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Original Article

Clinical significance of bendopnea in heart failure—Systematic review and meta-analysis

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ABSTRACT

Background: Bendopnea is a symptom mediated by increased ventricular filling pressure during bending forward. Presence of bendopnea in patients can be easily evaluated without additional maneuver in several countries whose norms, habits, culture, and occupation relates to a higher frequency of bending forward. This information may prove valuable in routine clinical practice. We aimed to analyze the latest evidence on bendopnea in order to further define the clinical significance of this symptom.
Methods: We performed a comprehensive search on bendopnea in heart failure from inception up until January 2019 through PubMed, EuropePMC, EBSCOhost, Cochrane Central Database, and ClinicalTrials.gov.
Results: There were 283 patients (31.76%) who have bendopnea, and a total of 891 patients from six studies were included. Bendopnea was associated with the presence of dyspnea [odds ratio (OR) 69.70 (17.35–280.07); <0.001], orthopnea [OR 3.02 (2.02–4.52); <0.001], paroxysmal nocturnal dyspnea [OR 2.76 (1.76–4.32); <0.001], and abdominal fullness [OR 7.50 (4.15–13.58); <0.001]. Association with elevated jugular venous pressure was shown in two studies. New York Heart Association (NYHA) functional class IV was more prevalent in patients with bendopnea [OR 7.58 (4.35–13.22); <0.001]. Bendopnea was also associated with increased mortality [OR 2.21 (1.34–3.66); 0.002].
Conclusion: Bendopnea is associated with the presence of several signs and symptoms. This study also showed that bendopnea is one of the signs and symptoms of advanced heart failure associated with increased mortality. However, owing to the limited number of studies, further investigation is needed before drawing a definite conclusion.

1. Introduction

Heart failure (HF) is a complex clinical syndrome and a final common pathway of most heart diseases that affect approximately 26 million people worldwide.[1] HF is classified into HF with reduced ejection fraction, mid-range ejection fraction, and preserved ejection fraction.[2] In 2014, Thibodeau et al.[3] proposed bendopnea, shortness of breath when bending forward, as a novel symptom of advanced HF. The symptom is mediated by increased ventricular filling pressure during bending, which exacerbates an already high filling pressure in patients with HF. It was also associated with a worse cardiac index (Fick's method), pulmonary capillary wedge pressure, right heart pressure, and pulmonary arterial pressure.[3]

Presence of bendopnea in the patients can be easily evaluated without additional maneuver in several countries whose norms, habits, culture, and occupation relate to a higher frequency of bending forward. This information may prove valuable in routine clinical practice. We aimed to analyze the latest evidence on bendopnea by performing a comprehensive search on studies relating to bendopnea in their research in order to further define the clinical significance of this symptom. Studies that explored these symptoms were limited, and to the best of our knowledge, there was no systematic review or meta-analysis on this subject.

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2. Methods

2.1. Search strategy

We performed a comprehensive search on bendopnea in HF with keywords [bendopnea] from inception up until January 2019 through PubMed, EuropePMC, EBSCOhost, Cochrane Central Database, and ClinicalTrials.gov and using the hand sampling from potential articles cited by other studies. We aimed to use the search keyword unrestricted to other terms in order to obtain the largest number of search results possible.

2.2. Inclusion and exclusion criteria

The inclusion criterion for this study was all the studies that assessed bendopnea in HF. Two authors (E.Y. and V.C.) independently screened for abstracts. Two independent authors (R.P. and B.B.S.) extracted and critically appraised the studies. We included all related clinical researches/original articles and research letters and excluded case reports and review articles.

2.3. Statistical analysis

To perform a meta-analysis, we used RevMan, version 5.3. We used the odds ratio and a 95% confidence interval as a pooled measure for dichotomous data. We used mean difference and its standard deviation as a pooled measure for the continuous data. The inconsistency index (I^2) test which ranges from 0 to 100% was used to assess heterogeneity across studies. A value above 50% or $p < 0.05$ indicates statistically significant heterogeneity. We used the Mantel–Haenzsel method (for odds ratio), and the inverse variance method (for mean difference) with a fixed-effect model for meta-analysis and a random-effect model were used in case of heterogeneity. All p values were two tailed with a statistical significance set at 0.05 or below.

