Article

The "Diabetes Comorbidome": A Different Way for Health Professionals to Approach the Comorbidity Burden of Diabetes

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Abstract: (1) Background: The disease burden related to diabetes is increasing greatly, particularly in
older subjects. A more comprehensive approach towards the assessment and management of diabetes'
comorbidities is necessary. The aim of this study was to implement our previous data identifying and
representing the prevalence of the comorbidities, their association with mortality, and the strength of
their relationship in hospitalized elderly patients with diabetes, developing, at the same time, a new
graphic representation model of the comorbidome called "Diabetes Comorbidome". (2) Methods:
Data were collected from the RePoSi register. Comorbidities, socio-demographic data, severity and
comorbidity indexes (Cumulative Illness rating Scale CIRS-SI and CIRS-CI), and functional status
(Barthel Index), were recorded. Mortality rates were assessed in hospital and 3 and 12 months after
discharge. (3) Results: Of the 4714 hospitalized elderly patients, 1378 had diabetes. The comorbidities
distribution showed that arterial hypertension (57.1%), ischemic heart disease (31.4%), chronic renal
failure (28.8%), atrial fibrillation (25.6%), and COPD (22.7%), were the more frequent in subjects with
diabetes. The graphic comorbidome showed that the strongest predictors of death at in hospital and
at the 3-month follow-up were dementia and cancer. At the 1-year follow-up, cancer was the first
comorbidity independently associated with mortality. (4) Conclusions: The "Diabetes Comorbidome"
represents the perfect instrument for determining the prevalence of comorbidities and the strength
of their relationship with risk of death, as well as the need for an effective treatment for improving
clinical outcomes.

Keywords: "Diabetes Comorbidome"; comorbidities; dementia; cancer; in-hospital mortality; 3-month
mortality; 1-year mortality

1. Introduction

Diabetes represents a major clinical and public health problem. According to the Inter-
national Diabetes Federation, diabetes was estimated to affect 451 million adults globally
in 2017, 1 in 11 adults aged 20 to 79 years [1], with a projected increase to 693 million by
2045 [2]. At this time, numerically, diabetes, if it were a nation, would be the third most
populated country in the world [3]. The World Health Organization considers that diabetes
will constitute the seventh leading cause of mortality worldwide in 2030. [4].

The burden of diabetes has increased significantly in recent decades and will continue to soar in the next few decades, especially in the older population. More than 20% of people aged 65 years and older have diabetes [5], and, among them, about 60% have at least one comorbidity [6], and up to 40% have four or more comorbidities [7].

Diabetes-related comorbidities are associated with a patient's quality of life, health status, hospitalization, and outcomes [8–10]. It is worth outlining that, in 2017, disability-adjusted life-years (DALYs) associated with diabetes were 67.9 million, with a projection to 79.3 million in 2025. [11]. For this reason, some authors [6] have suggested a more comprehensive approach to the diagnosis, assessment, and management of diabetes and its comorbidities in older adults. In this sense, the utilization of a specific tool such as "comorbidome" could be helpful. The "comorbidome" is a graphic representation of the prevalence and the risk of death of comorbidities, similar to the solar system, developed by Divo and colleagues that identified the comorbidities related to an increased mortality in COPD [12].

According to the original design of Divo et al., the size of the circles expresses the prevalence of the single disease, while the distance to the center indicates the risk of death (the closer the comorbidity is to the center, the higher the risk of death).

The importance of this graphic representation lies in the fact that it is possible to identify the most relevant and statistically important comorbidity. Recent studies have used comorbidome to represent associations between sex-specific comorbidities and mortality in COPD subjects [13], as well as comorbidities associated with higher risk of acute heart failure [14] Moreover, other approaches, such as a comorbidity network, have been used to develop a diabetes-risk prediction model [15]

In the light of the above reasons, the aim of this study was to investigate the prevalence of diabetes in the REPOSI population, focusing on comorbidities, and to study their association with mortality in-hospital, at a 3-month follow-up, and at a 1-year follow-up, utilizing, concomitantly, a new graphic representation model of comorbidome.

