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RESEARCH ARTICLE

Use of SGLT2 Inhibitors in Frail Older Adults is Associated with Increased Survival: A Retrospective Study

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Abstract: Background: In recent years, sodium-glucose co-transporter 2 inhibitors (SGLT2i) have emerged as a valuable treatment for type 2 diabetes (T2D) and heart failure. Despite these medications seeming to be safe in older people, the literature about SGLT2i and frailty is still limited. This study aims to evaluate whether SGLT2i use is associated with increased survival in older adults and if frailty can affect the findings.

Materials and Methods: We enrolled over 65 patients admitted to the Geriatrics Wards at the University Hospital 'P. Giaccone' in Palermo, Italy, between December 2022 and May 2023. After 12 months of follow-up, various outcomes were assessed, including mortality, hospitalization, glycemic dysregulation, urinary tract infections, and falls. The association between SGLT2i use and mortality was analyzed and reported as hazard ratios (HRs) with their 95% confidence intervals (CIs).

Results: A total of 80 patients were included in the study (mean age 79.5 ± 8.5 years; 50% were women). Patients using SGLT2i had a higher prevalence of T2D ($p = 0.02$) and cirrhosis ($p = 0.001$). After adjusting for potential confounders, SGLT2i use was significantly associated with a reduced mortality risk (HR = 0.53; 95% CI: 0.20-0.93; $p = 0.02$). When stratified by the presence of multidimensional frailty, SGLT2i use was significantly associated with a lower risk of mortality in frail patients (HR = 0.27; 95% CI: 0.06-0.88; $p = 0.008$), but not in robust ones.

Conclusion: In older frail patients, the use of SGLT2i is associated with reduced mortality after 12 months of follow-up. Further larger studies are needed to evaluate the role of these medications in older adults.

Keywords: Diabetes, aging, SGLT2 inhibitors, multidimensional frailty, sodium-glucose co-transporter 2 inhibitors, multidimensional prognostic index (MPI).

1. INTRODUCTION

Type 2 diabetes (T2D) in older persons is a major health issue characterized by the body's failure to effectively regulate blood sugar levels and vascular complications. As people get older, the likelihood of developing T2D rises [1] due to a mix of factors such as lower insulin sensitivity, decreased physical activity, and changes in body composition, including more abdominal fat [2]. The number of individuals aged 65 to 99 with T2D is expected to rise dramatically, reaching 195.2 million by 2030 and 276.2 million by 2045, while the countries with the highest expected numbers of seniors with T2D will be China, the United States, and India [3].

In the past decades, new therapeutic classes against T2D were developed, such as the SGLT2i, which represents one of the most beneficial medications after metformin failure [4] in patients with a history of cardiovascular (CV) or renal disease who need further hemoglobin A1c reduction [5]. They have been investigated in randomized, controlled, CV outcome trials, revealing how SGLT2i

were associated with a reduced risk of CV events and all-cause mortality [6-9]. The Kidney Disease Improving Global Outcomes Guidelines recommend using SGLT2i as first-line therapy for patients with chronic kidney disease (CKD). This recommendation underscores the efficacy of SGLT2i not only in managing CKD but also in addressing various conditions associated with metabolic syndrome [10].

Frailty, traditionally defined as a geriatric syndrome associated with a decreased reserve of acute events [11], is a very common condition among older patients with T2D [12]. It is estimated that the prevalence of frailty is three to five times higher in persons with T2D compared to those without [13]. Both individually and together, T2D and frailty significantly affect health service provision [14], leading to increased overall healthcare costs [15]. The combination of frailty and DM negatively impacts mortality, psychosocial well-being, and quality of life [16].

The implementation of deprescribing processes could be extremely beneficial to older patients living with T2D worldwide [17]; for example, insulin treatment is considered one of the most common causes of hypoglycemic episodes in frail older adults due to cognitive decline or excessive number of administrations during the day [18]. Treatments with SGLT2i might be considered safer in

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these patients [19], with an administration once a day instead of insulin administration sometimes four times a day.