3. Results

We found a total of 85 results. We screened 42 records after removing duplicates. Eight were relevant titles/abstracts. After assessing eight full-text studies for eligibility, we excluded two because of full-text unavailability. We included six studies in the qualitative synthesis and five studies in meta-analysis.[3–8] (Fig. 1)

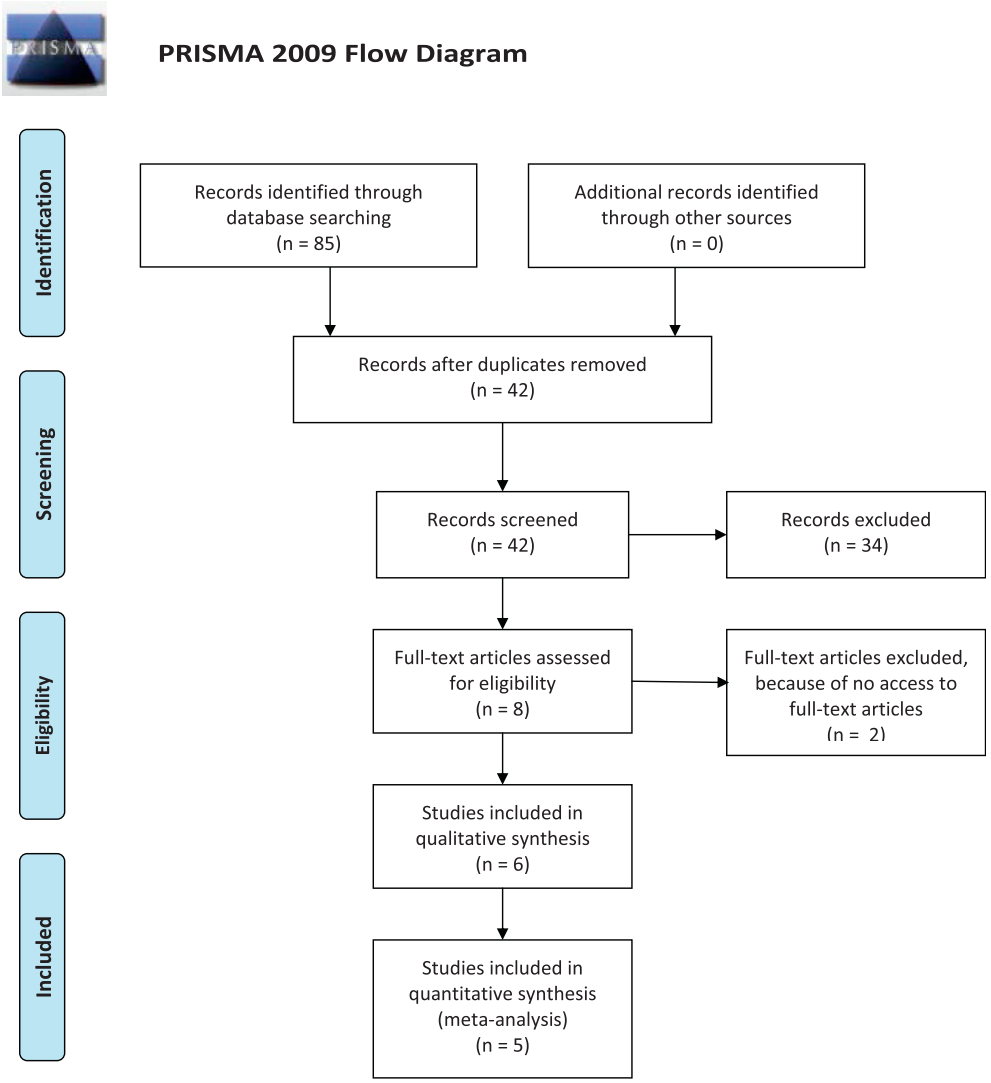

Fig. 1. Prisma flow diagram.

Three studies are a prospective cohort, and three are cross-sectional. There were a total of 891 patients from six studies. There were 283 patients (31.76%) who have bendopnea.