2. Materials and Methods

2.1. Data Collection and Study Population

Data concerning patients were extracted retrospectively from the frame of the RePoSI project. REPOSI is an independent and collaborative register, organized by the Italian Society of Internal Medicine (SIMI), the Fondazione Ca' Granda Ospedale Maggiore Policlinico, and the Mario Negri Institute for Pharmacological Research. The introduction of the register was aimed at recruiting, monitoring, and evaluating older hospitalized patients aged 65 or over admitted to 102 Italian internal medicine and geriatric wards, with data collected every 2 years from 2008 onwards. The project's design has been previously described in detail [16,17]. For this study, all 4713 patients recorded in the REPOSI Register between 2010 and 2016 were considered. All patient with and without diabetes were included in the present analysis. All patients provided informed consent. Data were collected in full compliance with the Italian law on personal data protection, and the REPOSI study was approved by the Ethics Committee of each participating center.

2.2. Socio-Demographic and Clinical Characteristics

Socio-demographic variables including age, sex, body mass index, and information about lifestyles were considered. The following clinical characteristics were evaluated: comorbidities and performance in activities of daily living at hospital admission (measured by means of the Barthel Index [BI] [18,19] and severity and comorbidity index (assessed by the Cumulative-Illness-Rating-Scale CIRS-s and CIRS-c, respectively) [20]. The association between comorbidities and in-hospital, 3-month, and 1-year mortality was analyzed.

2.3. Statistical Analysis

Stata Statistical Software2016, Release14 (Stata-Corp, College-Station, TX, USA) was used for database management and all analyses. Quantitative variables were summarized

as mean (95% confidence intervals) and categorical variables as percentage. A Fisher's exact-test for contingency tables, a z test, and a non-parametric Mann–Whitney-U-test were used when appropriate. Comorbidity distributions with a prevalence equal to or greater than 3% were reported.

The "Diabetes Comorbidome"

The "comorbidome" is the graphic representation of comorbidities and their association with mortality by Odds Ratio [OR]. The diameters of colored circles are functions of the prevalence of each comorbidity. The dotted-line circle represents the OR equal to 1, the outside area corresponds to OR < 1, and the inner area corresponds to OR > 1. All circles associated with a statistically significant increase in mortality are fully inside the dotted orbit. Mortality is set at the center (with the higher value = 4). The proximity to the center represents the stronger positive association with mortality. The comorbidities are represented graphically clockwise, from the first with the highest prevalence to the last with the lowest prevalence in patients with diabetes. The association with mortality was represented during hospitalization (panel A), at a three-month follow-up (panel B), and at a 1-year follow-up (panel C).

3. Results

As previously described [9], of 4714 hospitalized patients aged 65 years or older recorded in the REPOSI register during the years 2010–2016, 1378 subjects were affected by diabetes (29.2%).