Despite these medications seeming to be safe in older people, the literature on SGLT2i use and frailty is still limited; an Italian study of 739 older participants revealed how SGLT2i were well-tolerated and safe in older people and appeared as an effective therapeutic option, but the study enrolled only outpatients, did not assess fall or cardiological and endocrinological evaluations during follow-up, and there was no clear definition of frail patients [20]. In a Spanish study of 750 older adults, SGLT2i use was associated with lower readmission rates and mortality at the 12-month follow-up in participants with multiple pathologies admitted with acute heart failure [21]; however, adverse effects secondary to the use of these drugs, falls, and urinary tract infections were not registered during follow-up, and also, in this case, there was no clear definition of frailty.

Given this background, this study aims to evaluate whether the use of SGLT2i is associated with increased survival in older adults affected by T2D and heart failure and if frailty can modify the findings.

2. MATERIALS AND METHODS

2.1. Participants

This study enrolled patients over the age of 65 who were admitted to the Geriatrics Wards at the University Hospital 'P. Giaccone' in Palermo, Italy, between December 2022 and May 2023. We included patients who were able to understand and sign the informed consent. For patients with dementia or unable to sign the informed consent, we obtained consent from their relatives. Since this is a retrospective study based on data already collected for clinical purposes, we formally notified our Institution's Ethical Committee (Comitato Etico Palermo 1 A.O.U.P. 'P. Giaccone') on July 04, 2024, according to the most recent Italian law. The study was conducted according to the principles of the Declaration of Helsinki. All patients were made to sign consent to participate in the study upon admission in the medical record; for patients who were unable to do so due to cognitive problems, relatives were asked to sign for them.

2.2. Exposure: SGLT2i use

We included participants in accordance to SGLT2i prescription allowed in Italy (Note 100) [22], where SGLT2i can be administered only in adult patients with T2D in inadequate glycemic control (glycated hemoglobin -HbA1c- greater than 53 mmol/mol or 7.0%); patients in secondary CV prevention, patients in primary CV prevention at high CV risk, patients with CKD (presence of glomerular filtration rate < 60 mL/min and/or micro or macro albuminuria), and patients with heart failure.

A prerequisite for these medications to be financed by the National Health Care System (NHCS) in Italy is that the patient must already be under metformin treatment without effective glycemic control (unless there are contraindications or intolerance to metformin). Prescription charged to the NHCS must be made in accordance with the indications contained in Note 100 and provide for completion of the Evaluation and Prescription Form by General Practitioners or Specialists.

The use of SGLT2i was evaluated at patients' admission in our department, according to the Italian Note 100 and the guidelines on the use of SGLT2i [23]. At discharge, we suggested home therapy with SGLT2i to all patients who met the previously reported condi-

tions (T2D, CV risk, heart failure). In patients who were not taking SGLT2i prior to admission and were prescribed it at discharge, the treatment plan was delivered. After 12 months of follow-up, we conducted phone calls to evaluate whether patients continued using SGLT2i and to identify any adverse effects and outcomes.

2.3. Covariates

Age was measured as a continuous variable; sex was specified as a binary indicator [women vs. men]. Medical conditions, such as T2D, heart failure, hypertension, CKD and cirrhosis were reported by the medical records during hospitalisation.

At hospital admission, all participants were assessed using the Multidimensional Prognostic Index (MPI), which was derived from information obtained through a standard Comprehensive Geriatric Assessment that considered the following domains [24]:

(1) Activities of Daily Living (ADL) Index: Measures the level of dependence or independence in six daily personal care activities: bathing, toileting, feeding, dressing, urine and bowel continence, and transferring (getting in and out of bed or a chair).

(2) Instrumental Activities of Daily Living (IADL): Evaluates eight activities that are more cognitively and physically demanding than ADLs, including managing finances, using the telephone, taking medications, shopping, using transportation, preparing meals, doing housework, and washing.