3.1. Patient characteristics

The inclusion and exclusion criteria enrolled in the studies were more or less similar; hence, the result of the study should not be obscured by different sample characteristics. The distribution of gender across the studies was similar. However, two studies reported a mean age of 80 years, and the rest of the studies reported around 57 years. All studies showed no significant association between age, gender, and the presence of bendopnea. On pooled analysis, gender and age were not significant for the presence of bendopnea (Table 1).

3.2. Prevalence of bendopnea

The inclusion criteria for these studies were mostly patients ≥18 years with systolic HF with LVEF ≤45%. From these six studies, the prevalence of bendopnea is 31.76%. The prevalence ranges from 18% to 48.8%. Age of the samples may be the cause of this discrepancy. Studies with a mean age of samples around 80 years have a higher prevalence of bendopnea (33.3% and 48%). When these two studies were omitted, the prevalence ranges from 18% to 31.6% (Table 2).

3.3. Comorbidities

A study by Baeza-Trinidad et al reported a significant association with atrial fibrillation (AF) and diabetes mellitus (DM) with the presence of bendopnea. Thibodeau et al also reported the significance of hypertension on bendopnea. However, upon pooled analysis from three studies, there was no significant difference between chronic obstructive pulmonary disease, AF, DM, and hypertension. Hence, comorbidities are not associated with the presence of bendopnea (Table 2).

3.4. Symptoms

Three studies that reported symptoms showed that dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and abdominal fullness were more frequent in patients with bendopnea.[3–5] Thibodeau et al reported more frequent symptoms of angina, weight gain, and palpitations. However, Baeza-Trinidad et al showed that palpitation was not significantly different in patients with or without bendopnea. Thibodeau et al and Dominguez-Rodriguez reported that ankle swelling was not different in patients with bendopnea or not. Early satiety and ascites were also not associated with bendopnea. Pooled analysis showed that dyspnea [odds ratio (OR) 69.70 (17.35–280.07); <0.001], orthopnea [OR 3.02 (2.02–4.52); <0.001] (Fig. 2A), paroxysmal nocturnal dyspnea [OR 2.76 (1.76–4.32); <0.001] (Fig. 2B), and abdominal fullness [OR 7.50 (4.15–13.58); <0.001] (Fig. 2C) were more frequent in patients with bendopnea (Table 2).

3.5. Signs

Two studies reported that elevated jugular venous pressure was more frequent in patients with bendopnea.[3,8] Baeza-Trinidad et al reported that hepatomegaly was more frequent in patients with bendopnea, but Dominguez-Rodriguez et al reported no difference. On pooled meta-analysis, we found that bendopnea was not associated with BMI, lower extremity edema, or pulmonary edema and/or rales. Hence, the only sign that is more frequent in patients with bendopnea is an elevated jugular venous pressure. However, meta-analysis cannot be done on this sign because there were only two studies (Table 2).

Table 1
Result of the studies included in the qualitative synthesis.

Author	Study design	Inclusion criteria	Exclusion criteria	Sample size (n)	Bendopnea	Mean age (bendopnea/no bendopnea)	Follow-up (mean)
Thibodeau 2017[7]	Cohort	≥18 years with systolic HF, defined as LVEF ≤45%, within 3 months of enrollment.	Active pulmonary infection; severe restrictive, obstructive, or interstitial pulmonary process; were on inotropic therapy; were non–English speaking; or were unable or unwilling to bend forward to assess for bendopnea.	179	39 (18%)	57 ± 12/58 ± 15	12
Baeza-Trinidad 2017[8]	Cohort	Decompensated HF, LVEF ≤45%	N/A	250	122 (48.8%)	81.1 ± 8.9/82.6 ± 7.5	6
Baeza-Trinidad 2018[4]	Cross section; research letter	Decompensated HF	N/A	60	20 (33.3%)	82.3 ± 7.8/81.3 ± 7.42	N/A
Sajeev 2017[6]	Cohort	Chronic systolic HF with EF <50% and satisfying Framingham's criteria and age >18 years.	acute coronary syndrome with HF, acute pulmonary thromboembolism, any acute-onset HF, and unable to provide written informed consent.	205	43 (21.2%)	N/A	12
Thibodeau 2014[3]	Cross section	≥18 years with systolic HF, defined as LVEF ≤45%, within 3 months of enrollment. Patients with systolic heart failure who were referred for right heart catheterization	Cardiac transplantation or required mechanical circulatory support with an intra-aortic balloon pump or ventricular assist device.	102	29 (28.4%)	58 (50,65)/64 (54,68)	N/A
Dominguez-Rodriguez 2016[5]	Cross section; research letter	Systolic HF referred for CPX	N/A	95	30 (31.6%)	57 ± 14/54 ± 14	N/A

CPX, cardiopulmonary exercise testing; HF, heart failure; LVEF, left ventricular ejection fraction.

