventions on interest: Australia Pharmaceutical Benefits Scheme (PBS) [19], Canadian Agency for Drugs and Technologies in Health (CADTH) [20], Institute for Clinical and Economic Review (US ICER) [21], National Center for Pharmacoeconomics (NCPE Ireland) [22], National Institute for Health and Care Excellence (NICE England) [23], Scottish Medicines Consortium (SMC) [24], and All Wales Medicines Strategy Group (AWMSG) [25].

2.2 Inclusion Criteria

The retrieved studies were screened against the predefined Population, Intervention, Comparison, Outcomes, and Study (PICOTS) criteria outlined in Table 1. Eligible publications focused on adult patients with PAH (defined as WHO Group 1 PH), and therefore, pediatric patients (< 18 years old) were excluded. Studies that reported on mixed populations of pediatric and adult PAH patients, or multiple WHO PH groups, were only included if the data were stratified to enable the extraction of relevant populations.

2.3 Study Selection and Data Extraction

Each study's eligibility, based on its alignment with the PICOTS (Table 1), was reviewed independently by two reviewers, with any discrepancies resolved by a third reviewer. Studies were reviewed in two stages: first, only the title and abstract were reviewed, followed by full-text review, with eligible studies progressed to data extraction. Each study was initially extracted by one reviewer, followed by verification by a second reviewer. For each eligible study, information was extracted on the study characteristics and design, population characteristics, as well as the prespecified outcomes of interest (Table 1). If data were stratified, provided it aligned with the PICOTS, all data were recorded, enabling comparison of economic burden outcomes for patients, stratified by different severity levels or treatment regimens.

Patient population sources were recorded for studies reporting costs and/or HCRU. Of note, several studies supplemented their outcome data with additional sources, such as government benefit registries through data linkage, which were not extracted as part of this review. Identified cost data were converted to 2024 US dollars (USD) using Campbell and Cochrane Economics Methods Group Evidence for Policy and Practice (CCEMG-EPPI)-Center Cost Converter v1.4; data are presented as such in this article to enable the comparison of values [26].

3 Results

3.1 Overview of SLR Findings

Across the database searches, 8924 studies were identified, and 2078 of these were removed owing to their being duplicates. Additionally, 67 studies were identified during the gray literature search. Following abstract and full-text screening, 148 studies were included in the SLR (Fig. 1). Of the included studies, 14 were economic evaluations, 24 were HTAs, and 110 were observational studies (Supplementary Tables 9–11). Of these studies, 34 reported total costs, 65 reported direct costs, and 7 reported indirect costs. Most of the studies were conducted in the USA; however, there were also multinational studies and studies from South America, Europe, and Asia–Pacific (Supplementary Tables 9–11). Studies that were comparative typically explored outcomes for different PAH subtypes or outcomes of different treatments. Less common comparators were WHO FC and risk scores. Outcomes were reported over a variety of timespans including monthly, annually, and over multiple years. Owing to the variety of outcomes, comparators, and timespans, the potential for direct comparisons across studies was limited.

3.2 HCRU and Associated Direct Costs

The literature search identified a large number of observational studies ($n = 110$) reporting on the economic burden of PAH, including HCRU ($n = 89$) and costs ($n = 65$) (Supplementary Table 9).

Across the studies identified, HCRU included the number of hospital admissions and length of stay (LOS) for both general and PAH-related reasons. The median annual number of hospitalizations was reported to be as high as 2.2 for the overall PAH population in a South Korean study [27] and a mean of 4.4 for patients with PAH-systemic sclerosis (SSc) in an Australian study [28]. The hospital LOS was reported to be as high as 7.6 days per hospitalization for the overall PAH population in a US study [29]. A subset of studies also reported more granular data, such as inpatient, ED, and ICU admissions. Data were also reported on physician and outpatient visits, enabling an overview of the impact of PAH on the entire HCRU spectrum, the specifics of which are discussed in relevant sections within this article.

Table 1 PICOTS criteria for study inclusion

Criteria	Included	Excluded
Population	• Patients aged ≥ 18 years with WHO Group 1 hypertension (pulmonary arterial hypertension), including all subtypes of PAH	• Patients without PAH or patients diagnosed with other groups of PH (WHO Groups 2–5) • Patients aged < 18 years • Mixed-age populations including children where data on patients age 18 or over cannot be stratified • Studies in animals but not humans
Interventions/comparators (applied to economic evaluations only)	• Any of the following as monotherapy or combined with any other, as per label (only riociguat and PDE5is would not be combined): - Sotatercept • Prostacyclin analogs or receptor agonists: - Epoprostenol - Iloprost - Treprostinil - Selexipag • PDE5is: - Sildenafil citrate - Tadalafil • Soluble guanylate cyclase stimulator: - Riociguat • ERAs: - Ambrisentan - Bosentan - Macitentan	Any interventions other than those identified in the inclusion criteria
Outcomes	• Direct costs of interest: - Medication costs (including the use of durable medical equipment) - Outpatient visit costs - Hospitalization costs (inpatient, emergency department, or hospital visits) - Laboratory costs - Diagnostic costs (e.g., MRI) - Physician costs - Cost per treatment success or per response or per QALY gained - Home healthcare costs - Skilled nurse facility costs • Indirect or other costs of interest: - Productivity losses of parents or caregivers (wages lost because of travel or because of absences from work or changes to work status) - Out-of-pocket expenses - Travel costs for patient and caregiver - Days lost from work for caregiver - Resource use estimates (e.g., number of hospitalizations and length of stay, drug utilization, and physician visits) • Utility outcomes: - EQ-5D - SF-6D - SF-36 and SF-12 - HUI - Any other preference-based utility measure	• Studies that report only clinical efficacy and safety data • Resource use or cost studies that do not report per-patient or per-health-state results (e.g., studies that report annual national disease costs only) • Studies reporting quality-of-life data but not health-utility estimates

Table 1 (continued)

Criteria	Included	Excluded
Study design	• Economic evaluations: - Cost-effectiveness analyses - Cost–benefit analyses - Cost–utility analyses - Cost-minimization analyses • Prospective studies reporting costs or resource utilization (e.g., observational studies) • Utility studies (including studies where utility weights were mapped from other instruments, e.g., disease specific patient-reported outcome measures) • Retrospective studies reporting costs or resource utilization (e.g., cost of illness, cross-sectional studies, and including surveys) • Systematic reviews of economic analyses, resource use, or cost studies[a]	• Commentaries • Letters • Case reports • Consensus reports • Nonsystematic reviews • Articles reporting cost estimates that are not based on data (e.g., commentaries making general reference to cost burden) • Clinical trials
Timeframe	• Database searches: 2012–2024 • Conference abstracts: 2020 to Q1 2024[b]	• Database searches: articles published before 2012 • Conference abstracts: abstracts published before 2020
Other	• No language limits applied for the searches. • Screening limited to English-language studies only.	• Non-English-language studies

