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Cost-of-disease of Heart Failure in Turkey: A Delphi Panel-based Analysis of Direct and Indirect Costs

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Background: Heart failure (HF) is considered a significant public health issue with a substantial and growing epidemiologic and economic burden in relation to longer life expectancy and aging global population

Aims: To determine cost-of-disease of heart failure (HF) in Turkey from the payer perspective.

Study Design: Cross-sectional cost of disease study.

Methods: In this cost-of-disease study, annual direct and indirect costs of management of HF were determined based on epidemiological, clinical and lost productivity inputs provided by a Delphi panel consisted of 11 experts in HF with respect to ejection fraction (EF) status (HF patients with reduced EF (HFrEF), mid-range EF (HFmrEF) and preserved EF (HFpEF)) and New York Heart Association (NYHA) classification. Direct medical costs included cost items on outpatient management, inpatient management, medications, and non-pharmaceutical treatments. Indirect cost was calculated based on the lost productivity due to absenteeism and presenteeism.

Results: 51.4%, 19.5%, and 29.1% of the patients were estimated to be HFrEF, HFmrEF, and HFpEF patients, respectively. The total annual direct medical cost per patient was $887 and non-pharmaceutical treatments ($373, 42.1%) were the major direct cost driver. Since an estimated nationwide number of HF patients is 1,128,000 in 2021, the total annual national economic burden of HF is estimated to be $1 billion in 2021. The direct medical cost was higher in patients with HFrEF than in those with HFmrEF or HFpEF ($1,147 vs. $555 and $649, respectively). Average indirect cost per patient was calculated to be $3,386 and was similar across HFrEF, HFmrEF and HFpEF groups, but increased with advanced NYHA stage.

Conclusion: Our findings confirm the substantial economic burden of HF in terms of both direct and indirect costs and indicate that the non-pharmaceutical cost is the major direct medical cost driver in HF management, regardless of the EF status of HF patients.

INTRODUCTION

Heart failure (HF) is considered an important public health problem with a substantial and growing epidemiologic and economic burden in relation to longer life expectancy and an aging global population.[1-3]

Given the substantial effect of HF costs on healthcare systems, having a nationwide estimate of the costs attributed to HF is considered an increasingly important for health policymakers to understand the aspects and specific drivers of the costs better and to optimize the allocation of healthcare spending and medical resources at a regional or country level.[3,4]

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Cost-of-disease studies having a robust methodology are considered valuable in this context and provide country-specific data regarding the economic burden of a particular disease and the cost drivers on the basis of cost components, which are transparent and detailed.[3,5] However, besides being highly limited to North America and Western Europe countries with high income[3], most of the available cost-of-disease studies have only estimated direct costs related to HF management.[3,4,6]

The accrual of costs related to HF management in a patient is considered likely to vary throughout a lifetime,[7] whereas an advanced New York Heart Association (NYHA) stage is suggested to be an important determinant of the rise in cost.[4] In addition, while the introduction of multiple evidence-based medicine and device treatments improved the results for outpatients with HF with a reduced ejection fraction (HFrEF), readmission and post-discharge mortality rates continue to be unacceptably high along with a growing increase in the proportion of HF patients with preserved EF (HFpEF) among hospitalized HF patients.[8] However, neither the NYHA stage nor the EF status has been sufficiently addressed in terms of their effect on cost drivers by cost-of-disease studies conducted in the HF setting.

Therefore, to determine the cost-of-disease of HF in Turkey in terms of direct costs from the payer perspective, as well as the indirect costs, and in relation to the EF status and NYHA functional classification, this cost-of-disease study, which is based on the Delphi panel, was designed.

MATERIAL AND METHODS

Design

In this cross-sectional cost-of-disease study, based on various inputs that mainly consisted of epidemiological, clinical, cost, and work productivity data, annual direct and indirect costs for HF management were determined. Epidemiological inputs, clinical inputs, and work productivity inputs were based on a Delphi panel that comprises 11 experts in HF who reached a consensus on real-life clinical practice patterns in HF management in Turkey with respect to EF status (HFrEF, mid-range ejection fraction [HFmrEF], and HFpEF) as well as work productivity with respect to EF and NYHA status. Cost inputs were gathered from retail prices from the price list of Turkish Medicines and Medical Devices Agency (local abbreviation: TİTCK), institutional discount list of national payor, Social Security Institute (local abbreviation: SGK), released on March 2021, and Declaration of Health Care Implementation (local abbreviation: SUT) and its annexes.[9,10]

Cardiology experts who participated in the Delphi panel were selected from tertiary care university hospitals (n = 7) or training and research hospitals (n = 4) located in different provinces (Eskisehir, Mersin, Ankara, Izmir, and Istanbul) from the main geographical regions of Turkey and based on their scientific background and clinical specialty.

