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Original Article

Incremental Healthcare Resource Utilization and Expenditures Associated with Cardiovascular Diseases in Patients with Diabetes: A Cross-Sectional Study

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Abstract

Background: Cardiovascular disease (CVD) is the most prevalent comorbid condition among patients with diabetes. The objective of this study is to determine the incremental healthcare resource utilization and expenditures (HRUE) associated with CVD comorbidity in diabetic patients.

Methods: In a cross-sectional study, patients receiving antidiabetic drugs were identified using the 2014 database of the Iran Health Insurance Organization of East Azerbaijan province (Iran). The frequency of HRUE was the main outcome. Outcome measures were compared between diabetic patients with and without CVD comorbidity during 2014-2016. The generalized regression model was used to adjust for cofounders because of a highly skewed distribution of data. Negative binomial regression and gamma distribution model were applied for the count and expenditure data, respectively.

Results: A total of 34,716 diabetic patients were identified, of which 21,659 (63%) had CVD comorbidity. The incremental healthcare resource utilization associated with CVD compared to non-CVD diabetic patients for physician services, prescription drugs, laboratory tests, and medical imaging was 5.9±0.34 (28% increase), 46±1.9 (46%), 12.9±0.66 (27%), and 0.16±0.40 (7%), respectively (all P<0.001). Similarly, extra health care costs associated with CVD comorbidity for physician services, prescription drugs, laboratory tests, and medical imaging were 10.6±0.67 million IRR (294.4±18.6 USD) (50% increase), 1.44±0.06 million IRR (40±1.6 USD) (32%), 8.36±0.57 million IRR (232.2±15.8 USD) (58%), 0.51±0.02 million IRR (14.1±0.5 USD) (24%), and 0.29±0.02 million IRR (8±0.5 USD) (22%), respectively (all P<0.001).

Conclusion: CVD comorbidity substantially increases HRUE in patients with diabetes. Our findings draw the attention of healthcare decision-makers to proactively prevent CVD comorbidity in diabetic patients.

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Keywords ● Diabetes mellitus ● Cardiovascular diseases ● Comorbidity ● Healthcare resources

What's Known

- Cardiovascular disease (CVD) is the most prevalent comorbidity among diabetic patients.
- In developing countries, data on diabetes with CVD comorbidity and the associated healthcare resource utilization and expenditures (HRUE) are scarce.

What's New

- Overall, 63% of patients treated for diabetes received concomitant cardiovascular medications.
- In all categories of healthcare services, comorbid conditions in patients with CVD substantially increase the HRUE of patients with diabetes.

Introduction

Diabetes mellitus (DM) is the most prevalent disorder with a high cost of care and a major public health issue worldwide. Globally,

in 2013, more than 380 million adults suffered from DM resulting in approximately 1.3 million deaths.[1, 2] It is projected that the number of DM patients will rise to more than 590 million by 2035.[1] The highest prevalence of DM is reported in the Middle East and North Africa.[1] Iran has the second-highest number of DM patients in the Middle East. An Iranian national survey conducted in 2011 reported that DM had affected over four million Iranians,[2] a two-fold increase in 40 years.[3] By 2030, it is estimated that around 9.2 million Iranians will suffer from DM.[4] In 2009, the total health care costs for Iranian DM patients were about 3.64 billion U.S. dollars (USD), consisting of direct (1.71 billion USD) and indirect (1.93 billion USD) costs.[4]

Cardiovascular disease (CVD) has a strong association with DM and is very common among people with diabetes.[5] During recent decades, there has been a substantial increase in the incidence of CVD with diabetes. A systematic review reported that, globally, CVD has affected about 32.2% of all people with type-2 diabetes, but the true estimate could be as high as 60%.[5] It has also been reported that CVD is the main cause of mortality in people with diabetes.[6] Some studies have shown that the incidence of CVD with diabetes has strongly contributed to the need to assess healthcare utilization and costs incurred by patients with diabetes.[7, 8]

Understanding various aspects of healthcare resource utilization and expenditures (HRUE) is important for healthcare policymaking, resource allocation process, and reducing the burden of this comorbidity. There have been few studies, in various medical settings, examining incremental HRUE in comorbid conditions in diabetic patients with CVD.[7, 9] However, very few have addressed this issue in the context of low- and middle-income countries, where 85% of deaths are due to non-communicable diseases. Since HRUE is country-specific information, its generalizability is questionable. A previous study estimated incremental HRUE in diabetic patients with CVD complications based on the direct attributable costs of the disease.[10] Such an approach underestimates the true incremental HRUE associated with comorbidity.[8] It is therefore important to use the net incremental cost of all HRUE irrespective of the underlying disease.

