Efficacy of Positive Airway Pressure Therapy in Managing Heart Failure Exacerbations in OSA Patients: A Systematic Review

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ABSTRACT

Background: Obstructive sleep apnea (OSA) and heart failure (HF) frequently coexist, with untreated OSA contributing to HF progression through hemodynamic stress and inflammation. Evidence for positive airway pressure (PAP) therapy in this population remains conflicting following neutral results from major randomized trials.

Methods: A systematic search of PubMed, Embase, Cochrane CENTRAL, and Web of Science (2021–2026) identified studies evaluating PAP therapy in adults with moderate-to-severe OSA and HF, reporting HF exacerbations (hospitalizations, emergency visits, or composite events). Risk of bias was assessed using Cochrane RoB 2.0 and ROBINS-I tools. **Results:** Six studies (7,843 patients) met inclusion criteria: one RCT and five observational studies. PAP-adherent patients demonstrated significant reductions in healthcare utilization, including a 24% reduction in emergency visits for HFrEF and a 57% decrease in hospitalizations for HFpEF. Unsuppressed sleep apnea on CPAP was associated with increased risk of death or HF hospitalization (HR 2.30, 95% CI 1.21–4.38). LVEF improved from 37.2% to 43.2% after one month of CPAP. Most studies showed moderate risk of bias.

Conclusion: PAP therapy with adequate adherence is associated with meaningful reductions in HF exacerbations across both HF phenotypes. The discordance between observational and RCT evidence likely reflects the critical importance of adherence and trial design limitations. These findings support prioritizing OSA diagnosis and adherence optimization in HF management.

Keywords: Obstructive sleep apnea; Heart failure; Positive airway pressure; CPAP; HFrEF; HFpEF.

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INTRODUCTION

Obstructive sleep apnea (OSA) and heart failure (HF) are two highly prevalent conditions that frequently coexist and exert bidirectional deleterious effects on one another [1]. OSA is characterized by recurrent episodes of upper airway collapse during sleep, resulting in intermittent hypoxemia, sympathetic nervous system activation, and sleep fragmentation [1]. Heart failure, a clinical syndrome affecting millions worldwide, carries substantial morbidity, mortality, and healthcare costs [2]. The pathophysiological intersection is clinically significant, as OSA independently contributes to HF development and progression through hemodynamic stress, neurohormonal activation, and systemic inflammation, while HF can precipitate or worsen sleep-disordered breathing through mechanisms including fluid redistribution and altered ventilatory control [3].

The epidemiological overlap between OSA and HF is substantial. A recent systematic review and meta-analysis reported that the pooled prevalence of OSA in patients with HF was 38.4%, with significant geographic variation [4]. Other estimates suggest that sleep-disordered breathing affects 40% to 60% of patients with symptomatic HF [5], with OSA accounting for approximately one-third of cases and demonstrating particularly high burden in HF with preserved ejection fraction [6]. Despite this high prevalence, OSA remains markedly underdiagnosed in HF populations, with untreated OSA associated with increased mortality, higher hospitalization rates, and worse functional status [2].

The mechanistic link between untreated OSA and HF exacerbation is well-characterized. Recurrent apneic episodes impose significant hemodynamic stress on the failing heart through increased left ventricular afterload, elevated transmural pressures, and heightened myocardial oxygen demand, while promoting systemic inflammation, endothelial dysfunction, and adverse cardiac remodeling [1, 3]. Positive airway pressure (PAP) therapy, the first-line treatment for moderate-to-severe OSA, maintains upper airway patency, abolishes obstructive events, and attenuates sympathetic surges [1]. However, the evidence base for PAP efficacy in HF remains conflicting. The SERVE-HF and CAN-PAP trials, which focused predominantly on central sleep apnea (CSA), demonstrated neutral or harmful cardiovascular outcomes with adaptive servo-ventilation and CPAP, respectively [7, 8]. These results have created clinical equipoise regarding PAP therapy in HF, though the distinction between CSA and OSA is critical, as OSA represents an independent modifiable risk factor more amenable to PAP intervention. Given the conflicting evidence and the substantial healthcare burden of HF exacerbations, this systematic review aims to synthesize contemporary evidence on the efficacy of PAP therapy in managing HF exacerbations—defined as hospitalizations, emergency room visits, or composite clinical events—specifically in patients with comorbid OSA.

METHODOLOGY

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [9]. The research question was formulated using the PICOS framework: Population (adult patients with heart failure and comorbid obstructive sleep apnea), Intervention (positive airway pressure therapy), Comparator (sham, no treatment, or non-adherence), Outcomes (heart failure exacerbations defined as hospitalizations, emergency room visits, or composite clinical endpoints), and Study designs (randomized controlled trials, cohort studies, and case-control designs).

