Journal Pharmaceutical Science and Application
Volume 7, Issue 2, Page 51-63, December 2025
E-ISSN: 2301-7708

A SYSTEMATIC REVIEW OF DIRECT MEDICAL COSTS AND COMORBIDITIES IN HEART FAILURE

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ABSTRACT

Background: Heart failure (HF) often coexists with multiple comorbidities, which may substantially increase healthcare resource use. However, economic evaluations often overlook the specific cost impact of comorbid conditions in HF patients. **Objective:** To systematically review and quantify the excess direct medical costs and markup factors associated with comorbidities in patients with heart failure. **Methods:** A structured literature search was conducted across four databases (PubMed, Embase, ScienceDirect, and Google Scholar) on June 28, 2025. Observational studies reporting direct medical costs of HF patients with and without comorbidities were included. All cost values were standardized to 2024 USD using the Consumer Price Index (CPI) and converted using average exchange rates. The methodological quality of included studies was assessed using criteria adapted from Huber et al. (2015). A total of six studies, all conducted in the United States, met the inclusion criteria. Narrative synthesis was performed due to heterogeneity in cost reporting. **Results:** Across the six studies, comorbidities significantly increased HF-related costs. Mark-up factors ranged from 0.64 to 2.15, with the highest excess costs observed in patients with hyperkalemia (USD 39,543), drug use disorder (USD 27,783), and cancer (USD 19,379). In contrast, some comorbidities, such as Alzheimer's disease, ischemic heart disease, and type 2 diabetes mellitus, were associated with lower costs, possibly due to end-of-life care patterns or system-level cost controls**. Conclusion:** Comorbidities impose a substantial and variable economic burden on HF patients. Findings highlight the need for multi-country studies, standardized cost methodologies, and the inclusion of indirect costs and HF severity stratification in future research.

Keywords: Comorbidities; Direct medical costs; Economic burden; Heart failure; Mark-up factor.

INTRODUCTION

Heart failure (HF) is a clinical syndrome characterized by complex signs and symptoms resulting from structural or functional cardiac impairment, which leads to reduced ejection or impaired filling of the ventricles[1]. According to the New York Heart Association (NYHA), heart failure is classified based on the degree of functional limitation experienced by the patient, ranging from Class I (no limitation) to Class IV (severe limitation)[1]. Globally, HF is a major public health burden, affecting approximately 64 million people worldwide[2].

DOI: https://doi.org/10.24843/JPSA.2025.v07.i02.p01

In clinical practice, heart failure is rarely seen in isolation and is frequently accompanied by comorbidities such as coronary artery disease, hypertension, atrial fibrillation, COPD, CKD, and diabetes mellitus[3]. These coexisting conditions worsen clinical outcomes, increase hospitalizations, and raise overall healthcare costs. Moreover, comorbidities may amplify each other's negative effects, leading to a cycle of worsening health and higher resource use[4-5].

Despite this impact, many economic evaluations often exclude patients with comorbidities, potentially underestimating the true cost of heart failure in real-world settings[6]. However, to date, no previous systematic review has specifically calculated the excess direct medical costs for individual heart failure comorbidities using markup factors. Therefore, this systematic review aims to analyse and quantify the excess healthcare costs due to comorbidities in patients with heart failure. This review addresses the following research question based on the PICOS framework: In patients with heart failure (P), how does the presence of comorbidities (I), compared to those without comorbidities (C), affect direct medical costs (O), as reported in analytical observational studies (S).

METHODS

1. Comorbidity, assessment, and markup factor

The definition and cost implications of comorbidities may vary depending on whether the comorbid condition is considered causally related to the index disease[7]. In this review, comorbidity is defined using the classical approach, treating heart failure as the index disease and any additional condition as comorbid.

The definition and evaluation of comorbidities remain an important consideration in health economic research. Comorbidities may be assessed either individually or through index-based methods. Quantitative indices simply count the number of comorbid conditions, while weighted indices such as the Charlson Comorbidity Index (CCI) assign scores based on the severity or mortality risk of each condition, with scores ranging from 1 to 6. These indices are commonly used to adjust for patient complexity or to match study populations.

In the context of cost analysis, comorbidity-related economic burden can be reported as excess costs, calculated as the difference in cost between patients with and without specific comorbidities. To further express the proportional impact, markup factors can be calculated by dividing the average cost per patient with comorbidities by the cost per patient without. This approach provides a clearer understanding of how comorbidities contribute to increased healthcare utilization.

