

Prevalence and comorbidities of known diabetes in northeastern Italy

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ABSTRACT

Aims/Introduction: We aimed at estimating the prevalence and at identifying the frequent comorbidities of diabetes mellitus in a region of northeastern Italy from administrative health data.

Materials and Methods: The prevalence was estimated according to two disease definitions, based on administrative health data. Association rule mining was used to detect comorbid diagnoses that coexisted with a diagnosis of diabetes among patients admitted to the regional hospitals.

Results: The prevalence of known diabetes in 2010 was 6.0–8.1%, with great variations by age class (from approximately 2% <60 years to more than 20% in some elderly age groups). Of 155,494 patients admitted to the hospital in 2011, 9,358 had a diagnosis of diabetes. A total of 12 rules satisfied our criteria for support (>0.5%) and confidence (>5%), and identified nine frequent isolated comorbidities and three pairs of comorbid diagnoses. The rule with the highest support (2.4%) and confidence (39.5%) identified the combination of diabetes and essential hypertension.

Conclusions: Association rule mining was useful, because it showed the complexity of diabetic patients. Clinical management of those patients cannot neglect comorbidities. (*J Diabetes Invest*, doi: 10.1111/jdi.12043, 2013)

KEY WORDS: Association rule mining, Diabetes mellitus, Hospital discharge data

INTRODUCTION

Diabetes mellitus is a common disease worldwide. Its prevalence is increasing, and varies greatly across geographical areas^{1–4}.

In Italy, the overall prevalence has been estimated to be approximately 5%⁵, but the country is geographically and culturally heterogeneous, and disparities exist in health-related factors⁶. Friuli Venezia Giulia (FVG) is a 1,200,000-inhabitant region located in northeastern Italy. In FVG, a regional health information system allows for comprehensive assessments of the health status of the population through the analysis of administrative health-related databases.

The objective of the present study was to estimate the prevalence of known diabetes mellitus in the FVG region based on the health information system, and to assess the relationships among the diseases that accompany diabetes mellitus using association rule mining (ARM) on the regional large administrative databases.

METHODS

Prevalence of Known Diabetes

The sources of information for estimating prevalence were the administrative health databases of the FVG region, included in

a regional repository of data for epidemiological studies: (i) hospital discharges; (ii) exemptions from medical charges (in Italy, diabetics can obtain medicines, visits and devices free of charge from the National Health System, after being certified); (iii) pharmaceutical prescriptions; and (iv) outpatient visits. In each database, patients are identified through an anonymous univocal identification number that allows individual linkage of records from different databases. Classification of type 1 and type 2 diabetes mellitus is not possible according to those sources, therefore, both types of diabetes are included in our estimates. However, according to the World Health Organization, type 2 diabetes comprises 90% of people with diabetes worldwide⁷.

The prevalence among residents in the region was estimated as of 31 December 2010, the most recent date when all databases were complete. The prevalence was calculated according to two different definitions:

1. Any hospital discharge from 2000 to 2010 with International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) = 250.xx in any diagnosis position; or being exempt from medical charges because of diabetes mellitus (regional codes 'P20','013'); or being prescribed ≥ 3 packages of medications with Anatomical Therapeutic Chemical (ATC)⁸ codes A10Axx or A10Bxx within 365 days;
2. Criteria in definition 1; OR ≥ 2 outpatient blood withdrawal for glycated hemoglobin (HbA_{1c}) measurement (regional code 90.28.1) within 365 days; or ≥ 1 medications with ATC

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codes A10Axx or A10Bxx and ≥ 1 outpatient blood withdrawal for HbA_{1c} measurement (regional code 90.28.1) within 365 days.

The use of different criteria based on different sources of information should minimize the possibility of underestimating the prevalence. A more accurate estimation will be possible when the actual HbA_{1c} concentration measured in blood is available for epidemiological analyses.

The prevalence of known diabetes was also estimated stratified by sex and age category (<60; 60–69, 70–79, ≥ 80 years). To allow for international comparison, we also calculated the directly standardized prevalence of known diabetes mellitus using the Segi world population as the standard⁹.