Despite the high prevalence of CVD in people with diabetes, only a limited number of studies have been conducted in Iran. Available studies have primarily investigated multimorbidity using self-report and epidemiological data rather than its association with HRUE.[11] In the present study, for the first time, the prevalence of CVD with diabetes in Iran during the fiscal year 2014 is examined. In addition, a comparison is made between HRUE over three years in diabetic patients with and without CVD comorbidity in a large outpatient population.

Materials and Methods

In a cross-sectional study, the database of the Iran Health Insurance Organization (IHIO) was used to identify patients with diabetes in 2014, and the frequency of HRUE during 2014-2016 was examined. The study protocol was approved by the Research Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran (code: IR.TBZMED.REC.1397.559). With a specific focus on the population of East Azerbaijan province (Iran), the records of all medical claims related to outpatient services were retrieved. East Azerbaijan is the fifth most populous province in Iran with approximately four million people, representing 5% of the total population of Iran.[12] The East Azerbaijan Health Insurance Organization (EAHIO) serves approximately 2.3 million people and has a business contract with roughly 90% of healthcare providers in the province.[13] As part of their service, they refund over 50% of the costs incurred by patients for physician services, laboratory tests, medical imaging, and prescription drugs.

All patients registered as diabetic in the IHIO database during 2014, prescribed hyperglycemic agents (e.g., insulin) twice within the year, and aged ≥18 years were included in the study. Pharmacy claims data were also used as a measure of the population's chronic disease status.[14, 15] Using the stratified sampling method, diabetic patients were assigned to two groups, namely patients receiving and those not receiving CVD medications.

Outcome Measures

The primary outcome of interest was the mean difference in direct HRUE per capita, both overall and by the type of healthcare service, between the two groups during 2014-2016 adjusted for demographic characteristics of patients. Outpatient services included services rendered in a physician's office, emergency department, medical imaging center, medical laboratory, pharmacy, other outpatient services covered by the insurance, and costs incurred by patients. Total expenditure was adjusted for 2016 inflation using the overall medical care component of the consumer price index (MCPI).[16] To compare expenditure data with other studies, the average US dollar to Iranian rial exchange rate in 2016 (1 USD equal to 36,000 IRR) was used [http://old.nasimonline.ir/Content/Detail/2066919]).

Key Explanatory Variables

Explanatory variables included age, sex, types of insurance funds, and chronic conditions. The most prevalent chronic conditions included diabetes, CVD, inflammatory bowel disease (IBD), chronic obstructive pulmonary disease (COPD); acid-related disorders, cancer, dementia, hyperlipidemia, migraine, thyroid disorders, schizophrenia and bipolar disorders; and depression, anxiety, and sleep-related disorders. For each of these conditions, pharmacy claims data from the insurance database were used to identify the corresponding patients. This approach has been proposed as a reliable indicator of underlying chronic conditions, for which patients are being treated.[14] In consultation with a panel of medical experts, specific drugs prescribed at least twice to patients for a specific chronic condition were used as an indicator of comorbidity. The other explanatory variable was related to the internal categorization of funds by IHIO, namely health insurance policy for government employees (fund two), the general public (fund three), private sector and specific public institutions (fund four), self-employed individuals (fund six), and rural and tribal populations (fund nine). Each category is designed to cover certain groups of people with specific reimbursement arrangements.