ERA endothelin receptor antagonist, *HUI* Health Utilities Index, *MRI* magnetic resonance imaging, *PH* pulmonary hypertension, *PAH* pulmonary arterial hypertension, *PDE5i* phosphodiesterase-5 inhibitor, *PICOTS* Population, Interventions, Comparators, Outcomes, and Study Types, *QALY* quality-adjusted life year, *SF 36* 36-item Short Form Survey, *SF-6D* SF-6D Health Survey, *WHO* World Health Organization

[a]Systematic reviews were included at level 1 screening, used for identification of primary studies, and then excluded at level 2 screening

[b]Conferences were searched from 2020 to 2023 during the first eSLR update, then from 2023 to Q1 2024 during the second eSLR update to ensure the most up-to-date information was captured

There were 35 studies that reported total healthcare costs, with annual total costs per patient with PAH as high as $160,335 (converted to USD 2024) in one US study [30]. Further, hospitalization costs were identified as a substantial contributor of total costs in DuBrock et al., a US study, constituting up to 50% of total costs (hospitalization cost versus total costs per patient per month (PPPM) for patients with a < 12 month diagnosis delay, 12–24 month diagnosis delay, and > 24 month diagnosis delay were $6303 versus $14,643, $9005 versus $17,958, and $9431 versus $18,506, respectively) [31]. This was supported by findings from Tsang et al., a US study, which reported mean per person per annum (PPPA) hospitalization costs versus total medical costs (not including pharmacy costs) for patients receiving selexipag and for patients not receiving any prostacyclin treatment ($13,686 versus $31,623 and $31,064 versus $58,073) [32]. A Spanish study reported mean PPPA hospitalization costs, accounting for a substantially lower proportion; however, these data were not directly measured and instead were calculated using PAH hospitalization data from literature and median hospitalization cost across differing communities [14].

Key comparisons of note across the SLR were PAH-specific treatment intervention and differing WHO FCs. Higher WHO FC was associated with higher economic burden [14, 33], and treatment with PAH-specific therapies was generally associated with reduced economic burden, particularly with reduced HCRU [32, 34–37].

3.3 Increased Economic Burden with Increased Disease Severity

Increasing economic burden for patients in higher WHO FCs (i.e., worse disease severity) was reported for total healthcare costs and HCRU. The total healthcare costs for PAH were stratified by WHO FC in four studies (Table 2) [14, 28, 33, 38], all of which reported a general increase in costs for patients in higher WHO FCs [14, 28, 33, 38]. Mean annual costs for WHO FC I versus WHO FC IV patients in the USA were $73,443 versus $175,368 (converted from monthly to annual for comparison) [38], and $6432 versus $8966 among Australian patients with PAH [28]. Further, within a cohort of Spanish patients with PAH, the annual mean total cost for WHO FC I–II versus WHO FC IV was $30,427 versus $112,845 for prevalent patients and $77,333 versus $247,556 for incident patients (Table 2) [39].

Two studies reported hospitalization costs stratified by WHO FC (Table 2) [14, 28], with mean annual hospitalization costs for WHO FC I versus WHO FC IV of $2652 versus $4314 in an Australian cohort and $10,174 versus $25,106 for Spanish patients with prevalent PAH (Table 2).

Upon examining granular HCRU types, such as hospitalization, pharmacy costs, ED admission, and outpatient visits, the trend remained the same, with higher costs associated