Following the methodology of this review included only studies that reported or allowed the calculation of comorbidity-specific excess costs were included. Retrospectively collected cost data from over a year prior to the study require adjustment, commonly referred to as cost standardization, using the Consumer Price Index (CPI) to account for inflation[7-8]. All cost data were adjusted for inflation to reflect 2024 U.S. dollars and were made using the official CPI inflation calculator from the U.S. Bureau of Labor Statistics (https://www.bls.gov/data/inflation_calculator.htm), according to the following formula:

$$Adjusted\ cost = Original\ cost\ x\ \frac{CPI2024}{CPIbase\ year}$$

To minimize bias, comorbidity-specific costs were analyzed separately, and study quality was assessed using criteria adapted

DOI: https://doi.org/10.24843/JPSA.2025.v07.i02.p01

from several validated assessment frameworks[7].

2. Database Sources, Search Strategy, Study Selection, and Data Extraction

On 28 June 2025, we conducted a structured literature search in PubMed, Embase, ScienceDirect, and Google Scholar. Embase was accessed via the Cochrane Library platform, while PubMed, ScienceDirect, and Google Scholar were accessed directly. The following search concept was used in PubMed and adapted for other databases: The PubMed search ("heart failure"[Title/Abstract]) AND ("comorbidity"[Title/Abstract] OR "multimorbidity"[Title/Abstract]) AND ("cost"[Title/Abstract] OR "economic burden"[Title/Abstract]).

The search was restricted to articles published between January 2010 and 28 June 2025, in English, involving human subjects, and limited to observational or economic evaluation studies reporting direct medical costs related to comorbidities in heart failure.

A total of 2,224 records were retrieved: PubMed (n=142), Embase (n=799), ScienceDirect (n=1,248), and Google Scholar (n=35). After importing all records into reference management software, duplicate entries were removed, especially overlapping records from PubMed and Embase.

Two independent reviewers screened titles, abstracts, and full texts. No prespecified protocol was registered [9]. Studies focusing solely on healthcare utilization without reporting cost outcomes were excluded. A total of 6 studies were included after full screening. Data extraction emphasized cost components attributable to comorbidities, and markup factors were calculated to express excess costs. Studies that described only healthcare utilization without reporting cost outcomes were excluded.

Ultimately, 6 studies met the eligibility criteria and were included in the final analysis. Data extraction focused on key variables, including comorbidity type, cost category, study design, and currency year. Markup factors were calculated where possible to quantify excess costs.

To standardize costs across studies, an inflation adjustment was performed using the Consumer Price Index for All Urban Consumers (CPI-U) with 2024 as the reference year, obtained from the U.S. Bureau of Labor Statistics. Subsequently, inflated values were converted to 2024 US dollars using the average exchange rate for 2024.

3. Quality Assessment

The methodological quality of included studies was assessed using a structured checklist adapted from Huber et al. (2015), who based their framework on previously published criteria by Husereau, McKeage, and Molinier[10–12]. The checklist consisted of 14 items, including study objectives, study perspective, epidemiological sources, costing components, and funding disclosure. Each item was scored as "Yes (✓)" if clearly addressed or "No (×)" if not.

4. Data Synthesis

Due to the heterogeneity of the included studies in terms of study design, populations, comorbidity types, and cost reporting methods, a meta-analysis was not feasible. Variations in the types of comorbidities evaluated, cost components included (e.g., inpatient vs. outpatient, direct vs. total costs), and differences in currency years and healthcare systems further limited statistical pooling.

Therefore, a narrative synthesis approach was employed. Key characteristics of each study, including country, sample

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size, comorbidity of interest, cost type, and reported cost values, were extracted and summarized in structured tables. Mark-up factors were calculated where possible to estimate the relative increase in cost due to comorbidities. Results were synthesized thematically according to comorbidity type and cost category, with a focus on excess direct medical costs.

6. Outcome Measures

The primary outcome in this review was the excess direct medical costs associated with comorbidities in patients with heart failure. This approach was adapted from the comparative cost analysis framework used by Huber et al. (2015), which compared costs between heart failure patients with and without comorbidities.

Excess cost was defined as the difference in annual direct medical costs between patients with comorbidities (CD case) and those without (base case):

Excess Cost Cost CD – Cost Base.