Statistical Analysis

Data analysis was performed using STATA/MP 14 (StataCorp LP, College Station, TX, USA). All continuous and categorical covariates were presented descriptively and expressed as means±SD, and proportions. The difference in baseline characteristics between diabetic patients with and without CVD comorbidity was examined using *t* test for continuous variables and the Chi squared test for categorical variables. Unadjusted difference in HRUE between the cohorts was determined using *t* test. The generalized linear regression model (GLM) was used to adjust for the potential confounding variables and to account for the common highly skewed distribution of the HRUE data.[17] This model is an effective alternative to ordinary least squares regression that corrects for heteroscedasticity and avoids re-transformation bias on log-transformed expenditures.[18] A negative binomial distribution was defined for the frequency of healthcare resource utilization. In order to analyze expenditure data, a two-part regression model was applied consisting of logistic models of all incurred costs and of a gamma model with log-link in the second part to model positive costs.[19] STATA software was used to execute the two-part regression model allowing the calculation of predictions and marginal effects and their standard errors from the combination of the first and second parts.[20] We reported the exponents of regression coefficients from the models representing a factor by which the groups differed in terms of costs (eform function in stata). For example, a covariate with an exponentiated coefficient of 1.25 is associated with a 25% increase in expenditure.[21]

The method of recycled predictions (also called predictive margins) was then used to obtain the incremental arithmetic mean cost/utilization between cohorts, rather than simply comparing the costs incurred by patients with diabetes with and without CVD. This approach is gaining increasing attention and is commonly used to calculate differences in absolute costs and utilization between groups in generalized linear models,[12, 22] as it presents the results of regression in a meaningful scale. We did not apply a matched control design because the method of recycled prediction controls for covariates. The predictive margin technique avoids the problem of covariate imbalance through the counterfactual prediction technique. Confidence intervals were calculated based on 1000 bootstrap replications using the percentile method. The goodness of fit of the regression models was examined using the Hosmer-Lemeshow test (STATA command: estat gof).

Results

Based on the IHIO database, during 2014, a total of 481,733 people filed insurance claims for the prescription of at least one drug. Of these, 34,176 cases were identified as diabetic patients, indicating a prevalence of 5.15% (95% CI: 5.09-5.20) of the total outpatient population. Among these, 21,659 (63.37%) were identified with CVD comorbidity. Characteristics of all diabetic patients with and without CVD comorbidity are presented in table 1. Overall, compared to diabetic patients without CVD, those with CVD were older with significant variations in acid-related disorders, schizophrenia and bipolar disorders, COPD, dementia; hyperlipidemia, thyroid disorders, and depression, anxiety, and sleep-related disorders.

Healthcare Resource Utilization

Unadjusted differences in the frequency of healthcare resource utilization in diabetic patients with and without CVD comorbidity are shown in table 2. The median of all HRUE categories, particularly in the case of prescription drugs, was significantly higher in diabetic patients with CVD than those without CVD comorbidity.

Table 1: Demographics and clinical characteristics of the study cohorts

Variables		Diabetic patients without CVD (n=12,517)	Diabetic patients with CVD (n=2,659)	P value
Demographic characteristics	Age (years; mean±SD)	50.59±15.99	63.48±11.80	<0.001[a]
	Female (n, %)	7,841 (62.64)	13,975 (64.52)	<0.001[b]
	Male (n, %)	4,676 (37.36)	7,684 (35.48)	<0.001[b]
Insurance fund (n, %)	Insurance fund 2	5,367 (42.88)	11,810 (54.53)	<0.001[b]
	Insurance fund 3	782 (6.25)	1,887 (8.71)	<0.001[b]
	Insurance fund 4	711 (5.68)	784 (3.62)	<0.001[b]
	Insurance fund 6	3,117 (24.90)	4,442 (20.51)	<0.001[b]
	Insurance fund 9	2,540 (20.29)	2,736 (12.63)	<0.001[b]
Other comorbidities (%)	IBD	0.21	0.32	0.052[b]
	Acid-related disorders	11.07	19.81	<0.001[b]
	Schizophrenia and bipolar disorders	4.35	5.07	0.002[b]
	Cancer	0.41	0.48	0.307[b]
	COPD	5.08	8.67	<0.001[b]
	Dementia	0.22	0.76	<0.001[b]
	Hyperlipidemia	22.40	58.01	<0.001[b]
	Migraine	0.06	0.03	0.197[b]
	Depression, anxiety, and sleep disorders	15.58	26.86	<0.001[b]
	Thyroid disorders	3.21	4.03	<0.001[b]

