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Letter to the Editor

## Impact of diabetes mellitus on survival in South East Asian patients with congestive heart failure due to left ventricular systolic dysfunction

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### Abstract

**Objective:** We assessed the impact of diabetes mellitus on survival in South East Asian patients with congestive heart failure.

**Methods:** 1668 consecutive patients with chronic heart failure (age  $65 \pm 13$  years, ejection fraction  $28 \pm 12\%$ , 67% male) were followed up for  $36 \pm 12$  months. 837 patients (50.2%) were diabetic and 1076 patients (65%) had ischemic cardiomyopathy. Primary outcome measure was all-cause mortality. Secondary outcome measures were heart failure readmission and the composite end-point.

**Results:** There were 223 (13.4%) deaths and 112 (7%) heart failure readmissions. Ischemic cardiomyopathy, renal failure, hypertension, cerebrovascular disease, peripheral vascular disease, and hyperlipidemia were more prevalent in diabetics (all  $p < 0.01$ ). All-cause mortality (17.3% vs 9.4%), heart failure readmission (8.1% vs 5.3%) and the composite end-point (21.9% vs 12.6%) occurred more frequently in diabetics (all  $p < 0.05$ ). Diabetes was an independent predictor of all-cause mortality (OR = 1.70,  $p = 0.01$ ), as were ischemic cardiomyopathy (OR = 1.85,  $p = 0.01$ ), hypertension (OR = 1.78,  $p = 0.01$ ), GFR (OR = 0.98,  $p < 0.01$ ), and beta-blocker use (OR = 0.55,  $p < 0.01$ ).

**Conclusions:** In spite of advances in heart failure treatment, the presence of diabetes mellitus significantly worsens survival in South East Asian patients with congestive heart failure.

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**Keywords:** Diabetes mellitus; Congestive heart failure; Death; Readmission; South East Asian population

### 1. Introduction

Diabetes mellitus (DM) is more prevalent in patients with congestive heart failure (CHF) (15–25%), compared to the

general population (4–6%) [1]. DM also increases the risk of developing CHF, the poorer the control, the greater the risk [1]. In patients with established CHF, randomized trials show that DM increases morbidity and mortality, especially in those with ischemic cardiomyopathy [2,3].

However, these studies were conducted in predominantly Caucasian CHF populations, most were retrospective [2–4], and some were conducted in a clinical trial setting [2,3], and hence may not represent CHF patients in the general population. Some studies were also performed before widespread use of ACEIs and beta-blockers [2,3], and the findings may not be applicable currently.

**Abbreviations:** CHF, congestive heart failure; DM, diabetes mellitus; LV, Left ventricular; EF, ejection fraction; NHYA, New York Heart Association; ACEI, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker; GFR, glomerular filtration rate.

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45 Accordingly, we conducted this prospective observational  
46 study to evaluate the impact of DM on survival in a large  
47 population of South East Asian patients with CHF on  
48 contemporary medical therapy.

## 49 2. Materials and methods

### 50 2.1. Study population

51 The study population consisted of 1668 consecutive CHF  
52 patients enrolled into the National Healthcare Group Multi-  
53 disciplinary Heart Failure Disease Management Program in  
54 Singapore from October 2002 to September 2004. The  
55 current study included approximately 20% of the CHF  
56 patients mentioned in an earlier report [4]. Patients were  
57 classified as diabetic if they were on oral hypoglycemic  
58 agents or insulin, or had a history of elevated ( $>126$  mg/dl)  
59 fasting blood glucose documented on at least two separate  
60 occasions. Patients were classified as having ischemic  
61 cardiomyopathy if they had previous myocardial infarction,  
62 severe multivessel coronary artery disease on coronary  
63 angiography, or previous coronary revascularization (percu-  
64 taneous coronary intervention or coronary bypass surgery).

### 65 2.2. Study design

66 In this prospective observational study, baseline demo-  
67 graphics and clinical data including information on medica-  
68 tions, New York Heart Association (NYHA) functional class  
69 and quality of life measures were recorded. Information on  
70 the number of hospitalizations and deaths were collected  
71 prospectively. Patients were followed up at one to six  
72 monthly intervals. Cardiac medications were uptitrated  
73 accordingly until maximal tolerated doses. This study was  
74 approved by the hospital ethics committee.