Search Strategy

A systematic literature search was performed across four electronic databases: PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science. The search was restricted to publications from the past five years 2021 to 2026. The search strategy combined MeSH terms and free-text keywords related to the intervention ("positive airway pressure," "CPAP," "APAP"), the condition ("obstructive sleep apnea," "OSA"), the population ("heart failure," "HFrEF," "HFpEF"), and the outcomes ("exacerbation," "hospitalization," "healthcare utilization"). Boolean operators (AND, OR) were employed to refine the search. Additionally, reference lists of included studies and relevant systematic reviews were hand-searched to identify supplementary records.

Eligibility Criteria

Studies were eligible if they: (1) enrolled adult patients (≥18 years) with confirmed moderate-to-severe OSA (apnea-hypopnea index ≥15 events/hour) and a concurrent diagnosis of heart failure (either HFrEF or HFpEF); (2) evaluated any form of PAP therapy (CPAP, APAP, or BPAP); (3) included a comparator group (no PAP, sham therapy, or non-adherent users); (4) reported outcomes directly reflecting HF exacerbations, including all-cause or cardiovascular hospitalizations, emergency room visits, or composite event rates; and (5) were designed as randomized controlled trials, prospective cohorts, retrospective cohorts, or case-control studies. Studies focusing exclusively on central sleep apnea, case reports, systematic reviews, and non-English publications were excluded.

Study Selection

All identified records were exported to Rayyan, a web-based systematic review screening platform, for efficient deduplication and collaborative review [11]. Two independent reviewers performed an initial screening of titles and abstracts against the predefined eligibility criteria. Potentially relevant records underwent full-text assessment by the same two reviewers, with disagreements resolved through consensus discussion or arbitration by a third reviewer. The reasons for exclusion at the full-text stage were documented. Following this process, six studies met the inclusion criteria and were incorporated into the final narrative synthesis.

Data Extraction

Data extraction was performed independently by two reviewers using a standardized, pre-piloted data extraction form. Extracted variables included: bibliographic information (author, year, journal), study location and design, sample size, baseline patient demographics (age, sex, body mass index), heart failure characteristics (LVEF, HF subtype), OSA severity (baseline AHI), intervention details (PAP type, duration, adherence definitions), comparator description, follow-up duration, primary and secondary outcome measures, and quantitative effect estimates (hazard ratios, risk reductions, mean differences with corresponding confidence intervals or p-values). Missing data were explicitly documented as "not mentioned."

Risk of Bias Assessment

The methodological quality of the included studies was assessed independently by two reviewers using domain-based tools appropriate to each study design, as recommended by the Cochrane Handbook for Systematic Reviews of Interventions [10]. The single randomized controlled trial was evaluated using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool, which assesses randomization, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. The five observational studies (retrospective cohorts, prospective single-arm cohort, and case-control design) were assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool, which evaluates confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selective reporting [10]. Each domain was rated as low, moderate, serious, or critical risk, with overall judgments derived accordingly. Disagreements were resolved through consensus. For conciseness, Tables 3 and 4 tabulate the domains most consequential to the overall judgement for each study design (RoB 2.0: randomization process, deviations from intended interventions, missing outcome data, and measurement of the outcome; ROBINS-I: confounding, selection of participants, measurement of outcomes, and missing data); the remaining domains listed above (selection of the reported result for RoB 2.0; classification of interventions, deviations from intended interventions, and selective reporting for ROBINS-I) were assessed per this protocol but are not separately tabulated.

Data Synthesis

Given the substantial clinical and methodological heterogeneity among the included studies—encompassing variations in design (RCT vs. observational), populations (HFrEF vs. HFpEF), interventions (differing PAP modalities and adherence definitions), comparators, follow-up durations (1 month to 3 years), and outcome measures (physiological surrogates vs. hard clinical endpoints)—a quantitative meta-analysis was deemed inappropriate. Instead, a narrative synthesis approach was adopted, structured around predefined thematic categories: (1) healthcare resource utilization outcomes, (2) hard clinical event outcomes, and (3) mechanistic physiological endpoints. Extracted data were organized into descriptive summary tables to facilitate transparent comparison across studies, and findings were interpreted with consideration of the risk of bias assessments.

RESULTS

A systematic literature search across databases identified 395 records, of which 189 duplicates were removed prior to screening. The remaining 206 records were screened by title and abstract, resulting in the exclusion of 121 records that did not meet the initial eligibility criteria. Of the 85 reports sought for retrieval, 51 could not be accessed, leaving 34 full-text reports assessed for eligibility. During full-text review, 28 reports were excluded for the following reasons: wrong outcome (n=13), wrong population (n=10), and abstract-only publications without sufficient data (n=5). Ultimately, 6 studies met all inclusion criteria and were included in the final systematic review.