[a]*t* test, [b]Pearson's Chi squared test, IBD: Inflammatory bowel disease, COPD: Chronic obstructive pulmonary disease, Statistical significance (P<0.005)

Table 2: Unadjusted healthcare resource utilization and expenditure outcomes

Categories	Diabetic patients without CVD	Diabetic patients with CVD	P value[a]
Healthcare resource utilization (median, IQR)			
Physician services	18 (9-30)	26 (16-40)	<0.001
Prescription drugs	43 (23-70)	81 (52-118)	<0.001
Laboratory tests	32 (11-64)	53 (24-88)	<0.001
Medical imaging	1 (0-3)	1 (0-3)	<0.001
Total	103 (53-165)	170 (110-242)	<0.001
[b]Expenditure (mean, IQR)			
Physician services	4.0 (1.4-5.2)	6.1 (2.6-7.7)	<0.001
Prescription drugs	14.5 (2.2-11.4)	22.0 (5.6-20.7)	<0.001
Laboratory tests	1.6 (0.3-2.3))	2.2 (0.7-3.0)	<0.001
Medical imaging	4.5 (1.5-5.8)	7.1 (2.8-9.1)	<0.001
Total	21.2 (0.57-21.5)	32.0 (11.5-34.5)	<0.001

[a]Mann-Whitney U test, [b]Expenditure in million IRR, IQR: Interquartile range, Statistical significance (P<0.005)

Table 3 presents the incidence rate ratio of prescribed healthcare services for diabetic patients with and without CVD comorbidity, adjusted for demographic characteristics and other comorbidities in the fitted regression model. Diabetic patients with CVD comorbidity received approximately 30% extra healthcare services (ratio=1.3, P<0.001) than those, who did not suffer from CVD comorbidity. The increase in incidence rate ratio was 28% in physician services (ratio=1.28, P<0.001), 46% in prescribed drugs (ratio=1.46, P<0.001), 27% in laboratory tests (ratio=1.27, P<0.001), and 7% in medical imaging (ratio=1.07, P<0.001).

Healthcare Expenditures

The unadjusted mean total expenditure is presented in table 2. The mean of total direct costs for diabetic patients with CVD comorbidity was 32 million IRR (888.9 USD) compared to 21.2 million IRR (588.9 USD) for those without CVD comorbidity, representing 51% higher medical expenditures.

The results of the regression models on healthcare expenditures are shown in table 4. Adjusting for confounding variables, the presence of CVD comorbidity showed a significant positive effect on both the probability of having at least one IRR expenditure and the amount of total expenditures for those with positive expenditures. In this regression model, having CVD comorbidity was associated with an increase in total expenditure by 50%. The costs were significantly higher in older patients,

Table 3: Regression coefficients (incident rate ratios) from negative binomial regression model on utilization, categorized by healthcare services (2014-2016)

Covariates	Physician services	Prescription drugs	Laboratory tests	Medical imaging	Overall utilization
Cohort (reference: Non-CVD comorbidity)	1.28***	1.46***	1.27**	1.07***	1.3***
Age	1.09***	1.01	1.08***	1.10***	1.16***
Sex (reference=female)	0.95***	0.92***	0.96**	0.79***	0.96***
Insurance fund (reference: Fund 2)					
Insurance fund 3	1.22***	1.3***	0.99	1.02	1.17***
Insurance fund 4	0.81***	0.93*	0.66***	0.56***	0.81***
Insurance fund 6	0.86***	0.91***	0.79***	0.72***	0.85***
Insurance fund 9	0.50***	0.60***	0.44***	0.48***	0.52***
Other comorbidities					
IBD	1.50***	1.48***	1.20	1.50**	1.40***
Acid-related disorders	1.30***	1.44***	1.1***	1.32***	1.30***
Schizophrenia and bipolar disorders	1.18***	1.32***	0.91***	0.94	1.15***
Cancer	1.59***	1.86***	2.14***	2.47***	1.90***
COPD	1.28***	1.41***	1.02	1.29***	1.25***
Dementia	0.93	0.99	0.8**	1.10	0.92
Hyperlipidemia	1.17***	1.27***	1.37***	1.11***	1.28***
Migraine	1.20	1.36	1.11	0.70	1.23
Depression, anxiety, and sleep disorders	1.25***	1.32***	1.12***	1.20***	1.23***
Thyroid disorders	1.10**	1.14***	1.35***	1.15***	1.20***

*P=0.05; **P=0.01; ***P<001; The P value for Hosmer-Lemeshow test is 0.23

Table 4: Regression coefficients of the two-part model on healthcare expenditures adjusted for covariates by health service category.