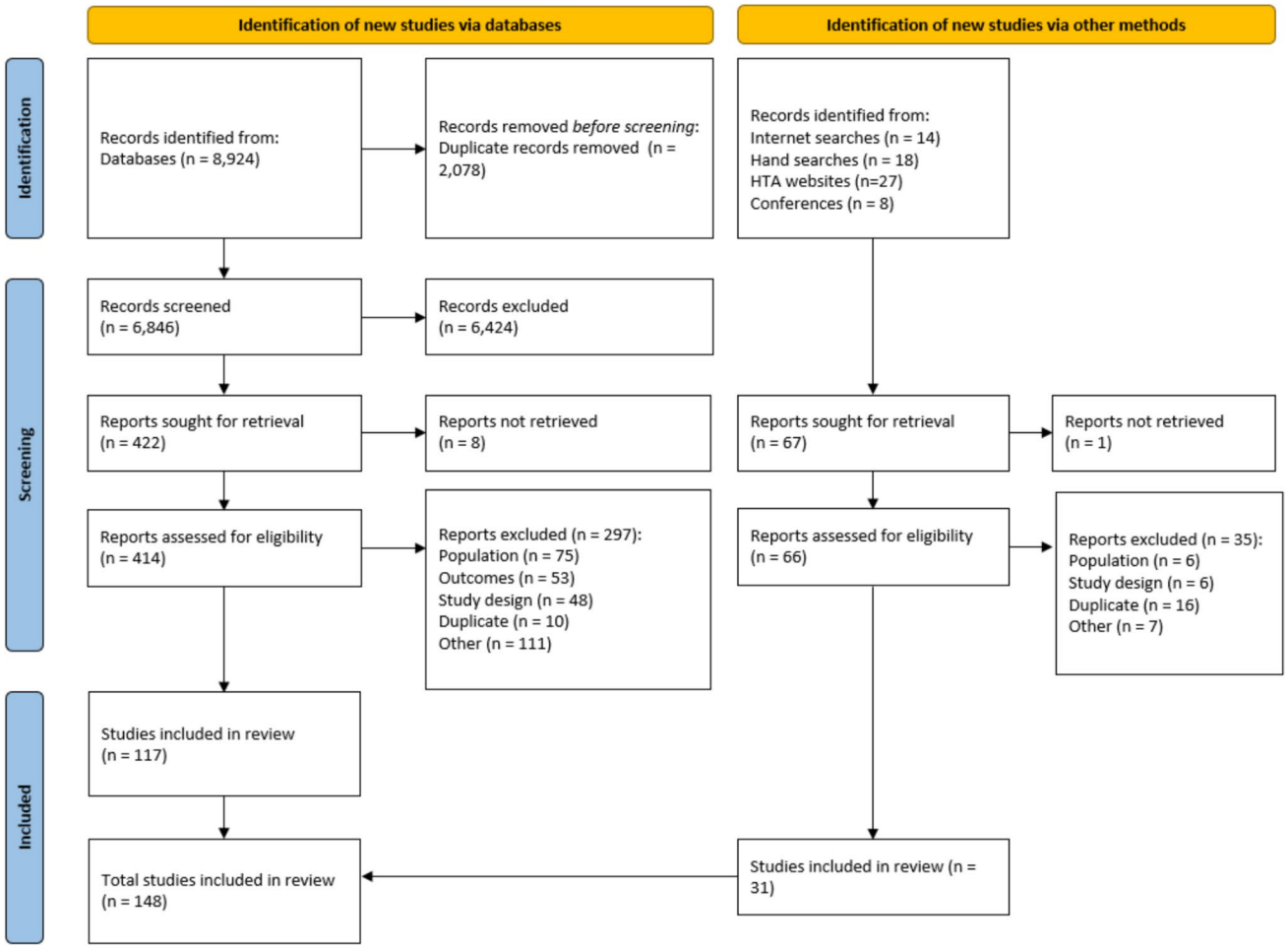

Fig. 1. PRISMA diagram showing overview of the SLR study selection

with higher WHO FCs (Table 2) [38, 39]. Alvarez-Albarran et al., a study from Mexico, was the only study that reported inconsistent data on the correlation between higher WHO FCs and higher HCRU. However, this publication was only a conference abstract, with no full-text publication available [40].

In addition, there were two studies identified in the SLR that reported economic burden data stratified by multicomponent risk score (an alternative measure of PAH severity). These studies were in agreement with those reporting WHO FC, with higher risk scores also corresponding to an increased number of hospitalizations and a longer LOS (22 versus 8 mean days per hospitalization for high- versus intermediate-risk patients) (Table 2) [41, 42].

3.4 Impact of Treatment on Economic Burden in Patients with PAH

In line with treatment escalation being an integral approach to PAH management, 28 studies across the SLR reported pharmacy costs or drug costs as contributors to overall direct costs, highlighting medication costs as an important aspect of the economic burden of PAH [13, 14, 17, 27, 28, 30, 31, 34, 38, 40, 43–60]. Furthermore, 21 studies reported comparative HCRU data for patients receiving treatment [15, 32, 35, 36, 46, 49, 51, 54, 58, 61–72], 8 of which reported comparative total cost data [32, 49, 51, 54, 58, 62, 64, 69]. Comparative data included subgroups of patients pre- and post-treatment initiation, patients receiving a specific PAH treatment on top of background therapy compared with only background therapy, and patients receiving different treatments. The SLR also identified 14 economic evaluations and 24 HTAs that examined the cost-effectiveness of differing PAH treatments (Supplementary Tables 10 and 11).

Table 2 Economic burden stratified by disease severity in patients with PAH

Author, year	Country	Population	Burden subtype	Severity measure	Outcome measure	Outcome value
WHO FC						
Total healthcare costs (converted to 2024 USD)						
Tassara, 2022 [33]	Argentina	PAH	Total costs	FC I	Cost range PPPA	$17,854.71–$28,616.31
				FC II		$59,436.89–$80,542.34
				FC III		$198,456–$284,320.35
				FC IV		$378,894.12–$555,042.92
ZoZaya, 2022 [14]	Spain	Prevalent PAH	Total costs	FC I–II	Mean PPPA	$77,333.19
				FC III		$122,978.18
				FC IV		$247,555.59
		Incident PAH		FC I-II		$30,426.83
				FC III		$52,952.36
				FC IV		$112,844.60
Morrisroe, 2019 [28]	Australia	PAH-Ssc	Healthcare costs	FC I	Mean (SD) PPPA	$6432.42 (3240.87)
				FC II		$6338.26 (2486.70)
				FC III		$9761.17 (5200.28)
				FC IV		$8965.75 (2996.95)
Dufour, 2017 [38]	USA	PAH	Total costs	FC I	Mean (SD) PPPM	$6120.24 (7473.65)
				FC II		$12,811 (21,076.64)
				FC III		$12,102.54 (9544.09)
				FC IV		$14,614.15 (9294.23)
Hospitalization costs (converted to 2024 USD)						
ZoZaya, 2022 [14]	Spain	Prevalent PAH	Hospitalization costs	FC I–II	Mean PPPA	$10,173.94
				FC III		$11,891.88
				FC IV		$25,106.09
		Incident PAH	Hospitalization costs	FC I–II		$5,087.88
				FC III		$5,946.85
				FC IV		$12,553.04
Morrisroe, 2019 [28]	Australia	PAH-Ssc	Hospitalization costs	FC I	Mean (SD) PPPA	$2651.94 (1579.95)
				FC II		$2777.91 (1566.94)
				FC III		$4671.57 (2739.71)
				FC IV		$4313.97 (1971.68)
Pharmacy costs (converted to 2024 USD)						
Dufour, 2017 [38]	USA	PAH	Pharmacy costs	FC I	Mean (SD) PPPM	$2994.40 (3579.60)
				FC II		$5874.29 (4315.27)
				FC III		$6111.13 (4518.28)
				FC IV		$5953.67 (5625.73)
Healthcare resource use						
Alvarez-Albarran, 2023 [40]	Mexico	PAH	Inpatient stays	FC II	Median PPPM	5.0
				FC III		7.5
				FC IV		8.0
			ICU admission LOS	FC III	Median LOS per stay (days)	8.8
				FC IV		3.5
ZoZaya, 2022 [14]	Spain	PAH	Hospitalizations	FC I-II	Mean PPPA	9.4
				FC III		10.8
				FC IV		22.8

Table 2 (continued)

Author, year	Country	Population	Burden subtype	Severity measure	Outcome measure	Outcome value
Dufour, 2017 [38]	USA	PAH	Inpatient stays	FC I	Mean (SD) PPPM	0.1 (0.1)
				FC II		0.1 (0.1)
				FC III		0.1 (0.2)
				FC IV		0.2 (0.2)
			Inpatient LOS	FC I	Mean days (SD) PPPM	0.5 (0.9)
				FC II		0.8 (2.0)
				FC III		0.9 (1.7)
				FC IV		1.9 (2.9)
			ED visits	FC I	Mean (SD) PPPM	0.2 (0.2)
				FC II		0.3 (0.5)
				FC III		0.3 (0.5)
				FC IV		0.6 (0.8)
			Outpatient visits	FC I	Mean (SD) PPPM	2.5 (1.4)
				FC II		3.2 (2.3)
				FC III		3.6 (2.5)
				FC IV		3.8 (2.8)
Risk score						
Healthcare resource use						
Kim, 2020 [41]	USA	PAH	Hospitalization rate	Low risk	Mean (95% CI) PPPA	0.29 (0.19–0.44)
				Intermediate risk		0.65 (0.52–0.81)
				High risk		1.49 (0.89–2.48)
Souza, 2020 [42]	Brazil	PAH	Hospital LOS	Intermediate risk	Mean LOS per hospitalization (days)	8
				High risk		22

Studies did not statistically compare disease severity; therefore, significance values were not reported.