Patients with diabetes had a significantly higher cumulative illness rating scale for the evaluation of severity and comorbidity index (1.80 (1.78–1.81) vs. 1.60 (1.59–1.61) and 3.81 (3.69–3.92) vs. 2.69 (2.62–2.75), respectively, ($p < 0.0001$)) and a lower BI score (76.7 (75,0–78.4) vs. 78.3 (77.1–79.4) ($p = 0.0019$)). Notably, a deeper novel analysis of CIRS-SI and CIRS-CI according to age groups showed that patients with diabetes had CIRS-SI and CIRS-CI scores significantly higher for all age classes (Figures 1 and 2).
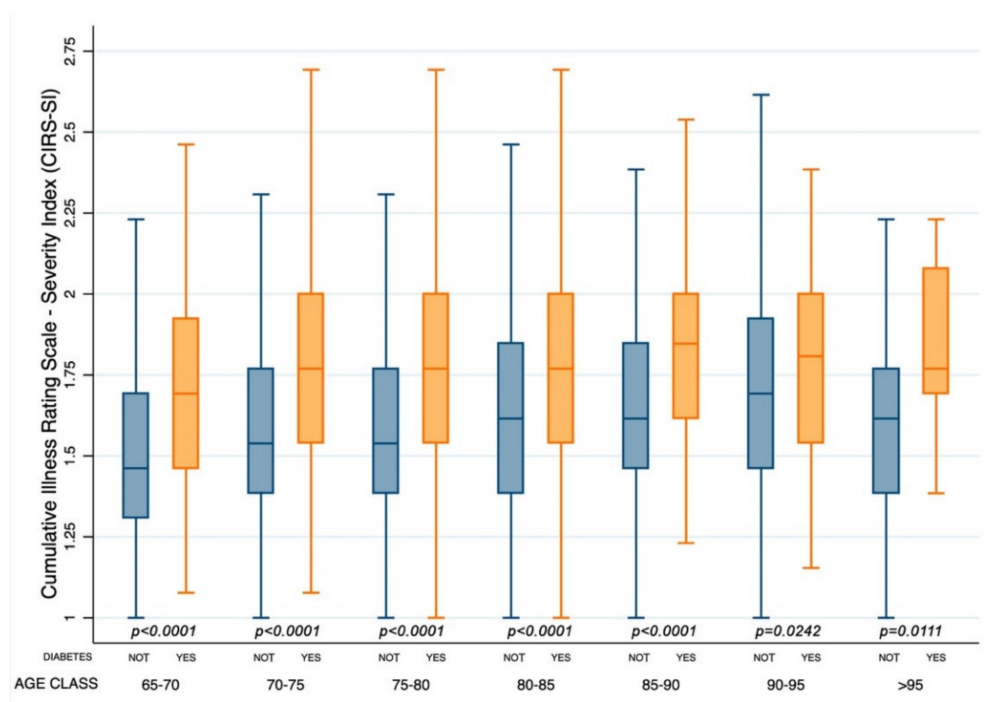
Figure 1. Box and whisker plot of the Cumulative Illness Rating Scale Severity Index [CIRS-SI] according to age classes in patients with or without diabetes (Yes or Not).
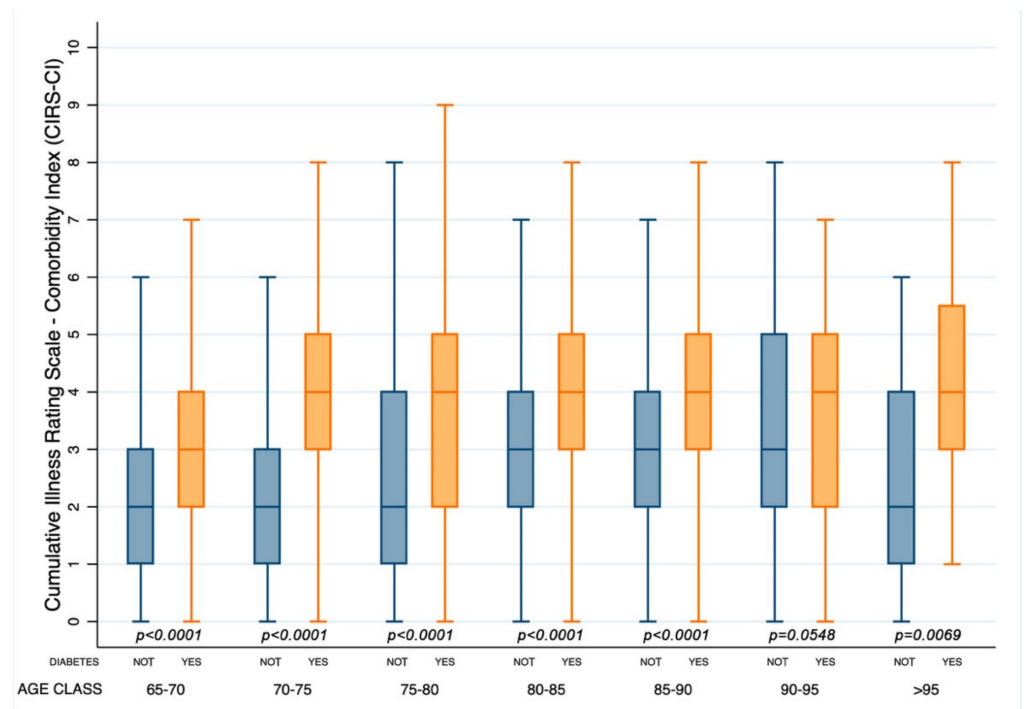
Figure 2. Box and whisker plot of the Cumulative Illness Rating Scale Comorbidity Index [CIRS-CI] according to age classes in patients with or without diabetes (Yes or Not).