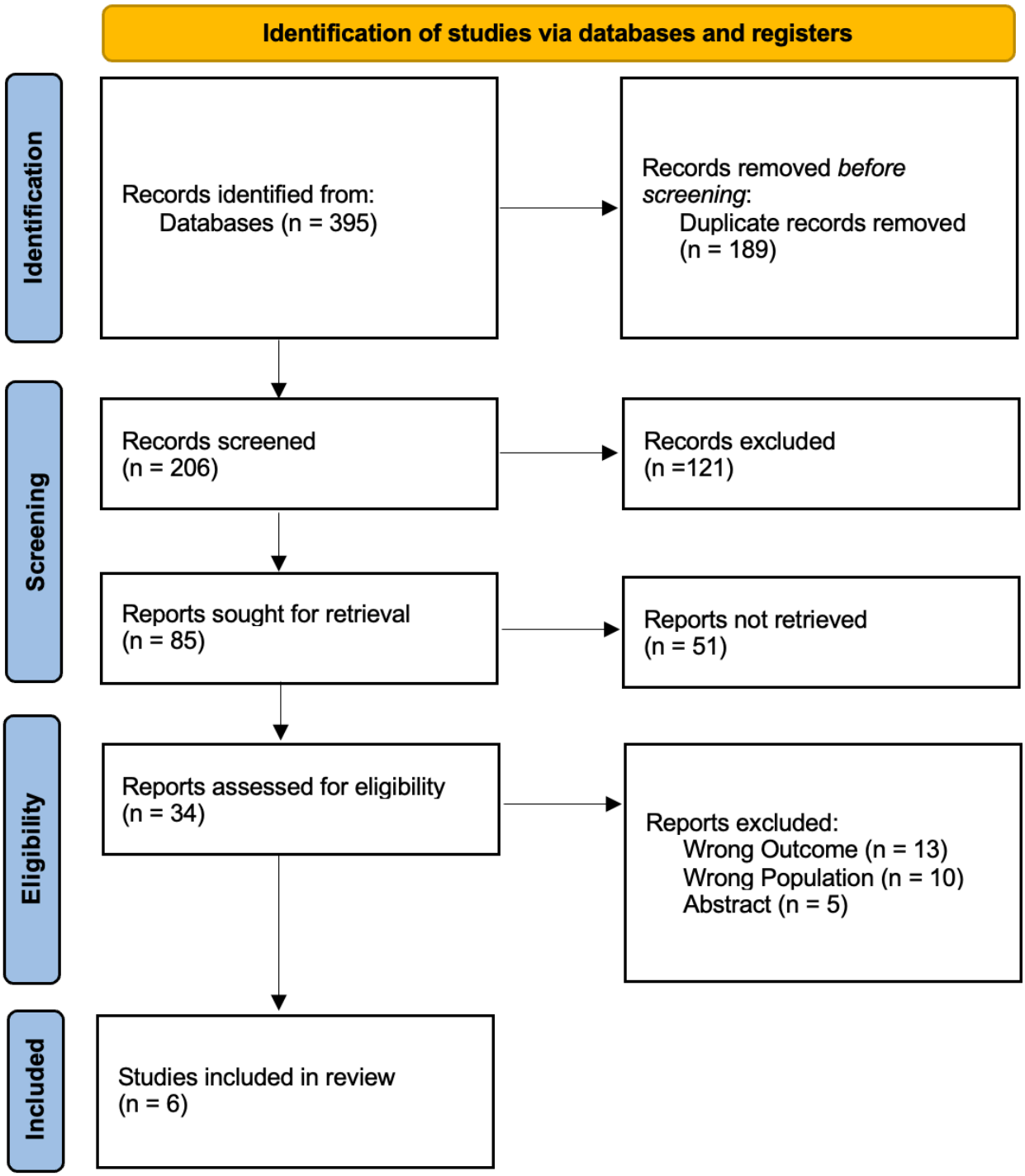

Figure 1. PRISMA Flow Diagram of Study Selection Process.

Table 1 summarizes the key demographic and baseline clinical features of the six included studies, revealing substantial heterogeneity in geographical origin, design, and population characteristics. Geographically, the studies were predominantly conducted in the United States, utilizing large administrative claims databases for the retrospective cohorts [13, 14], and in Japan, where single-center hospital-based cohorts were enrolled [15–17]; the only randomized controlled trial did not specify its location [12]. The study designs varied considerably, ranging from a pilot randomized controlled trial [12] and a prospective single-arm interventional study [15] to large retrospective cohort analyses [13, 14, 16] and a case-control investigation [17], which collectively provided both high-level experimental evidence and real-world observational data. Notably, the sample sizes displayed extreme variation, with the smallest cohort comprising only 55 patients [15] and the largest encompassing over 4,200 patients [14], thereby offering a broad spectrum of statistical power and generalizability across different healthcare settings.