Table 2
Summary of analysis.

Variable	Odds ratio (95% CI); *p*-value/mean difference (mean difference ± SD)	Heterogeneity (I^2, *p*-value)	Number of studies
Patient characteristics			
Gender	NS	–	Five
Age	NS	–	Five
Comorbidities			
Chronic obstructive pulmonary disease	NS	–	Three
Atrial fibrillation	NS	–	Three
Diabetes mellitus	NS	–	Three
Hypertension	NS	–	Three
Chronic kidney disease[a]	NS	–	One
Symptoms			
Dyspnea	69.70 [17.35–280.07]; <0.0001	42; 0.18	Three
Orthopnea	3.02 [2.02–4.52]; <0.0001	0; 0.78	Three
Paroxysmal nocturnal dyspnea	2.76 [1.76–4.32]; <0.0001	0; 0.44	Three
Abdominal fullness	7.50 [4.15–13.58]; <0.0001	0; 0.51	Three
Early satiety[a]	NS	–	One
Palpitation[a]	41% vs 18%; 0.01 and NS	–	Two
Syncope[a]	NS	–	One
Signs			
BMI	NS	–	Three
Elevated jugular venous pressure[a]	36.1% vs 21.1%; 0.008, and 10 cm vs 7 cm; 0.01	–	Two
Third heart sound[a]	NS	–	Two
Hepatomegaly[a]	32% vs 20%; 0.038, and NS	–	Two
Ascites[a]	NS	–	One
Rales/edema	NS	–	Three
Lower extremity edema	NS	–	Three
Laboratory values			
Anemia	NS	–	Three
Creatinine and e-GFR[a]	NS		Two
NT-pro BNP	NS	–	Three
Echocardiographic parameter			
LVEF	NS	–	Four
NYHA classification			
NYHA I	0.16 [0.03–0.83]; 0.03	0; 0.80	Three
NYHA II	0.19 [0.07–0.50]; <0.0001	47; 0.15	Three
NYHA III	0.56 [0.34–0.92]; 0.02	0; 0.73	Three
NYHA IV	7.58 [4.35–13.22]; <0.0001	49; 0.14	Three
Outcome			
Rehospitalization	NS	–	Three
Mortality	2.21 [1.34–3.66]; 0.002	0; 0.79	Three
Drugs Used			
Angiotensin-converting enzyme inhibitor	NS	–	Three
Angiotensin receptor blocker	NS	–	Three
Aldosterone antagonist	NS	–	Three
B-blocker	NS	–	Three
Digoxin	NS	–	Three
Diuretic	NS	–	Three

Summary of analysis: Presence of bendopnea was associated with dyspnea, orthopnea, paroxysmal nocturnal dyspnea, abdominal fullness, NYHA class IV, and mortality.
NS, not significant; CI, confidence interval; SD, standard deviation; NYHA, New York Heart Association.
[a] Meta-analysis was not performed in this category because there were less than 3 studies.

3.6. Laboratory findings

Two studies reported that there was no association between creatinine, Estimated Glomerular Filtration Rate (eGFR), and bendopnea. Our pooled analysis showed that there was no association between anemia, NT-pro BNP, and the presence of bendopnea (Table 2).

3.7. Echocardiographic findings

Although one study reported a lower cardiac index measured by Fick's method by cardiac catheterization,[3] four studies showed no significant difference in the left ventricular ejection fraction evaluated using echocardiography in those with or without bendopnea. The pooled analysis yielded a similar result (Table 2).

