Diabetes as a Predictor of In-Hospital and One-Year Outcomes After Decompensated Heart Failure

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Abstract: Diabetes and heart failure are closely interdependent, but its significance in decompensated heart failure (DHF) is not uniformly accepted. *Objective:* To compare mortality between diabetics and nondiabetics with DHF. *Methods and Results:* In-hospital and 1-year mortality of 1004 consecutive patients with DHF: 25.6% diabetics; median age was 81, 53% male. Diabetics were younger, more often male, with higher prevalence of ischemic etiology and reduced ejection fraction. Congestion was the most prevalent finding in both groups. In hospital mortality was 6.3% vs 6.6 % in nondiabetics and diabetics respectively and 1-year mortality was 35.77% in nondiabetics and 29.3% in diabetics. There were no significant differences in mortality at univariate and multivariate analyses. We applied a propensity score restricted to 378 patients, 189 (50%) diabetics and 189 (50%) and no significant differences were found. *Conclusion:* Diabetes had no impact on prognosis in DHF. Advanced age may played a major role in outcomes i thus making less relevant the presence of diabetes. (Curr Probl Cardiol 2021;46:100579.)

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There is a close dependence between diabetes and heart failure, from pathophysiological as well as epidemiologic and clinical aspects.[1,2]

The mechanisms by which diabetes is associated with heart failure are not only related to a higher prevalence of coronary artery disease and hypertension but also a direct causative effect of diabetes in the development of heart failure with and without reduced ejection fraction.[3,4]

The prevalence of heart failure is higher among diabetic patients[5,6] and diabetes is also more prevalent in patients with heart failure.[2]

As a risk factor, diabetes is more significant in women. According to a classic Framingham analysis, diabetes doubles the risk of heart failure in males and triples the risk in females.[7]

Diabetes worsens the prognosis of chronic heart failure[2] and conversely heart failure itself is a predictor of increased diabetic risk.[8,9]

Heart failure is the first cause of admission for patients older than 65 years and this has a clear negative impact in prognosis.[10-12]

In diabetic patients, heart failure is the main cardiovascular cause of hospital admissions even more prevalent than myocardial infarction or stroke.[13]

The prognostic impact of diabetes in patients admitted with decompensated heart failure is not coincident among different authors.

The objective of this study is to evaluate an unselected population representative of daily clinical practice admitted to a coronary care unit with decompensated heart failure in order to compare differences in mortality between diabetics and nondiabetics during the in-hospital phase and at 1 year.

Methods

Between February 2010 and December 2017, all patients with decompensated heart failure admitted to the coronary care unit at 2 private institutions of Buenos Aires (Argentina) were consecutively recruited with a prospective data collection system. A comparison between diabetics and nondiabetics was retrospectively carried out.

Assessment of in-hospital and 1-year survival was evaluated by personal or telephonic contact.

The diagnosis of heart failure was made by the treating physician adopting criteria similar to the European Society of Cardiology Guidelines[14]: *Rapid onset or worsening of symptoms and/or signs of heart failure either with preserved or reduced ejection fraction*. We included both patients with *de novo* heart failure or with decompensated chronic heart

failure. Laboratory diagnostic criteria included the presence of elevated natriuretic peptides at admission (B type natriuretic peptide (BNP) > 100 pg/ml or NTproBNP> 300 pg/ml). The area of hospital admission was also a decision of the treating physician according to the severity of the disease and the therapeutic requirements.

Acute pulmonary edema, anasarca, or cardiogenic shock were considered as a severe presentation profile.

According to medical history and/or the use of antidiabetic drugs (insulin or oral antidiabetics) patients were divided as diabetics or nondiabetics.

Ejection fraction by Sympson method was evaluated in every patient and those <45% were considered to have heart failure with reduced ejection fraction; otherwise they were defined as having preserved ejection fraction.

Statistical Analysis

Categorical variables are presented as percentages, while continuous variables are presented as means and standard deviation if normally distributed or as median and interquartile range if not.