### 2.3. Statistical analysis

75

Continuous variables in text and tables are expressed as  
76 mean  $\pm$  standard deviation and compared by Kruskal–Wallis  
77 test. Chi-square test was used to test associations between  
78 categorical variables. Multiple logistic regression was applied  
79 to identify independent predictors of all-cause mortality.  
80

Survival analysis was performed using the Kaplan–Meier  
81 method. The log rank test was used to compare differences  
82 between strata. Statistical analysis was performed using the  
83 statistical package Stata 9.0 (Stata Corp, Texas, USA). Statistical  
84 significance was defined as a two tailed  $p$  value of  $<0.05$ .  
85

## 3. Results

86

1668 consecutive patients with CHF were followed up for  
87 a mean duration of 36 months. Follow-up was complete for  
88 all study patients. 837 patients (50.2%) were diabetic and  
89 1076 patients (65%) had ischemic cardiomyopathy. At the  
90 end of follow-up, 223 patients (13.4%) died and 112 patients  
91 (7%) were readmitted for CHF.  
92

Ischemic cardiomyopathy (77.5% vs 60.7%), hyperten-  
93 sion (81.6% vs 59.9%), cerebrovascular disease (15.5% vs  
94 8.2%), peripheral vascular disease (4.2% vs 1.2%) and  
95 hyperlipidemia (66.2% vs 46.6%) were more prevalent  
96 among diabetics (all  $p < 0.01$ ).  
97

At 3 years, all-cause mortality (17.3% vs 9.4%), CHF  
98 readmission (8.1% vs 5.3%) and the composite end-point  
99 (21.9% vs 12.6%) were greater in diabetics compared to non-  
100 diabetics (all  $p < 0.05$ ). Diabetic patients had a worse all-  
101 cause mortality free survival compared to non-diabetics (log  
102 rank = 18.48,  $p < 0.001$ ) (Fig. 1).  
103

The univariate and multivariate predictors of all-cause  
104 mortality are shown in Table 1. In a logistic regression  
105 analysis, DM was an independent predictor of all-cause  
106

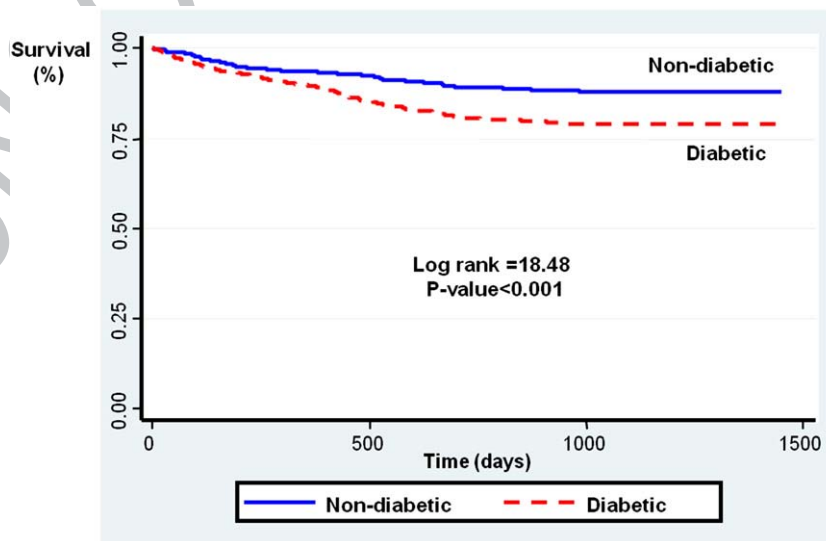


Fig. 1. Kaplan–Meier survival curves comparing all-cause mortality free survival between diabetic and non-diabetic CHF patients.