(3) Short Portable Mental Status Questionnaire (SPMSQ): A ten-item questionnaire that assesses orientation, memory, attention, calculation, and language. Validated versions were used in each local language.

(4) Cumulative Illness Rating Scale (CIRS): Uses a 5-point ordinal scale (scores range from 1 to 5) to estimate the severity of pathology in each of 13 systems: cardiac, vascular, respiratory, eye-ear-nose-throat, upper and lower gastrointestinal, hepatic, renal, genitourinary, musculoskeletal, skin disorders, nervous system, endocrine-metabolic, and psychiatric behavioral disorders.

(5) Mini Nutritional Assessment (MNA) Short Form (SF): A brief questionnaire that includes anthropometric measurements combined with questions regarding loss of appetite, recent weight loss, mobility, acute distress, and neuropsychological problems.

(6) Exton Smith Scale (ESS): A five-item questionnaire that assesses physical and mental condition, activity, mobility, and incontinence to indicate the risk of pressure sores.

(7) Number of medications taken at hospital discharge.

(8) Cohabitation status: Categorized as living alone, in an institution, or with family members.

Each domain was scored using a tripartite hierarchy: 0 = no problems, 0.5 = minor problems, and 1 = major problems, based on conventional cut-off points derived from the literature for each item [25]. The total scores from the eight domains were summed and divided by eight to obtain a final MPI risk score ranging from 0 (no risk) to 1 (higher risk of mortality) [25]. Traditionally, the MPI is divided into three categories: MPI-1 (low risk of mortality, robustness): MPI score < 0.33; MPI-2 (intermediate risk, pre-frailty): MPI score between 0.33 and 0.66; MPI-3 (high risk, frailty): MPI score > 0.66. In our study, we divided MPI into < 0.56 (robustness) and > 0.56 (frailty) due to the limited sample size. On average, the execution of the MPI takes about 15 minutes. The software for calculating the MPI can be downloaded for free at the following address: <https://multiplat-age.it/index.php/en/tools>. Table S1 details how the MPI is constructed.

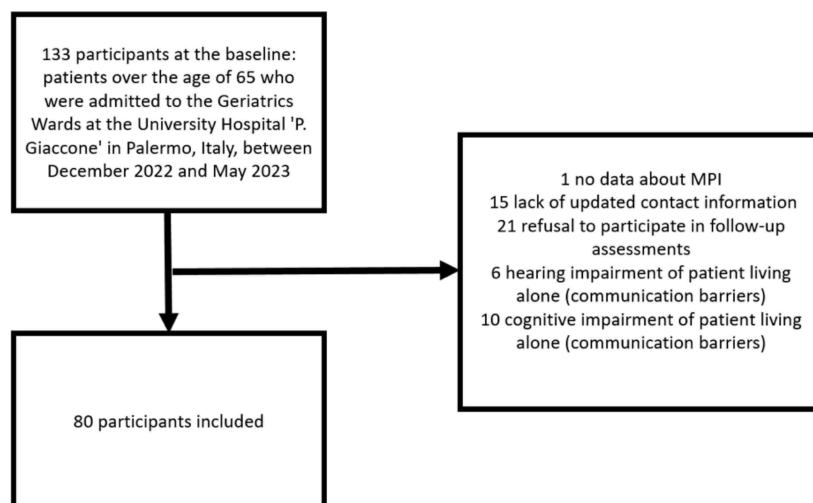


Fig. (1). Flow-chart of participants included in the study.

2.4. Outcomes

One year after discharge, patients received a phone call made by post-graduate students in Geriatrics in the third or fourth year of their course. During the phone call, a questionnaire was used to research the outcomes of clinical interest and possible adverse effects of SGLT2i, such as mortality, hospitalisation, glycaemic dysregulation, urinary tract infections, falls, cardiological and diabetological examinations. All data were self-reported by patients or their relatives. Table S2 shows the telephone questionnaire.