3.8. NYHA classification

Four studies reported that bendopnea was associated with the NYHA functional class IV, and patients without bendopnea were more likely to have NYHA functional class I, II, or III than patients with bendopnea (Fig. 3). On pooled analysis, the OR of bendopnea patient having NYHA IV was 7.58 (4.35–13.22); <0.001 (Fig. 3D), while the OR of bendopnea patient having NYHA I, II, or III were 0.16 (0.03–0.83); 0.03 (Figs. 3A), 0.19 (0.07–0.50); <0.001 (Figs. 3B), and 0.56 (0.34–0.92); 0.02 (Fig. 3C), respectively (Table 2), showing that bendopnea is a sign of advanced HF.

3.9. Outcome

Sajeev et al reported that patients without bendopnea were associated with a higher rate of HF readmission.[6] However, two other studies reported no significant difference. A pooled analysis showed that the rate of readmission was not associated with bendopnea.

Two studies by Sajeev et al and Thibodeau et al (both have a follow-up period of 12 months) reported no significant difference between mortality in patients with bendopnea. A study by Baeza-Trinidad et al, which has a significantly larger sample and event rate, showed that bendopnea was associated with higher mortality (6-month follow-up). A pooled analysis showed that bendopnea was associated with increased mortality with an OR of 2.21 (1.34–3.66); 0.002 (Table 2, Fig. 4). However, Baeza-Trinidad sample has a mean age of 81 years, and this may indicate that the mortality outcome is more relevant in the elderly. Sensitivity analysis by omission of Baeza-Trinidad et al study still results in a significant outcome with OR of 2.84 (1.16–6.93); 0.02. It is also still significant if the random-effect model is used.

Funnel plot analysis across most analysis of studies that are included within this meta-analysis reveals symmetry in the plot. This finding has positive implications on our meta-analysis due to symmetry in funnel plots, which indicates a lower risk of publication bias and heterogeneity (Figs. 2C, 3A-D). However, funnel plot analysis of association of bendopnea with orthopnea and bendopnea with paroxysmal nocturnal dyspnea indicated risk of publication bias (Fig. 2A and B); then again, with the small number of studies included in this meta-analysis, possible risk of publication bias cannot be dismissed. We acknowledge that the small numbers of studies included within funnel plot analyses in this study might pose a certain amount of inaccuracy in its interpretation.