CI confidence interval, *ED* emergency department, *FC* functional class, *ICU* intensive care unit, *LOS* length of stay, *NR* not reported, *PAH* pulmonary arterial hypertension, *PPPA* per person per annum, *PPPM* per person per month, *Ssc* systemic sclerosis, *SD* standard deviation, *USD* US dollar, *WHO* World Health Organization

3.4.1 Economic Burden Pre- and Post-treatment Initiation

Several studies reported on costs before and after treatment initiation (Table 3) [34, 50, 51, 56, 57]. In line with an expected increase in drug costs with PAH disease management, two studies by Runheim et al. [56, 57] quantified the increase in drug costs, moving from an average of $4481 per patient over the 5-year period before PAH diagnosis to $143,506 for the 5-year period after diagnosis, with the total sum of drug costs over 5 years considerably higher post- compared with pre-diagnosis (Table 3) [56]. As patients diagnosed with PAH are likely to initiate PAH-specific therapies, this increase is likely due to the high costs of these therapies, as well as the fact that, once initiated, PAH therapies will be continued for a patient's lifetime.

The studies captured by the review indicate that the high cost of PAH therapies can be balanced by a reduction of other costs following proper disease management. For example, Burger et al., a US study, reported an increase in total costs posttreatment initiation with prostacyclin from $78,909 to $153,691 per patient per 6 months, which was largely driven by an increase in medication costs, from $25,648 to $101,672 (Table 3) [34]. However, this study reported a decrease in the total healthcare contact costs from $46,200 to $41,623, indicating that the decrease in HCRU can offset the increased pharmacy costs to a degree [34]. These findings were supported by two other US-based studies that demonstrated statistically significant reductions in costs associated with inpatient admissions post-PAH-specific treatment initiation (average $42,062 to $24,115 and $112,097 to $36,135 per patient per 6 months, respectively) (Table 3) [50, 51]. Meanwhile the Runheim studies, which reported data from Sweden, did not show a decrease in other healthcare costs such as hospitalizations [56, 57]. Nonetheless, one of the

Table 3 Economic burden for patients pre- and post-treatment initiation

Author, year	Population	Country	Treatment	Outcome	Outcome measure	Outcome value	Significance
Costs (converted to 2024 USD)							
Burger, 2018 [34]	PAH	USA	Prostacyclin (preindex)	Total costs	Mean (SD) per patient per 6 months	$78,909.06 (93,332.06)	< 0.001
			Prostacyclin (postindex)			$153,691.18 (154,854.66)	
			Prostacyclin (preindex)	Medication costs		$25,648.05 (30,103.54)	< 0.001
			Prostacyclin (postindex)			$101,672.25 (70,117.91)	
			Prostacyclin (preindex)	Healthcare contact costs		$46,200.25 (85,487.93)	0.326
			Prostacyclin (postindex)			$41,623.65 (137,914.01)	
Burger, 2018 [51]	PAH	USA	Pre-PAH-specific treatment initiation	Inpatient admission costs	Mean (SD) per patient per 6 months	$42,062.19 (144,440.60)	< 0.001
			Post-PAH-specific treatment initiation			$24,115.29 (103,834.61)	
			Pre-PAH-specific treatment initiation	Pharmacy costs	Mean (SD) per patient per 6 months	$4235.89 (7920.01)	NR
			Post-PAH-specific treatment initiation			$25,976.22 (24,361.25)	
Runheim, 2023 [56]	PAH	Sweden	Pre-PAH diagnosis	Societal costs	Mean (95% CI) per patient over 5 years	$116,858.00 (105,096.82–128,773.93)	NR
			Post-PAH diagnosis			$269,766.31 (244,714.40–294,818.22)	
			Pre-PAH diagnosis	Hospitalization costs		$1539.96 (1376.42–1703.49)	NR
			Post-PAH diagnosis			$3924.85 (3584.15–4279.18)	
			Pre-PAH diagnosis	Outpatient care costs		$8751.23 (7690.48–10,077.18)	NR
			Post-PAH diagnosis			$19,093.60 (17,767.65–20,684.73)	
			Pre-PAH diagnosis	Drug costs		$4480.55 (3072.38–6016.74)	NR
			Post-PAH diagnosis			$143,505.60 (128,655.78–158,355.43)	
			Pre-PAH diagnosis	Productivity loss costs		$89,056.49 (78,516.35–99,749.38)	NR
			Post-PAH diagnosis			$43,535.33 (32,231.42–54,686.49)	

Table 3 (continued)

Author, year	Population	Country	Treatment	Outcome	Outcome measure	Outcome value	Significance
Runheim, 2022 [57]	PAH	Sweden	Pre-PAH diagnosis	Inpatient care costs	Sum of costs over 5 years	$14,871.52	NR
			Post-PAH diagnosis			$41,358.47	
			Pre-PAH diagnosis	Outpatient care costs		$4399.26	NR
			Post-PAH diagnosis			$12,237.13	
			Pre-PAH diagnosis	Drug costs		$4730.30	NR
			Post-PAH diagnosis			$207,032.50	
			Pre-PAH diagnosis	Disability costs		$115,819.12	NR
			Post-PAH diagnosis			$132,594.15	
			Pre-PAH diagnosis	Sick leave costs		$30,207.58	NR
			Post-PAH diagnosis			$61,839.97	
Sikirica, 2014 [50]	PAH	USA	Pre-first PAH-related medical or pharmacy claim	Total costs	Mean (SD) per patient per 6 months	$160,334.74 (505,808.63)	< 0.0001
			Post-first PAH-related medical or pharmacy claim		Mean (SD) PPPA	$134,998.55 (151,999.28)	
			Pre-first PAH-related medical or pharmacy claim	Pharmacy costs	Mean (SD) per patient per 6 months	$8,849.39 (16,746.51)	< 0.0001
			Post-first PAH-related medical or pharmacy claim		Mean (SD) PPPA	$52,923.20 (47,843.05)	
			Pre-first PAH-related medical or pharmacy claim	Inpatient costs	Mean (SD) per patient per 6 months	$112,097.32 (490576.41)	< 0.001
			Post-first PAH-related medical or pharmacy claim		Mean (SD) PPPA	$36,135.47 (106,442.78)	
			Pre-first PAH-related medical or pharmacy claim	ER costs	Mean (SD) per patient per 6 months	$670.57 (1720.41)	0.7
			Post-first PAH-related medical or pharmacy claim		Mean (SD) PPPA	$743.40 (2437.70)	
HCRU							
Pan, 2022 [36]	PAH	USA	Parenteral prostacyclin (preindex)	ED visits	Visits (IQR) per patient per 6 months	1 (0–3)	0.14
			Parenteral prostacyclin (preacclimation[a])			0.25 (0–2)	
			Parenteral prostacyclin (preindex)	Outpatient visits		1 (0-2)	NR
			Parenteral prostacyclin (preacclimation[a])			2 (1-3)	NR