2.5. Statistical Analysis

The demographic and clinical characteristics of the patients are presented as mean and standard deviations for continuous variables, or as frequency and percentage for categorical variables.

The association between SGLT2i use and the outcomes of interest was analysed using adjusted logistic regression, with the results reported as hazard ratios (HRs) with 95% confidence intervals (CIs), with a significance level set at $p < 0.05$. This analyses were adjusted for confounding factors, such as age, sex, and MPI, which were carefully selected based on existing literature and their established relevance to both SGLT2i use and mortality in older adults. While we acknowledge that more granular adjustments for specific conditions such as cardiovascular or renal health could provide additional insights, the limited sample size restricted our ability to adjust for a larger number of variables without overfitting the model. All analyses were conducted using SPSS 26.0 for Windows (SPSS Inc., Chicago, Illinois). All statistical tests were two-tailed, and a p -value of <0.05 was considered statistically significant.

3. RESULTS

Out of the 133 patients initially evaluated for this study, we ultimately included 80 older patients. We excluded 52 patients who were lost during follow-up since they did not answer our invitation or died and one patient because there was insufficient information available about MPI at discharge (Fig. 1). The participants in the study had an average age of 79.5 years (SD = 8.5, range: 65-98), and 50% were women.

Table 1 provides a descriptive analysis of the population based on the use of SGLT2i. Among the 32 participants using SGLT2i, 14

participants were discharged with canagliflozin, 13 with dapagliflozin, four with empagliflozin and one with ertugliflozin. Those who used SGLT2i during their hospitalization and at discharge did not differ in terms of gender ($p = 0.17$), age ($p = 0.36$), ADL ($p = 0.19$), comorbidities ($p = 0.22$), and other domains of multidimensional frailty, finally leading to similar values in MPI ($p = 0.23$). Regarding biochemical tests and medical conditions, participants using SGLT2i had similar HbA1c values ($p = 0.34$) and renal function ($p = 0.27$) to their counterparts not using these types of medication. Patients using SGLT2i had a higher prevalence of T2D ($p = 0.02$) and cirrhosis ($p = 0.001$) and a similar prevalence of heart failure ($p = 0.16$). No significant differences were found in the prevalence of hypertension and CKD ($p > 0.05$ for these comparisons). During the follow-up period, a consistent part of the baseline population died (=33.8% of the initial population).

Seventeen patients were already taking SGLT2i at the time of admission, 16 patients received the SGLT2i prescription for the first time and one patient was instead taken off the medication. All patients who were prescribed SGLT2i at the time of discharge were still taking them at 12-month follow-up, and of the 27 patients who died in total, only 5 were taking SGLT2i. Fig. (2) reports outcomes during one year of follow-up. Participants taking SGLT2i showed significantly lower mortality after 12 months of follow-up ($p = 0.02$), whilst other outcomes investigated, such as diabetological and cardiological examinations, falls, glycaemic dysregulation, and hospitalisations did not differ between the two groups ($p > 0.05$ for these comparisons).

Table 2 presents the association between baseline use of SGLT2i and mortality, adjusted for potential confounders (survival curves are reported in Fig. (3)). After adjusting for age, sex, and MPI, SGLT2i use was significantly associated with a reduced risk of mortality (HR = 0.53; 95% CI: 0.20-0.93; $p = 0.02$), highlighting the protective effect of these antidiabetic medications. When stratified for the presence or absence of multidimensional frailty, SGLT2i use was significantly associated with a lower risk of mortality in frailer patients (HR = 0.27; 95% CI: 0.06-0.88; $p = 0.008$) but not in more robust ones ($p = 0.97$) (Table 2).

4. DISCUSSION

This study aimed to evaluate whether the use of SGLT2i was associated with increased survival in older hospitalized adults and

Table 1. Descriptive characteristics of the population.