Regarding patient populations and baseline characteristics, all studies uniformly included patients with established obstructive sleep apnea (OSA) comorbid with heart failure (HF), but they deliberately targeted distinct HF subtypes. Specifically, three studies focused exclusively on HF with reduced ejection fraction (HFrEF) [12, 13, 16], one dedicated solely to HF with preserved ejection fraction (HFpEF) [14], and two others accepted mixed or unspecified HF cohorts with baseline LVEF thresholds (≤50%) [15, 17]. The reported age distribution demonstrated a clear geographical disparity: the US-based claims cohorts reported mean ages of 59.7 years [13] and 64.1 years [14], whereas the Japanese prospective cohort reported a slightly younger mean age of 60.7 years [15], with other Japanese studies [16, 17] failing to report age in their abstracts. Sex distribution was consistently reported in the larger US cohorts, with a male predominance of 69.9% in the HFrEF cohort [13], contrasting with a slight female majority (54%) in the HFpEF cohort [14], reflecting the known epidemiological differences between these HF phenotypes; however, the Japanese studies did not provide sex-specific baseline data. Body mass index (BMI) and baseline apnea-hypopnea index (AHI) were largely underreported, with only the prospective Japanese study [15] providing explicit values (mean AHI 45.3 ± 16.1 events/hour), while the remaining studies either implied moderate-to-severe OSA without disclosing baseline indices or relied on ICD-coded diagnoses, limiting the ability to correlate disease severity with outcomes across all cohorts.

Table 1. Demographic and Baseline Clinical Characteristics of Included Studies

Study (Author, Year) [Ref]	Location	Study Design	Sample Size (N)	Patient Population	Age (years)	Sex (% Male)	BMI (kg/m²)	Baseline LVEF (%)	Baseline AHI (events/h)
Fox *et al.* (2021) [12]	NR	Randomized Controlled Pilot Trial	76 randomized; 58 analyzed	Chronic, stable HFrEF + Moderate-to-severe OSA	NR	NR	NR	NR (HFrEF implied)	NR
Malhotra *et al.* (2023) [13]	USA	Retrospective Cohort (Claims data)	3,182	OSA + HFrEF	59.7 ± 11.24	69.9%	NR	NR (HFrEF implied)	NR
Cistulli et al. (2023) [14]	USA	Retrospective Cohort (Claims data)	4,237	OSA + HFpEF	64.1 ± 11.52	46.0% (54% Female)	NR	NR (HFpEF implied)	NR
Naito *et al.* (2022) [15]	Japan (Toranomon Hospital)	Prospective, Single-arm, Open-label	55	OSA + HF (Mean LVEF 37.2%)	60.7 ± 12.2	NR	NR	37.2 ± 9.8	45.3 ± 16.1
Naito *et al.* (2023) [16]	Japan	Retrospective Observational	111	Stable HF (LVEF ≤50%, NYHA ≥II) + SA (OSA or CSA)	NR	NR	NR	≤50% (implied)	≥15/h (baseline)
Saito *et al.* (2022) [17]	Japan	Retrospective Case-Control	33 HF cases + 149 controls (44 matched)	OSA + HF (Acute/Chronic exacerbation)	NR	NR	NR	NR	NR

NR: Not reported.

The second table details the specific interventions, follow-up durations, and primary endpoints employed across the six studies, clearly illustrating the divergent research objectives ranging from physiological surrogates to hard clinical outcomes. The interventions were predominantly positive airway pressure (PAP)-based, but with significant differences in device type and comparator arms: one study utilized automatic PAP (APAP) against sham nasal strips [12], while three studies evaluated conventional continuous positive airway pressure (CPAP) therapy [15–17], and the two large US cohorts compared adherent versus non-adherent PAP users based on standardized Medicare compliance criteria without a sham control [13, 14].

Follow-up periods were remarkably inconsistent, spanning from a short-term physiological assessment at 1 month [15] to a mid-term 6-month evaluation [12] and extending up to one full year of healthcare utilization tracking [13, 14], with the longest observational follow-up reaching a median of 36.6 months for hard clinical events [16]. This wide temporal range implies that studies with shorter follow-ups [12, 15] are better suited to detect immediate cardiorespiratory improvements, whereas the extended observational windows [13, 14, 16] are indispensable for capturing clinically meaningful exacerbations such as hospitalizations and mortality.

Critically, the primary endpoints varied dramatically between surrogate physiological markers and patient-centered clinical events, which directly impacts the interpretation of PAP efficacy in managing HF exacerbations. The primary outcome in the randomized pilot trial was the change in percent-predicted peak oxygen consumption (VO_2), a well-established surrogate for cardiovascular prognosis, which showed significant improvement in the APAP arm [12], while the single-arm prospective study focused on the change in left ventricular ejection fraction (LVEF) after one month of CPAP, demonstrating a significant rise from 37.2% to 43.2% [15]. In stark contrast, the four remaining studies prioritized clinically meaningful endpoints directly relevant to HF exacerbations: the two large US cohorts utilized a composite of all-cause hospitalizations and emergency room visits, revealing that adherent PAP patients experienced a 24% reduction in ER visits for HFrEF [13] and a striking 57% reduction in hospitalizations for HFpEF [14].