Covariates	Part 1: Probability of observing a positive versus zero expenditures (logistic regression model[a])			Part 2: Amount of expenditures for those with positive expenditures (GLM with the log-link and gamma distribution[b])				
	Physician services	Laboratory tests	Medical imaging	Physician services	Drugs [c]	Laboratory tests	Medical imaging	Total
Cohort (reference: Non-CVD comorbidity)	1.27***	1.35***	1.12***	1.32***	1.59***	1.23***	1.26***	1.50***
Age	1.01**	1.03	1.01***	1.02***	1.04***	1.01***	1.03***	1.02***
Sex (reference=female)	0.52***	0.70***	0.76***	1.01	1.12***	1.02	0.95**	1.09***
Insurance fund (reference: Fund 2)								
Insurance fund 3	0.90	0.80**	1.04	1.1***	1.1	0.97	1.03	1.09*
Insurance fund 4	0.39***	0.43***	0.49***	0.8***	0.95	0.72***	0.74***	0.89*
Insurance fund 6	0.60**	0.62***	0.67***	0.93***	1.12***	0.84***	0.88***	1.03
Insurance fund 9	0.16***	0.27***	0.43***	0.67***	0.92*	0.54***	0.76***	0.8***
Other comorbidities								
IBD	1.68*	2.1	2.18**	1.56***	3.05***	1.12	1.2	2.5***
Acid-related disorders	1.01	1.08	1.44***	1.23***	1.14***	1.1***	1.1***	1.17***
Schizophrenia and bipolar disorders	5.4*	0.78**	0.88*	1.1***	1.03	0.9***	0.98	1.03
Cancer	2.5***	1.9***	3.9***	1.83***	19.73***	2.4***	2.75***	3.27***
COPD	1.5	0.9	1.42***	1.23***	1.53***	1.05*	1.20***	1.41***
Dementia	0.5	0.45***	1.20	1.01	1.43*	0.92	0.90	1.24
Hyperlipidemia	3.5***	2.44***	1.23***	1.21***	1.32***	1.21***	1.13***	1.29***
Migraine	1.03	1.20	1.4	1.22***	0.70	1.06	0.60	0.84
Depression, anxiety, and sleep disorders	2.07*	1.35***	1.40***	1.24***	1.23***	1.1***	1.13***	1.22***
Thyroid disorders	1.4	3.07***	1.22**	1.11***	1.25***	1.4***	1.1*	1.25***

*P=0.05; **P=0.01; ***P<0.001; The P value for Hosmer-Lemeshow test is 0.19; [a]Odds ratio; [b]Exponentiated coefficients; [c]The first part is skipped due to patients with positive drug expenditures; GLM: Generalized linear model

men, insurance fund two, and patients with other chronic comorbidities (except for migraine and schizophrenia/bipolar disorders).

The total three-year incremental costs for diabetic patients with CVD was 10.6±0.67 million IRR (294.4±18.6 USD) (95% CI: 8.6-11 million IRR, P<0.001). A similar effect was observed for all types of healthcare services. The marginal/