Comorbidities of Diabetes

To assess the relationships among the diseases that occur in association with diabetes mellitus, we used ARM. Association rules are of the form if A then B (A \Rightarrow B). ARM is widely used by marketing professionals to recognize affinities among products, but it can also be applied to medical histories of patients to detect particular combinations of conditions or diagnoses (Dx)^{10–12}.

The algorithm rules specify when a certain item set A (DxA) appears in a database and another item set (DxB) appears in association with it. The rules are evaluated by support, confidence and lift. Support is the percentage of occurrences of DxA and DxB out of all diseases. It can be seen as the probability of the co-occurrence of DxA and DxB, and is direction independent. Confidence is the ratio of the support of the co-occurrence of DxA and DxB to the occurrences of DxA, and can be seen as a direction-dependent conditional probability. To take a rule into consideration, we impose a minimum support (s0); that is, a reasonably large amount of data about the rule, and a minimum confidence (c0); that is, a reasonably good predictivity of the rule. A strong rule is one with support $> s0$ and confidence $> c0$. Interesting rules, however, should also show a reasonable lift or improvement, which is the ratio of the support of the co-occurrence of DxA and DxB to the product of the support of DxA, and the support of DxB. A lift > 1 indicates that the association between DxA and DxB is due to more than just chance alone.

The analysis of comorbidities was based on hospital discharges in 2011, the most recent available year. All the patients who were admitted to any of the FVG hospitals and discharged in the year 2011 were included in the analysis.

Five-digit ICD-9-CM codes were recoded into three-digit codes, because more specific codes would have given low support item sets. Duplicate records (i.e. those with the same diagnosis for the same patient) were removed from the analysis. The association rules were determined by the RapidMiner 5.2.008 free software (Rapid-I GmbH, Dortmund, Germany). The threshold for values was established as $s0 > 0.5\%$ for support and $c0 > 5\%$ for confidence. The statistical significance of the rules identified by ARM was tested through chi-square tests.

RESULTS

The regional prevalence of known diabetes mellitus as of 31 December 2010 was 6.0% according to definition 1 and 8.1% according to definition 2. Using the Segi world population, the directly standardized prevalence of known diabetes according to definition 2 was 3.7%. There was great variability of age- and sex-specific prevalences, as shown in Table 1, with diabetes being relatively rare in people aged younger than 60 years. In all sex and age groups, the prevalence estimated according to definition 2 was 30–40% higher than according to definition 1.

In 2011, 155,494 patients were admitted to the regional hospitals at least once, totalling 416,396 diagnostic records with non-duplicate three-digit ICD-9-CM codes. The number of patients with a diagnosis of diabetes was 9,358, with 46,897 diagnostic records with non-duplicate three-digit ICD-9-CM codes and 659 distinct three-digit ICD-9-CM codes other than 250 (diabetes mellitus).

The diagnoses that were most frequently associated with diabetes mellitus are shown in Table 2. We obtained 12 rules between diabetes mellitus and comorbid diagnoses (Table 3). The rule with the highest support and confidence was diabetes mellitus \Rightarrow essential hypertension. Three rules identified two comorbid diagnoses simultaneously associated with diabetes mellitus.

Persons discharged from the hospital with a diagnosis of diabetes mellitus are significantly more likely than the others to have the comorbid discharge diagnosis sets identified through the ARM process (Table 4).

Table 1 | Sex and age-specific prevalence of diabetes in Friuli Venezia Giulia, northeastern Italy, 31 December 2010

Sex and age (years)	Diabetes definition 1†		Diabetes definition 2‡	
	n	Prevalence (%)	n	Prevalence (%)
Females				
0–59	7,976	1.9	11,551	2.7
60–69	7,556	9.1	10,558	12.7
70–79	9,792	13.8	13,668	19.3
≥ 80	9,288	15.5	12,283	20.4
Males				
0–59	9,774	2.2	13,121	3.0
60–69	12,294	15.8	16,280	21.0
70–79	11,827	21.0	16,120	28.6
≥ 80	5,294	19.2	6,985	25.4
Total	73,801	6.0	100,566	8.1