Delphi Panel Method

The Delphi panel technique is a structured process that asks experts to participate in a series of rounds to collect the required information on a study question and refine it until they reach an agreement.[11] In this study, the Delphi panel was implemented in three rounds, and discussions on the questionnaire were completed within 2 months (November and December 2020).

Epidemiological and Clinical Inputs

Epidemiological and clinical inputs were retrieved via a standardized questionnaire that elicited items on epidemiological and clinical features of patients with HF. An independent consultant prepared the questionnaire under the supervision of an expert panelist who represented the group. It was designed to cover all direct HF cost items and thus prepared through a detailed examination of literature data on the subject and HF guidelines prepared by Turkish Society of Cardiology[12], European Society of Cardiology[13], and American College of Cardiology/American Heart Association.[14]

Accordingly, estimates for the distribution among age categories, sex, primary diagnosis (ischemic and non-ischemic), EF category (HFrEF, HFmrEF, and HFpEF), comorbidities and NYHA class (I-IV), and clinical inputs (outpatient and inpatient management, medications, and non-pharmaceutical treatments) were based on the consensus achieved through the Delphi panel (Suppl. Tables 1a, 1b, 2a, 2b, 3a, 3b, 4a, 4b).

Estimates of productivity loss, including data on labor loss due to absenteeism (percentage worktime missed due to disease) plus presenteeism (decreased productivity due to disease while at work), was obtained by the Delphi panel using a modified version of the Work Productivity and Activity Impairment Questionnaire: General Health V2.0 (WPAI:GH).[15]

Data Management and Analysis

Direct medical costs were calculated by taking the costs related to outpatient management (visits, consultations, and tests), inpatient management (hospital stay, consultations, and tests), medications, and non-pharmaceutical treatments. Indirect cost was calculated based on the productivity loss that was derived from absenteeism and presenteeism.

Average direct medical costs per patient were calculated considering the cost of outpatient visits, consultations and tests, hospitalizations, inpatient consultations and tests, and treatments from the perspective of payers in Turkey (only direct medical costs using prices of the public payer), using cost-of-disease methodology. Inputs for direct costs were derived from the drug price list of TİTCK and Declaration of Health Care Implementation (SUT) and its supplements, released by SGK on March 2021.[9,10] Prices of medications were used as public prices, i.e., the money out of SGK's pocket, which were calculated by using the drug prices published by TİTCK and institutional discounts published by SGK. Productivity loss calculations were based on inputs derived from modified the WPAI:GH Questionnaire.[15]

Unit prices of health resources, consultations, laboratory tests, medications, and non-pharmaceutical treatments were taken from SUT annexes (Anx-2A, Anx-2A-1, Anx-2A-2, Anx-2B, Anx-2C, Anx-3H, and Anx-3I) (Suppl. Tables 5a-5c).

The cost analysis did not include direct non-medical costs of various origins (e.g., home care, transfers of patients and caregivers for examinations and/or hospitalization, etc.) and intangible costs. The outcomes of the practice patterns for HF management were summarized using descriptive statistics. The study's key cost-analysis-related parameter was expenses associated with HF management. A cost model was formed considering the following equation:

Cost (Turkish Lira [TL]/year) = ∑ [(Frequency of usage of resource; amount per year) × (Unit price of the resource; TL) x (proportion of patients who used the resource; %)].

The analysis was executed from the reimbursement institution's (SGK) perspective, and costs were provided in TL. In October 1, 2021, the exchange rate was 8.8628 $/TL, which was used to convert the monetary results.

RESULTS

Epidemiological Characteristics

Based on the Delphi panel consensus, 51.4%, 19.5%, and 29.1% of the patients were diagnosed with HFrEF, HFmrEF, and HFpEF, respectively. The ischemic etiology was considered in 64.9%, 61.2%, and 35.9% of patients with HFrEF, HFmrEF, and HFpEF, respectively (Table 1).

