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CLINICAL STUDY

# Absence of interaction of diabetes mellitus with chronic kidney disease on mortality in acute heart failure

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**Abstract**

*Objectives*: To evaluate how chronic kidney disease (CKD) and diabetes mellitus (DM) influence in-hospital mortality in patients urgently admitted for acute heart failure (HF). *Methods*: We used data from the Spanish "Minimum Basic Data Set" for 2006–2007 to evaluate clinical differences and crude mortality rates for patients having versus non-having CKD or DM. We tested pre-specified predictive factors of in-hospital mortality in a multivariate logistic regression model, which included age, sex, CKD, DM, acute respiratory failure, a modified Charlson Comorbidity Index—excluding CKD/DM- and a CKD × DM-interaction variable. *p* Values < 0.05 were considered significant. *Main findings*: A total of 275,176 episodes of acute HF were analyzed (47.9% male, mean age 76.2 ± 12.8 years). CKD patients ($N = 25{,}174$, 9.1%) were older (78.4 ± 10.1 vs. 76.0 ± 13.1 years; $p < 0.001$) and more frequently had coexisting medical conditions. DM patients ($N = 88{,}994$, 32.3%) more often had vascular risk factors and CKD (11.4% vs. 8.1%; $p < 0.001$). Overall in-hospital mortality rate for admitted HF patients was 10.4%. Mortality was lower for DM versus non-DM patients (9.2% vs. 11.0%; $p < 0.001$), but higher for CKD versus non-CKD patients (14.1% vs. 10.0%; $p < 0.001$). No interaction effect was found between CKD and DM on survival for a HF episode (odds ratio; OR = 1.01, 95% CI: 0.91–1.10; *p* for interaction = 0.73). DM remained protective (OR = 0.85, 95% CI: 0.82–0.87; $p < 0.001$), while CKD was associated with increased mortality (OR = 1.46, 95% CI: 1.39–1.53; $p < 0.001$). *Conclusions*: In patients urgently admitted for HF, the association of CKD with higher in-hospital mortality was homogeneous irrespectively of the absence or presence of DM.

**Keywords**

Chronic, diabetes mellitus, hospitalization, heart failure, mortality, renal insufficiency, type 2 diabetes

**History**

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## Introduction

Episodes of acute heart failure (HF) remain a major health problem.[1] The clinical burden of HF can be aggravated by the fact that chronic HF patients very often have coexisting medical conditions, such as chronic kidney disease (CKD) and diabetes mellitus (DM). The prevalence rate of DM in patients admitted for HF can be as high as 42%[2] and that of CKD can reach 60%.[3]

Prevalent CKD and DM can influence the in-hospital mortality rate associated with HF. It has been reported that CKD[4] and worsening of baseline renal function[5] are associated with higher mortality rates in HF patients. Furthermore, although some studies had shown higher mortality rates in diabetic patients admitted for HF,[6–8] additional work has found lower mortality rates.[9,10] Ritchie et al.[11] described a higher mid-term mortality rate in ambulatory chronic HF patients with both CKD and DM. However, few studies have evaluated the combined simultaneous effect of prevalent CKD and DM on the short-term prognosis of hospitalized HF patients. If an interaction effect between both conditions were present, we might then identify a higher-risk group of patients who would benefit from specific strategies designed to improve their outcomes. The possibility of an interaction effect, that is, an eventual heterogeneous influence when both CKD and DM are present on survival for HF, has not been adequately addressed in the literature.

Therefore, as our main hypothesis, we evaluated the possible interaction effect of CKD with DM on mortality in patients admitted to the hospital for an episode of acute HF.

## Methods

### Data and variables

We analyzed data coming from the Minimum Basic Data Set (in Spanish, Conjunto Mínimo Básico de Datos) for patients urgently admitted for acute HF to internal medicine departments as reported by all hospitals within the Spanish National Health System between 2006 and 2007. We got the data on

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special request for research purposes. The Minimum Basic Data Set is a mandatory information system to which all hospitals must submit periodic reports to the Ministry of Health, Social Services and Equality.[12] These databases use the coding system established by the International Classification of Diseases, 9th Revision Clinical Modification (ICD-9-CM).[13] We grouped patient discharges by associated diseases according to the classification system of Diagnosis-Related Groups, version 21.0 (SPSS Inc., Version 15.0, Chicago, IL). We removed patient identifiers as to keep patients' identities anonymous. We preserved data confidentiality at all times. Given the anonymous and compulsory nature of the database, patients' informed consent was not deemed necessary.