Moreover, subjects with diabetes between 65 and 80 years old had Barthel Index scores lower than people without diabetes (Figure 3).
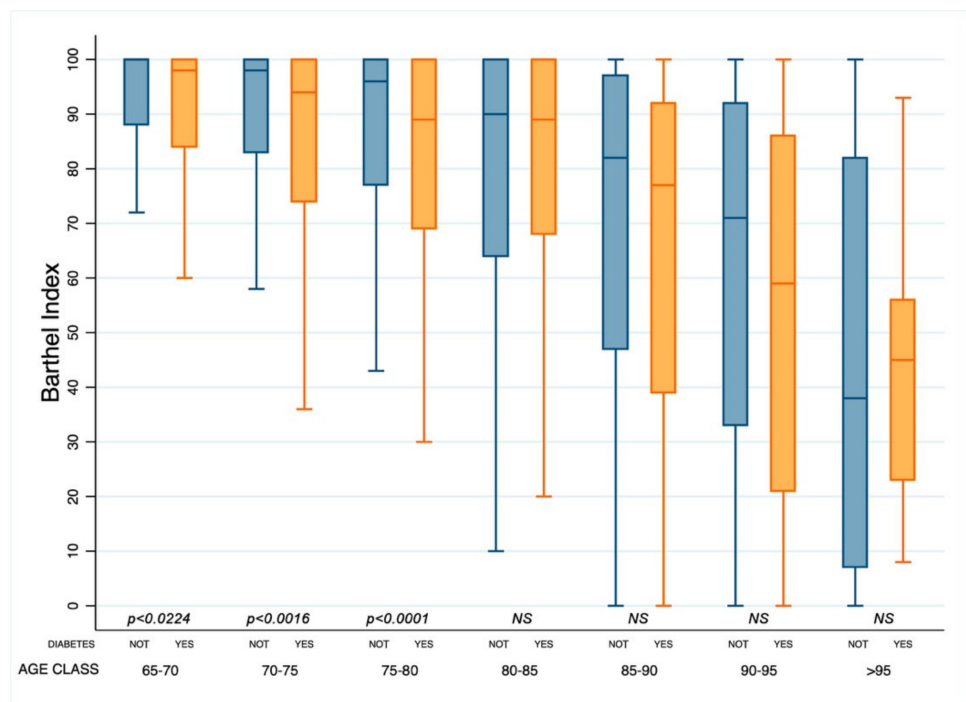
Figure 3. Box and whisker plot of the Barthel index according to age classes in patients with or without diabetes (Yes or Not). NS: not significant.