Table 3 (continued)

Author, year	Population	Country	Treatment	Outcome	Outcome measure	Outcome value	Significance
Burger, 2018 [34]	PAH	USA	Prostacyclin total (preindex)	Inpatient LOS	Mean days per patient per 6 months (95% CI)	5.8 (12.5)	0.773
			Prostacyclin total (postindex)			5.7 (13.4)	
			Prostacyclin total (preindex)	Number of inpatient visits	Mean days per patient per 6 months (95% CI)	1.1 (1.1)	0.402
			Prostacyclin total (postindex)			1.0 (1.3)	
			Prostacyclin total (preindex)	Number of ED visits	Mean days per patient per 6 months (95% CI)	0.9 (1.3)	0.053
			Prostacyclin total (postindex)			0.8 (1.3)	
Berger, 2012 [35]	PAH	USA	Sildenafil (preindex)	Hospitalizations	Mean per patient per 6 months (95% CI)	0.5 (0.4–0.6)	0.180
			Sildenafil (postindex)			0.5 (0.4–0.5)	
			Sildenafil (preindex)	Hospital LOS	Mean days per patient per 6 months (95% CI)	4.3 (3.5–5.1)	0.060
			Sildenafil (postindex)			3.9 (3.0–4.7)	
			Sildenafil (preindex)	ED visits	Mean per patient per 6 months (95% CI)	0.7 (0.6–0.8)	< 0.010
			Sildenafil (postindex)			0.5 (0.4–0.7)	
			Sildenafil (preindex)	Outpatient visits		10.1 (9.4–10.9)	0.520
			Sildenafil (postindex)			10.3 (9.5–11.1)	
Sikirica, 2014 [50]	PAH	USA	Pre-first PAH-related medical or pharmacy claim	Inpatient stays	Mean (SD) per patient per 6 months	1.38 (2.03)	< 0.001
			Post-first PAH-related medical or pharmacy claim		Mean (SD) PPPA	0.91 (1.59)	
			Pre-first PAH-related medical or pharmacy claim	ED visits	Mean (SD) per patient per 6 months	1.56 (2.95)	0.032
			Post-first PAH-related medical or pharmacy claim		Mean (SD) PPPA	1.55 (3.17)	

Index refers to the treatment start date

CI confidence interval, *ED* emergency department, *IQR* interquartile range, *LOS* length of stay, *NR* not reported, *PAH* pulmonary arterial hypertension, *SD* standard deviation

[a]Acclimation phase refers to the period < 6 months posttreatment initiation

studies did report a decrease in productivity loss, from an average of $89,056 per patient over 5 years prediagnosis to $43,535 over the 5 years after diagnosis (Table 3) [56].

In line with potential broader economic offsets, Berger et al. and two other US studies reported a decrease in HCRU following treatment initiation (Table 3) [35, 36, 51]. Berger et al. assessed resource use 6 months prior and following treatment with sildenafil, reporting a decrease in the total LOS following treatment from 4.3 days to 3.9 days [35], although the mean number of hospitalizations remained the same (Table 3). Burger et al. reported a suggestive decrease in HCRU across measures, with a mean inpatient admissions per 6 months reduction from 1.1 to 1.0 for those receiving parenteral prostacyclin and from 0.5 to 0.4 for those

Table 4 Economic burden for PAH therapies on top of background therapy compared with background therapy only

Author, year	Country	Treatment	Outcome	Outcome measure	Outcome value	Significance
Costs (converted to 2024 USD)						
Tsang, 2023 [32]	USA	Selexipag	Total medical costs	Mean PPPA	$31,622.61	$p = 0.002$
		Background with no prostacyclin pathway agents			$58,072.67	
		Selexipag	Hospitalization costs		$13,686.20	$p = 0.0001$
		Background with no prostacyclin pathway agents			$31,064.16	
Tsang, 2022 [37]	USA	Selexipag	Hospitalization costs	Mean PPPA	$14,949.61	NR
		Background with no selexipag			$30,994.46	NR
		Selexipag	Outpatient costs	Mean PPPA	$19,708.04	NR
		Background with no selexipag			$31,550.04	NR
HCRU						
Shankar, 2023 [66]	USA	Background with anticoagulant	Hospital LOS	Mean per hospitalization	6.04	$p < 0.001$
		Background with no anticoagulant			7.03	
Garry, 2022 [72]	USA	Background with anticoagulants	Number of hospitalizations	Mean PPPA	0.44	NR
		Background with no anticoagulants			0.34	NR
		Background with anticoagulants	Hospital LOS	Mean days PPPA	3.39	NR
		Background with no anticoagulants			2.71	NR
		Background with anticoagulants	ED visits	Mean PPPA	1.03	NR
		Background with no anticoagulants			0.76	NR
Corkish, 2019 [61]	USA	Background with aldosterone receptor antagonists	Number of hospitalizations	Mean (SD) per patient per 6 months	1.91 (1.37)	1
		Background with no aldosterone receptor antagonists			1.91 (1.04)	

ED emergency department, *HCRU* healthcare resource utilization, *LOS* length of stay, *NR* not reported, *PAH* pulmonary arterial hypertension, *PPPA* per person per annum, *SD* standard deviation, *USD* United States dollar

receiving nonparenteral prostacyclin. In addition, a decrease in the mean inpatient LOS per patient per 6 months, from 5.8 to 5.7 days, was reported following treatment with a prostacyclin [51].

