

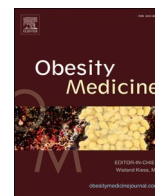


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Diabetic women: Inpatient mortality risk before SARS-CoV-2

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ABSTRACT

Background: Type 2 diabetes mellitus is a major driver of mortality worldwide. To assess the risk factors associated with diabetes that increase in-hospital mortality.

Methods: A retrospective cohort study was conducted using the National Hospital Morbidity with a sample of 3904 diabetic women admitted (2018–2019) in public hospitals, in Portugal. The type of comorbidities and the severity of the main disease – type 2 diabetes mellitus – was assessed based on the International Classification of Diseases (ICD-9) and Disease Staging. Cox proportional hazard was used to assess mortality during hospitalization. Mortality rates and mortality risk were the main outcome measures.

Results: In a total of 3904 diabetic women three hundred and eighty-nine (10.0%) died during hospitalization. Comorbidities bacterial pneumonia and coronary artery disease contributed 73% [Hazard ratio (HR) 1.73, 95% CI 1.32–2.27] and 37% [HR 1.37, 95% CI 1.03–1.81] respectively, to the risk of mortality, as did age over 65 years and severity 3 of the main disease.

Conclusions: Women with advanced type 2 diabetes mellitus, advanced age, and with comorbidities such as pneumonia and coronary artery disease admitted urgently have a higher risk of mortality during hospitalization.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a growing public health problem ([International Diabetes Federation, 2019](#)), resulting in part of the morbidity and mortality. By 2021, about 6.7 million adults (12%) over the age of 20 years will die from diabetes or its complications, excluding the mortality risks associated with SARS-CoV-2 ([International Diabetes Federation, 2021](#)). About 1/3 (32.6%) of all diabetes deaths occur in people of working age (<60 years) ([International Diabetes Federation, 2021](#)). Between the ages of 60 and 69 years, approximately 600.000 diabetic women die and increases to 2.000.000 from the age of 70 years ([International Diabetes Federation, 2021](#)).

When mortality is adjusted for age, mortality in the diabetic population doubles compared with those without diabetes so some factors associated with T2DM may contribute to this increase, such as cardiovascular risk factors ([Rawshani et al., 2017](#); [Einarson et al., 2018](#)) such as hypertension and dyslipidemia. Some studies ([Peters et al., 2014](#); [Wang et al., 2019](#)) have established a relationship between excessive risk of cardiac death in diabetic women with higher risk of cardiovascular heart disease than men, especially after menopause ([Peters et al., 2014](#); [De Paoli and Werstuck, 2020](#)).

Community-acquired pneumonia has been identified as one of the key factors associated with mortality ([Kofteridis et al., 2016](#);

Abbreviations: T2DM, type 2 diabetes mellitus; NSH, National Service Health.

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Huang et al., 2021) in diabetic women with advanced age and often requires hospital admission (Lopez-de-Andres et al., 2021). Some authors (Chen et al., 2015) justify this by the fact that diabetes inhibits host histiocytic cell defense functions, such as chemotaxis, phagocytosis, and bactericidal activity. According to Smerdely (2020), diabetes does not have a negative impact on mortality or length of stay in hospitalized older adults from data derived from hospital administrative records.

Data regarding the outcomes of hospitalization after community-acquired pneumonia and cardiovascular diseases in diabetic women remain scarce in Portugal. This study aimed to investigate the mortality rates and associated factors that increase the mortality risks of hospitalized diabetic Portuguese women.

2. Materials and methods

In this retrospective cohort study, 3904 diabetic women aged ≥ 18 years from 45 public hospitals in Portugal who were diagnosed with T2DM were included. We used medical data from the National Hospital Morbidity database between December 25, 2018, and December 29, 2019. We used (1) the Diagnosis Related Group (DRG) to identify T2DM episodes (DX codes 250,00) as the main diagnosis and (2) Disease Staging (Thomson Reuteurs, 2009) to identify the severity of T2DM, and comorbidities. Exclusion criteria were patients with type 1 diabetes mellitus, gestational diabetes, and patients with T2DM admitted to oncology and mental health hospitals. The selected comorbidities are those that represent a major burden for diabetes.