Continuous variables were compared by the *t* test or Wilcoxon test according to normally distribution or not. Categorical variables were compared by the x^2 test or exact Fisher test.

For the evaluation of prognostic implications of diabetes for in-hospital and 1-year mortality we performed a propensity score (PS) and a multivariable analysis (logistic regression). All the significant variables at univariate analysis including diabetes entered the model. Age and systolic blood pressure were considered as continuous variables.

The association between diabetes and in-hospital and 1-year all-cause mortality was assessed by Cox regression models in a 1:1 propensity score matched cohort and in prespecified subgroups. The PS for diabetes was calculated in each imputed dataset for each patient by a logistic regression model including 15 clinically relevant covariates (sex, age, hypertension, dyslipidemia, chronic obstructive pulmonary disease, peripheral artery disease, ischemic heart disease, valvular heart disease, history of chronic heart failure, atrial fibrillation, coronary etiology, systolic dysfunction, chronic kidney disease, systolic blood pressure at admission, and comorbidities average) and then averaged across the imputed datasets. Diabetics were matched 1:1 to nondiabetics by their PS, using the nearest neighboring method with a caliper of 0.2 and no replacement.

For 1-year all-cause mortality analysis, events occurred beyond 1 year were censored.

Cox proportional hazard analyses were performed to evaluate the hazard ratio (HR) for events at 1 year.

We also analyzed the propensity score value as a covariable for prediction of in-hospital and 1-year mortality.

Differences were considered statistically significant at P value <0.05.

Analysis was performed with the Epi Info 7.0 system software. PS was constructed with SPSS 23.

Data collection and protocol design were approved by the Ethics and Scientific Committees of both institutions.

Results

During the enrolment period, 1004 patients (25.6% diabetics) were admitted. In-hospital outcome information was obtained in all patients, and at 1-year follow-up in 91.15%. Patients lost to follow-up presented similar characteristics than the rest. Main characteristics of the patients are detailed in Table 1. Median age was 81 years (interquartile range 25-75: 73-87) and 53% were male. Diabetics were younger, more often male, with higher prevalence of ischemic etiology and also presented more prevalence of heart failure with reduced ejection fraction. Congestion was the most prevalent clinical profile at admission in both diabetics and nondiabetics without significant differences. Mean length of stay was 6 days in each group. There were no significant differences in hospital mortality:6.3% vs 6.6 % in nondiabetics and diabetics respectively. At one-year follow-up mortality was 35.77% in nondiabetics and 29.3% in diabetics (P: 0.046).

History of chronic kidney disease, age, valvular disease, average patient comorbidities, systolic blood pressure at admission, mechanical ventilation and use of intravenous inotropes were predictors of in-hospital death at the univariate analysis. At multivariate analysis including all the significant predictors in the univariate and diabetes; age, valvular disease, systolic blood pressure at admission, mechanical ventilation, and intravenous inotropes remained as independent predictors (Table 2). As regards 1-year mortality after discharge: age, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, valvular disease, history of chronic heart failure, atrial fibrillation, average patient comorbidities, systolic blood pressure at admission, mechanical ventilation, severe admission profile, and the use of intravenous inotropes at in-hospital period were associated with mortality at univariate analysis. At