The age groups of 60-69 years and ≥ 70 years among patients with HFrEF, HFmrEF, and HFpEF were estimated to consist of 32.3%, 32.7%, and 32.7% of patients and 23.6%, 21.6%, and 36.7% of patients, respectively. Patients with NYHA class II were estimated to represent 49.1%, 44.7%, and 45.9% of the patients with HFrEF, HFmrEF, and HFpEF, respectively (Table 1).

TABLE 1. Average Values of Responses of Panelists on Heart Failure Epidemiology

	HFrEF	HFmrEF	HFpEF
Heart failure patients, (%)	51.4%	19.5%	29.1%
Age			
<40 years	7.0%	5.2%	3.1%
40-49 years	13.5%	12.9%	7.8%
50-59 years	23.6%	27.5%	19.6%
60-69 years	32.3%	32.7%	32.7%
≥70 years	23.6%	21.6%	36.7%
Sex			
Male	63.4%	54.5%	42.5%
Female	36.6%	45.5%	57.5%
Underlying cause of heart failure			
Ischemic	64.9%	61.2%	35.9%
Non-ischemic	35.1%	38.8%	64.1%
Concomitant diseases			
Hypertension	48.6%	57.3%	77.5%
Diabetes mellitus	32.5%	35.5%	45.0%
Coronary heart disease	63.0%	61.4%	44.3%
Chronic renal failure	31.4%	25.0%	37.5%
Atrial fibrillation	32.0%	25.0%	38.9%
Stroke	10.7%	7.1%	13.2%
COPD	16.8%	19.1%	22.3%
Hyperlipidemia	32.7%	41.8%	38.6%
Obesity	28.9%	33.2%	52.0%
NYHA class			
NYHA-I	15.2%	30.2%	19.2%
NYHA-II	49.1%	44.7%	45.9%
NYHA-III	27.7%	19.8%	27.1%
NYHA-IV	8.0%	5.3%	7.8%

COPD, chronic obstructive pulmonary disease; HFmrEF, mid-range ejection fraction; HFpEF, preserved ejection fraction; HFrEF, reduced ejection fraction; NYHA, New York Heart Association

Outpatient Management

The average annual utilization of a healthcare resource was calculated by multiplying the proportion of patients who used the resource with the number of times the resource was used. When all patients are considered together (weighted by the proportions of patients with HFrEF, HFmrEF, and HFpEF), the estimated average annual number of visits to the cardiology, internal medicine, cardiovascular surgery, and pulmonology outpatient clinics are 2.30, 0.48, 0.09, and 0.15, respectively (Suppl. Table 1b).

The total annual cost of outpatient management per patient was calculated as $81 for all patients and $83 for HFrEF, $74 for HFmrEF, and $82 for HFpEF. The major driver in the cost of outpatient management was tests, which amounted to $61, $55, and $59 for patients with HFrEF, HFmrEF, and HFpEF, respectively (Suppl. Table 6).

Inpatient Management

The average total duration of hospital stay per year is calculated by multiplying the percentage of patients who are hospitalized at least once a year, by the number of hospital stays of these patients and by the length of each stay.

Accordingly, the total annual duration of hospital stay for an average patient with HFrEF, HFmrEF, and HFpEF are 7.30, 3.27, and 3.66 days. These figures correspond to an average of 5.45 days per year for an average patient with HF regardless of the EF status (Table 2, Suppl. Table 2b).

The total annual cost of inpatient management per patient was calculated as $148 for all patients and $208, $77, and $89 for patients with HFrEF, HFmrEF, and HFpEF, respectively. The major driver in the cost of inpatient management was hospitalization, which amounted to $149, $45, and $58 for patients with HFrEF, HFmrEF, and HFpEF, respectively (Suppl. Table 7).

Medications

Beta-blockers (outpatient, 86.8%, 75.7%, and 65.2%; inpatient, 86.4%, 79.3%, and 66.8%), ACE inhibitors (outpatient, 78.2%, 66.4%, and 56.8%; inpatient, 72.7%, 65.5%, and 60.9%), diuretics (outpatient, 75.9%, 55.5%, and 61.8%; inpatient, 84.1%, 64.1%,

TABLE 2. Estimates of Hospital Stays, Calculated Based on Average Values of Responses of Panelists