2.1. Statistical analysis

The baseline characteristics were expressed as mean \pm standard deviation for continuous variables and as the frequency with percentages for categorical variables. The continuous variables were compared using Student's t-test, and the categorical variables were compared using the chi-squared test. The Kaplan–Meier method and log-rank test were used to assess mortality according to the age and duration of hospitalization, and the Cox proportional hazard model was used to predict mortality by adjusting the covariates to account of effect age, length of hospitalization, the severity of T2DM (stage 1, stage 2, and stage 3) (Thomson Reuteurs, 2009), the comorbidities (essential hypertension, stroke, dyslipidaemia, obesity, bacterial pneumonia, coronary artery disease, congestive heart failure, renal failure, other disorders of the respiratory system, rhino, adeno, and corona virus infections, malignant neoplasm of colon and rectum, malignant neoplasm of the lungs, bronchi, or mediastinum, and malignant neoplasm of stomach), type of treatment (medical and surgery), and type of admission (urgent and elective). OR values were presented with their respective 95% confidence intervals (CI). The p-value set to indicate statistical significance was $p < 0.05$. All statistical analyses were performed using the IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY: IBM Corp.).

Table 1
Baseline characteristics of hospitalized diabetic women.

Characteristics	All subjects (3904)	Survivors (3515)	Non-survivors (389)
Age, n (%)			
Mean \pm SD	73.36 \pm 12.29	72.47 \pm 13.39	81.38 \pm 9.07
Median, IQR	76, 18-89	75, 65-82	83, 78-87
<65	954 (24.4)	929 (97.4)	25 (2.6)
≥ 65	2950 (75.6)	2586 (87.7)	364 (12.3)
Severity of type 2 diabetes mellitus, n (%)			
Stage 1	237 (6.1)	231 (97.5)	6 (2.5)
Stage 2	1364 (34.9)	1313 (96.3)	51 (3.7)
Stage 3	2303 (59.0)	1971 (85.6)	332 (14.4)
Comorbidity, n (%)			
Essencial hypertension	3101 (79.4)	694 (86.4)	109 (13.6)
Stroke	3464 (88.7)	378 (85.9)	62 (14.1)
Dyslipidemia	2792 (71.5)	1023 (92.0)	89 (8.0)
Obesity	3123 (80.0)	731 (93.6)	50 (6.4)
Bacterial pneumonia	3693 (94.6)	145 (68.7)	66 (31.3)
Coronary artery disease	3477 (89.1)	368 (86.2)	59 (13.8)
Congestive heart failure	3621 (92.8)	240 (84.8)	43 (15.2)
Renal failure	3684 (94.4)	189 (85.9)	31 (14.1)
Other disorders of the respiratory system	3706 (94.9)	160 (80.8)	38 (19.2)
Rhino, adeno, and corona virus infections	3790 (97.1)	95 (83.3)	19 (16.7)
Malignant neoplasm of colon and rectum	3857 (98.8)	40 (85.1)	7 (14.9)
Malignant neoplasm of the lungs, bronchi, or mediastinum	3894 (99.7)	9 (90.0)	1 (10.0)
Type of treatment, n (%)			
Medical	3219 (82.5)	2878 (89.4)	341 (10.6)
Surgery	685 (17.5)	637 (93.0)	48 (7.0)
Type of admission, n (%)			
Urgent	3343 (85.6)	2965 (88.7)	378 (11.3)
Elective	561 (14.4)	550 (98.0)	11 (2.0)

3. Results

3.1. Study population

A total of 3904 female T2DM patients aged 18 years admitted to public hospitals were selected from the NHS database; their mean age was 73.36 years, and the mean duration of hospitalization was 10.99 ± 14.18 days. The main comorbidities present in non-surviving diabetic women were bacterial pneumonia in 31.3% and other respiratory system diseases in 19.2% of patients. Of 3219 patients undergoing medical treatment, 341 patients (10.6%) did not survive, 48 patients (7.0%) undergoing surgical treatment did not survive, and 378 (11.3%) patients who had urgent hospitalization did not survive. Patient characteristics are shown in [Table 1](#).