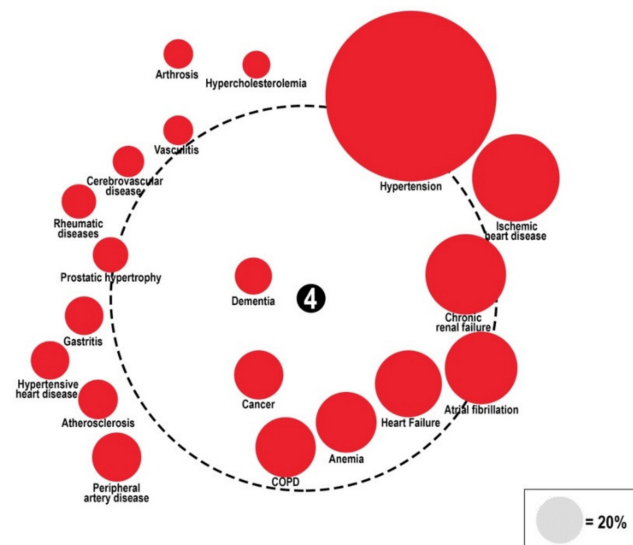To evaluate the relationship between comorbidities and mortality during hospitalization and at follow-up, a graphic representation called the comorbidome was plotted (Figures 4–6).
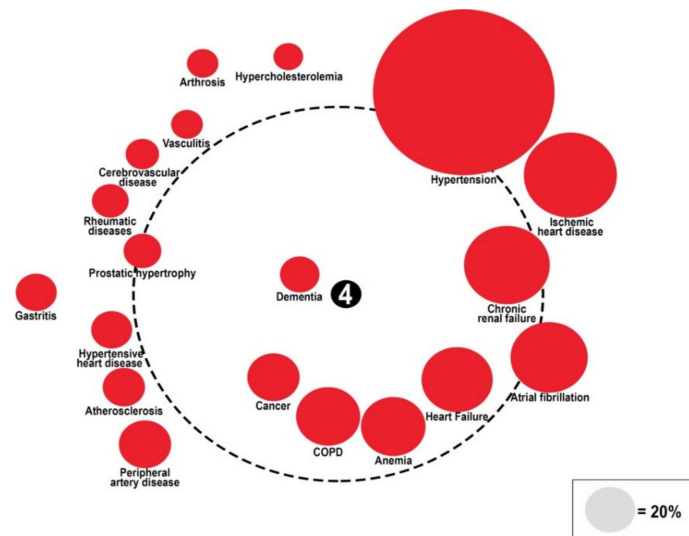
Figure 4. Comorbidome representation of in-hospital mortality in the RePoSI population with diabetes. Diameter of colored circles is function of the prevalence of each comorbidity. The dotted-line circle represents the OR equal to 1, the outside area corresponds to OR < 1, and the inner area correspond to OR > 1. All circles associated with a statistically significant increase in mortality are fully inside the dotted orbit. Mortality is set at the center (with the higher value = 4). The proximity to the center represents the stronger positive association with mortality. The comorbidities are represented graphically clockwise, from the first with the higher prevalence to the last with the lower prevalence in patients with diabetes.

Figure 5. Comorbidome representation of 3-month mortality in the RePoSI population with diabetes. Diameter of colored circles is function of the prevalence of each comorbidity. The dotted-line circle represents the OR equal to 1, the outside area corresponds to OR < 1, and the inner area correspond to OR > 1. All circles associated with a statistically significant increase in mortality are fully inside the dotted orbit. Mortality is set at the center (with the higher value = 4). The proximity to the center represents the stronger positive association with mortality. The comorbidities are represented graphically clockwise, from the first with the higher prevalence to the last with the lower prevalence in patients with diabetes.
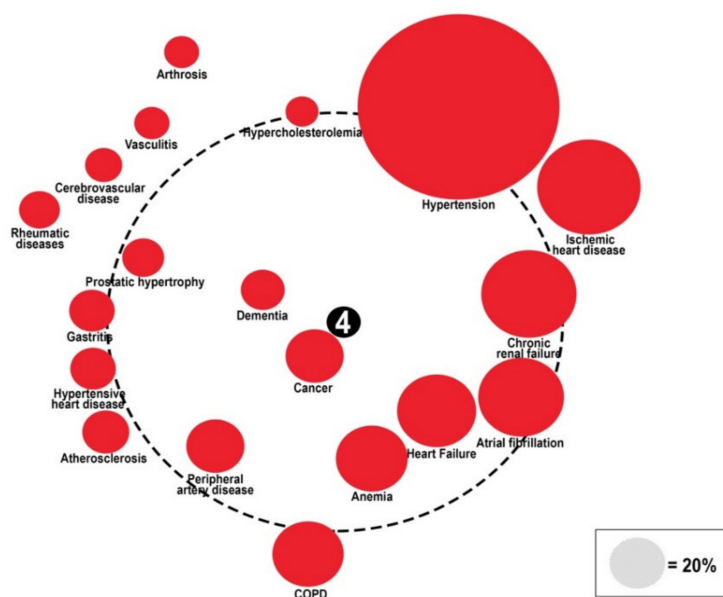
Figure 6. Comorbidome representation of 1-year mortality in the RePoSI population with diabetes. Diameter of colored circles is function of the prevalence of each comorbidity. The dotted-line circle represents the OR equal to 1, the outside area corresponds to OR < 1, and the inner area correspond to OR > 1. All circles associated with a statistically significant increase in mortality are fully inside the dotted orbit. Mortality is set at the center (with the higher value = 4). The proximity to the center represents the stronger positive association with mortality. The comorbidities are represented graphically clockwise, from the first with the higher prevalence to the last with the lower prevalence in patients with diabetes.