Notably, four studies reported a decrease in the number of ED visits following treatment, with ranges from 0.7–1.56 and 0.25–1.55 for pretreatment and posttreatment, respectively (Table 3) [34–36, 50]. In total, two studies reported an increase in the mean number of outpatient visits per 6 months following treatment, from 10.1 to 10.3 (pretreatment to posttreatment) and from 1 to 2 (pretreatment to posttreatment) [34, 36]. Overall, these results suggest a switch from inpatient to outpatient management with treatment intervention.

3.4.2 Impact of Treatment Escalation on Economic Burden

Treatment escalation is recommended for patients at intermediate or high risk or for those who remain within a WHO FC group higher than FC II [7]. However, treatment escalation can lead to higher costs, as seen in Pizzicato et al., a 2022 US study that reported an increase in the mean total costs PPPM with each subsequent treatment line (defined by any modification to the treatment regime or a treatment gap

of more than 60 days) from $18,120 for first-line therapy to $29,682 for fourth-line therapy [54].

Certain treatment pathways were also associated with higher costs. In the economic evaluations identified in the SLR, typically, therapies targeting the prostacyclin pathway were associated with higher costs than therapies targeting other pathways, with pharmacy costs being noted as a key driver in multiple studies [73–75]. A total of two US studies identified in the SLR reported a comparison of economic burden outcomes in patients receiving both selexipag and background therapy and those receiving background therapy alone (Table 4) [32, 37]. Significantly lower total medical cost PPPA of $31,623 was reported by Tsang et al. (2023) for patients receiving selexipag compared with $58,073 for the patients not receiving prostacyclin pathway treatment ($p = 0.002$) [32]. Similarly, a significantly lower hospitalization cost PPPA of $13,686 was reported in the same study for the selexipag group compared with $31,064 for the group not receiving prostacyclin ($p = 0.0001$) [32]. Tsang et al. (2022) reported lower hospitalization costs PPPA of $14,950 for the selexipag group compared with $30,994 for the non-prostacyclin group. In addition, they reported lower outpatient costs of $19,708 for the selexipag group compared with $31,550 for the nonprostacyclin group [37]. p values were not reported for the comparison of costs between these patient groups. These findings indicate that escalation of therapy to include selexipag, while increasing pharmaceutical costs, can reduce HCRU costs.

A total of three US studies compared patients receiving conventional treatment, such as anticoagulants and background therapy, with those receiving background therapy alone. None of these studies reported a decrease in economic burden outcomes for patients receiving conventional PAH therapies, highlighting the particular benefit of PAH-specific treatment intervention (Table 4) [61, 66, 72]. One study reported a mean number of hospitalizations of 1.91 per patient per 6 months for both patients receiving aldosterone receptor antagonists and those not receiving aldosterone receptor antagonists [61]. Another reported a higher mean LOS per hospitalization of 7.03 days in patients not receiving anticoagulants compared with 6.04 for those receiving anticoagulants, on the basis of the 2019 Nationwide Inpatient Sample database [66]. The final study reported 0.34 hospitalizations per person-year for those not receiving anticoagulants compared with 0.44 for those receiving anticoagulants. In addition, it detailed a lower hospital LOS per person-year of 2.71 days compared with 3.39 days [72].

These findings indicate that PAH-specific treatments such as selexipag, while more expensive than conventional treatments, may reduce the economic burden of PAH through improved HCRU outcomes. Similar improvements in patient outcomes for those receiving PAH-specific therapy were reported in two economic evaluations [76, 77]. Villaquiran-Torres et al. reported an improvement of 8.195 disability-adjusted life years (DALYs) in Colombian patients with PAH who received a PAH-specific treatment compared with those who did not [76]. McLaughlin et al. reported a gain of 11.5 life-years (LYs) among US patients receiving sotatercept and PAH-specific background therapy compared with those receiving PAH-specific background therapy alone [77].

Similarly, Tran-Duy et al., an Australian economic evaluation, reported a significant improvement in LYs and quality-adjusted life years (QALYs) gained for patients with PAH-SSc receiving combination therapy compared with monotherapy [78]. Despite these benefits, combination therapy was not cost-effective owing to the large direct treatment costs [78].

3.4.3 Impact of Early PAH Diagnosis on Economic Burden

There were four studies identified that reported on the impact of diagnostic timing on economic burden (Table 5). The SLR identified one study that reported on diagnostic timing, which indicated that earlier diagnosis leads to marginal improvements in HCRU [31]. The study compared US patients who received a PAH diagnosis with a < 12-month delay, 12–24-month delay, and a > 24-month delay. Mean hospitalizations PPPM increased in patients with a longer delay prior to diagnosis (0.12, 0.16, and 0.19, respectively), as did the number of ICU stays (0.07, 0.1, and 0.14, respectively) and ED visits (0.1, 0.12, and 0.15, respectively) (Table 5). However, this trend was not observed for ICU LOS (1.36, 2.27, and 1.73) and hospital LOS (1.78, 2.69, and 2.09) [31].

Additionally, two studies reported the annual cost of ED visits for five years post-diagnosis. Fischer et al., a US study, and Morrisroe et al., an Australian Study, reported a decrease in mean annual ED visit costs between the first year following diagnosis to the fifth year postdiagnosis. In both cases, the trend was a decrease in visit costs over time, indicating that actively managed PAH leads to a reduced number of serious hospitalizations (Table 5) [28, 45].

Finally, Bergot et al., a French study, compared hospitalizations for monitoring (e.g., short LOS, admitted for exploratory care or right heart catheterization) and hospitalization for disease worsening (i.e., longer LOS or admission with death of patient). Those hospitalized for monitoring had lower annual hospital costs of $1,180,184 compared with $2,797,61 for those hospitalized for disease worsening, and a lower hospital LOS per stay of 2.1 days compared with 12.9 days for those hospitalized for disease worsening, indicating that stable PAH reduces economic burden (Table 5) [79].