TABLE 1. Baseline characteristics

	TOTAL n: 1004	Non DBT n: 747 (74.4%)	DBT n: 257 (25.6%)	*P*
Gender (male)	532 (53%)	369 (49.4%)	163 (63.4%)	<**0.001**
Age (years), median (IQR)	81 (73-87)	83 (75-88)	77 (69-83)	<**0.001**
Hypertension	794 (79%)	571 (76.4%)	223 (86.8%)	<**0.001**
Dyslipidemia	363 (36%)	234 (31.3%)	129 (50.2%)	<**0.001**
Chronic Kidney Disease	241 (24%)	172 (23%)	69 (26.8%)	NS
COPD	159 (15.8%)	106 (14.2%)	53 (20.6%)	**0.008**
Arterial disease	123 (12.2%)	77 (10.31%)	46 (17.9%)	**0.001**
Ischemic heart disease	335 (33.4%)	215 (28.8%)	120 (46.7%)	<**0.001**
Valvular disease	211 (21%)	176 (23.5%)	35 (13.6%)	<**0.001**
History of chronic heart failure	582 (58%)	425 (56.9%)	157 (61%)	NS
Atrial fibrillation	325 (32.4%)	254 (34%)	71 (27.6%)	**0.03**
Coronary etiology	258 (25.7%)	158 (21.1%)	100 (38.9%)	<**0.001**
Admission depressed ejection fraction	486 (49.9%)	340 (47%)	146 (58.2%)	**0.001**
Avg patient comorbidities, median (IQR)	4 (2-5)	3 (2-5)	5 (4-6)	<**0.001**
Congestion at admission	646 (64.3%)	488 (65.3%)	158 (61.5%)	NS
Severe presentation profile	358 (35.6%)	259 (34.7%)	99 (38.5%)	NS
Systolic blood pressure at admission, median (IQR)	140 (120-170)	140 (120-170)	143 (130-180)	**0.016**

COPD, chronic obstructive pulmonary disease.

multivariate analysis: age, chronic obstructive pulmonary disease, systolic blood pressure at admission, severe admission profile, and the use of intravenous inotropes at in-hospital period remains as independent predictors (Table 3).

For the PS matching, the analysis was restricted to 378 patients, 189 (50%) diabetics and 189 (50%) nondiabetics. In this analysis, baseline characteristics were equally distributed between both study groups (Table 4). In the hospital phase there were no differences in the rate of use of diuretics, inotropes, intravenous vasodilators, or mechanical ventilation assistance (Fig 1). In addition, there were no significant differences at one-year mortality between diabetics and nondiabetics for the prespecified subgroups (Fig 2). Also, there were no significant differences in hospital mortality: 5.8% vs 4.76% for nondiabetics and diabetics respectively. At 1 year follow-up mortality was 35.4% in nondiabetics and 28.9% in diabetics (*P*: NS; Table 5). We also analyzed the PS score

TABLE 2. Univariate and multivariate analysis of in-hospital mortality

	Univariate analysis			Multivariate analysis		
	In-hospital death: 64 (6.37%)	**Alive at discharge: 940 (93.63%)**	**P**	**Odds ratio**	**95% CI**	***P***
Gender (male)	32 (50%)	500 (53.19%)	0.35	–	–	–
Age (years), median (IQR)	85 (79.5-88)	81 (73-87)	**0.005**	**1.05**	**1.02-1.08**	**0.0007**
Diabetes	17 (26.5%)	240 (25.5%)	0.47	1.37	0.67-2.78	0.37
Hypertension	49 (76.56%)	745 (79.2%)	0.35	–	–	–
Dyslipidemia	25 (39%)	338 (36%)	0.35	–	–	–
Chronic Kidney Disease	27 (42.2%)	214 (22.8%)	<**0.001**	1.93	0.99-3.72	0.0501
COPD	12 (18.75%)	147 (15.6%)	0.3	–	–	–
Arterial Disease	9 (14%)	114 (12.1%)	0.38	–	–	–
Ischemic heart disease	19 (29.7%)	316 (33.6%)	0.3	–	–	–
Valvular disease	25 (39%)	186 (19.8)	<**0.001**	**1.93**	**1-3.71**	**0.047**
History of chronic heart failure	43 (67.2%)	539 (57.3%)	0.07	–	–	–
Atrial fibrillation	23 (35.9%)	302 (32.1%)	0.3	–	–	–
Coronary etiology	14 (21.9%)	244 (26%)	0.28	–	–	–
Admission depressed ejection fraction	35 (54.7%)	463 (50%)	0.27	–	–	–
Avg patient comorbidities, median (IQR)	4 (3-6)	4 (2-5)	**0.017**	0.98	0.82-1.18	0.89
Systolic blood pressure at admission, median (IQR)	130 (119-150)	140 (121-170)	**0.006**	**0.98**	**0.98-0.99**	**0.021**
Mechanical ventilation	32 (50%)	166 (17.6%)	<**0.001**	**4.17**	**2.23-7.78**	≤**0.001**
Severe admission profile	23 (35.9%)	335 (35.6%)	0.52	–	–	–
Intravenous inotropes	32 (50%)	89 (9.5%)	<**0.001**	**5.58**	**2.99-10.4**	≤**0.001**