3.2. Mortality rate and related risk during the length hospitalization

The average mortality rate was 9.9% and the average length of hospital stay was 12.2 ± 17.4 days in non-survivor patients. The risk of mortality during hospitalization increased with age ≥ 65 years (RR 0.21, 95% CI 0.14–0.31), in stage 3 severity of type 2 diabetes mellitus (RR 0.17, 95% CI 0.07–0.38), in those who underwent medical treatment (RR 0.66, 95% CI 0.49–0.88) and were admitted urgently to the hospital (RR 0.17, 95% CI 0.09–0.31). The related mortality risk was 1.56 (95% CI 0.23–10.22) when patients were obese and increased to 1.24 (95% CI 0.19–8.10) when they had dyslipidemia, however these results were not statistically significant ([Table 2](#)).

3.3. Risk factors for mortality in diabetic women

The adjusted mortality rate increased to 3.57 (95% CI 2.37–5.36) when diabetic patients were 65 years or older and 3.63 (95% CI 1.61–8.16) when the severity of type 2 diabetes mellitus was in stage 3 compared to stage 1 of the main disease, and when patients were admitted urgently. In the presence of bacterial pneumonia and coronary artery disease, the mortality rate of patients increased to 1.73 (95% CI 1.32–2.27) and 1.37 (95% CI 1.03–1.81), respectively ([Table 3](#)). As the length of hospitalization by age, the survival rate of patients decreased significantly (Log rank $< p.0001$) ([Fig. 1](#)). The ROC curve showed that it is a useful indicator of in-hospital mortality (0.759) ([Fig. 2](#)).

4. Discussion

This study showed the clinical significance of bacterial comorbidities pneumonia and coronary artery disease, including T2DM severity and advanced age being associated with mortality during hospitalization, based on Portuguese national data for a study period from 2018 to 2019, before SARS-CoV-2. The hazard model and survival analysis could be used as tools for risk stratification of these patients to improve the medical care strategy to prevent adverse events associated with Diabetes mellitus. Diabetic women with

Table 2
Mortality rate and related risk by patient characteristics.

Characteristics	Cases/Controls (n)	Mortality rate (%)	RR (95% CI)
Age, n			
< 65 (Ref.)	25/929	2.6	
≥ 65	364/2586	12.3	0.21 (0.14–0.31) ^a
Severity of type 2 diabetes mellitus, n			
Stage 1 (Ref.)	6/231	2.5	
Stage 2	51/1313	3.7	0.67 (0.29–1.56)
Stage 3	332/1971	14.4	0.17 (0.07–0.38) ^a
Comorbidity, n			
Malignant neoplasm of the lungs, bronchi, or mediastinum (Ref.)	1/9	0.03	
Malignant neoplasm of colon and rectum	7/40	0.18	0.67 (0.09–4.86)
Rhino, adeno, and corona virus infections	19/95	0.50	0.60 (0.08–4.02)
Other disorders of the respiratory system	38/160	1.03	0.52 (0.07–3.41)
Renal failure	31/189	0.84	0.70 (0.10–4.68)
Congestive heart failure	43/240	1.19	0.65 (0.10–4.31)
Coronary artery disease	59/368	1.70	0.72 (0.11–4.71)
Bacterial pneumonia	66/145	1.79	0.31 (0.04–2.07)
Obesity	50/731	1.60	1.56 (0.23–10.22)
Dyslipidemia	89/1023	3.19	1.24 (0.19–8.10)
Stroke	62/378	1.79	0.70 (0.10–4.62)
Essencial hypertension	109/694	3.51	0.73 (0.11–4.76)
Type of treatment, n			
Surgery (Ref.)	48/637	7.01	
Medical	341/2878	10.59	0.66 (0.49–0.88) ^a
Type of admission, n			
Elective (Ref.)	11/550	1.96	
Urgent	378/2965	11.31	0.17 (0.09–0.31) ^a

^astatistically significant.