Hypertension was the comorbidity with the highest prevalence (57.1%), while heart failure (22.6%), anemia (22%), COPD (22.7%), cancer (17.5%), and dementia (9.1%) were the strongest predictors of mortality (OR > 1) in-hospital (OR 1.27, 1.11, 1.31, 1.74, 3.32, respectively) and at the 3-month follow-up (OR 1.36, 1.33, 1.12, 2.02, 2.39, respectively). At the 1-year follow-up, heart failure, anemia, cancer, and dementia, along with peripheral artery disease (17.3%), and prostatic hypertrophy (13.2%), were independently associated with mortality (OR 1.50, 1.29, 3.62, 2.10, 1.13, 1.14, respectively). See Table A1

4. Discussion

Despite the considerable clinical and economic burden of diabetes in older popula-tions, clinical trials have historically excluded the oldest patients, particularly those with comorbidities [21]. For this reason, there is a need to have an effective approach to co-morbidities to improve the care and outcomes for older patients with diabetes, especially at this time, where it the risk of hospitalization and death in patients with COVID-19 is always high [22]. The first important finding of our analysis regards the importance of the utilization of the CIRS assessment of comorbidities in the diabetic population.

Our data are consistent with a recent analysis that showed that the CIRS assessment of comorbidity burden represents the more useful clinical tool for the evaluation all-cause mortality in hospitalized elderly patients [23]. According to a recent study, CIRS-SI and CIRS-CI were higher in subjects with pneumonia than patients without pneumonia [24], and a CIRS index value >3 is significantly associated with gastrointestinal bleeding in elderly patients [25]. It is worth outlining the importance of CIRS as instrument of choice for multimorbidity assessment in clinical trials and its benefit to predict mortality, hospital readmission, and prolonged hospital stays [26,27]. Another important finding concerns the role of the Barthel index. A Barthel Index value ≤ 40, along with CIRS-SI and glycemia level ≥ 250 mg/dL, was the strongest predictor of in-hospital mortality for patients aged 65 years and older admitted in internal and geriatric wards [28].

According to recent studies, hyperglycemia was an independent predictor of the functional outcomes of ischemic patients measured by the Barthel index on admission [29].

In a longitudinal cohort study with a long follow-up of 11 years, the BI at admission to geriatric department is associated with short- and long-term mortality in both genders [30]. The most important innovation of our study is represented by the utilization of a novel modified data visualization: the "Diabetes comorbidome ".

The comorbidities are represented graphically clockwise, from the first with the highest prevalence to the last with the lowest prevalence.

The center represents mortality. The proximity to the center shows the strength of the association between the comorbidity and the risk of death. In our opinion, this is a simple tool that allows the researcher to understand, at a glance, the prevalence and impact of every single comorbidity. The utilization of the comorbidome, representative of the study of comorbidity patterns, may be useful in improving the clinical management of each specific subgroup of patients with a given index disease such as diabetes. Moreover, the knowledge of the possible physio-pathological interactions among comorbidities can contribute to the improvement of prevention and treatment strategies. As highlighted in different studies, the comorbidome is an effective tool to represent the comorbidities related to an increased mortality in COPD [12], the associations between sex specific comorbidities, and the mortality in COPD subjects [13], as well as comorbidities associated with higher risk of acute heart failure [14].

Our findings for the co-morbidity burden of diabetes are expected to be representative for a hospitalized-care setting and might be more useful for those taking strategic decision to reduce the length of hospital stays and unplanned readmission to hospital and create successful transitions from hospitals to local services or homes.

In our analysis heart failure, anemia, COPD, cancer, and dementia were strongly associated with in-hospital and 3-month mortality.

A possible explanation involved the role of a chronic low-grade inflammation state that is present in age-associated chronic conditions and, in particular, in diabetes [31].