TABLE 3. Univariate and multivariate analysis of 1 year after discharge mortality

	Univariate analysis			Multivariate analysis		
	1 year follow up death: 290 (34%)	**Alive at 1 year: 561 (65.9%)**	***P***	**Odds ratio**	**95% CI**	***P***
Gender (male)	130 (44.8%)	261 (46.5%)	0.36	–	–	–
Age (years), median (IQR)	83 (75-88)	79 (71-85)	**<0.0001**	**1.04**	**1.02-1.05**	**≤0.0001**
Diabetes	65 (22.4%)	157 (28%)	**0.046**	0.81	0.55-1.19	0.29
Hypertension	230 (79.3%)	444 (79.14%)	0.51	–	–	–
Dyslipidemia	130 (36.7%)	207 (36.9%)	0.5	–	–	–
Chronic Kidney Disease	81 (27.9%)	109 (19.4%)	**0.003**	1.41	0.97-2.05	0.067
COPD	65 (22.4%)	74 (13.2%)	**0.0004**	**1.73**	**1.14-2.63**	**0.009**
Arterial Disease	51 (14.4%)	64 (11.4%)	0.1	–	–	–
Ischemic heart disease	126 (35.6%)	181 (32.2%)	0.16	–	–	–
Valvular disease	97 (27.4%)	102 (18.2%)	**0.0007**	1.34	0.92-1.95	0.12
History of chronic heart failure	223 (63%)	316 (56.3%)	**0.02**	1.06	0.76-1.49	0.7
Atrial fibrillation	128 (36.1%)	168 (30%)	**0.03**	0.91	0.64-1.27	0.59
Coronary etiology	93 (26.3%)	145 (25.8%)	0.47	–	–	–
Admission depressed ejection fraction	181 (51.6%)	276 (50.1%)	0.35	–	–	–
Avg patient comorbidities, median (IQR)	4 (3-6)	4 (2-5)	**0.0003**	1.05	0.94-1.19	0.33
Systolic blood pressure at admission, median (IQR)	140 (120-160)	145 (126-170)	**0.001**	**0.99**	**0.98-0.99**	**0.0005**
Mechanical ventilation	88 (24.8%)	94 (16.7%)	**0.0019**	1.39	0.94-2.05	0.09
Severe admision profile	138 (39%)	186 (33.1%)	**0.04**	**1.66**	**1.17-2.36**	**0.0045**
Intravenous inotropes	76 (21.5%)	37 (6.6%)	**<0.0001**	**3.03**	**1.88-4.88**	**≤0.001**

TABLE 4. Propensity score matched cohort

	TOTAL n: 378	No DBT n: 189 (50%)	DBT n: 189 (50%)	*P*
Gender (male)	221 (58.47%)	110 (58.20%)	111 (58.73%)	0.5
Age (years), median (IQR)	79 (70-84)	79 (69-85)	78 (71-83)	0.43
Hypertension	317 (83.86%)	155 (82%)	162 (85.7%)	0.2
Dyslipidemia	173 (45.77%)	84 (44.44%)	89 (47.09%)	0.33
Chronic Kidney Disease	97 (25.66%)	48 (25.4%)	49 (25.93%)	0.5
COPD	70 (18.52%)	36 (19.05%)	34 (18%)	0.44
Arterial Disease	53 (14%)	21 (11.1%)	32 (16.9%)	0.07
Ischemic heart disease	152 (40.2%)	73 (38.6%)	79 (41.8%)	0.3
Valvular disease	58 (15.34%)	31 (16.4%)	27 (14.3%)	0.33
History of chronic heart failure	210 (55.5%)	105 (55.5%)	105 (55.5%)	0.5
Atrial fibrillation	108 (28.57%)	50 (26.46%)	58 (30.7%)	0.21
Coronary etiology	118 (31.2%)	55 (29.1%)	63 (33.3%)	0.21
Admission depressed ejection fraction	209 (55.3%)	101 (53.44%)	108 (57.14%)	0.26
Avg patient comorbidities, median (IQR)	4 (3-6)	4 (3-6)	5 (3-6)	0.27
Congestion at admission	245 (64.8%)	126 (66.6%)	119 (62.9%)	0.25
Acute pulmonary edema at admission	124 (32.8%)	56 (29.6%)	68 (36%)	0.11
Severe presentation profile	133 (35.2%)	63 (33.3%)	70 (37%)	0.25
Systolic blood pressure at admission, median (IQR)	140 (127-170)	140 (121-170)	140 (130-180)	0.34