We had access to basic individual information, such as age and gender, and to several outcomes (mortality and length of stay). We selected cases of urgent hospitalization with a HF code as the primary or a secondary diagnosis (ICD-9-CM: 398.91, 404, 402.11, 402.91 and 428–428.9). We identified patients coded for CKD (ICD-9-CM: 585–586.99, 582.0–582.9, 583.0–583.7 and 588.0–588.9) or DM (ICD-9-CM: 250.00–250.99) upon admission according to responsible physicians' criteria. We specifically evaluated CKD irrespectively of superimposed acute renal failure, since both diagnoses were not mutually exclusive. We also collected information on additional variables using the same methodology: hypertension, anemia, smoking status, atrial fibrillation, ischemic heart disease, obesity, hypercholesterolemia, heart valve disease and acute respiratory failure during admission.

We calculated the Charlson Comorbidity Index, developed in 1987 to show the association between coexisting medical conditions and one-year mortality rates in different cohorts of patients.[14] The index, which has been adapted for use in administrative databases,[15] evaluates the presence of 19 different medical conditions, with a weight of 1–6 and a total score that varies between 0 and 37. Scores higher than 2 have been associated with a one-year mortality rate greater than 50%.[14] A limitation of this is that the Charlson Comorbidity Index does not discriminate between acute and chronic renal disease. We used modified indexes excluding DM and CKD as appropriate in the univariate analyses, since people having these conditions unevenly add to the score when compared with people not having these diagnoses.

### Statistical analyses

We performed descriptive analyses of the data and compared demographic and clinical variables between CKD versus non-CKD patients and between DM versus non-DM patients. We used the chi-square test for categorical variables with the Yates correction if needed and the Student *t*-test for quantitative variables. We analyzed crude mortality rates for patients having versus non-having CKD or DM.

We then evaluated pre-specified predictive factors of in-hospital mortality in a multivariate logistic regression model according to significance in the univariate analyses or due to clinical relevance. It included age, sex, a categorical ($\leq 2$ vs. $>2$) modified Charlson Comorbidity Index that excluded the terms CKD and DM, onset of acute respiratory failure, CKD, DM and a first-order interaction CKD-by-DM variable. The odds ratios (ORs) and 95% confidence intervals (95% CI) were estimated using the regression coefficients. In a secondary analysis, we excluded the interaction variable to evaluate main effects.

In additional sensitivity analyses, we used a continuously distributed modified Charlson Comorbidity Index that excluded the items CKD and DM and a categorical variable ($<75$ vs. $\geq 75$ years) for age distribution of the population instead of continuously distributed age.

A $p$ value $<0.05$ was considered statistically significant in the association tests. We used SPSS version 15.0 (released 2006, SPSS Inc., Chicago, IL) for the statistical analyses.

### *A priori* statistical power calculations

Based on our prevalence rates for CKD (around 9%) and for DM (around 32%), for an estimated 10% in-hospital mortality rate, and according to a previously reported 50% higher mortality rate for CKD patients[4] and 16% lower mortality rate for the diabetic population,[9] we estimated that our sample size would have 80% statistical power to detect a CKD-by-DM interaction OR below 1.15 and ORs below 1.06 for main effects at a two-tailed type I error rate of $<0.05$.

## Results

### Baseline characteristics of the whole population of acute HF patients

During the study period (2006–2007), a total of 275,176 admissions for acute HF were reported in hospitals from our country, which represented around 11.9% of the total number of admissions. Of them, 25,174 (9.1%) had been coded for CKD and 88,994 (32.3%) for DM. Demographic baseline characteristics are listed in Table 1.

### CKD patients admitted for acute HF

CKD diagnosis in acute HF was more frequent in older patients ($78.4 \pm 10.1$ vs. $76.0 \pm 13.1$ years; $p < 0.001$) (Table 1; Supplemental Digital Content Table S1 lists coding for CKD according to age) and in men (54.5% vs. 47.2%; $p < 0.001$). Obesity was less prevalent in CKD patients (9.3% vs. 12.2%; $p < 0.001$). When comparing both groups, more CKD patients had a modified Charlson Comorbidity Index $>2$ (not including CKD; 35.8% vs. 28.1%; $p < 0.001$).

### DM patients admitted for acute HF

DM diagnosis in acute HF was more frequent in females (55.6% vs. 50.4%; $p < 0.001$), but age did not differ between DM and non-DM patients ($76.3 \pm 9.6$ vs. $76.2 \pm 14.2$ years, mean $\pm$ standard deviation; $p = 0.07$) (Table 1; Supplemental Digital Content Table S1 lists coding for DM according to age). More DM subjects were obese (17.5% vs. 9.3%; $p < 0.001$), had hypertension (44.9% vs. 33.7%; $p < 0.001$) and CKD (11.4% vs. 8.1%; $p < 0.001$). In addition, more DM patients admitted for HF had a modified Charlson Comorbidity Index $>2$ (not including diabetes), reflecting a higher number of coexisting conditions (26.7% vs. 21.9%; $p < 0.001$).