To standardize the relative impact of comorbidities, we also calculated the markup factor, which represents the proportional increase in cost due to comorbidities:

Markup Factor = Cost CD/Cost Base

These outcomes were calculated on a per-patient per-year basis and were used to compare the cost burden across different comorbidities and studies[7].

RESULTS

A total of 2,224 records were identified through database searching, including PubMed, Embase, ScienceDirect, and Google Scholar. After removing 588 duplicates and excluding an additional 87 records through automation tools and other preliminary checks, 2,137 unique records remained for screening. Following the title and abstract assessment, 2,081 records were excluded for not meeting the predefined eligibility criteria. Fifty-six full-text articles were subsequently retrieved and evaluated for eligibility, of which 44 were excluded with documented reasons. Ultimately, six studies met all inclusion criteria and were incorporated into the final qualitative synthesis. The detailed study identification and selection process is illustrated in Figure 1.

All six included studies were conducted in the United States, reinforcing the predominance of cost-of-illness research in high-income countries [13–18] All studies used real-world data from large databases such as MEPS[13], NIS [14], Premier [15]Tufts Medical Center[16], the VA system[17], and US insurance claims [18]

In terms of sample characteristics, the smallest cohort included 307 patients [13]while the largest exceeded 899,000 [14]. Four studies reported a mean patient age ≥70 years [13,15,16,19]. Gender was mostly balanced except in the VA and insurance-based datasets, which had predominantly male populations [17,18]

The most prominent excess cost was observed in patients with hyperkalemia, where annual costs rose from USD 69,625 to USD 109,168, resulting in an excess cost of USD 39,543 and a mark-up factor of 1.57 [18]Another notably high increase was seen in patients with drug use disorder, where costs rose from USD 57,791 to USD 85,574 (excess: USD 27,783; mark-up: 1.48) [17]Comorbid renal failure (RF) and other psychiatric disorders also led to substantial excess costs of USD 17,568 and USD 19,224, respectively (Table 1).

For diabetes mellitus (T2DM), higher excess costs in patients with HFrEF (USD 5,199; mark-up 1.36) than those with HFpEF (USD 4,120; mark-up 1.29). The lowest additional burden was observed in patients with acute myocardial infarction (AMI), where excess cost was only USD 2,655 (mark-up 0.88)[15-16].

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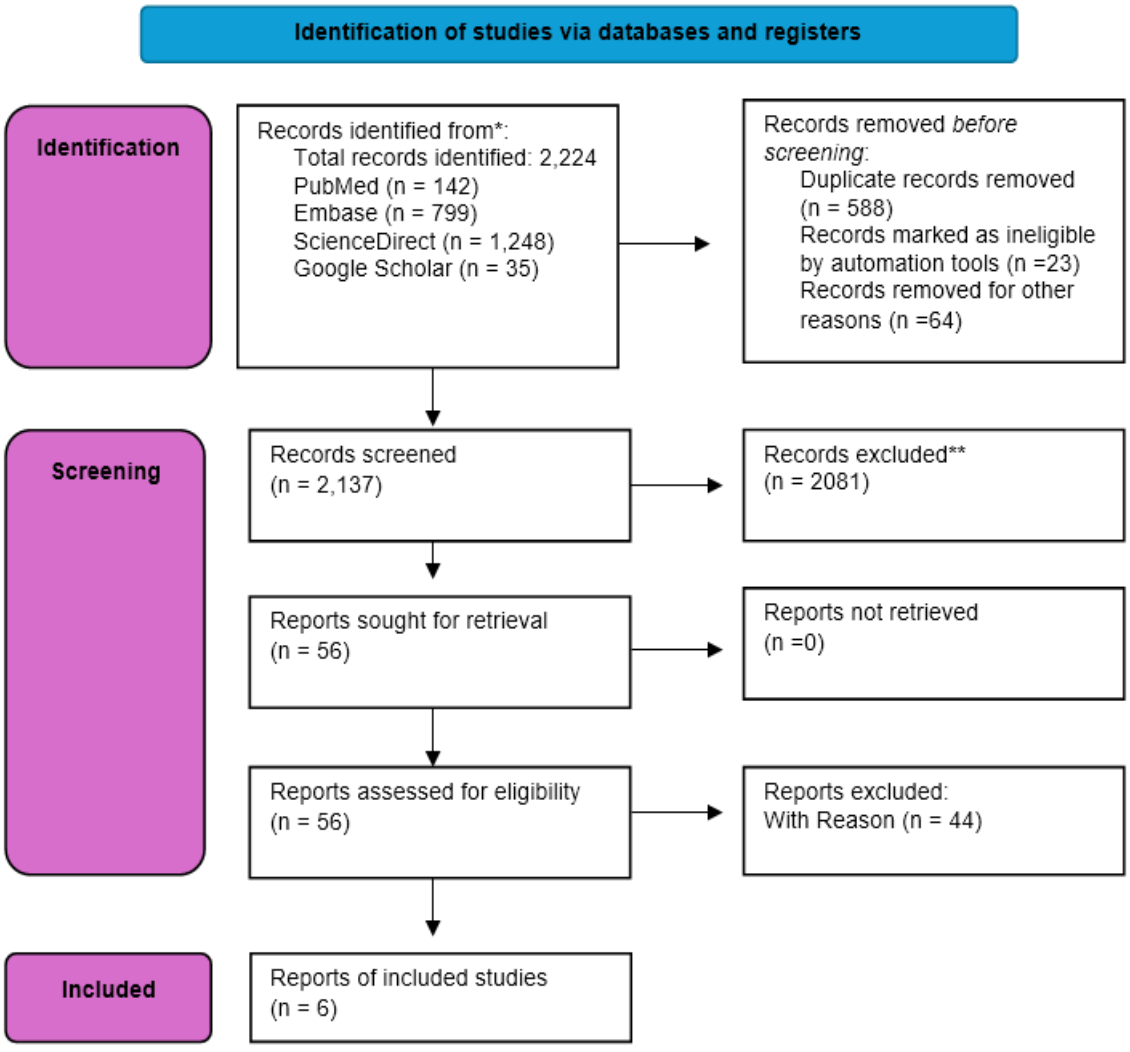