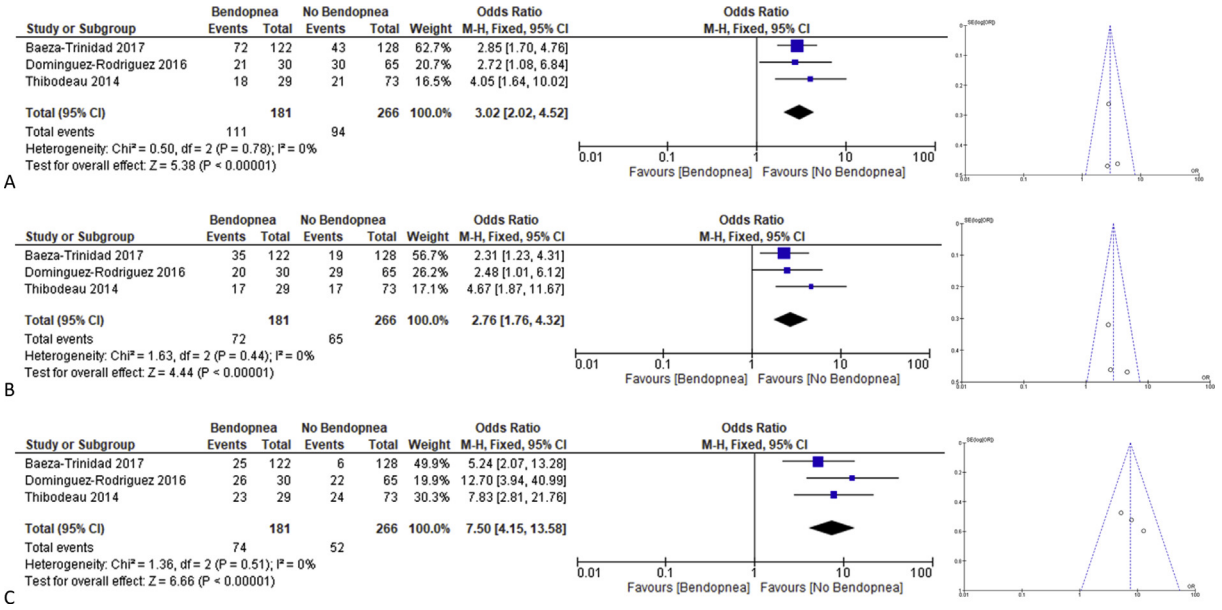

Fig. 2. Pooled analysis of the association between bendopnea and symptoms. Forest plots showing the association between bendopnea and orthopnea (A), paroxysmal nocturnal dyspnea (B), and abdominal fullness (C). Bendopnea is associated with above symptoms. CI, confidence interval.

4. Discussion

Bendopnea was associated with the presence of dyspnea [OR 69.70 (17.35–280.07); <0.001], orthopnea [3.02 (2.02–4.52); <0.001], paroxysmal nocturnal dyspnea [OR 2.76 (1.76–4.32); <0.001], and abdominal fullness [OR 7.50 (4.15–13.58); <0.001]. Association with elevated jugular venous pressure was shown in two studies. NYHA functional class IV was more prevalent in patients with bendopnea [OR 7.58 (4.35–13.22); <0.001]. Bendopnea was also associated with increased mortality [OR of 2.21 (1.34–3.66); 0.002]. Three studies were cohort, and three were cross-sectional. These cohort studies only followed up the patient