COPD, chronic obstructive pulmonary disease.

value for diabetes in all patients and this was not associated with in-hospital or 1-year mortality.

Discussion

An outstanding observation from our analysis on real world evidence refers to the fact that diabetes does not impact on prognosis (neither in hospital nor at 1-year follow-up).

Our study shares similarities with other databases in that admission criteria are nonrestrictive and broad. This explains in part the characteristics of the population admitted with heart failure: advanced age, similar gender distribution, high prevalence of comorbidities, and a substantial number of patients with preserved ejection fraction. Many of these variables

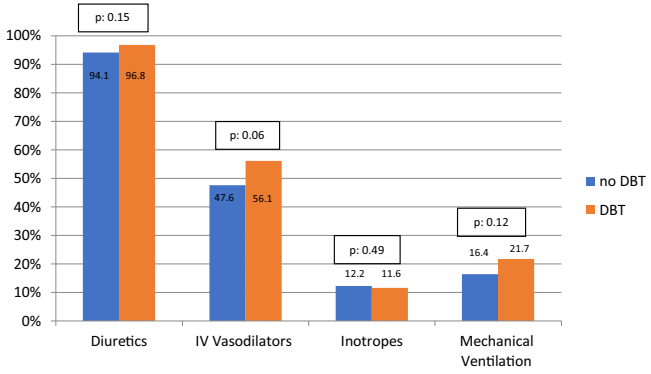

FIG 1. In-hospital therapy.

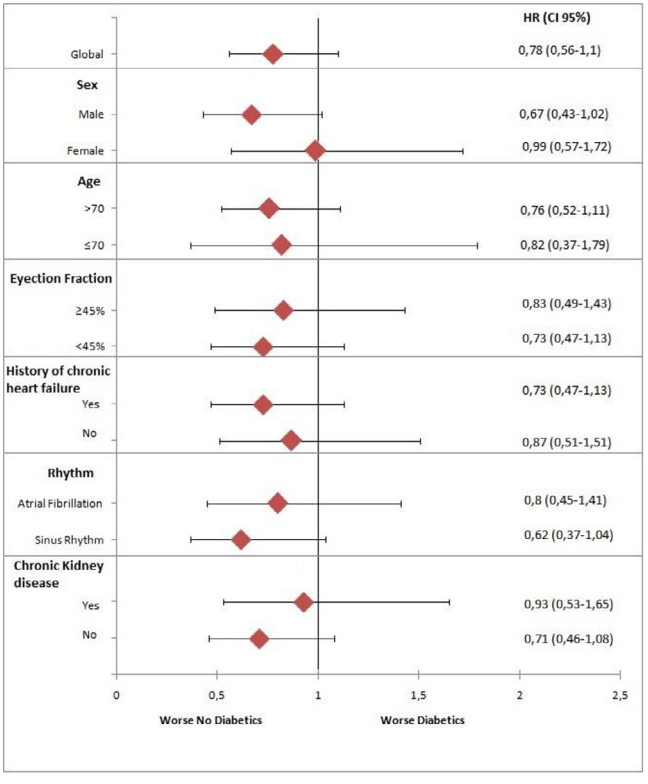

FIG 2. Subgroup analysis of 1-year mortality between diabetics and nondiabetics.