Figure 1. Flow Diagram of the Study Selection Process

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

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Table 1. Characteristics of Heart Failure Studies, Cost Categories, Excess Costs, and Corresponding Mark-up Factors

No	Study	Country Sample size Source Adjusment method	Gender (%) Mean Age (+- SD) Saverity of HF Prevalence of Comorbidities	Comorbiditiy of Interest and Evaluated Cost Category	Base case per patient and year	CD case per patient and year	Excess cost with CD	Mark-up Factor
1	[13]	USA	(ACS+HF) Female| Male: 50.1%| 49.9% (ACS+HF): 70.8 % SE 1.02;	**ACS + HF (All Cause Total)**	$ 25,108	$ 45,970	$ 20,862	1.83
		(ACS+HF): 307	n/a	**ACS + HF (Cardiovascular related)**	$ 8,662	$ 18,619	$ 9,957	2.15
		Medical Expen-diture Panel Survey (MEPS) database from 1998 through 2009 Tobit Model and Negative Binomial Regression	ACS+HF 6.01 SE 0.2					
2	[14]	USA	Female No HF| HF: 50.2% | 46.3%	**Cancer + HF**	$ 33,813	$ 52,490	$ 18,677	1.55
		No HF| HF: 834,900 (92.8%) |64,740 (7.2%)	No HF| HF: 63.9 (14.1) | 73.7 (11.3)					
		National Inpatient Sample (NIS) Logistic regression (cluster-adjusted) for mortality; age-standardization for costs/LOS	n/a					
3	[15]	USA	Male No HF| HF: 47.2 | 43.3	**AMI + HF**	$ 20,332	$ 22,987	$ 2,655	1.13
		No HF| HF: 425708 | 42946	Age No HF| HF: 82.2 (4.7) | 83.2 (4.7)					
		Premier Healthcare Database (Premier Inc., Charlotte, NC)	n/a					