Table 1. Descriptive characteristics of our whole population admitted for heart failure (HF) and stratified by chronic kidney disease (CKD) and diabetes mellitus (DM) status.

| | HF, global $N = 275,176$ | HF/CKD $N = 25,174$ | HF/non-CKD $N = 250,002$ | $p$-Value (CKD vs. non-CKD) | HF/DM $N = 88,994$ | HF/non-DM $N = 186,182$ | $p$-Value (DM vs. non-DM) |
|---|---|---|---|---|---|---|---|
| Age in years, mean ± SD | 76.2 ± 12.8 | 78.4 ± 10.1 | 76.0 ± 13.1 | <0.001 | 76.3 ± 9.6 | 76.2 ± 14.2 | 0.067 |
| Male sex, % | 47.9 | 54.5 | 47.2 | <0.001 | 44.3 | 49.5 | <0.001 |
| Hypertension, % | 37.3 | 34.1 | 37.7 | <0.001 | 44.9 | 33.7 | <0.001 |
| Diabetes mellitus, % | 32.3 | 40.2 | 31.6 | <0.001 | NA | NA | NA |
| Chronic kidney disease | 9.1 | NA | NA | NA | 11.4 | 8.1 | <0.001 |
| Obesity, % | 11.9 | 9.3 | 12.2 | <0.001 | 17.5 | 9.3 | <0.001 |
| Hypercholesterolemia, % | 15.1 | 14.4 | 15.2 | 0.001 | 22.7 | 11.5 | <0.001 |
| Smokers, % | 7.4 | 3.5 | 7.7 | <0.001 | 5.7 | 8.1 | <0.001 |
| Atrial fibrillation, % | 40.4 | 41.2 | 40.4 | 0.010 | 40.6 | 40.4 | 0.329 |
| Coronary artery disease, % | 19.1 | 25.3 | 18.5 | <0.001 | 24.4 | 16.5 | <0.001 |
| Heart valve disease, % | 8.9 | 9.0 | 8.9 | 0.561 | 8.3 | 9.1 | <0.001 |
| Acute respiratory failure, % | 42.4 | 28.4 | 43.9 | <0.001 | 36.0 | 45.4 | <0.001 |
| Anemia, % | 14.9 | 27.9 | 13.6 | <0.001 | 17.0 | 13.8 | <0.001 |
| Charlson Comorbidity Index > 2, %[a] | 31.1 | 35.8 | 28.1 | <0.001 | 26.7 | 21.9 | <0.001 |
| Hospitalization days, mean ± SD | 8.9 ± 7.9 | 9.9 ± 9.0 | 8.8 ± 7.8 | <0.001 | 9.2 ± 7.9 | 8.7 ± 7.9 | <0.001 |
| Mortality rate, % | 10.4 | 14.1 | 10.0 | <0.001 | 9.2 | 11.0 | <0.001 |

Notes: HF, heart failure; CKD, chronic kidney disease; DM, diabetes mellitus; SD, standard deviation; and
[a]Modified Comorbidity Charlson Indexes exclude CKD when comparing CKD versus non-CKD patients and DM when comparing DM versus non-DM patients.
$p$ Values <0.05 denote statistical significance.

Table 2. Crude mortality rates for patients admitted for acute decompensated heart failure (HF) according to prevalent chronic kidney disease (CKD) and diabetes mellitus (DM) status.

| | DM present | DM absent |
|---|---|---|
| CKD present | Total: $N = 10,110$<br>Die: $N = 1223$ (12.1%) | Total: $N = 15,064$<br>Die: $N = 2328$ (15.5%) |
| CKD absent | Total: $N = 78,884$<br>Die: $N = 6966$ (8.8%) | Total: $N = 171,118$<br>Die: $N = 18,109$ (10.6%) |

Notes: DM, diabetes mellitus and CKD, chronic kidney disease.
$p$ Values< 0.001 for all comparisons.

Table 3. Interaction test in a multivariate logistic regression model including pre-specified predictive factors of in-hospital mortality.

| | In-hospital mortality | | |
|---|---|---|---|
| Multivariate model | Odds ratio | 95% CI | $p$ Value |
| Number of subjects | | $N = 275,176$ | |
| Sex, male | 0.99 | 0.96–1.01 | 0.29 |
| Age, years | 1.04 | 1.03–1.04 | <0.001 |
| Modified Charlson Comorbidity Index[a] | 1.74 | 1.69–1.79 | <0.001 |
| Acute respiratory failure | 1.59 | 1.55–1.63 | <0.001 |
| CKD | 1.46 | 1.39–1.53 | <0.001 |
| DM | 0.85 | 0.82–0.87 | <0.001 |
| CKD-by-DM | 1.01 | 0.94–1.10 | 0.73 |

Notes: CI, confidence interval; CKD, chronic kidney disease; DM: diabetes mellitus.
[a]Modified Charlson Comorbidity Index: it excludes CKD and DM.
$p$ Values <0.05 denote statistical significance.