RR, Related risk; CI, Confidence interval; Ref., Reference group.

Table 3
Hazard ratio of mortality.

Characteristics	Mortality adjusted HR (95% CI)
Age	
<65	Reference
≥65	3.57 (2.37–5.36)
Severity of type 2 diabetes mellitus	
Stage 1	Reference
Stage 3	3.63 (1.61–8.16)
Comorbidity	
Coronary artery disease (without)	Reference
With	1.37 (1.03–1.81)
Bacterial pneumonia (without)	Reference
With	1.73 (1.32–2.27)
Type of admission	
Elective	Reference
Urgent	2.79 (1.52–5.12)

HR, Hazard ratio; CI, Confidence interval.

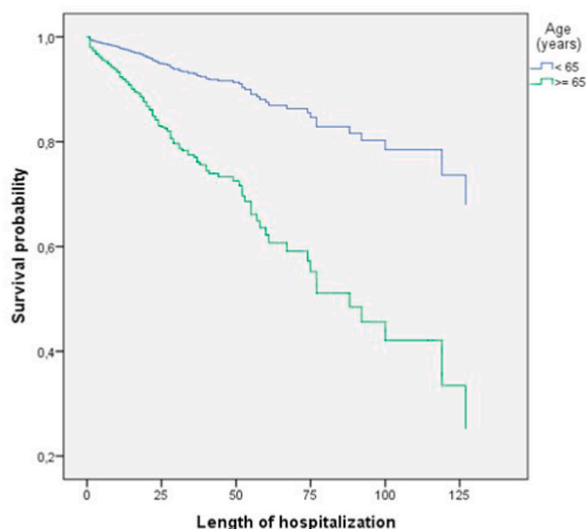


Fig. 1. Kaplan-Meier survival curves stratified by age of diabetic women.

comorbidities such as bacterial pneumonia and coronary artery disease increase their risk of mortality to 73% and 37% and decrease their survival during prolonged hospitalization, as well as when admitted urgently. The greater the age of diabetic women and the severity of T2DM the greater the risk of increased mortality. [Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration, 2014](#) As the burden of disease increases, so do mortality and medical costs ([Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration, 2014](#); [Khan et al., 2020](#); [Li et al., 2021](#)). Control of diabetes and blood glucose is crucial in diabetic patients to decrease hospitalization and mortality rates ([Erener, 2020](#); [Hine et al., 2017](#); [Mor et al., 2017](#)).

The mortality rate in our study was 9.9%. Based on another study ([Emami et al., 2021](#)), the mortality rate in patients with diabetes infected with SARS-CoV-2 was 10.9% (8.6% without other comorbidities and 12.1% with comorbidities). One explanation for this similar rate is the use of metformin ([Hariyanto and Kurniawan, 2020](#)) and GLP-1R agonists ([Pang et al., 2021](#)) and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), which have benefits in reducing mortality from COVID-19 ([Pang et al., 2021](#)). Contradicting these results, [Guo et al. \(2020\)](#) found a mortality rate of 16.5% in diabetic patients without other comorbidities justifying this with the fact that diabetics are more likely to be malnourished.

Studies have reported that patients with diabetes over the age of 65 have an increased risk of up to 1.4 for pneumococcal disease, including community-acquired pneumonia ([Cheng et al., 2020](#); [Torres et al., 2015](#)). Other studies have shown a significant association between admission glucose and the outcome of mortality from community-acquired pneumonia ([Jensen et al., 2017](#)), even in non-diabetic patients ([Lepper et al., 2020](#); [López-de-Andrés et al., 2017](#); [Wang et al., 2020](#)). However, the risk of diabetes-related pneumonia hospitalization is higher in those without other comorbidities and those with a longer duration of diabetes and/or poor blood glucose control (based on A1C levels) ([Torres et al., 2015](#)).