DOI: https://doi.org/10.24843/JPSA.2025.v07.i02.p01

No	Study	Country Sample size Source Adjustment method	Gender (%) Mean Age (+- SD) Severity of HF Prevalence of Comorbidities	Comorbidity of Interest and Evaluated Cost Category	Base case per patient and year	CD case per patient and year	Excess cost with CD	Mark-up Factor
4	[16]	US	Female 238 (44%)	**HFrEF + DM**	$ 14,707	$ 19,948	$ 5,241	1.36
		N = 544	Age 71.04 (15.13)	**HFpEF + DM**	$ 14,147	$ 18,301	$ 4,154	1.29
		Tufts Medical Center cost accounting system	HFrEF 161; (HFrEF+C) 124; HFpEF 146; (HFpEF+C) 113					
5	[17]	Texas	Female 2.299 (2) | 115.585 (98)	**HF + HT**	$ 57,847	$ 49,216	$ -8,631	0.85
		N = 117,870	Age <50 2088 (2) | 50-59 12428 (11) | 60-69 37014 (31) |70-79 29421 (25) | 80+ 36934 (31)	**HF + IHD**	$ 57,847	$ 52,270	$ -5,577	0.90
		Veterans Affairs (VA) system.	N/A	**HF + T2DM**	$ 57,847	$ 51,124	$ -6,723	0.88
		regression analysis	HT 89014 (76) | IHD 62143 (53) | T2DM 57672 (49) | RF 24187 (21) |Depression 17361 (15) | Post-traumatic Stress Disorder 8158 (7) |Alcohol Use Disorders 3851 (3) |Other Psychiatric Disorder 4035 (3)|Drug Use Disorder 2457 (2) | Alzheimer's Disease 854 (1)	**HF + RF**	$ 57,847	$ 75,431	$ 17,584	1.30
		VA National Patient Care Database and Fee Basis files		**HF + Depression**	$ 57,847	$ 60,194	$ 2,347	1.04
				HF + post-traumatic stress disorder	$ 57,847	$ 61,111	$ 3,264	1.06
				HF + Drug use disorder	$ 57,847	$ 85,656	$ 27,809	1.48
				HF + Alcohol use disorder	$ 57,847	$ 69,695	$ 11,848	1.20
				HF + Other psychiatric disorder	$ 57,847	$ 77,089	$ 19,242	1.33
				HF + Alzheimer's disease	$ 57,847	$ 52,005	$ -5,842	0.90

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No	Study	Country Sample size Source Adjustment method	Gender (%) Mean Age (+- SD) Severity of HF Prevalence of Comorbidities	Comorbidity of Interest and Evaluated Cost Category	Base case per patient and year	CD case per patient and year	Excess cost with CD	Mark-up Factor
6	[18]	US N (c) 4426; N = 4426 US insurance claims database	Men 2391 (54.0) Age 63.7 (15.6) Patients with yperkalemia-related hospitalizations 1473 (33.3); Patients with index hospitalization unrelated to hyperkalemia 1473(33.3)	**HF + Hyperkalemia**	$ 68,770	$ 107,827	$ 39,057	1.57

All costs were adjusted to 2024 USD using the Consumer Price Index (CPI) via the CPI inflation calculator. ACS = Acute Coronary Syndrome; HF = Heart Failure; AMI = Acute Myocardial Infarction; HT = Hypertension; IHD = Ischemic Heart Disease; T2DM = Type 2 Diabetes Mellitus; RF = Renal Failure; DM = Diabetes Mellitus; HFrEF = Heart Failure with Reduced Ejection Fraction; HFpEF = Heart Failure with Preserved Ejection Fraction; Depression = Major Depressive Disorder; PTSD = Post-Traumatic Stress Disorder; Drug Use Disorder = Substance Use Disorder involving illicit or prescription drugs; Alcohol Use Disorder = Chronic alcohol misuse with clinical diagnosis; Other Psychiatric Disorder = Includes anxiety, bipolar disorder, schizophrenia, and unspecified psychiatric conditions; Alzheimer's Disease = A neurodegenerative disorder causing progressive dementia; Hyperkalaemia = Elevated blood potassium levels; "All-cause total" = Includes all medical cost components regardless of disease origin; "Cardiovascular-related" = Includes only costs directly related to cardiovascular conditions