Ward	HFrEF			HFmrEF			HFpEF			All patients
	% pts	Use (per/stay)	Length of stay (days/patient-year)	% pts	Use (per/stay)	Length of stay (days/year)	% pts	Use (per/stay)	Length of stay (days/year)	Length of stay (days/year)
Emergency ward	27.8%	1.85 stays/year (1.30 days/stay)	0.67 days	16.5%	1.50 stays/year (1.11 days/stay)	0.27 days	19.6%	1.67 stays/year (1.20 days/stay)	0.39 days	0.51 days
Cardiology CU (CCU)	17.3%	1.60 stays/year (3.80 days/stay)	1.05 days	9.8%	1.40 stays/year (3.00 days/stay)	0.41 days	13.2%	1.30 stays/year (2.45 days/stay)	0.42 days	0.74 days
Secondary ICU	15.9%	1.80 stays/year (5.00 days/stay)	1.43 days	5.9%	1.30 stays/year (3.40 days/stay)	0.26 days	11.0%	1.33 stays/year (3.45 days/stay)	0.50 days	0.93 days
Tertiary ICU	5.1%	1.18 stays/year (5.45 days/stay)	0.33 days	2.5%	1.22 stays/year (4.33 days/stay)	0.13 days	2.7%	1.11 stays/year (4.11 days/stay)	0.12 days	0.23 days
Regular ward	37.5%	1.64 stays/year (6.23 days/stay)	3.82 days	28.0%	1.70 stays/year (4.61 days/stay)	2.19 days	29.3%	1.40 stays/year (5.41 days/stay)	2.22 days	3.04 days
Total			7.30 days			3.27 days			3.66 days	5.45 days

CCU, cardiology care unit; HFmrEF, mid-range ejection fraction; HFpEF, preserved ejection fraction; HFrEF, reduced ejection fraction; ICU, intensive care unit

and 78.6%), and MRAs (outpatient, 55.0%, 34.5%, and 24.6%; inpatient, 63.2%, 45.0%, and 32.4%) were considered the most common medications in patients with HFrEF, HFmrEF, and HFpEF, respectively (Suppl. Table 3a). Medications constitute almost one-third of the total cost in all patient groups with any EF status (Suppl. Table 8).

Non-pharmaceutical Treatments

Continuous positive airway pressure-bilevel positive airway pressure (11.2%, 6.4%, and 9.5%) was considered the most common non-pharmaceutical palliative treatment during inpatient management (for 3.08, 3.17, and 2.83 days), following oxygen treatment, in patients with HFrEF, HFmrEF, and HFpEF, respectively (Suppl. Table 4a).

Coronary intervention (25.7%, 23.7%, and 26.4% per 5 years) was considered the most common non-pharmaceutical treatment categorized under pharmaceutical permanent/continuous treatment in patients with HFrEF, HFmrEF, and HFpEF, respectively (Table 3, Suppl. Table 4a). The total annual cost related to treatment per patient was calculated as $887 for all patients and $857, $404, and $478 for patients with HFrEF, HFmrEF, and HFpEF, respectively. The cost of non-pharmaceutical treatments was $373 for all patients (42.1% of the total cost) and $495, $206, and $270 for patients with HFrEF, HFmrEF, and HFpEF, respectively (Suppl. Table 9).

Direct Medical Costs

The total annual direct cost-of-disease per patient was calculated as $887 from the payer perspective. Non-pharmaceutical treatments ($373 and 42.1%) were the major direct cost driver (Table 4).

The total annual direct cost-of-disease per patient was higher in patients with HFrEF ($1,147) than in those with HFmrEF ($555) or HFpEF ($649), whereas non-pharmaceutical treatments were still the major direct cost driver (43.2% [$495], 37.1% [$206], and 41.5% [$270], respectively) in each group (Table 4).

Indirect Costs

Based on the opinions of the experts in the Delphi panel, the proportions of patients actively not working and the degree of absenteeism, presenteeism, and overall work impairment in employed HF patients was estimated according to the EF status and NYHA classification (Table 5). The overall absenteeism regardless of EF status and NYHA classes was 14.8%. Absenteeism, which was as low as 3.6% in NYHA class I, increased to 9.4%, 21.6%, and 55.0% in NYHA classes II, III, and IV, respectively. The overall presenteeism regardless of the EF status and NYHA classes was 38.3%. Presenteeism, which was 17.9% in NYHA class I, increased to 29.8%, 56.8%, and 81.4% in NYHA classes II, III, and IV, respectively. The overall work impairment regardless of the EF status and NYHA classes was 45.2%. The overall work impairment, which was 20.8% in NYHA class I, increased to 36.4%, 66.1%, and 91.6% in NYHA class II, III, and IV, respectively.