In our opinion, our results can be justified by (i) not introducing pneumococcal vaccines in diabetic patients only if they have underlying respiratory diseases, such as chronic obstructive pulmonary disease or severe asthma, regardless of age and (ii) delayed administration of appropriate antibiotic therapy in the emergency department. We think that pneumococcal vaccination should be

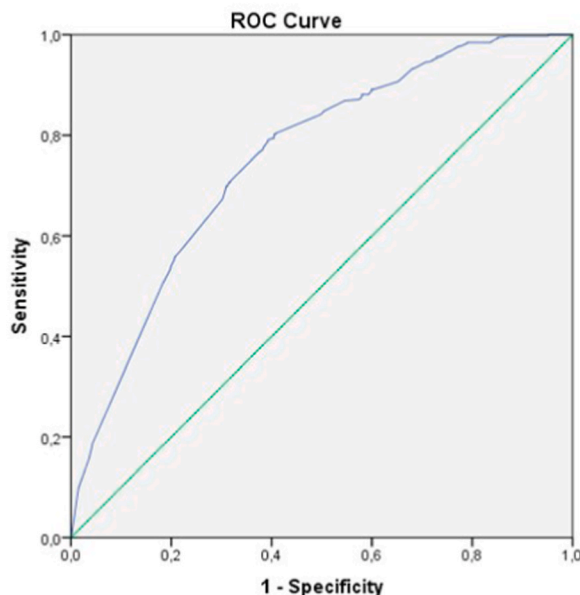


Fig. 2. Receiver operating characteristics curve for in-hospital mortality of diabetic women.

introduced for all diabetic patients from the age of 65, regardless of whether they have underlying respiratory diseases, in order to reduce the long-term risk of infection and there should be more effective protocols for antibiotic therapy in the emergency department and follow up during hospitalization.

Diabetes mellitus has been described as an important risk factor associated with mortality from coronary heart disease (particularly, when there is involvement of the left main coronary artery, stenosis of distal arterial segments, presence of atherosclerotic plaques with vascular and calcified thrombosis) (Bednarska et al., 2017), especially in postmenopausal (Miao Jonasson et al., 2020) women (Shaw et al., 2018; Wong et al., 2020). There is a correlation between the severity of glucose metabolism disturbances in patients without diabetes and in diabetic patients (poor glycemic control) and the risk of long-term mortality due to coronary heart disease (Dal Canto et al., 2019; Djupsjo et al., 2020; Rosengren, 2018). Other studies (Arnold et al., 2020; Gyldenkerne et al., 2019; Katsiki et al., 2020; Rezende et al., 2018) have shown that very tight control of glucose levels can reduce microvascular complications, but because of the risk of severe hypoglycemia the risk of coronary heart disease may increase.

We speculated that our results can be justified by (i) severe hypoglycemic episodes on admission to the emergency department, (ii) some patients may be on corticoid therapy which leads to increased hyperglycemia, so it is advisable during hospitalization to monitor glucose levels at least four times a day, and (iii) poor control of atherosclerosis for coronary artery disease in diabetic women with advanced T2DM severity.

5. Conclusions

In this retrospective cohort study using the National Hospital Morbidity, including severity 3 of type 2 diabetes mellitus, advanced age, and the comorbidities pneumonia and coronary artery disease were responsible for the mortality of diabetic women during hospitalization who were urgently hospitalized. In future work, we suggest conducting in-hospital mortality studies in diabetic women infected with SARS-CoV-2 in order to understand the characteristics that have contributed to their increased mortality in Portugal.

6. Limitations

Our study has several limitations. First, we could not analyse the clinical test results of glycosylated haemoglobin and blood glucose because it is not a hospital electronic medical record, as well as the patients' treatment. Second, we could not use the information on vaccination and smoking status from the administrative data. Third, we did not have access to the coronary artery obstruction score and how many of these patients underwent percutaneous revascularization. Finally, due to the cross-sectional design of this study and the use of administrative data, it cannot be applied to other populations.

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CRediT authorship contribution statement

Maria Cristina Carrondo: Conceptualization, Methodology, Software, Data curation, Writing – original draft, preparation,

Visualization, Investigation, Validation, and, Writing – review & editing, No funding received.

Declaration of competing interest

No conflict of interest.

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