t1.1 Table 1  
t1.2 Univariate and multivariate predictors of all-cause mortality in the study population

t1.3 Variables	Total cohort (n=1668)	Dead (n=223)	Alive (n=1445)	Univariate <i>p</i> -value OR (95% CI)	Multivariate <i>p</i> -value OR (95% CI)
t1.4 <i>Demographics</i>					
t1.5 Age: mean (sd) yrs	64.9 (13.0)	70.5 (11.0)	64.2 (12.9)	<0.01 1.04 (1.03–1.06)	0.12 1.02 (1.00–1.04)
t1.6 Sex (proportion males)	67.0%	61.4%	67.9%	0.06 0.75 (0.56–1.01)	
t1.7 Single	8.2%	4.0%	8.8%	0.02 0.43 (0.22–0.87)	0.28 0.61 (0.25–1.49)
t1.8 Income (>\$1000)	41.8%	40.8%	42.0%	0.85 1.03 (0.66–1.42)	
t1.9 Education	25.7%	19.3%	26.7%	0.02 0.66 (0.46–0.94)	0.89 1.04 (0.62–1.74)
t1.10 <i>Race</i>					
t1.11 Chinese (reference)	65.1%	62.8%	65.5%	1.00	
t1.12 Malay	20.7%	22.0%	20.5%	0.54 1.12 (0.79–1.59)	
t1.13 Indian	12.3%	12.6%	12.2%	0.76 1.07 (0.69–1.66)	
t1.14 Others	1.9%	2.6%	1.8%	0.34 1.56 (0.63–3.87)	
t1.15 <i>Comorbidities</i>					
t1.16 Ischemic cardiomyopathy	67.2%	80.7%	65.0%	<0.01 2.25 (1.59–3.20)	0.01 1.85 (1.14–2.99)
t1.17 Diabetes	50.2%	65.0%	47.9%	<0.01 2.02 (1.51–2.71)	0.01 1.70 (1.19–2.66)
t1.18 Hypertension	68.4%	76.7%	69.9%	0.04 1.42 (1.02–1.97)	0.01 1.78 (1.13–2.54)
t1.19 Hyperlipidemia	54.5%	57.0%	56.3%	0.86 1.03 (0.77–1.36)	
t1.20 CVA	11.5%	18.8%	10.8%	<0.01 1.92 (1.32–2.79)	0.66 1.12 (0.68–1.84)
t1.21 PVD	2.6%	3.6%	2.6%	0.38 1.42 (0.65–3.08)	
t1.22 CRF	10.0%	13.9%	9.8%	0.06 1.49 (0.98–2.27)	
t1.23 Previous CABG	5.7%	4.5%	5.0%	0.75 0.90 (0.45–1.76)	
t1.24 Previous PCI	5.4%	4.5%	4.8%	0.82 0.92 (0.47–1.82)	
t1.25 Previous AICD	0.9%	0.5%	0.8%	0.61 0.59 (0.08–4.57)	
t1.26 <i>EF</i>					
t1.27 0–19%	23.5%	26.4%	23.0%	0.11 1.60 (0.89–2.87)	
t1.28 20–29%	37.5%	42.0%	36.8%	0.10 1.59 (0.91–2.77)	
t1.29 30–40%	27.2%	22.8%	27.9%	0.66 1.14 (0.63–2.06)	
t1.30 >40% (reference)	11.8%	8.8%	12.3%	1.00	
t1.31 GFR: mean (sd) ml/min	53.4 (29.7)	38.5 (21.8)	55.9 (30.2)	<0.01 0.97 (0.96–0.98)	<0.01 0.98 (0.97–0.99)
t1.32 <i>NYHA class</i>					
t1.33 I (reference)	16.8%	8.2%	18.2%	1.0	1.0
t1.34 II	57.2%	57.3%	57.4%	<0.01 2.22 (1.32–3.71)	0.19 1.48 (0.82–2.65)
t1.35 III and IV	25.9%	34.6%	24.5%	<0.01 3.13 (1.83–5.37)	0.27 1.33 (0.70–2.55)