The annual cost for productivity loss per patient was calculated as $1,648 (assumed to be 0, $684, $3,418, and $5,888 in NYHA classes I, II, III, and IV, respectively) due to nonworking HF patients. This figure was $471 ($227, $526, $620, and $220 for NYHA classes I, II, III, and IV, respectively) due to absenteeism and $1,267 ($1,084, $1,512, $1,279, and $147 for NYHA classes I, II, III, and IV, respectively) due to presenteeism. The average cost of productivity loss per patient (loss of labor force due to all working or nonworking patients) was calculated to be $3,386, which increased from $1,311 in NYHA class I to $2,722, $5,317, and $6,255 in NYHA classes II, III, and IV, respectively) (Table 6).

DISCUSSION

In this cost-of-disease study, the total annual direct medical cost of HF management was calculated as $887 per patient, from the payer perspective. Non-pharmaceutical treatment constituted the main direct cost driver, with 42.1% of the total cost-of-disease. The management of patients with HFrEF was associated with a higher direct medical cost than those with HFmrEF or HFpEF,

TABLE 3. Average Values of Responses of Panelists and Average Annual use of Non-pharmaceutical Treatments Categorized Under Permanent/Continuous Treatments

Non-pharmaceutical treatments	HFrEF			HFmrEF			HFpEF			All patients
	% pts	Duration (per year)	Amount usage (per patient-year)	% pts	Duration (per year)	Amount usage (per patient-year)	% pts	Duration (per year)	Amount usage (per patient-year)	Amount usage (per patient-year)
CPAP-BiPAP	0.3%	300 days	0.82	0.2%	300 days	0.55	0.2%	300 days	0.55	0.69
Peritoneal dialysis	1.6%	122 days	2.00	0.6%	122 days	0.73	1.3%	122 days	1.56	1.63
Hemodialysis	3.0%	122 days	3.66	2.0%	122 days	2.43	3.3%	122 days	3.98	3.51
CRT-P	2.41%	per 5 years	0.0048	-	-	-	-	-	-	0.0025
CRT-D	10.6%	per 5 years	0.0211	0.22%	per 5 years	0.0004	0.09%	per 5 years	0.0002	0.0110
ICD	20.9%	per 5 years	0.0419	2.11%	per 5 years	0.0042	0.77%	per 5 years	0.0015	0.0228
CABG	7.4%	per 5 years	0.0049	7.3%	per 15 years	0.0049	5.4%	per 15 years	0.0036	0.0045
Coronary intervention	25.7%	per 5 years	0.0514	23.7%	per 5 years	0.0473	26.4%	per 5 years	0.0527	0.0510
LVAD	0.036%	per 1 year	0.0004	-	-	-	-	-	-	0.0002
Heart transplantation	0.015%	per 1 year	0.0001	-	-	-	-	-	-	0.0001
Heart valve surgery	2.83%	per 15 years	0.0019	2.00%	per 15 years	0.0013	2.84%	per 15 years	0.0019	0.0018
Mitraclip	0.24%	per 15 years	0.0002	0.01%	per 15 years	0.0000	0.09%	per 15 years	0.0001	0.0001
TAVI	1.88%	per 8 years	0.0023	2.23%	per 8 years	0.0028	2.89%	per 8 years	0.0036	0.0028
AF ablation	3.01%	per 5 years	0.0060	2.67%	per 5 years	0.0053	2.78%	per 5 years	0.0056	0.0058
VT ablation	2.23%	per 5 years	0.0045	1.25%	per 5 years	0.0025	1.01%	per 5 years	0.0020	0.0034
Physical therapy	14.3%	per 10 sess.	1.43	3.0%	per 10 sess.	0.30	9.8%	per 10 sess.	0.98	1.08

AF, atrial fibrillation; BiPAP, bilevel positive airway pressure; CABG, coronary artery bypass grafting; CPAP, continuous positive airway pressure; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; HFmrEF, mid-range ejection fraction; HFpEF, preserved ejection fraction; HFrEF, reduced ejection fraction; ICD, implantable cardioverter defibrillator; LVAD, left ventricular assist device; TAVI, transcatheter aortic valve implantation; VT, ventricular tachycardia

as expected. The indirect cost per patient (cost of productivity loss, $3,386) outweighed the direct cost and was similar across the HFrEF, HFmrEF, and HFpEF groups, but increased with an advanced NYHA class.