This phenomenon is exacerbated by hospitalization, determining a progressive decline of cognitive and clinical status and quality of life [32,33]. Heart failure, anemia, COPD, cancer, and dementia str characterized by low-grade inflammation and are often associated with diabetes [12,34–37]. Evidence indicate that inflammation and, in particular, high levels of TNF-α, IL-β and IL-6 are factors involved in the development of type-1 diabetes [31,38], and TNF- α, IL-1, IL-6, IL-10, leptin, and adiponectin are the factors involved in the development of type-2 diabetes [31,39].

In addition, other studies showed the role of adiponectin and its relationship with cardiometabolic comorbidities [40–43] and the impact of chronic disease such as diabetes and cancer on the health-related quality of life in elderly population [33].

Although hypertension, ischemic heart disease, chronic renal failure, and atrial fibrillation are highly prevalent, the risk of death that these comorbidities give is not significant. In our opinion, the most likely reason is that these comorbidities are more often highlighted and treated by physicians, even if they are risk factors for the development of more lethal diseases such as heart failure and cardio-renal syndrome. Hypertension, particularly, is the most prevalent comorbidity, but there is no correlation with the risk of death; on the contrary, it has a protective role, particularly during hospitalization.

Our results are in agreement with previous studies that showed an inverse association between hypertension and mortality in older people [44,45].

At a 1-year follow-up, peripheral artery disease and prostatic hypertrophy were associated with mortality along with cancer, dementia, heart failure, and anemia.

Type-2 diabetes, along with obesity, is associated with prostatic hypertrophy [46]. Prostatic hypertrophy increases with age and may affect three out of four men in people aged 60 and older [47], and men with higher fasting glucose or with a diagnosis of diabetes may have a significant 3-fold and 2.3-fold higher risk of benign prostatic hypertrophy, respectively [48]. A likely explanation is that the diagnosis of prostatic hypertrophy in

this subgroup of patients subsequently evolves into a cancer. In men with type-2 diabetes, benign prostatic hypertrophy could be a risk factor for bladder cancer [49].

Regarding the role of peripheral artery disease, it is well known that diabetes mellitus increases the incidence of peripheral artery disease, accelerates disease progression, and increases disease severity. Patients affected by peripheral artery disease and diabetes mellitus are at high risk for amputation. According to a recent meta-analysis, diabetes is associated with an increased risk of mortality in peripheral vascular disease, particularly in patients with critical limb ischemia [50]. Subjects with peripheral artery disease are at higher risk of cardiovascular events, particularly a 14.2% increase in risk for every percentage point increase in HbA1c, [51]. Dementia was strongly associated with mortality both in-hospital and at follow-up. Hanyu [52] identified a subgroup of patients with diabetes and dementia characterized by specific diabetes-related metabolic abnormalities such as advanced age, high hemoglobin A1c level, long course of diabetes, high frequency insulin treatment, low apolipoprotein E4 carrier, less-severe medial temporal lobe atrophy, impaired attention and executive function, less-impaired word recall, and slow progression of cognitive impairment. Moreover, a recent meta-analysis showed that diabetes increases the risk of cognitive impairment (cognitive impairment and dementia) by 1.25 to 1.91 times [53]. Our results are consistent with previous studies that showed dementia in type-2 diabetes is associated with an increasing risk of death during a follow-up of 12.7 ± 5.9 years [54]. Finally, cancer was associated with in-hospital and follow-up mortality. Particularly, it is the strongest comorbidity associated with the risk of mortality at 1-year follow-up. In this sense, our data are in agreement with previous studies, which showed a strongly association between diabetes and different malignancies such as breast cancer [55], pancreatic [56], liver [57], kidney [58], endometrial [59], colorectal [60], bladder [61] cancers, and non-Hodgkin's lymphoma [62,63].

Hyperglycemia represents one of the key factors in the hypothesis that diabetes raises the cancer risk for both men and women [64–66]. Hyperglycemia can promote the cancer cells' proliferation, invasion, and migration; it induces the apoptotic resistance and the metastatic effect and enhances the chemoresistance of tumor cells [67–69].