(continued on next page)

t1.64 Table 1 (continued)

t1.65 Variables	Total cohort (n=1668)	Dead (n=223)	Alive (n=1445)	Univariate <i>p</i> -value OR (95% CI)	Multivariate <i>p</i> -value OR (95% CI)
t1.66 <i>Medications</i>					
t1.67 ACEI/ARB	79.1%	75.0%	79.5%	0.18 0.77 (0.53–1.13)	t1.68
t1.69 Spironolactone	52.3%	50.0%	52.9%	0.49 0.89 (0.38–1.24)	t1.70
t1.71 Beta-blockers	64.3%	50.6%	66.0%	<0.01 0.53 (0.38–0.73)	t1.72 0.55 (0.37–0.81)

t1.73 Income = monthly income >SGD\$1000; single = unmarried; education = greater than secondary school level education; CVA = cerebrovascular accident; PVD = peripheral vascular disease; CRF = chronic renal failure; EF = ejection fraction; GFR = glomerular filtration rate; NYHA = New York Heart Association; CABG = coronary bypass surgery; PCI = percutaneous coronary intervention; AICD = implantable defibrillator; ACEI/ARB = angiotensin converting enzyme inhibitor/angiotensin receptor blocker; OR = odds ratio; 95% CI = 95% confidence intervals.

107 mortality (OR=1.70, *p*=0.01), as were ischemic cardiomyo-  
108 pathy (OR=1.85, *p*=0.01), hypertension (OR=1.78,  
109 *p*=0.01), GFR (OR=0.98, *p*<0.01), and beta-blocker use  
110 (OR=0.55, *p*<0.01).

#### 111 4. Discussion

112 Our study is the first in reported literature to prospectively  
113 evaluate the prognostic impact of DM in a large population  
114 of South East Asian patients with CHF on contemporary  
115 medical therapy. In spite of advances in CHF treatment, DM  
116 was associated with an increased risk for all-cause mortality,  
117 CHF readmission and the composite end-point.

118 Mortality rate in our study (13.4%), was lower compared  
119 to previous studies by Domanski et al. (32%) and Kamalesh  
120 et al. (32%) [2,6]. Our patients had less advanced CHF at  
121 enrollment, with a lower proportion in NYHA class III/IV  
122 (25%) compared to patients in de Groote's (28%) and Varela-  
123 Roman et al.'s (67%) studies [5,7]. Greater use of beta-  
124 blockers and/or ACEI/ARB (64% and 79%) in our patients,  
125 compared to those in the SOLVD (25% and 50%) and BEST  
126 trials (50% and 91%), and the benefits of a multidisciplinary  
127 CHF disease management program could also have  
128 contributed to the better outcome [2,3].

129 Our diabetic CHF patients had a 84% higher all-cause  
130 mortality rate, 53% higher CHF readmission rate and 74%  
131 higher composite end-point rate compared to non-diabetics,  
132 confirming the findings of earlier studies [2,3,6,7]. Kamalesh  
133 et al.'s study [6] demonstrated a 30% higher mortality in  
134 diabetic compared to non-diabetic CHF patients. Varela-  
135 Roman et al.'s study [7] showed a worse survival at 1, 3 and  
136 5 years among diabetics (78.9%, 57.2% and 39.0%),  
137 compared to non-diabetics (84.7%, 68.3% and 52.7%). In  
138 De Groote et al.'s study [5], DM was not associated with  
139 increased cardiovascular mortality in the overall study cohort.  
140 Although DM predicted an increased cardiovascular mortal-  
141 ity in the ischemic cardiomyopathy subgroup, DM was  
142 surprisingly associated with decreased cardiovascular mortal-  
143 ity in those with non-ischemic cardiomyopathy. This  
144 finding together with the lower prevalence of ischemic  
145 cardiomyopathy in their study compared to ours (45% vs

65%) may have reduced the negative prognostic impact of  
DM in their overall study population.

The reasons for a negative impact of DM on survival in  
patients with CHF are multifactorial. In our study, DM was  
associated with an increased prevalence of other comorbidities  
such as ischemic cardiomyopathy, renal failure, cerebrovascular  
disease, peripheral vascular disease and hypertension. Due to  
more extensive coronary disease, diabetics with acute coronary  
syndromes have higher reinfarction rates, and hence greater  
long-term mortality [8]. Recurrent myocardial infarction could  
also worsen outcome in CHF patients with DM. Furthermore, a  
specific diabetic cardiomyopathy may occur in some patients  
[1], and certain anti-diabetic drugs especially insulin and  
glitazone may adversely affect myocardial function [9].

#### 160 5. Conclusions

In spite of advances in CHF treatment, the presence of  
DM worsens survival in South East Asian patients with CHF,  
which reinforces the need for aggressive preventive  
strategies to improve outcomes in these patients.

#### 165 Acknowledgements

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