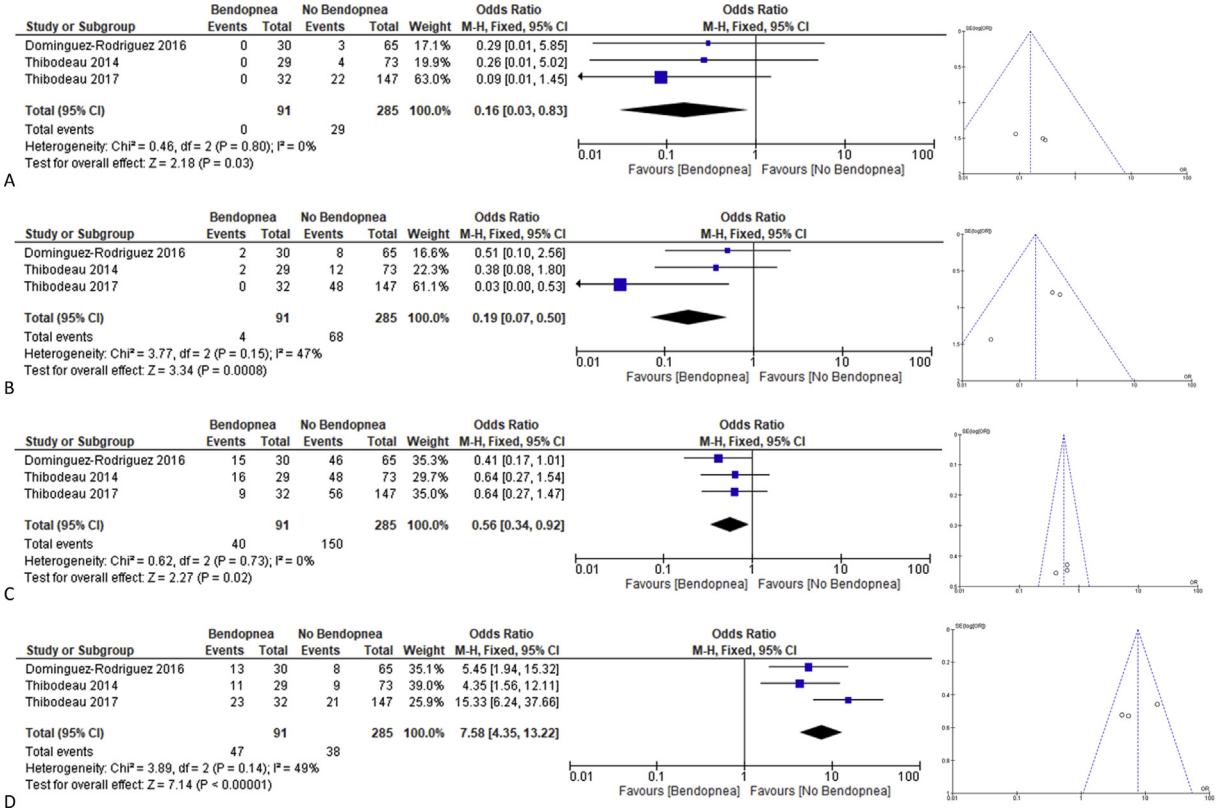

Fig. 3. Pooled analysis of the association between bendopnea and NYHA classification. Forest plots showing the association between bendopnea and NYHA class I (A), class II (B), class III (C), and class IV (D). Bendopnea was associated with NYHA class IV and is inversely associated with NYHA I, II, and III. CI, confidence interval.

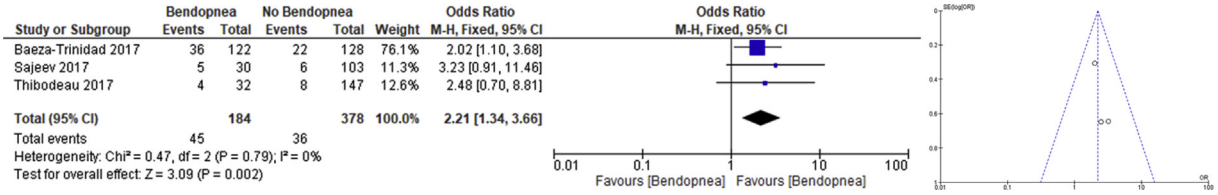

Fig. 4. Pooled analysis of the association between bendopnea and mortality. Forest plots showing the association between bendopnea and mortality. CI, confidence interval.

to up to 12 months, and two only included mortality and readmission as the outcome/endpoint. Hence, the studies lacked data for a long term outcome. They also did not include other important endpoints such as major adverse cardiovascular events, myocardial infarction, stroke, documented arrhythmia or ICD shocks. They also did not separate mortality into the cardiovascular cause of mortality and all-cause mortality. All of the studies included subjects with HF, two studies by Baeza-Trinidad specify a decompensated HF and the other four studies listed systolic HF as their inclusion criteria. Four studies reported similar inclusion criteria, although one of them has a different threshold of LVEF (50% compared to 45% in other studies). The exclusion criteria are clear in three studies and not available on the paper of the other three studies. Also, two studies were published as a research letter/letter to the editor, unlike the other four studies. Two studies reported a mean age of 80 years and the rest of the studies reported around 57 years, although the omission of these two studies did not alter the result of the pooled analysis.

Bendopnea was strongly associated with shortness of breath, dyspnea, orthopnea, and paroxysmal nocturnal dyspnea.[3,5,8] It was expected that bendopnea is related with orthopnea and paroxysmal nocturnal dyspnea due to a similar mechanism of increased ventricular filling pressure due to the position. Bendopnea was strongly associated with abdominal fullness although the association with hepatomegaly was not clear. Interestingly, NT-pro BNP was not significantly associated with bendopnea. NYHA class IV was more frequent in patients with bendopnea, and class I, II, and III were inversely correlated.[3,5,7] This may explain that although bendopnea may be present in all stages of HF, it is more specific for advanced HF.

Baeza-Trinidad et al[4,8] studies reported a mean age of 80 years, and the rest of the studies reported around 57 years;[3,5,7] they also specify decompensated HF as their inclusion criteria, and this may lead to a higher odds ratio in mortality outcome. We can see from Fig. 4 that Baeza-Trinidad et al[8] has the narrowest confidence interval, although the omission of this study also resulted in a significant pooled analysis. Baeza-Trinidad also had the highest events, and thus contributing to the bulk of study weight. Use of random-fixed model also yielded a similar result. The result may especially be relevant for the elders. A study that we excluded because of inaccessible full text (and Russian language full text if accessible) reported higher mortality in elderly patients with bendopnea.[9]

The anti-HF drugs were reported to be similar in patients with or without bendopnea; however, the dose was not reported. It is possible that the difference between the patients with and without bendopnea lies in the drug dosages. Because bendopnea is higher in NYHA class IV, it is possible that patient will be more likely to get a higher dosage of anti-HF medicine. Also, the device used such as a pacemaker or implantable cardioverter defibrillator was not addressed in these studies.