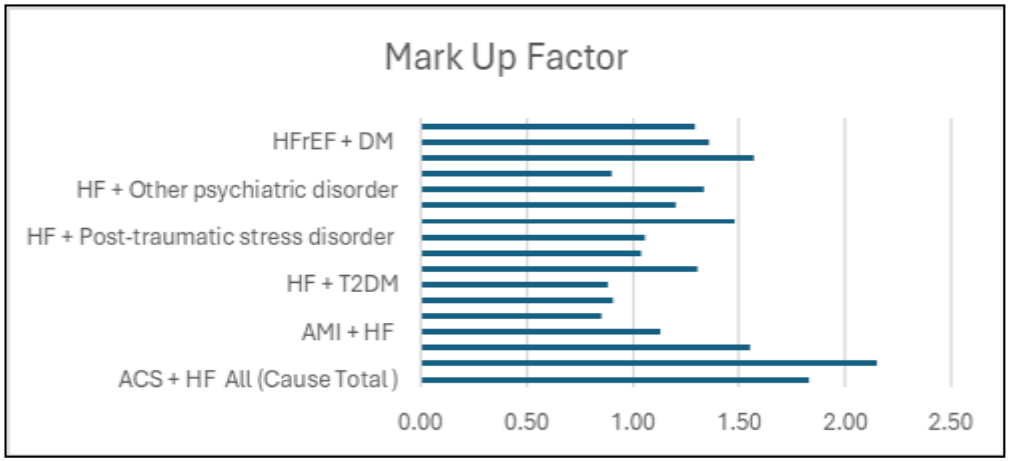

Figure 2. Mark-Up Factors of Medical Costs Due to Comorbidities in HF

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Table 2. Quality Criteria and Their Implementation in HF Comorbidity Studies

No	Items/ Studies	[13]	[14]	[18]	[15]	[17]	[16]
1	Purpose of the study explained	✓	✓	✓	✓	✓	✓
2	Setting and location	✓	✓	✓	✓	✓	✓
3	The study perspective is stated directly or indirectly.	✓	✓	✓	✓	✓	✓
4	The epidemiology source was carefully described.	✓	✓	✓	✓	✓	✓
5	Were the Inclusion criteria for patient groups clear and sufficient?	✓	✓	✓	✓	✓	×
6	Was the severity of HF assessed or indicated?	×	×	×	×	×	×
7	Was the index used to indicate the prevalence and severity of comorbidities among the group?	✓	✓	✓	✓	×	×
8	Were the prevalences for single additional comorbidities stated?	✓	✓	✓	✓	✓	✓
9	Was the comparison group matched for characteristics?	✓	✓	✓	✓	✓	✓
10	Did the outcome include direct costs?	✓	✓	✓	✓	✓	✓
11	Was the price date stated?	×	✓	✓	✓	✓	✓
12	Were the study limitations stated?	✓	✓	✓	✓	✓	✓
13	Was the source of funding stated?	✓	✓	✓	✓	✓	×
14	Was a possible conflict of interest stated?	✓	✓	✓	✓	✓	✓

✓: Yes; ×: No

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Interestingly, several comorbidities, such as Alzheimer's disease, hypertension, and ischemic heart disease, were associated with negative excess costs, indicating lower costs than for HF alone. For example, HF + Alzheimer's disease showed an excess cost of –USD 5,836 (mark-up 0.90), while ischemic heart disease showed –USD 5,572[17].

Notably, found that cancer comorbidity was associated with a reduction in cost, from USD 54,461 (HF only) to USD 35,082 (HF + cancer), producing a negative excess cost of –USD 19,379 and a mark-up of 0.64, the lowest among all included studies[19].

Statistical methods used included Tobit and negative binomial regression[13], cluster-adjusted logistic regression[19], and multivariate models across other studies. All adjusted for demographic and clinical covariates. However, no study reported HF severity, and a few did not disclose price year or funding source, as noted in Table 2.

They found a cost increase from USD 20,328 to USD 22,983 (excess cost of USD 2,655), resulting in a lower mark-up factor of 0.88 (Pasala et al., 2022). Another study by Yoon (2016) utilized data from the Veterans Affairs (VA) system in Texas, USA. This study examined various comorbidities in HF patients, including hypertension (HT), ischemic heart disease (IHD), type 2 diabetes mellitus (T2DM), renal failure (RF), and psychiatric disorders. The results varied widely depending on the type of comorbidity. For instance, HF patients with drug use disorder had the highest excess cost of USD 27,783 and a mark-up factor of 1.48. Conversely, patients with Alzheimer's disease experienced a reduction in costs, with a negative excess cost of USD –5,836 and a mark-up factor of 0.90.

Betts (2018) investigated the effect of hyperkalemia on HF patients and found a substantial cost increase from USD 69,625 to USD 109,168, yielding an excess cost of USD 39,543 and a mark-up factor of 1.57. This study used insurance claims data from the United States[18].

Finally, compared the impact of type 2 diabetes mellitus (T2DM) in two types of heart failure: HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). The results showed that patients with HFrEF and DM had an excess cost of USD 5,199 with a mark-up factor of 1.36, while those with HFpEF and DM had an excess cost of USD 4,120 and a mark-up factor of 1.29 (Figure 2). The cost data were obtained from the Tufts Medical Center cost accounting system[16].