†Diabetes definition 1: any hospital discharge from 2000 to 2010 with International Classification of Diseases, ninth revision, Clinical Modification = 250.xx in any diagnosis position; or being exempt from medical charges because of diabetes mellitus (regional codes 'P20';013'); or being prescribed ≥ 3 medications with Anatomical Therapeutic Chemical (ATC) codes A10Axx or A10Bxx within 365 days. ‡Diabetes definition 2: criteria in definition 1; or ≥ 2 outpatient blood withdrawal for glycated hemoglobin (HbA_{1c}) measurement (regional code 90.28.1) within 365 days; or ≥ 1 medications with ATC codes A10Axx or A10Bxx and ≥ 1 outpatient blood withdrawal for HbA_{1c} measurement (regional code 90.28.1) within 365 days.

Table 2 | Comorbid discharge diagnoses frequently associated with diabetes (International Classification of Diseases, Ninth Revision, Clinical Modification code 250) among patients discharged from hospital in Friuli Venezia Giulia, northeastern Italy, in 2011

ICD-9-CM	Diagnosis name	<i>n</i>	Diabetic patients (%)
401	Essential hypertension	3,692	39.5
427	Cardiac dysrhythmias	2,058	22.0
414	Other forms of chronic ischemic heart disease	2,031	21.7
428	Heart failure	1,848	19.8
402	Hypertensive heart disease	1,530	16.4
585	Chronic kidney disease	1,272	13.6
491	Chronic bronchitis	1,082	11.6
272	Disorders of lipid metabolism	953	10.2
518	Other diseases of lung	860	9.2
278	Overweight, obesity and other hyperalimentation	733	7.8
440	Atherosclerosis	715	7.6
437	Other ill-defined cerebrovascular disease	643	6.9
571	Chronic liver disease and cirrhosis	592	6.3

n = 9,358. ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

DISCUSSION

In this region of northeastern Italy, 73,000–100,000 of the 1,200,000 inhabitants are estimated to have known diabetes mellitus. Our prevalence estimates (6.0–8.1%) were much higher than those reported in the national official statistics: 4.9% according to the Italian National Institute of Statistics⁵ in 2011, as reported by the citizens interviewed in the national survey Indagine Multiscopo ‘Aspetti della vita quotidiana’, and 5% as estimated by the national health surveillance system (Progressi delle Aziende Sanitarie per la Salute in Italia [PASSI])¹³. However, the study designs used for the national statistics are different from ours (surveys of population samples and self-reports vs analysis of administrative health databases with full coverage of the population), and the resulting estimates are hardly comparable.

In contrast, methods similar to ours were used in a recent study carried out in the northern Italian region of Lombardy¹⁴. The sources of information were hospital discharge data (DRG), exemptions from medical charges and medicine prescriptions. The crude prevalence of type 1 and type 2 diabetes mellitus in that study was 4.2% – much lower than ours. However, all age-specific frequencies were higher than in FVG. This suggests that the crude prevalence of known diabetes mellitus in FVG is higher than in other Italian regions because of the age structure of the population. In fact, FVG has one of the highest ratios of residents aged ≥65 years over those aged 0–14 years in the country¹⁵.

Table 3 | Association rules between diabetes (International Classification of Diseases, Ninth Revision, Clinical Modification code 250) and comorbid discharge diagnoses, support, confidence and lift in Friuli Venezia Giulia, northeastern Italy, in 2011