## Mortality in acute HF patients

In-hospital mortality rate for the overall cohort of HF patients was 10.4% (Table 1), and was significantly lower in DM patients (9.2% vs. 11.0%; $p < 0.001$), but higher for CKD patients (14.1% vs. 10.0%; $p < 0.001$) (Tables 1 and 2). These results persisted significant after adjusting for older age (data not shown).

We then evaluated pre-specified predictive factors of in-hospital mortality in a multivariate logistic regression model, which included age, sex, a categorical ($\leq 2$ vs. $> 2$) modified Charlson Comorbidity Index that excluded the terms CKD and DM, acute respiratory failure, CKD, DM and a first-order interaction CKD-by-DM term. No interaction effect was found between CKD and DM on survival for a HF episode (OR = 1.01, 95% CI: 0.91–1.10; $p$ for interaction = 0.73). DM remained protective (OR = 0.85, 95% CI: 0.82–0.87; $p < 0.001$), while CKD was associated with increased mortality (OR = 1.46, 95% CI: 1.39–1.53; $p < 0.001$) (Table 3). Results were almost identical when excluding the interaction term of the model (Supplemental Digital Content Table S2).

We got consistently similar ORs and $p$ values in the sensitivity analyses done accounting for age categorically distributed and a continuous modified Charlson Comorbidity Index (data not shown).

## Discussion

In this study, we describe the general characteristics of the subset of the Spanish population urgently admitted for HF during a two-year period of time. In-hospital mortality rate for HF admission was slightly higher than in some previously reported similar cohort studies, but the mean age of our population was higher[16], and a higher number of patients were found to have coexisting medical conditions, such as CKD and DM.[17]

As reflected by the non-significant interaction $p$ value, the effect of combined CKD and DM resulted from simply adding the separate contribution of each condition, thus ruling out any heterogeneity effect. Had we eventually detected an interaction effect, that might have explained a

hypothetical relevant blunting of the protective effect on behalf of DM by coexisting CKD, thus allowing the identification of a special high-risk group of HF patients.

CKD patients suffered from a higher number of medical conditions. Their mortality rate was a 46% higher than for non-CKD patients, reinforcing previously highlighted data in the literature.[18] It is worth mentioning that CKD coding in our database very probably reflects long-standing impaired renal function confirmed by attending physicians, as opposed to reversible renal dysfunction during admission, which is amenable to improve and has been evaluated as a predictive factor in HF by other authors.[19]

Our diabetic patients admitted for HF presented with a higher number of established cardiovascular risk factors and coexisting medical conditions. In spite of this, in-hospital mortality rate turned out a significantly 15% lower for the diabetic population. The explanation for this remains speculative. It has been suggested that diabetic patients go to hospital earlier after the development of HF symptoms, or that physicians are more prone to assist DM patients earlier when registered in the emergency department due to the prioritization inherent to the triage process at registering, but unknown patho-physiological mechanisms could also be operating.

We were concerned about a possible worse baseline glycemic control for CKD patients, with less stringent HbA1C targets. This tailored clinical management might have otherwise had a negative impact on mortality.[20] However, the persistently protective effect for DM in the model even after including the interaction variable seemed to rule out this possibility.

Our database includes data from the whole population of our country in an unbiased manner; our large sample size conferred a high statistical power to detect associations; we had access to information on a wide range of potential confounders and ascertainment of the main outcome—mortality—was accurately obtained from the National data submitted to the authorities. Yet, some limitations of this study should be pointed out: we relied on administrative data, which might have included coding errors or low codification for some of the variables (i.e., obesity); however, we have extensively used this database for other research purposes,[21,22] and similar administrative databases have been used seeking results for hypotheses related to ours.[9] Data pertained to internal medicine departments and might not exactly reflect data from other different medical specialties. Residual unaccounted confounding might partly explain the significant associations, as we were not able to adjust for some possibly underreported conditions, such as functional status, socio-sanitary situation or cognitive status. Finally, some other variables could not be accounted for, such as left ventricular ejection factor, etiology of the renal insufficiency, type, duration and severity of DM, the type of drug therapies prescribed during admission, body mass index or malnutrition. The groups of diabetic and non-diabetic patients may not be balanced regarding the percentage of undernourished patients and malnutrition has been reported to increase cardiovascular mortality in CKD patients.[23]

## Conclusion

In summary, the influences that both CKD and DM exert on prognosis are homogeneous in HF patients admitted to the hospital. The diabetic patients who are admitted to the hospital for HF seem to have a significantly lower probability of dying during hospital admission, whereas CKD patients admitted for HF apparently have significantly higher mortality rates.

## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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## Supplementary material available online

Supplemental digital content Table S1 and S2