Overall, the findings presented in this table highlight that certain comorbidities can substantially increase the cost of care for patients with heart failure. The magnitude of this increase depends on the specific comorbid condition and the cost evaluation method used.

DISCUSSION

To assess the methodological quality of the included studies, a structured set of quality criteria was applied to each publication. These criteria included clarity of study objectives, identification of epidemiological sources, study perspective, and inclusion of direct medical costs. As summarized in Table 2, most studies met most criteria, suggesting good methodological rigor. However, common limitations were observed: none of the studies reported the severity of HF, and some did not clearly state the period of time or funding sources. This quality assessment enhances transparency and contextualizes the interpretation of excess costs and markup factors across various HF comorbidities.

Across the studies, for example, none of them reported the severity of heart failure

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(HF) in their analyses, and several did not clearly specify the price year or funding sources, limiting full transparency. This evaluation is important to contextualize the interpretation of excess costs and mark-up factors across comorbid conditions in HF patients.

When compared to other systematic reviews of chronic disease cost burdens, such as in chronic obstructive pulmonary disease (COPD)[7] a similar pattern emerges where comorbidities drive significant increases in direct medical costs. In both HF and COPD, conditions like renal failure, psychiatric disorders, and diabetes are consistently associated with substantial economic burden.

Interestingly, not all comorbidities led to higher costs. Some conditions, particularly Alzheimer's disease, ischemic heart disease (IHD), and type 2 diabetes mellitus (T2DM) in Veterans Affairs (VA) populations, showed negative excess costs and mark-up factors <1. These counterintuitive results could reflect end-of-life care pathways where therapeutic intensity is reduced, or differences in cost coverage structures, such as bundled services or capitated care models, which are common in VA systems.

From a policy and clinical standpoint, the findings highlight the need to prioritize interventions for comorbidities with high excess costs and strong mark-up factors, including hyperkalemia [18], acute coronary syndrome [13] and cancer [19]Proactive screening, comorbidity-specific care pathways, and multidisciplinary outpatient management may help reduce avoidable hospitalizations and control cost escalation in these populations.

Several limitations must be acknowledged. First, the review only includes studies from the United States, limiting its external generalizability. Second, publication bias may be present, as studies with non-significant or negative findings might be underrepresented. Third, there was substantial heterogeneity in cost components, with some studies reporting all-cause costs, others limiting to cardiovascular-related costs, and few clarifying whether overhead or indirect costs were included.

Fourth, none of the studies evaluated indirect costs (e.g., productivity loss, caregiver burden), which likely results in underestimation of total burden. Finally, although one study stratified by HFpEF and HFrEF, this was limited, and HF severity was not reported in any included study, restricting clinical interpretability.

Future economic evaluations in HF should adopt standardized costing frameworks, consider indirect costs, and include diverse health system settings. Stratification by HF subtype, severity class, and comorbidity clusters may also provide more actionable insights for policy and practice.

Additionally, no prior registration of the systematic review protocol was made in PROSPERO, as the review was initiated retrospectively, and the data collection process had already begun before registration could be completed. This lack of registration may limit transparency and reproducibility and should be acknowledged as a limitation of the current review.

CONCLUSION

This systematic review found that comorbidities in heart failure (HF) patients are associated with substantial increases in direct medical costs. The mark-up factors ranged from 0.64 to 2.15, indicating that costs for HF patients with comorbidities can be more than double those without. The highest excess costs were observed in comorbid hyperkalemia (USD 39,543), cancer (USD 19,379), and drug use disorder (USD 27,783). Conversely, comorbidities

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such as Alzheimer's disease, ischemic heart disease, and type 2 diabetes mellitus showed negative excess costs, potentially due to care intensity differences or system-level cost controls.

To improve future research and policy impact, we recommend: Conducting multi-country studies to enhance generalizability beyond the U.S. Adopting standardized cost reporting, including inflation and currency adjustments. Incorporating indirect costs (e.g., productivity loss) and HF severity or subtype stratification to ensure more comprehensive economic evaluations.

CONFLICT OF INTEREST

The author would like to express sincere gratitude to the supervising lecturer and all staff of the Faculty of Pharmacy, Universitas Gadjah Mada, for their valuable guidance and support throughout the completion of this research article.

ACKNOWLEDGEMENT

The authors declare that there are no conflicts of interest related to this research. This article was written independently, without any financial or personal influence from external parties.