TABLE 5. In-hospital and 1-year mortality in the propensity score matched groups

	TOTAL n: 378	No DBT n: 189 (50%)	DBT n: 189 (50%)	Hazard ratio (95% CI)	*P*
In-hospital mortality	20 (5.29%)	11 (5.8%)	9 (4.76%)	0.8 (0.32-2)	0.4
1 year mortality (n: 358)	115 (32.12%)	63 (35.4%)	52 (28.9%)	0.77 (0.54-1.12)	0.18

are associated with a poor outcome, mainly at 1 year.[15] In this context, it is reasonable that the prognostic impact of diabetes could be reduced by the burden of other diseases.

Current available data are principally derived from interventional trials or heart failure registries in which patients were younger than in our study[16-22] thus explaining the differences with the present analysis.

The prevalence of diabetes is a critical issue. It ranges from 13%[20,23] to 50%[11,24] in different series. In our population it reached 25%. This broad range of prevalence can be attributed to heterogeneous population characteristics and different diagnostic criteria of diabetes. Diagnostic criteria based on patient report probably underestimates the true prevalence of the disease.

Due to a dichotomic analysis, every patient not assigned as diabetic was considered nondiabetic and this could attenuate clear cut differences between both populations. In this sense, using HbA1C as a diagnostic tool would allow identification of diabetics who ignore their condition improving diagnostic accuracy.[25,26]

In our study, diabetic patients compared to nondiabetics were: younger, with more prevalence of coronary artery disease and worse systolic ventricular function; however, this was not associated with a different outcome either in propensity score or multivariate analysis.

In reviewing literature, prognostic significance of diabetes is variable among different authors but in general it is associated with a worse outcome.

MacDonald et al in Glasgow[20] found a prevalence of diabetes of only 13%. Surprisingly diabetic patients evidenced a better outcome during the in-hospital phase that reversed in long term follow-up. In addition the deleterious consequences of diabetes seemed to be more prominent in younger patients.

A comparative subanalysis of the EVEREST trial[17] in patients with a median age of 66 years and 40% diabetics found that diabetes was associated with a worse outcome (all-cause mortality and cardiovascular mortality plus heart failure hospitalization) over a median follow up of 9.9 months.

The outcome of diabetes was analyzed in the European Registry of Heart Failure[11]; mean age was 69 years, lower than in our study and also the diagnostic criteria were more sensitive. Therefore the prevalence of diabetes was 49%. In this case diabetes was associated with a worse outcome both in short and long term follow-up.

The OPTIMIZE[18] is a large registry that compared diabetics vs nondiabetics. The prevalence of diabetes was 42%; diabetics were younger (71 vs 74) and with a high prevalence of coronary etiology. No differences in hospital mortality were observed. At 60 and 90 days follow-up, there were no mortality differences, but diabetes was associated with rehospitalization.

Kosiborod et al[27] analyzed a cohort of more than 50.000 patients more than 65 years admitted with decompensated heart failure. In this group glycemia was not a predictor of worse outcome at 30 days and at 1 year.

These studies encompass different patient populations in terms of age and prevalence of diabetes (due to patient characteristics and diagnostic criteria). As regards the influence of age on prognosis, small differences between diabetics and nondiabetics were observed with age increase. This is probably explained by the higher prevalence of comorbidities and frailty with increasing age that attenuates the prognostic impact of diabetes. This was also seen in our population of diabetic patients. Despite the younger age of diabetics than their nondiabetic counterparts the overall population was old and therefore with similar outcomes.

These results should be interpreted with caution due to several limitations. Diabetes adjudication criteria relied on patient reference and this could have underestimated the exact prevalence of the disease. In addition, the number of patients recruited was probably insufficient to detect significant difference at 1 year.

In conclusion, in this study diabetes had no impact on prognosis. It is possible that advanced age played a major role in outcomes in the overall population thus making less relevant the presence of diabetes.

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