Rule	<i>n</i>	Support	Confidence	Lift
ICD-9-CM 250 (diabetes mellitus) ⇒ ICD-9-CM 401 (essential hypertension)	3692	2.4	39.5	3.968
ICD-9-CM 250 (diabetes mellitus) ⇒ ICD-9-CM 427 (cardiac dysrhythmias)	2058	1.3	22.0	2.975
ICD-9-CM 250 (diabetes mellitus) ⇒ ICD-9-CM 414 (other forms of chronic ischemic heart disease)	2031	1.3	21.7	4.360
ICD-9-CM 250 (diabetes mellitus) ⇒ ICD-9-CM 428 (heart failure)	1848	1.2	19.7	3.918
ICD-9-CM 250 (diabetes mellitus) ⇒ ICD-9-CM 402 (hypertensive heart disease)	1530	1.0	16.3	4.118
ICD-9-CM 250 (diabetes mellitus) ⇒ ICD-9-CM 585 (chronic kidney disease)	1272	0.8	13.6	4.888
ICD-9-CM 250 (diabetes mellitus) ⇒ ICD-9-CM 491 (chronic bronchitis)	1082	0.7	11.6	3.548
ICD-9-CM 250 (diabetes mellitus) ⇒ ICD-9-CM 272 (disorders of lipid metabolism)	953	0.6	10.2	3.782
ICD-9-CM 250 (diabetes mellitus) ⇒ ICD-9-CM 518 (other diseases of the lung)	860	0.6	9.2	2.878
ICD-9-CM 250 (diabetes mellitus) ⇒ ICD-9-CM 427 (cardiac dysrhythmias), ICD-9-CM 428 (heart failure)	859	0.6	9.2	3.964
ICD-9-CM 250 (diabetes mellitus) ⇒ ICD-9-CM 401 (essential hypertension), ICD-9-CM 414 (other forms of chronic ischemic heart disease)	829	0.5	8.9	4.017
ICD-9-CM 250 (diabetes mellitus) ⇒ ICD-9-CM 427 (cardiac dysrhythmias)	852	0.5	9.1	5.443

n = 155,494. ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

Table 4 | Statistical significance of the associations rules between diabetes (International Classification of Diseases, Ninth Revision, Clinical Modification code 250) and comorbid discharge diagnoses in Friuli Venezia Giulia, northeastern Italy, in 2011

ICD-9-CM	Diagnosis name	Subjects with ICD-9-CM 250 discharge diagnosis		Subjects with no ICD-9-CM 250 discharge diagnosis		χ^2 P-value
		N	%	N	%	
401	Essential hypertension	3,692	39.5	11,769	8.1	<0.0001
427	Cardiac dysrhythmias	2,058	22.0	9,437	6.5	<0.0001
414	Other forms of chronic ischemic heart disease	2,031	21.7	5,709	3.9	<0.0001
428	Heart failure	1,848	19.8	5,990	4.1	<0.0001
402	Hypertensive heart disease	1,530	16.4	4,644	3.2	<0.0001
585	Chronic kidney disease	1,272	13.6	3,052	2.1	<0.0001
491	Chronic bronchitis	1,082	11.6	3,985	2.7	<0.0001
272	Disorders of lipoid metabolism	953	10.2	3,234	2.2	<0.0001
518	Other diseases of lung	860	9.2	4,106	2.8	<0.0001
427,428	Cardiac dysrhythmias, heart failure	859	9.2	2,742	1.9	<0.0001
401,414	Essential hypertension, other forms of chronic ischemic heart disease	852	9.1	1,749	1.2	<0.0001
401,427	Essential hypertension, cardiac dysrhythmias	829	8.9	2,600	1.8	<0.0001

n = 155,494. ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

The validity of identifying cases of diabetes from administrative data is still unknown in Italy. A review of international studies showed that administrative databases were adequately sensitive and highly specific¹⁶. In Canada, recent research showed that, relative to three standard definitions of diabetes based on laboratory data, the use of a combination of administrative hospital discharge data and physician claims data underestimated the prevalence of diagnosed diabetes by at least 20%¹⁷. In the present study, we used multiple data sources, which should minimize the possibility of underestimating the prevalence. The estimated prevalence increased by more than 30% when we included among the criteria for case identification having at least two measurements of HbA_{1c} in 365 days, consistently with current clinical recommendations¹⁸. An improvement in case ascertainment validity will be possible through the individual linkage with the HbA_{1c} values actually measured in our patients, currently not available for epidemiological analyses. Of course, the administrative databases that we used will never capture cases of diabetes that are clinically unrecognized.