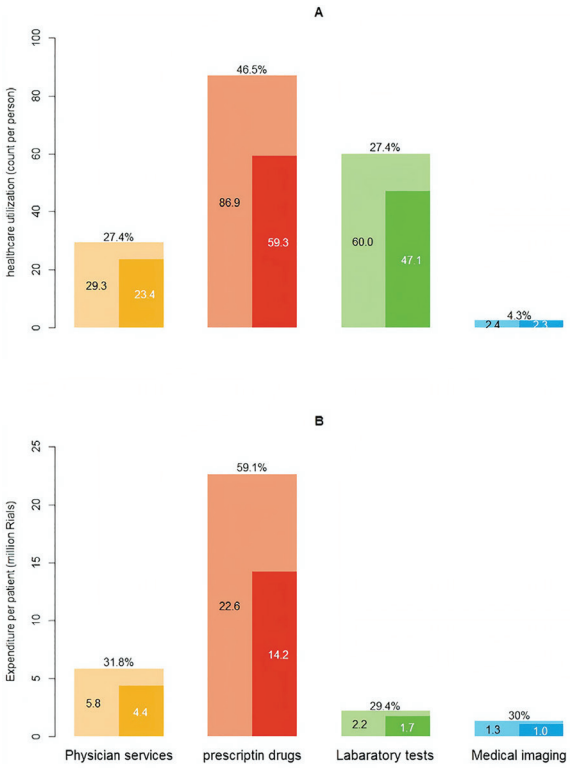

Figure 1: The figure demonstrates the marginal effect of CVD comorbidity in patients with diabetes on healthcare resource utilization (A) and expenditure (B), categorized by healthcare service. Light colors: Healthcare resource utilization patterns for diabetic patients with CVD comorbidity; Dark colors: Healthcare resource utilization patterns for diabetic patients without CVD comorbidity; Percentages: The difference in marginal effects among diabetic patients with and without CVD comorbidity.

incremental healthcare expenditure was 1.44±0.06 million IRR (40±1.6 USD) for physician services (32% increase), 8.36±0.57 million IRR (232.2±15.8 USD) for drug prescriptions (58% increase), 0.51±0.02 million IRR (14.1±0.5 USD) for laboratory costs (24% increase), and 0.29±0.02 million IRR (8±0.5 USD) for medical imaging (22% increase) (all Ps<0.001).

The marginal effect of CVD comorbidity in patients with diabetes on healthcare resource utilization (A) and expenditures (B) per healthcare category is shown in figure 1.

Discussion

It is known that comorbidities, such as CVD in diabetic patients, will result in a substantial increase in HRUE. However, an accurate estimate of the increase in the context of low- and middle-income countries is not known. This information is important in the assessment of healthcare policies, resource allocation, and planning.

Based on the IHIO database, our results showed that 63% of patients receiving drugs to treat diabetes were concurrently prescribed medications for CVD. In line with our results, several studies have reported the same percentages for such comorbidities. Referring to the Australian National Health Survey 2004-2005, a previous study also reported that over 60% of patients with diabetes had at least one form of CVD comorbidity.[23] Another study in Germany reported that 64% of the patients with diabetes had concurrent CVD complications.[24] A study in Saudi Arabia reported that over 78% of diabetic patients only suffered from hypertension.[25] In contrast, some other studies have reported a lower prevalence of CVD comorbidity with diabetes,[26, 27] which could be attributed to the absence of hypertension as a separate classification of CVD complications. According to a recent systematic review,[8] most studies have classified hypertension as part of CVD rather than a separate comorbid condition. In line with the results of a previous study, we found that diabetic patients with CVD were about 13 years older than those without CVD comorbidity.[28]

Our results showed that after adjusting for various covariates, CVD comorbidity in patients with diabetes was associated with increased use of healthcare resources. We estimated the adjusted mean overall healthcare expenditure for diabetic patients with CVD at 32 million IRR per patient, almost 50% higher than diabetic patients without CVD (21.4 million IRR). Furthermore, in line with the results of other studies, the mean overall records of healthcare utilization in diabetic patients with CVD was 178 entries per patient compared to 132 entries in those without CVD (34% increase). In a retrospective analysis of the Medicaid insurance claims in the state of West Virginia in 2002, Mody and colleagues reported that diabetes with CVD comorbidity resulted in 39% higher healthcare expenditure per patient.[9] Similarly, Erwin and colleagues reported a 58% increase in total expenditure in elderly patients with type 2 diabetes with at least one CVD complication compared to those without.[29] Compared to our results, some studies have reported much higher estimates for the incremental costs of CVD comorbidity in patients with diabetes. For example, health insurers in the United States reported that among the claims of 7,109 diabetic patients in managed care organizations, patients with CVD comorbidity had up to 150% higher direct medical costs than those without.[30] Such higher percentages in adjusted marginal health care costs can be attributed to the fact that estimates were based on total healthcare expenditures, including inpatient costs. One should remember

that hospitalization is the most expensive part of healthcare expenditures in diabetic patients with CVD comorbidity.