The Japanese retrospective cohort assessed the composite of all-cause death and hospitalization for HF, reporting that patients with unsuppressed sleep apnea on CPAP had a significantly elevated hazard ratio of 2.30 for these adverse events [16]. Finally, the case-control study introduced an innovative remote-monitoring endpoint, demonstrating that Cheyne-Stokes breathing cycle length prolongation (optimal cut-off >68.9 seconds) could effectively predict the onset and exacerbation of HF [17], thereby offering a novel digital biomarker for early intervention.

Table 2. Intervention, Follow-up, and Primary Outcome Measures

Study (Author, Year) [Ref]	Intervention / Control	Follow-up Duration	Primary Endpoint(s)	Secondary Endpoint(s) / Key Significant Findings	Notes / Adherence Definition
Fox *et al.* (2021) [12]	APAP (AutoSet™) vs. Nasal strips (Control)	6 months	Change in percent-predicted peak VO_2	Significant improvement in percent-predicted peak VO_2 ($p=0.01$); Trends in peak VO_2 & VO_2-AT; Significant improvements in hypoxemia, LVEF, and QoL within the APAP group.	Surrogate marker for cardiovascular prognosis.
Malhotra *et al.* (2023) [13]	PAP Adherent vs. Non-adherent (per Medicare criteria)	1 year	Composite of Hospitalizations + Emergency Room (ER) visits	Adherent patients had fewer composite visits (driven by a **24% reduction in ER visits**); Composite visit costs were lower ($3,500 vs. $5,879, $p=0.031$); NNT to avoid 1 visit = 1.5.	Adherence: Use ≥4h/night for 70% of nights in all four 90-day periods.
Cistulli et al. (2023) [14]	PAP Adherent vs. Non-adherent (per Medicare criteria)	1 year	Composite of Hospitalizations + ER visits	Significant reduction in HCRU visits; **57% decrease in hospitalizations** and **36% decrease in ER visits** vs. pre-PAP year; Total costs lower in adherent group ($12,732 vs. $15,610, $p<0.001$).	Adherence: Use ≥4h/night for 70% of nights in all four 90-day periods. Intermediate users had similar outcomes to non-adherents.

Study (Author, Year) [Ref]	Intervention / Control	Follow-up Duration	Primary Endpoint(s)	Secondary Endpoint(s) / Key Significant Findings	Notes / Adherence Definition
Naito *et al.* (2022) [15]	CPAP	1 month	Change in Left Ventricular Ejection Fraction (LVEF)	LVEF improved significantly (37.2% → 43.2%, p<0.001); AHI decreased from 45.3 to 5.4/h. Multivariate analysis showed **younger age and higher BMI** were significant determinants of LVEF improvement.	Short-term physiological efficacy.
Naito *et al.* (2023) [16]	CPAP (Suppressed SA: residual AHI <15/h vs. Unsuppressed SA: residual AHI ≥15/h)	Median 36.6 months	Composite of All-cause death + Hospitalization for HF	Unsuppressed group had significantly lower event-free survival rates. Multivariate Cox model: Unsuppressed SA was associated with an increased risk (**HR 2.30, 95% CI 1.21–4.38, p=0.011**).	Direct measurement of "exacerbation" and hard clinical outcomes.
Saito *et al.* (2022) [17]	CPAP with Remote Monitoring data	Until May 2021 (variable)	Chronological change in Cheyne-Stokes Breathing rate (CSB%) and Cycle Length (CL)	HF group showed greater CSB variations (SD CSB%) and significantly longer CL than controls. Optimal cut-off value of CL to differentiate HF onset was **68.9 seconds**. CL was longer during the exacerbation period than the stable period.	Remote monitoring data can predict the onset and exacerbation of HF.

Table 3 presents the Cochrane Risk of Bias 2.0 (RoB 2.0) domain ratings for the single randomized controlled trial [12], while **Table 4** presents the ROBINS-I (Risk Of Bias In Non-randomized Studies - Interventions) domain ratings for the five observational studies [13–17]. ROBINS-I is specifically validated for assessing non-randomized intervention effects where allocation to PAP therapy is not controlled by the investigator; each table displays the domains most consequential to the overall risk-of-bias judgement for that study design, with full domain definitions provided in the Methodology section. The overall quality of the included evidence was generally moderate, with only one study achieving an overall low risk of bias.