Overall, it is apparent that appropriate disease management, i.e., timely diagnosis and consistent postdiagnosis

Table 5 Economic burden for disease management over time

Author, year	Country	Patient population	Outcome	Outcome measure	Outcome value
DuBrock, 2024 [31]	USA	PAH patients with ≤ 12-month diagnosis delay	Hospitalizations	Mean (SD) PPPM	0.12 (0.15)
		PAH patients with 12–24-month diagnosis delay			0.16 (0.18)
		PAH patients with > 24-month diagnosis delay			0.19 (0.25)
		PAH patients with ≤ 12-month diagnosis delay	Hospital LOS (days)		1.78 (3.53)
		PAH patients with 12–24-month diagnosis delay			2.69 (5.31)
		PAH patients with > 24-month diagnosis delay			2.09 (3.37)
		PAH patients with ≤ 12-month diagnosis delay	ICU stays		0.07 (0.1)
		PAH patients with 12–24-month diagnosis delay			0.1 (0.13)
		PAH patients with > 24-month diagnosis delay			0.14 (0.25)
		PAH patients with ≤ 12-month diagnosis delay	ICU LOS (days)		1.36 (3.14)
		PAH patients with 12–24-month diagnosis delay			2.27 (5.08)
		PAH patients with > 24-month diagnosis delay			1.73 (3.28)
		PAH patients with ≤ 12-month diagnosis delay	ED visits		0.1 (0.14)
		PAH patients with 12–24-month diagnosis delay			0.12 (0.16)
		PAH patients with > 24-month diagnosis delay			0.15 (0.36)
Bergot, 2019 [79]	France	PAH hospitalized for monitoring[a]	Hospital LOS	Mean (SD) per stay	2.1 (0.9)
		PAH hospitalized for worsening[a]			12.9 (12.9)
		PAH hospitalized for monitoring	Total hospitalization costs	Total annual cost (SD)	$1,180,183.66
		PAH hospitalized for worsening			$2,797,610.93 (549,725.37)
Morrisroe, 2019 [28]	Australia	PAH patients 1 year after diagnosis	ED visits	Mean (SD) PPPA	$230.00 (508.77)
		PAH patients 2 years after diagnosis			$180.43 (368.17)
		PAH patients 3 years after diagnosis			$236.50 (520.15)
		PAH patients 4 years after diagnosis			$161.73 (308.02)
		PAH patients 5 years after diagnosis			$144.67 (351.91)

Table 5 (continued)

Author, year	Country	Patient population	Outcome	Outcome measure	Outcome value
Fischer, 2018 [45]	USA	PAH patients year 1 after diagnosis	ED visits	Mean cost (SD) PPPA	$1026.76 (3543.57)
		PAH patients year 2 after diagnosis			$914.85 (5571.07)
		PAH patients year 3 after diagnosis			$1021.56 (5500.80)
		PAH patients year 4 after diagnosis			$451.57 (1139.98)
		PAH patients year 5 after diagnosis			$474.99 (1335.18)

None of these studies reported associated significance values for these outcomes

ED emergency department, *LOS* length of stay, *NR* not reported, *PAH* pulmonary arterial hypertension, *PPPA* per person per annum, *PPPM* per person per month, *SD* standard deviation

[a]Bergot et al. categorized hospitalizations for monitoring as those with short LOS, hospital admissions for exploratory care or right heart catheterization, and hospitalization for disease worsening as longer stays, and admissions resulting in death of the patient. See publication for full classification of monitoring versus worsening stays [79]

monitoring, led to reduced HCRU, resulting in lower costs and lower total economic burden.

3.5 Indirect Costs

Few studies identified in the SLR explored the indirect burden of PAH ($n = 7$) [39, 40, 47, 50, 56, 57, 60] on the outcomes of total indirect costs, societal costs, productivity loss due to sick leave and disability, cost due to lost work days and early retirement, and out-of-pocket costs.

A total of two Swedish studies reported on costs due to sick leave and disability costs in the 5 years before PAH diagnosis and the 5 years after diagnosis [56, 57]. One study reported an increase in both disability and sick leave total costs in the 5 years after diagnosis from $979,673 to $1,121,567 and from $255,515 to $523,061, respectively [57]. However, Runheim et al. (2023) reported a decrease in total costs related to the combination of sick leave and disability costs in the 5 years after diagnosis compared with the 5 years before diagnosis from $69,114 to $33,786; this study stated that this may be due to an aging cohort, leading to an increased proportion of deceased or retired patients [56]. Importantly, the costs were higher than those reported for non-PAH controls in both studies both pre- and post-diagnosis. In Runheim et al. (2023), the productivity loss costs over 5 years were reported to be $33,786, which is almost equivalent to the hospitalization costs of $34,142 for the same period [56], indicating the importance of indirect costs when determining the economic burden of PAH. Another study from Spain reported an increase in annual total indirect costs at higher WHO FCs, from $47,007 for patients in WHO FC I–II to $174,336 for patients in WHO FC IV [14], aligned with other aspects of economic burden.

Regarding specific treatment intervention, the economic evaluation conducted by Jandhyala et al. investigated the impact of an earlier market launch of the PAH-specific therapy ambrisentan in the UK using a Markovian-like transition model. The study reported an increased survival rate and a potential increase in earnings of £43,598 per patient, largely due to the potential lives saved, highlighting how the consideration of indirect costs is particularly important in PAH [80].

4 Discussion

This SLR has demonstrated the large economic burden of PAH, largely driven by HCRU costs. Common HCRU reported included outpatient visits, ED visits, and ICU stays, as well as high medication costs, indicating the different support requirements of PAH patients and reflecting the serious nature and broad spectrum of PAH and its management. Previous SLRs have reported a similarly large economic burden [81, 82], with costs related to HCRU associated with a large proportion of this burden [81]. To the best of our knowledge, this is the first SLR to provide a comprehensive synthesis of the global economic burden of PAH, including direct and indirect cost and HCRU, across multiple comparators including disease severity and the broader impact of treatment intervention on other aspects of economic burden. Overall, our findings and those in the wider literature indicate a need for improvement along the spectrum of PAH care encompassing earlier diagnosis, improved risk assessment,

and guideline-directed treatment strategies to reduce the overall burden on the healthcare system. This sentiment is echoed by Watzker et al., who conducted a retrospective cohort study of adult patients with PAH in US Medicare and Commercial databases during 2018–2020 (published October 2024, after the SLR cutoff date). Watzker et al. reported overall "persistent unmet need in terms of outcomes, such as hospitalizations" leading to "high inpatient admission rates and associated costs" [83].

Based on studies reporting data stratified by WHO FC and risk score, there was a higher reported economic burden in patients with greater disease progression and severity. This is in agreement with the outcome described in Wronski et al., which stated that "FC also predicted health care resource utilization and costs," following analysis of the impact of WHO FC on economic outcomes [84]. Of note, the disparity between cost ranges by country in this review was not intended to reflect any differences in PAH management and is believed to be primarily due to the differences inherent to the healthcare systems. For example, healthcare costs in the USA are higher than other geographic regions owing to the healthcare system complexity. The cost trends resulting from comparative data, for example, from increasing severity (i.e., WHO FC and risk score progression), therefore reflect the relevant outcomes of this analysis.