Knowing that there are at least 73,000 diabetic patients in the FVG region, and that most of them are elderly, is important from the public health standpoint and for the regional health policy planning. Other information that is extremely important for organizing healthcare and management of diabetics regards comorbidities. For this reason, we studied through ARM the comorbidities that are often associated with diabetes mellitus.

Association rule mining proved efficient and effective in identifying new and interesting patterns in health data^{19,20}, and

in particular in comorbidity studies using large health databases^{10–12}. This method has some limitations, such as the lack of uniform criteria for setting thresholds for support and lift²⁰, and the generation of superfluous patterns²¹. Nonetheless, it was useful to confirm in an Italian context associations between diabetes mellitus and comorbid diagnoses, most of which had been shown in other settings¹⁰.

Diabetes mellitus is frequently associated with essential hypertension. Patients with both conditions are much more likely to have coronary heart disease, and to experience more severe cardiomyopathy and complications than those with either one²², and should be treated to control both blood pressure and glucose levels.

We noticed an association of diabetes mellitus with different heart diseases. In regard to dysrhythmias, diabetes mellitus has been shown to significantly alter the cardiac electrophysiology²³ and, in particular, the association of diabetes with increased risk of atrial fibrillation is well known²⁴. Several mechanisms have been proposed, however, not one has been demonstrated²⁴. Heart failure was reported to have worse outcomes among diabetic patients than among the others, and diabetes might influence the clinical choice of carrying out revascularization in case of ischemic heart failure²⁵. Recognizing diabetic status is fundamental for the correct management and treatment of patients with heart failure²⁶. Hypertensive heart disease was also common in our cohort. Diabetes mellitus affects the pattern of left ventricular hypertrophic response to hypertension²⁷, and good glycemic control reduces left ventricular hypertrophy both in patients with type 2 diabetes and in those with type 1 diabetes^{28,29}.

Chronic kidney disease is another condition that is often associated with diabetes. Diabetes is a frequent cause of kidney disease, and is the primary cause of kidney failure for many patients who receive dialysis. Patients with a combination of the two conditions are at a higher risk of cardiovascular events than the others and need to be carefully treated. However, the clinical management of those patients is difficult; kidney dysfunction might impose an adjustment of the medication therapy to control diabetes³⁰.

Regarding the association with chronic bronchitis and other diseases of the lung, in the Women's Health Study, women with chronic obstructive pulmonary disease were shown to have an increased risk of developing type 2 diabetes mellitus, independent of smoking status and other known risk factors for diabetes³¹. A possible explanation for this association is the existence of a common inflammatory basis between the two conditions. Behaviors that reduce diabetes risk among patients with chronic lung disease should be encouraged.

In our diabetic population, disorders of lipid metabolism were also common. Impaired insulin action modifies the adipocyte metabolism, ultimately leading to an alteration of plasma lipids, with increased very-low-density lipoproteins, decreased high-density lipoprotein, and small and dense low-density lipoprotein³², and increased risk of cardiovascular events. Correcting dyslipidemia in diabetic patients is, therefore, particularly important.

In addition to the aforementioned associations, ARM identified three rules in which two comorbid diagnoses were associated with diabetes mellitus. Although the mechanisms underlining such associations are not always fully explained and more research is required to clarify them, the present study shows that diabetics are undoubtedly complex patients and reminds us that their clinical management cannot neglect comorbidities. In this perspective, the association rules generated in the present study might be regarded as useful; they are not trivial, because the comorbidities of diabetes had never been studied before in this population; they are not inexplicable, because they have plausible explanations; they are actionable.

The results of our ARM, however, should not be generalized to the overall population of diabetics. In fact, patients who are admitted to the hospital are likely to be different from those who do not require hospitalization, who are the majority. They might differ in a number of aspects, such as disease seriousness, socioeconomic and marital status, and comorbidity pattern.

In conclusion, we estimated that 6–8% of the population of FVG has known diabetes mellitus, with great variations by age group. Among diabetics who are admitted to the hospital, comorbidities are frequent and should be taken into consideration in the clinical management of those patients.

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