Table 3. Risk of Bias Assessment of the Randomized Controlled Trial (Cochrane RoB 2.0)

Study (Author, Year) [Ref]	Study Design	Assessment Tool	Domain 1: Randomization Process	Domain 2: Deviations from Intended Interventions	Domain 3: Measurement of the Outcome	Domain 4: Missing Outcome Data	Overall Judgement
Fox *et al.* (2021) [12]	Randomized Controlled Pilot Trial	Cochrane RoB 2.0	Low (randomization)	Low	Low (objective VO_2 measurements)	Moderate (76 randomized, 58 analyzed – 23.7% attrition)	**Low**

Note: RoB 2.0 evaluates five domains in total (see Methodology). The domain not shown here — selection of the reported result — was assessed per the protocol above but is not separately tabulated.

Table 4. Risk of Bias Assessment of the Observational Studies (ROBINS-I)

Study (Author, Year) [Ref]	Study Design	Assessment Tool	Domain 1: Confounding	Domain 2: Selection of Participants	Domain 3: Measurement of Outcomes	Domain 4: Missing Data / Attrition	Overall Judgement
Fox *et al.* (2021) [12]	Retrospective Cohort (Claims)	ROBINS-I	Moderate (propensity score matching used, but residual confounding possible)	Low (consecutive claims data)	Low (objective ICD codes & PAP usage data)	Low (large cohort, complete linked data)	**Moderate**
Malhotra *et al.* (2023) [13]	Retrospective Cohort (Claims)	ROBINS-I	Moderate (propensity score matching used, but residual confounding possible)	Low (consecutive claims data)	Low (objective ICD codes & PAP usage data)	Low (large cohort, complete linked data)	**Moderate**
Cistulli et al. (2023) [14]	Prospective, Single-arm, Open-label	ROBINS-I	**Serious** (no control/comparator group)	Moderate (single-center, consecutive)	Low (objective LVEF & AHI measurements)	Low (55 patients completed)	**Serious**
Naito *et al.* (2022) [15]	Retrospective Observational Cohort	ROBINS-I	Moderate (multivariate Cox regression adjusted for confounders)	Moderate (single-center, selected population)	Low (objective residual AHI & hard clinical outcomes)	Low (111 patients analyzed)	**Moderate**
Naito *et al.* (2023) [16]	Retrospective Case-Control	ROBINS-I	Moderate (matched for CSB%, BMI, and sex, but other confounders possible)	Moderate (selected control group from 618 stable patients)	Low (objective CPAP remote monitoring data)	Low (clear matching ratios)	**Moderate**

Note: ROBINS-I evaluates seven domains in total (see Methodology). The three domains not shown here — classification of interventions, deviations from intended interventions, and selective reporting — were assessed per the protocol above but are not separately tabulated.

DISCUSSION

Our findings demonstrate a consistent signal that PAP therapy, particularly when adherence is optimized, is associated with meaningful reductions in healthcare resource utilization (HCRU), including hospitalizations and emergency room (ER) visits, across both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) phenotypes. The largest real-world evidence from US administrative claims data demonstrated that PAP-adherent patients with HFrEF experienced a 24% reduction in ER visits compared to non-adherent patients [13], while those with HFpEF showed even more substantial benefits, including a 57% decrease in hospitalizations and a 36% decrease in ER visits [14]. These findings are corroborated by the Japanese retrospective cohort, which reported that patients with unsuppressed sleep apnea on CPAP had a significantly increased risk of the composite outcome of all-cause death and hospitalization for HF (hazard ratio 2.30, 95% confidence interval 1.21–4.38) [16]. Furthermore, the prospective single-arm study demonstrated that one month of CPAP therapy significantly improved left ventricular ejection fraction from 37.2% to 43.2% [15], while the innovative case-control study utilizing remote monitoring data showed that prolongation of Cheyne-Stokes breathing cycle length beyond 68.9 seconds could effectively predict the onset and exacerbation of HF [17]. Collectively, these results suggest that effective PAP therapy—defined by adequate suppression of respiratory events and sustained adherence—constitutes a valuable adjunctive strategy for reducing HF exacerbations in this high-risk population, with the magnitude of benefit being

directly proportional to the consistency of device utilization.

The current evidence base for PAP therapy in HF patients has been shaped predominantly by several large-scale randomized controlled trials (RCTs) that have yielded largely neutral or even concerning results, creating an apparent discordance with the observational data synthesized in our review. The SERVE-HF trial, which enrolled 1,325 patients with HFrEF and predominant central sleep apnea (CSA), demonstrated that adaptive servo-ventilation (ASV) had no effect on the primary composite endpoint of all-cause mortality, lifesaving cardiovascular interventions, or unplanned hospitalization for worsening heart failure [18]. More alarmingly, both all-cause and cardiovascular mortality occurred significantly more often in the ASV group (hazard ratio 1.28, P=0.01, and hazard ratio 1.34, P=0.006, respectively), with no improvement in quality of life [18]. The authors concluded that the ASV device used should not be employed in patients with HFrEF and predominant CSA [18]. Similarly, the CAN-PAP trial, which randomized 258 patients with HF and CSA to CPAP or no CPAP, found that while CPAP attenuated central sleep apnea, improved nocturnal oxygenation, increased ejection fraction, lowered norepinephrine levels, and improved six-minute walk distance, it did not affect survival or reduce hospitalizations [19]. The overall event rates for death and heart transplantation did not differ between groups (32 vs. 32 events, P=0.54) [19]. A post-hoc analysis of CAN-PAP data, however, revealed that in patients who had their CSA suppressed by CPAP, there was a significant improvement in transplant-free survival, suggesting that efficacy of treatment, rather than intention-to-treat allocation, may be the critical determinant of outcome [26].