We found that the incremental HRUE associated with diabetic patients with CVD comorbidity widely varied among the main categories of outpatient care. Higher expenditure on prescription drugs was the prime contributor to the overall incremental healthcare expenditure. Our results showed that 8.6 (81%) of the 10.6 million IRR of total incremental expenditure was due to prescription drugs. Moreover, after adjusting for several covariates, the number of prescribed drugs in diabetic patients with CVD was almost 60% higher than those without CVD (figure 1). This is indicative of the intensive pharmaceutical treatment of CVD as well as the overall management of diabetic patients with CVD comorbidity. The second highest contributor to the overall incremental healthcare expenditure was due to the services provided by physicians, accounting for 1.4 million IRR (13%) of the total 10.6 million IRR.

The extra HRUE for treating patients with concurrent diabetes and CVD underlines the immediate need for effective and efficient management of such patients. This puts a heavy financial burden on healthcare systems, especially in the Middle East, where an increase in the number of patients with such comorbidities is anticipated in the coming decades.[1]

Healthcare systems that are fragmented and primarily able to deal with only a single disease at a time are not tailored to respond to multiple episodes of care and are unprepared to manage multimorbidity. It has been reported that patients with multimorbidity often receive fragmented, inefficient, incomplete, ineffective, and duplicative health care.[31, 32] This is the result of poor coordination among healthcare services, which often undermines synergy between interventions and can even put patients at risk. Some developed countries have recently initiated certain actions to develop evidence-based guidelines addressing the co-management of diabetes and CVD.[33] In contrast, developing countries such as Iran are yet to address this issue.

Effective management of the multimorbid nature of diabetes requires the adoption of a multi-dimensional strategy. Healthcare systems should adopt a more comprehensive approach instead of focusing on a single disease, whereby care is coordinated by a single or a team of healthcare providers with the primary focus on the difficulties and needs of patients with multimorbidity. Such a comprehensive approach will satisfy the treatment needs of patients and reduce the burden of the concurrent presence of chronic conditions, e.g., CVD in diabetic patients.

Our findings highlight the importance of managing medication usage among diabetic patients with CVD comorbidity. As mentioned earlier, over 80% of the total incremental outpatient healthcare expenditure was due to prescription drug costs. Considering the marginal effect of CVD comorbidity on the number of drugs used, we can conclude that the higher expenditure is to a large degree driven by a higher volume of prescriptions. This situation may trigger an increase in the dangers of polypharmacy among patients. An association between diabetes and polypharmacy can be detected early, but morbidity can exacerbate potential dangers and increase the risk of drug adverse effects.[34, 35] Therefore, taking multimorbidity into account, a comprehensive assessment of the prescribed drugs is required for each patient.

To the best of our knowledge, this is the first population-based study in a low- and middle-income country that comprehensively examined excessive HRUE of CVD in patients with diabetes. By using data from a large and continuous administrative database, we avoided the drawbacks of alternative data sources (e.g., self-reports) such as recall bias, non-response bias, attrition, and under-representation of high-cost cases. An additional strength of the present study was in developing a comprehensive list of other chronic conditions and the use of robust statistical techniques (GLM, recycled predictions method) in estimating an incremental increase in HRUE. Nonetheless, there are several limitations to our study. First, although the use of pharmacy claims data is recommended as an alternative indicator to identify diseases,[36, 37] the data lacks information on the definitive diagnosis. However, this approach is customary and used in several other studies. Secondly, the IHIO database lacks important confounding variables (e.g., socio-economic status, educational level, and accessibility to care) for HRUE. Moreover, this database does not include information related to inpatient healthcare services, which is a major contributor to HRUE. Lastly, in the absence of relevant information in the IHIO database, we could not adjust our estimates for the duration and severity of comorbidity.

Conclusion

In contrast with the implicit assumption made by the Iranian healthcare system, it is shown that the concurrence of diabetes and CVD is common in Iran and that the associated outpatient HRUE is substantial. The incremental increase in HRUE

is primarily due to prescription drugs followed by physician services. Our findings draw the attention of healthcare decision-makers to proactively prevent CVD comorbidity in diabetic patients. Further research is required to examine the potential effect of this comorbidity on other aspects of healthcare services such as quality and continuity of care.

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