REFERENCES

1. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. 2022.
2. Shahim B, Kapelios CJ, Savarese G, Lund LH. Global Public Health Burden of Heart Failure: An Updated Review. Card Fail Rev 2023;9(Icd).
3. Paolillo S, Scardovi A, Campodonico J. Role of comorbidities in heart failure prognosis Part I: Anaemia, iron deficiency, diabetes, atrial fibrillation. Eur J Prev Cardiol [Internet] 2020;27:27–34. Available from: https://consensus.app/papers/role-of-comorbidities-in-heart-failure-prognosis-part-i-paolillo-scardovi/00f2dbd96b10589f82808faedec00f3d/
4. Bozkurt B, Ahmad T, Alexander K, Baker WL, Bosak K, Breathett K, et al. HF STATS 2024: Heart Failure Epidemiology and Outcomes Statistics An Updated 2024 Report from the Heart Failure Society of America. J Card Fail 2024;00.
5. Screever EM, van der Wal MHL, van Veldhuisen DJ, Jaarsma T, Koops A, van Dijk KS, et al. Comorbidities complicating heart failure: changes over the last 15 years. Clin Res Cardiol [Internet] 2023;112(1):123–33. Available from: https://doi.org/10.1007/s00392-022-02076-1
6. Jackson SL, Tong X, King RJ, Loustalot F, Hong Y, Ritchey MD. National Burden of Heart Failure Events in the United States, 2006 to 2014. Circ Heart Fail 2018;11(12):e004873.
7. Huber MB, Wacker ME, Vogelmeier CF, Leidl R. Excess Costs of Comorbidities in Chronic Obstructive Pulmonary Disease : A Systematic Review. 2015;1–17.
8. Rascati KL. Essenstials of Pharmacoeconomic Second Edition. Lippincott Williams Wilkins, a Wolters Kluwer Bus 2014;
9. Salampessy RB. Pengolahan Bandeng Presto Di Ukm Mandala Presto, Sukaraja, Kab. Bogor - Jawa Barat. Marlin 2022;3(1):217.
10. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic

DOI: https://doi.org/10.24843/JPSA.2025.v07.i02.p01

Evaluation Reporting Standards (CHEERS) statement. BMJ 2013;346(March):1–6.
11. McKeage K, Lyseng-Williamson KA. Trastuzumab. Pharmacoeconomics [Internet] 2008;26(8):699–719. Available from: https://doi.org/10.2165/00019053-200826080-00006
12. Molinier L, Bauvin E, Combescure C, Castelli C, Rebillard X, Soulié M, et al. Methodological considerations in cost of prostate cancer studies: A systematic review. Value Heal [Internet] 2008;11(5):878–85. Available from: http://dx.doi.org/10.1111/j.1524-4733.2008.00327.x
13. Ghushchyan V, Nair K V., Page RL. Indirect and direct costs of acute coronary syndromes with comorbid atrial fibrillation, heart failure, or both. Vasc Health Risk Manag 2014;11:25–34.
14. Tuzovic M, Yang EH, Sevag Packard RR, Ganz PA, Fonarow GC, Ziaeian B. National Outcomes in Hospitalized Patients With Cancer and Comorbid Heart Failure. J Card Fail 2019;25(7):516–21.
15. Pasala S, Cooper LB, Psotka MA, Sinha SS, deFilippi CR, Tran H, et al. The influence of heart failure on clinical and economic outcomes among older adults ≥75 years of age with acute myocardial infarction. Am Heart J 2022;246:65–73.
16. Olchanski N, Vest AR, Cohen JT, Denofrio D. Comparing inpatient costs of heart failure admissions for patients with reduced and preserved ejection fraction with or without type 2 diabetes. Cardiovasc Endocrinol Metab 2020;9(1):17–23.
17. Yoon J, Zulman D, Scott JY, Maciejewski ML. Costs associated with multimorbidity among VA patients. Med Care 2014;52(3 SUPPL. 2):31–6.
18. Betts KA, Woolley JM, Mu F, Xiang C, Tang W, Wu EQ. The Cost of Hyperkalemia in the United States. Kidney Int Reports 2018;3(2):385–93.
19. Tuzovic M, Yang EH, Sevag Packard RR, Ganz PA, Fonarow GC, Ziaeian B. National Outcomes in Hospitalized Patients With Cancer and Comorbid Heart Failure. J Card Fail 2019;25(7):516–21.

DOI: https://doi.org/10.24843/JPSA.2025.v07.i02.p01