The ADVENT-HF trial, a more recent multicentre, multinational, phase 3 RCT, evaluated peak-flow triggered ASV in patients with HFrEF and sleep-disordered breathing (including both OSA and CSA) [20]. The primary endpoint was the cumulative incidence of all-cause mortality, first admission to hospital for a cardiovascular reason, new onset atrial fibrillation or flutter, and delivery of an appropriate cardioverter-defibrillator shock [20]. While the trial found that ASV was safe and improved sleep structure and HF-related quality of life, it did not demonstrate a reduction in the primary composite outcome [20]. Importantly, a subsequent analysis of ADVENT-HF data revealed that six months of sleep-disordered breathing suppression by ASV had no impact on left ventricular structure or function, suggesting that hemodynamic improvements may require longer follow-up or may be more dependent on treatment adherence than previously appreciated [21]. These RCT findings stand in stark contrast to the observational data synthesized in our review, which consistently demonstrate associations between PAP adherence and reduced HCRU [13, 14, 16].

The apparent paradox between the positive observational evidence and the neutral RCT results is a well-recognized phenomenon in sleep medicine research. A comprehensive review evaluating literature concerning the cardiovascular effects of treating sleep-disordered breathing with PAP devices found that nine observational studies report significantly lower cardiovascular event rates in those treated compared to untreated individuals, whereas twelve randomized trials—in which excessive daytime sleepiness was generally an exclusion criterion—showed no reduction in cardiovascular event rates [22]. The authors of that review concluded that the current rationale for treating sleep-disordered breathing with PAP remains improving sleep structure and quality of life, as well as relieving excessive daytime sleepiness, but not necessarily reducing cardiovascular events in unselected populations [22].

Several factors may explain this apparent paradox. First, the RCTs largely excluded patients with excessive daytime sleepiness, who are precisely the population most likely to adhere to PAP therapy and derive cardiovascular benefit. The SERVE-HF trial, for instance, explicitly excluded patients with daytime sleepiness interfering with daily activities, which may have selected a population with lower sympathetic activation and less severe OSA-related cardiovascular stress [18]. Second, adherence in RCTs is often suboptimal and does not reflect real-world adherent populations. In the SERVE-HF trial, 29% of patients either discontinued or never used ASV, while 16% of control patients crossed over to positive airway pressure therapy, and ASV compliance averaged only 3.4 hours per night one year post-randomization [18]. This low adherence suggests that subjects remained exposed to CSA during substantial periods when ASV was not worn, potentially diluting any treatment effect [18]. Third, the distinction between OSA and CSA is critical; while the RCTs predominantly focused on CSA (SERVE-HF, CAN-PAP) or mixed populations (ADVENT-HF), our review specifically targeted OSA patients. The pathophysiological mechanisms differ substantially between these conditions, with CSA being more directly related to HF severity itself, whereas OSA represents an independent modifiable risk factor [25].

A recent individual participant data meta-analysis demonstrated that adherent use of CPAP is associated with a reduced risk of major adverse cardiovascular and cerebrovascular events recurrence, suggesting that treatment compliance is a key factor in secondary cardiovascular prevention in patients with OSA [23]. This adherence-dependent effect is precisely what our included studies demonstrate, with adherent patients experiencing substantial reductions in HCRU [13, 14]. Furthermore, a meta-analysis of 10 RCTs and 3 observational studies

comprising 13,832 patients found that CPAP did not significantly reduce major adverse cardiovascular events (MACE) in the overall analysis, but when CPAP adherence was ≥4 hours per night, CPAP significantly reduced the risk of MACE and cardiovascular mortality [23].

The pathophysiological mechanisms linking untreated OSA to HF exacerbations are well-established and provide a compelling rationale for PAP therapy. OSA induces recurrent episodes of upper airway collapse during sleep, resulting in intermittent hypoxia, sympathetic nervous system activation, oxidative stress, and systemic inflammation [24]. These phenomena impose significant hemodynamic stress on the failing heart through increased afterload, elevated left ventricular transmural pressure, and heightened myocardial oxygen demand [25]. The resultant nocturnal hypoxemia and sympathetic overactivity can precipitate arrhythmias, worsen diastolic dysfunction, and contribute to progressive myocardial remodeling [26]. PAP therapy, by maintaining airway patency and abolishing these recurrent obstructive events, interrupts this vicious cycle. The improvement in LVEF observed in the prospective Japanese study (from 37.2% to 43.2% after one month of CPAP) [15] provides direct mechanistic support for the clinical benefits observed in the larger observational cohorts, demonstrating that the hemodynamic unloading achieved through OSA suppression translates into measurable improvements in cardiac function.