When compared with earlier cost analysis studies for HF conducted in 2008,[16] 2013,[17] and 2016[18] in Turkey, our findings indicate much higher annual direct cost related to HF management, supporting the substantial and growing economic burden of HF on health care systems.[3,4]

In a retrospective cost-of-disease study performed in Turkey by Sozmen et al.[16] in 2008, the total cost per admission was reported to be $1,055 *(2,351 TL >> 9,349 TL [inflation adjusted])* for HF. In an expert panel-based cost analysis study performed in Turkey by Fak et al.[17] in 2013, the total HF cost on average was reported to be $1,376 *(4,524 TL >> 12,196 TL [inflation adjusted])* based on the expert's view. In another Delphi panel-based cost-of-disease study performed in Turkey by Aras et al.[18] in 2016, the total annual cost per patient was reported as $369 *(1,537 TL >> 3,272 TL [inflation adjusted])* overall and to be $514 *(2,141 TL >> 4,558 TL [inflation adjusted])* for patients with HFrEF. The authors also noted that the interventional treatments amounted to $122 *(506 TL >> 1,077 TL [inflation adjusted])* and $218 *(906 TL >> 1929 TL[inflation adjusted])* and medications to $97 *(404 TL >> 860 TL [inflation adjusted])* and $104 *(435 TL >> 926 TL [inflation adjusted])* for overall and HFrEF, respectively, were the key cost drivers that corresponds 42% and 20% of the total cost, respectively.[18] The discordance between current and former cost-of-disease studies in Turkey may be explained by the inclusion of more detailed cost items specifically related to HF management in the present study and the potential differences in patient population characteristics used in the cost analyses. Essentially, by providing data on modern treatment approaches in HF, our findings also emphasize the increase in unit costs of model inputs over time and more prevalent use of high-cost instrumental interventions among the other modern treatment approaches in real-life practice.

TABLE 4. Annual Direct Medical Cost Components Related to Heart Failure Management

Direct cost components	Annual costs ($/patient-year)			
	HFrEF	HFmrEF	HFpEF	All patients
Non-pharmaceutical treatments	495	206	270	373
Medications	361	198	209	285
Inpatient management	208	77	89	148
Outpatient management	83	74	82	81
Total cost	**1,147**	**555**	**649**	**887**

HFmrEF, mid-range ejection fraction; HFrEF, reduced ejection fraction; HFpEF, preserved ejection fraction

TABLE 5. Delphi Panel-based Employment Status and Productivity Loss Input

Working status and productivity loss	All patients	NYHA-I	NYHA-II	NYHA-III	NYHA-IV	HFrEF	HFmrEF	HFpEF
% pts currently not working	51.5%	34.3%	41.4%	70.0%	95.8%	-	-	-
In actively working patients with HF								
Absenteeism (% of time being absent at the work)	14.8%	3.6%	9.4%	21.6%	55.0%	15.6%	12.5%	15.2%
Presenteeism (% of time with loss of productivity at the work)	38.3%	17.9%	29.8%	56.8%	81.4%	39.6%	34.3%	38.8%
Overall work impairment (absenteeism plus presenteeism)	45.2%	20.8%	36.4%	66.1%	91.6%	46.7%	40.5%	45.8%

HFmrEF, mid-range ejection fraction; HFpEF, preserved ejection fraction; HFrEF, reduced ejection fraction; NYHA, New York Heart Association functional classification

TABLE 6. Indirect Cost Components

	Annual costs ($/patient-year)							
	All patients	NYHA-I	NYHA-II	NYHA-III	NYHA-IV	HFrEF	HFmrEF	HFpEF
Loss of work productivity caused by nonworking patients	1,648	0	684	3,418	5,888	1,754	1,294	1,700
Loss of work productivity caused by working patients								
Due to absenteeism	471	227	526	620	220	483	439	471
Due to presenteeism	1,267	1,084	1,512	1,279	147	1,273	1,264	1,260
Due to overall work impairment	1,738	1,311	2,038	1,899	367	1,755	1,703	1,730
Loss of work productivity caused by all (non-working and working) patients	3,386	1,311	2,722	5,317	6,255	3,510	2,997	3,430

HFmrEF, mid-range ejection fraction; HFpEF, preserved ejection fraction; HFrEF, reduced ejection fraction; NYHA, New York Heart Association functional classification

The cost estimates achieved in the present study are within the range of annual costs related to HF management reported in systematic reviews including data from several countries.[4,6] In a systematic review of 35 cost-of-disease studies on HF between 2003 and 2015, Shafie et al. reported the annual cost per patient to range from international dollars (Int $) 908 to Int $84,434 and indicated hospitalization costs (ranging Int $3780 to Int $34,233) as the major cost driver to the total healthcare spending.[6] In another systematic review of 16 cost-of-disease studies on HF between 2004 and 2016, Lesyuk et al.[4] reported the annual cost per patient to differ from $868 in South Korea to $25,532 in Germany and indicated hospital admission costs as the most expensive cost element.