This study had some limitations. First, no specific information about diabetes duration is available. Second, HbA1c, the better indicator of chronic glycemic levels and risk for long-term complications, is lacking. Third, the REPOSI register was not specifically designed to evaluate clinical information. Fourth, our study population was different from the BODE cohort of Divo that included predominantly stable outpatients with COPD from pulmonary clinics with fewer comorbidities at initial recruitment.

Our population consisted of hospitalized elderly patients in internal medicine and geriatric wards with multiple and more severe diseases. The major strength of this study is the multicenter design of the REPOSI.

5. Conclusions

In summary, our analysis opens up new scenarios about the assessment of the burden of comorbidities that afflicted patients with diabetes through the identification of subsets of patients by comorbidities using the modified comorbidome as graphic representation. The most relevant aspect concerns the utilization of a tool such as the modified comorbidome as graphic representation of the prevalence of comorbidities and related outcomes. It could represent a perfect instrument for determining the importance of each comorbidity and the need of an effective treatment for the improvement of clinical outcomes. Our data should be considered by health authorities for the creation of discharge plans in agreement with local services in order to improve the quality of life and reduce mortality and the burden on the health system caused by re-hospitalizations. Further studies about complex and chronic diseases would use this graphic tool as an expression of the prevalence of comorbidities and the strength of their association with risk of death-related outcomes.

Appendix A

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Table A1. Univariate analysis.

Variables	Inpatient with Diabetes (%)	O.R. In-Hospital Mortality	O.R. 3-Months Mortality	O.R. 12-Months Mortality
Hypertension	57.1	**0.53 (0.33–0.84)**	**0.60 (0.44–0.99)**	0.67 (0.49–1.11)
Ischemic heart disease	31.3	**0.55 (0.31–0.97)**	0.71 (0.54–1.43)	0.64 (0.26–1.49)
Chronic renal failure	28.9	1.19 (0.73–1.95)	1.17 (0.72–1.87)	1.13 (0.41–2.23)
Atrial fibrillation	26.0	0.92 (0.54–1.57)	1.07 (0.74–1.96)	1.28 (1.05–5.07)
COPD	22.7	1.31 (0.77–2.23)	1.12 (0.58–1.71)	0.79 (0.04–1.01)
Heart Failure	22.6	1.27 (0.77–2.13)	1.36 (0.81–2.20)	1.50 (0.85–4.38)
Anemia	22.0	1.11 (0.64–1.92)	1.33 (0.83–2.32)	1.29 (0.54–3.21)
Peripheral artery disease	17.6	0.61 (0.30–1.26)	**0.53 (0.22–0.98)**	1.13 (0.54–2.87)
Cancer	17.5	**1.74 (1.01–3.04)**	**2.02 (1.28–3.52)**	**3.62 (1.49–9.78)**
Atherosclerosis	14.2	0.74 (0.33–1.66)	0.60 (0.19–1.27)	0.78 (0.31–3.13)
Hypertensive heart disease	13.9	0.81 (0.40–1.65)	**0.36 (0.03–0.50)**	0.88 (0.37–1.13)
Gastritis	13.8	**0.17 (0.42–0.72)**	0.78 (0.34–2.07)	0.87 (0.19–2.43)
Prostatic hypertrophy	12.7	1.02 (0.52–2.03)	0.96 (0.52–1.89)	1.14 (0.70–4.78)
Rheumatic diseases	12.4	0.59 (0.23–1.51)	**0.40 (0.09–0.98)**	**0.32 (0.13–1.56)**
Cerebrovascular disease	11.3	0.59 (0.07–4.64)	0.89 (0.38–2.94)	0.57 (0.21–2.09)
Vasculitis	10.7	0.62 (0.15–2.69)	0.96 (0.48–2.60)	0.54 (0.23–2.34)
Arthrosis	10.6	0.33 (0.10–1.06)	**0.26 (0.08–0.79)**	**0.23 (0.14–0.78)**
Hypercholesterolemia	10.0	0.47 (0.17–1.32)	0.62 (0.34–1.70)	0.94 (0.33–4.77)
Dementia	9.1	**3.32 (1.95–5.66)**	**2.39 (1.01–2.83)**	**2.10 (1.03–3.53)**

Data statistically significant ($p < 0.05$) were reported in bold.

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