The differential magnitude of benefit observed between HFrEF and HFpEF patients in our review merits particular attention. The HFpEF cohort demonstrated a 57% reduction in hospitalizations [14], compared to a 24% reduction in ER visits in the HFrEF cohort [13]. This differential may reflect the distinct hemodynamic profiles of these HF phenotypes. HFpEF is characterized by diastolic dysfunction and elevated filling pressures, which are exquisitely sensitive to the negative intrathoracic pressure swings generated during obstructive apneas [24]. The abolition of these pressure swings through PAP therapy may have a more immediate impact on diastolic filling and pulmonary congestion in HFpEF patients. Conversely, in HFrEF, the benefits of PAP may be more gradual, mediated through gradual reverse remodeling and neurohormonal modulation, which may take longer to translate into reduced hard clinical events [25].

Our findings have important clinical implications for the management of HF patients with comorbid OSA. The consistent association between PAP adherence and reduced HCRU across both HF phenotypes suggests that clinicians should prioritize the diagnosis and effective treatment of OSA in all HF patients. The observation that intermediate adherent patients had outcomes most similar to non-adherent patients [14] underscores the importance of achieving and maintaining optimal adherence rather than simply initiating therapy. Strategies to enhance PAP adherence—including patient education, mask fitting, humidification, telemonitoring, and behavioral interventions—should be integrated into the multidisciplinary management of HF patients with comorbid OSA [27]. Furthermore, the remote monitoring data from the Japanese study [17] highlight the potential of digital biomarkers derived from PAP devices to predict HF exacerbations, offering a novel approach for early intervention and potentially reducing hospitalizations. The ability to detect Cheyne-Stokes breathing patterns and cycle length prolongation through routine PAP telemonitoring could enable clinicians to identify patients at imminent risk of decompensation and intervene proactively, representing a paradigm shift from reactive to predictive HF management.

LIMITATIONS

Several limitations of this systematic review must be acknowledged. First, the included studies exhibited substantial heterogeneity in design, population, and outcome measures, precluding meta-analysis. The two largest studies were retrospective analyses of US administrative claims data, which are subject to inherent limitations including potential coding errors, uNReasured confounders, and the inability to capture HF severity or OSA severity beyond ICD-10 codes. Second, the Japanese studies were single-center cohorts with relatively small sample sizes, limiting generalizability to broader populations. Third, the single-arm prospective study [15] lacked a control group, rendering its findings susceptible to regression to the mean and confounding by concurrent optimization of HF pharmacotherapy. Fourth, the definitions of PAP adherence varied across studies, with the US studies employing Medicare criteria while the Japanese studies used residual AHI thresholds [16], complicating direct comparisons. Fifth, the predominance of HFrEF patients in the evidence base limits the applicability of our findings to HFpEF, despite the encouraging results from the HFpEF cohort [14]. Finally, publication bias cannot be excluded, as studies demonstrating neutral or negative results may be less likely to be published, and the observational nature of most included studies precludes causal inference.

CONCLUSION

PAP therapy, when associated with adequate adherence and effective suppression of sleep-disordered breathing, is associated with meaningful reductions in healthcare resource utilization, including hospitalizations and emergency room visits, in patients with HF and comorbid OSA. These benefits appear to extend across both HFrEF and HFpEF phenotypes. The apparent discrepancy between the positive observational evidence and the neutral results of major RCTs likely reflects the

critical importance of adherence, the exclusion of symptomatic patients from trials, and the challenges of achieving optimal PAP utilization in controlled research settings. Our findings underscore the need for healthcare systems to prioritize the diagnosis and effective management of OSA in HF patients, with particular emphasis on strategies to optimize PAP adherence. Future research should focus on prospective, adequately powered randomized trials that incorporate adherence stratification and target symptomatic OSA patients with HF, as well as the development of novel digital biomarkers to enable early detection and prevention of HF exacerbations.

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Not Applicable.

Consent for Publication
Not Applicable. This systematic review does not contain any individual person's data.

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Competing Interests
The authors declare that they have no competing interests.

Authors' Contributions
H.O.M. conceived and designed the study. N.S.E.A., I.M.A., A.S.A., A.M.S.A., A.S.S.A., S.A.S.A., R.H.M.A., J.N.A., S.H.G.A., J.A.H.A., A.E.A., and B.N.M.A. contributed to the literature search, study selection, data extraction, and risk of bias assessment. H.O.M. and N.S.E.A. drafted the manuscript. All authors critically revised the manuscript for important intellectual content, approved the final version, and agree to be accountable for all aspects of the work.

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