In contrast to the aforementioned systematic reviews, in the present study, inpatient management comprised only 16.7% of the total cost. This finding also contradicts data from studies in high-income countries, indicating that hospitalization comprised the largest share among the direct costs, accounting for 65%-70% of the total HF cost.[1,2,6,19-21]

Total HF-associated expenses were reported as 15,373 Euros per person in a retrospective population-based analysis using the BIG-PAC database on 17,163 patients who received care for HF between 2015 and 2019 in Spain.[22] The investigators also reported that cardiovascular disease hospitalizations (75.8%), especially HF hospitalizations (51%), were the most important determinant, whereas drug expenses accounted for only a small proportion (7%) of the overall cost.[30] As a result, the use of medicines that reduces HF hospitalization is considered likely to improve HF management and reduce HF burden.[22]

Indeed, a significant increase in HF cost is projected over the next decades based on an increase in HF prevalence and related hospitalizations,[20,23] and a shift in the care model toward a reduction in hospitalizations is suggested to have a major effect on the trajectory of overall HF costs.[20,24] Apart from a few exceptions, the majority of medications and non-pharmaceutical treatments used in HF management have given evidence to be cost effective.[25-27] Hence, prevention through treatment of predisposing conditions such as hypertension, coronary artery disease, and diabetes mellitus, the use of newer treatment modalities (i.e.,., cardiac resynchronization therapy, implantable cardioverter defibrillators, and left ventricular assist devices), and improved implementation of guideline-based therapies such as the use of β-blockers, angiotensin receptor blockers, or angiotensin-converting enzyme inhibitors are considered among the key cost-saving strategies in HF.[20,21,23,28] This explanation can be applied quite precisely to our analysis, since concomitant diseases (which can also be defined as predisposing or underlying diseases) are quite highly prevalent in our HF population, i.e., hypertension, 49%, 57%, and 78%; diabetes mellitus, 32%, 36%, and 45%; and coronary artery disease, 63%, 61%, and 44% in patients with HFrEF, HFmrEF, and HFpEF, respectively.

However, underutilization of evidence-based HF therapies has been consistently reported in real-life clinical practice,[20,28-30] despite the likelihood of using an optimal treatment and delaying disease progression by prophylaxis to reduce the predicted increase in total costs of HF in the next decades.[20] Notably, in an expert panel-based cost analysis study conducted in Turkey by Fak et al.[17] in 2013, authors noted that when guideline recommendations were considered in cost calculations, real-life management of HF costs in total were determined to be nearly half of the cost that was estimated according to the expert's view.

Accordingly, while being consistent with the expected increase in the economic burden of HF with an aging, rapidly growing, and industrializing population.[3,4] an increase in HF expenses over time in Turkey should be interpreted in the light of the possibility that cost increments may also indicate poor adherence to guidelines among clinicians and the evidence of certain practices considered unnecessary per clinical guidelines in real-life HF management.[17]

In a global analysis of the total cost of HF among 197 countries by Cook et al.[3] in 2012, the estimated economic cost of HF in total was $108 billion per year with direct and indirect costs corresponding to approximately 60% ($65 billion) and 40% ($43 billion) of the total cost, respectively. In addition, they have published that while a greater proportion of direct costs was spent by high-income countries (direct/indirect cost ratio 2:1), the pattern is the opposite for countries having low and middle income (direct/indirect cost ratio 1:9).[3] According to direct, indirect, and overall cost of HF estimated per country in the global analysis by Cook et al.,[3] Turkey ($59 million, $474 million, and $533 million, respectively) was the sixth among the medium- and low-income countries in terms of the highest total costs of HF, after China ($480 million, $4,936 million, and $5,416 million), Brazil ($226 million, $1,352 million, and $1,578 million), India ($80 million, $1,105 million, and $1,186 million), Mexico ($82 million, $706 million, and $788 million), and Indonesia ($27 million, $527 million, and $554 million).[3] The authors considered the differences in indirect and direct costs of HF to be particularly important given that more than 80% of the world's population is from low- and middle-income countries.[3]