Limitation of this systematic review includes a selection bias. The number of studies was also limited and varied on the variables measured; this may lead to a limited conclusion of the study. Two studies have a different mean age compared to the other four included studies. The exclusion criteria of the studies included also differs. These may contribute to heterogeneity in our study. The limited number of studies included also limits the power of our funnel plot analysis and may obscure the bias assessment. We also encountered two potential articles that were excluded because of inaccessible and non-English language full text. We could have a higher number of pooled events if we would have included those two studies, assuming the data are complete.

5. Conclusion

Bendopnea is statistically associated with the presence of dyspnea, orthopnea, paroxysmal nocturnal dyspnea, abdominal fullness, and elevated jugular venous pressure in this study. Patients with bendopnea are also more likely in a NYHA functional class IV group and are also associated with mortality. This systematic review demonstrated that bendopnea is potentially one of the signs and symptoms of advanced HF that is associated with increased mortality. However, owing to the limited number of studies, further investigation is needed before drawing a definite conclusion. We encourage further research on this topic because of the limited number of studies. We also suggest the symptom 'bendopnea' be included in HF registries to obtain a larger sample and to evaluate its association with a vast number of variables that are available in HF registries. We also suggest future research to include a complete report on symptoms, signs, laboratory values, echocardiographic values, drug dosages, devices used, and additional outcomes such as major adverse cardiovascular events with a longer follow-up. We also suggest the labeling of ischemic and non-ischemic cardiomyopathy for the etiology of HF.

Conflict of interest

All authors have none to declare.

References

1. Ponikowski P, Anker SD, AlHabib KF, et al. Heart failure: preventing disease and death worldwide. *ESC Hear Fail.* 2014;1(1):4–25. https://doi.org/10.1002/ehf2.12005.
2. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2016;37(27):2129–2200. https://doi.org/10.1093/eurheartj/ehw128.
3. Thibodeau JT, Turer AT, Gualano SK, et al. Characterization of a novel symptom of advanced heart failure: bendopnea. *JACC Hear Fail.* 2014;2(1):24–31. https://doi.org/10.1016/j.jchf.2013.07.009.
4. Baeza-Trinidad R, Mosquera-Lozano JD, Gómez-Del Mazo M, Ariño-Pérez de Zabalza I. Evolution of bendopnea during admission in patients with decompensated heart failure. *Eur J Intern Med.* 2018;51(February):e23–e24. https://doi.org/10.1016/j.ejim.2018.02.026.
5. Dominguez-Rodriguez A, Thibodeau JT, Abreu-Gonzalez P, et al. Association between bendopnea and key parameters of cardiopulmonary Exercise testing in patients with advanced heart failure. *J Card Fail.* 2016;22(2):163–165. https://doi.org/10.1016/j.cardfail.2015.12.013.
6. Sajeev CG, Rajan Nair S, George B, Rajesh GN, Krishnan MN. Demographical and clinicopathological characteristics in heart failure and outcome predictors: a prospective, observational study. *ESC Hear Fail.* 2017;4(1):16–22. https://doi.org/10.1002/ehf2.12119.

7. Thibodeau JT, Jenny BE, Maduka JO, et al. Bendopnea and risk of adverse clinical outcomes in ambulatory patients with systolic heart failure. *Am Heart J*. 2017;183:102–107. https://doi.org/10.1016/j.ahj.2016.09.011.
8. Baeza-Trinidad R, Mosquera-Lozano JD, El Bikri L. Assessment of bendopnea impact on decompensated heart failure. *Eur J Heart Fail*. 2017;19(1):111–115. https://doi.org/10.1002/ejhf.610.
9. Larina VN, Bart BY, Chukaeva II, Karpenko DG, Zacharova MI, Kulbachinskaya OM. Bendopnea: association with echocardiographic features and clinical outcomes in elderly patients with chronic heart failure. *Kardiologiia*. 2018;58(12):36–44. https://doi.org/10.18087/cardio.2018.12.10190.