This SLR also provided data on the importance of PAH-specific treatment in reducing broader economic burden, despite being associated with an inherent cost. Multiple studies indicated a decrease in overall HCRU following treatment initiation, including reduced hospital LOS and reduced ED admissions. Interestingly, it was reported that there was an increase in outpatient visits following treatment. This could indicate that treatment initiation lowers the severity of PAH, leading to a transition from inpatient stays to outpatient visits.

Most studies assessed costs from a payer perspective and therefore did not account for indirect costs in their totals. This meant that the economic impact of improved quality of life through retained work productivity was not accounted for. In addition, the possibility that increased costs were a result of PAH treatments extending patient life, and thus necessitating longer management periods, was also not accounted for. Furthermore, limited longitudinal analysis was undertaken to determine how HCRU and costs changed over time with treatment intervention. Indirect costs are an understudied area within PAH research [53]. However, research published since the completion of the SLR database search has reported a loss of $340–$1071 PPPM due to lost workdays for a US population including 1174 patients with PAH between 2019 and 2021 [85]. The few studies that did include indirect costs reported a substantial contributor to overall economic burden, with a Swedish study reporting that the indirect costs associated with productivity loss were equivalent to the direct costs of hospitalization, emphasizing that these data should not be overlooked [57]. Adopting a societal perspective of economic burden of PAH would include indirect costs, thereby providing a more holistic view of the disease, which would lead to improved accuracy in determining the cost offsets to pharmaceuticals used in PAH management.

Despite the lack of indirect cost reporting, the findings highlight the value of treatment escalation to therapies with higher associated costs due to the greater per unit pharmaceutical costs being somewhat offset by a reduction in overall HCRU. This was evident from two studies conducted by Tsang et al., which showed that selexipag, typically initiated after patients fail several therapy lines [86], had a beneficial effect on cost and HCRU outcomes [32, 37]. This suggests that earlier treatment escalation may lead to reduced economic burden for patients with PAH despite the increased pharmaceutical costs and that it may be even more evident if all indirect costs were accounted for. This is consistent with previous SLRs that reported that the pharmaceutical costs of expensive PAH therapies were partly offset by the reduced HCRU [81, 87].

Studies included in this SLR consistently showed that early and effective disease management positively impacted the economic burden of PAH. As indicated in this review, early initiation of PAH management can lead to reduced economic burden through a reduction in hospitalizations [31]. This may be due to patients with earlier PAH diagnoses presenting with lower severity of disease, who are therefore more easily managed. These findings are similar to those of Burger et al. [87], an SLR that investigated early intervention in the management of PAH and showed a reduction in hospitalizations in PAH patients of mild severity (WHO FC I and WHO FC II) after treatment initiation [87]. These studies support the importance of early intervention and optimal management in reducing the economic burden imparted through HCRU.

The results of this review highlight several implications for real-world treatment practice, including taking a holistic view of the improved burden of PAH with respect to reduced HCRU and cost offsets with earlier treatment initiation or escalation. Furthermore, this highlights the need for treatment costs being incorporated with other metrics when determining treatment strategies.

Overall, the SLR identified a substantial economic burden, including high treatment costs. Although treatment costs might appear high, these need to be examined in the broader framework of value and the improvement the treatment provides to the patient and society. Based on these SLR findings, broader benefits that may go underappreciated include reduced indirect costs and improvements in patient survival impacting economic outcomes (note, survival was only considered within context of cost-effectiveness analysis

(CEA) outputs in this SLR) [77, 78, 80, 88]. Of note, a UK economic evaluation conducted by Jandhyala et al., identified in this SLR, reported that the earlier launch of a specific PAH treatment would improve survival rate and increase earning potential by £43,598 per patient [80], highlighting the importance of considering indirect costs and survival within treatment value in PAH [80].

As identified by this SLR, the indirect burden of PAH requires further research to fully characterize; therefore, it may not be accurately considered during evaluation of PAH treatment. Similarly, higher treatment costs due to improved patient survival and prolonged period of treatment receipt may not be fully recognized, for example, within conventional cost-effectiveness modeling frameworks.

An economic modeling study identified in this SLR, conducted by Tran-Duy et al., demonstrated that combination treatment in place of monotherapy led to increased LYs among Australian patients with PAH-SSc, but with considerably higher treatment costs [78]. However, Tran-Duy et al. noted that the severity of PAH-SSc and the unmet need within the Australian patient population warranted a higher willingness-to-pay threshold for the more clinically effective combination treatments. Further, they noted that earlier initiation of combination therapy would result in cost offsets associated with reduced HCRU and employment-related costs [78]. These data support the limitation of cost-effectiveness analyses in orphan disease.

The findings of this SLR suggest further research is required into how to estimate the true economic impact of PAH as a rare and progressive disease and assess treatment value across the spectrum of patients with differing disease severity. This includes whether as PAH treatment escalates, increasing value should be placed on factors other than treatment cost to prevent the undervaluation of the treatment needs of patients with increasing severity of disease.

4.1 Limitations

A limitation of this SLR is the lack of direct comparison between studies due to population differences (e.g., comorbidities, age, and background therapy) and outcome reporting (e.g., timepoint, statistical measures, and units). While this is a challenge, it is not atypical for SLRs, and to mitigate this issue, study and population details were presented in detail. Furthermore, most studies identified were US-based, which may impact the generalizability of the findings to other geographic regions.

There were limited studies identified that compared patients pre- and post-treatment escalation and by timepoint of PAH diagnosis and treatment initiation. Additionally, comparison between studies was limited by patients receiving different degrees and combinations of background therapy.

As noted previously, few studies reported indirect costs ($n = 7$), and of these, varying outcomes limited comparison. This was expected, as indirect costs in PAH are generally understudied.

Finally, many studies did not report statistical significance, with some estimates also lacking confidence intervals or dispersion measures, making it difficult to determine the strength of the findings.

5 Conclusions

This SLR demonstrated the high economic burden of PAH and showed that HCRU is a key driver of this burden. It provided evidence that disease severity increases the economic burden of patients with PAH and that effective treatment has a positive impact on economic burden despite potentially increased medication costs. Specifically, it shows that treatment escalation can reduce the economic burden of PAH, particularly when viewed holistically, accounting for indirect costs and prolonged patient life. Finally, the SLR indicates that early and consistent initiation of treatment can reduce the overall economic burden.

Based on these findings, there is a need to view the economic burden of PAH from a more holistic perspective to accurately determine the value of new treatments. Further investigation is needed, particularly related to indirect costs and specific treatment comparisons, to inform real-world PAH management.

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Declarations

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Consent for publication Not applicable.

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