Likewise, indirect costs outweighed the direct costs of HF management in the present study resulting in 3.8-fold higher estimates in the total study population and 3.0-fold, 5.4-fold, and 5.2-fold higher estimates in patients with HFrEF, HFmrEF, and HFpEF, respectively. Indeed, the considerable effect of HF on work capabilities and detachment from the workforce has also been emphasized with substantially lower employment income in patients with HF already had at the time of diagnosis and return to the workforce by less than 70% of patients 1 year after first HF hospitalization.[31]

Our results bring out a higher annual direct medical cost per patient in HFrEF ($1,147) than in HFmrEF ($555) or HFpEF ($649). The non-pharmaceutical treatment costs in patients with HFrEF were 2.4-fold and 1.8-fold higher than in those in patients with HFmrEF and HFpEF, respectively. Considering outpatient and inpatient management costs, outpatient management cost was similar across EF subgroups, while inpatient management costs in patients with HFrEF were 2.7-fold and 2.3-fold higher than in patients with HFmrEF and HFpEF, respectively. Similarly, in a study by Murphy et al.[32] conducted in Ireland in 2016, the annual cost per patient was reported to be 12,206 € for patients with HFpEF and 13,011 € for patients with HFrEF. However, in a study by Dunlay et al.[2] on multivariable predictors of lifetime costs related to HF, HFpEF (≥ 50%) was reported to be associated with an increase of 21% and 24% in inpatient and overall costs, respectively, compared with HFrEF, while Liao et al.[33] reported no major difference between patients with HFpEF and HFrEF in terms of the 5-year cumulative costs.

The presence of a higher NYHA stage has been associated with an increase in HF-related costs.[4,6,34] Notably, the overall productivity loss (loss of labor due to work impairment) per patient was comparable across EF subgroups, whereas it was higher for advanced NYHA stages in the present study. In this regard, our findings support that the costs increase with advanced HF stages, emphasizing the importance of preventing HF progression to more advanced and highly symptomatic forms.[4]

Given the 2.84% prevalence of HF in Turkey,[35] the nationwide number of HF patients is estimated as 1,128,000 in 2021, taking the number of the population aged >35 years as 39,723,000 in 2021 (see Suppl Table 10 for the calculations). Based on these figures, the total annual national economic burden of HF is approximately $1 billion in 2021. The actual burden must be even much higher than this since this amount does not include the burden of patients with HF younger than 35 years of age. This amount corresponds to at least $12 annual burden per capita. This is quite notable, given the $8,599 (76,211 TL) per capita gross domestic product in Turkey (2020) and $403 (2,434 TL >> 3,573 TL [inflation adjusted]) per capita health expenditure (2019).[36,37]

The main strength of the present study appears to be its examination of not only direct but also indirect costs (productivity loss due to illness), as well as the inclusion of EF status and NYHA as subgroup criteria, which likely avoids a downward bias in our estimations of the economic cost of HF. On the contrary, this study has certain limitations that should be taken into account. First, while the model is based on a structured Delphi panel method, which is commonly used in health management, concerns may be raised about the validity and reliability of data due to the use of expert consensus data rather than a nationwide database on practice patterns as model inputs. Second, while a cost-of-disease study provides a point of view on the economic burden of HF in a population, the events in individual patient and family are not reflected in these studies. Nonetheless, our findings highly contribute to the literature by providing cost estimates for HF management in Turkey based on EF and NYHA subgroups.

Our findings verify the considerable economic burden of HF in terms of both direct and indirect costs and indicate that the non-pharmaceutical cost is the major direct medical cost driver in HF management, regardless of the EF status of patients with HF. HFrEF and an advanced NYHA class appear to be associated with the likelihood of cost increments related to direct and indirect expenses, respectively. In this regard, our findings underline the importance of adopting improved prevention, management, and surveillance strategies and delaying disease progression by implementing guideline-based therapies in real-life management of HF to enable cost savings for advanced disease management, hospitalization spending, or workforce loss. With further research addressing the economic burden of indirect costs of HF, considering the indirect costs with the assessment of the total productivity lost in planning cost-saving approaches appears crucial to support decision makers in resource allocation.

Ethics Committee Approval: This is a Delphi Panel, so ethics committee approval is not needed.

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Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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