Variable	SGLT2i Use (No = 48, Yes = 32)	Mean Values or Frequency (% or SD)	p-value
General Characteristics			
Age (mean, SD)	No	81.1 (9.4)	0.36
	Yes	76.9 (6.4)	
Women (N, %)	No	27 (56.3)	0.17
	Yes	13 (40.6)	
SPMSQ (mean, SD)	No	2.6 (2.9)	0.51
	Yes	2.3 (3.3)	
Exton Smith Scale (mean, SD)	No	13.3 (4.4)	0.67
	Yes	14.5 (4.5)	
ADL (mean, SD)	No	3.4 (2.5)	0.19
	Yes	4.4 (2.3)	
IADL (mean, SD)	No	2.9 (2.5)	0.96
	Yes	4.7 (2.8)	
CIRS Severity Index (mean, SD)	No	1.8 (0.3)	0.22
	Yes	1.9 (0.2)	
MNA short (mean, SD)	No	8.2 (3)	0.54
	Yes	9.6 (3.5)	
MPI (mean, SD)	No	0.58 (0.2)	0.23
	Yes	0.52 (0.1)	
Biohumoral Tests			
HbA1c (mean, SD)	No	6.2 (0.8)	0.34
	Yes	7 (1.8)	
Creatinine clearance (mean, SD)	No	64.6 (29.7)	0.27
	Yes	56 (22)	
Medical Conditions			
Diabetes (N, %)	No	26 (54.2)	0.02
	Yes	28 (87.5)	
Heart Failure (N, %)	No	30 (62.5)	0.16
	Yes	15 (46.9)	
Hypertension (N, %)	No	28 (58.3)	0.64
	Yes	17 (53.1)	
Chronic Kidney Disease (N, %)	No	14 (29.2)	0.9
	Yes	9 (28.1)	
Cirrhosis (N, %)	No	3 (6.3)	0.001
	Yes	11 (34.4)	

Abbreviations: ADL: Activity Daily Living; CIRS: Cumulative Illness Rating Scale; HbA1c: hemoglobin A1C; IADL: Instrumental Activity Daily Living; MNA: Mini Nutritional Assessment; MPI: Multidimensional Prognostic Index; SGLT2i: sodium-glucose co-transporter 2 inhibitors; SPMSQ: Short-Portable Mental Status Questionnaire.

Table 2. Association between SGLT2i use and mortality in the whole sample and by presence or absence of multidimensional frailty.

-	Unadjusted Model	p-value	Adjusted	p-value
All samples	0.42 (0.17-0.86)	0.007	0.53 (0.20-0.93)	0.02
MPI ≤ 0.56 (N=48)	1.2 (0.26-5.47)	0.80	0.97 (0.19-4.93)	0.97
MPI > 0.56 (N=31)	0.27 (0.06-0.89)	0.008	0.27 (0.06-0.88)	0.008

Note: Data are reported as hazard ratios (HRs) with their 95% confidence intervals (CIs). The fully-adjusted model was adjusted for age, sex and MPI in the sample as whole.

Abbreviations: MPI: Multidimensional Prognostic Index; SGLT2i: sodium-glucose co-transporter 2 inhibitors.

if frailty could affect these findings. Moreover, we evaluated as secondary outcomes the association between many crucial aspects for older patients, such as falls, hospitalisation, urinary tract infections, glycaemic dysregulation and diabetological or cardiological evaluations, and use of SGLT2i. We found that after adjusting for potential confounders, SGLT2i use was significantly associated with a reduced mortality risk considering all participants, while considering separately frail and robust patients, the results were similarly significant for frail participants but the significance was lost for robust participants.

We believe that our findings are novel for several reasons. Firstly, frailty was assessed using the MPI, a tool that integrates biological, functional, cognitive, psychological, and socio-economic information. This approach provides a more comprehensive evaluation of frailty in older adults. Secondly, to the best of our knowledge, there are only a few studies about the association between frailty and SGLT2i, and most of them are only reviews or updates about SGLT2i use.

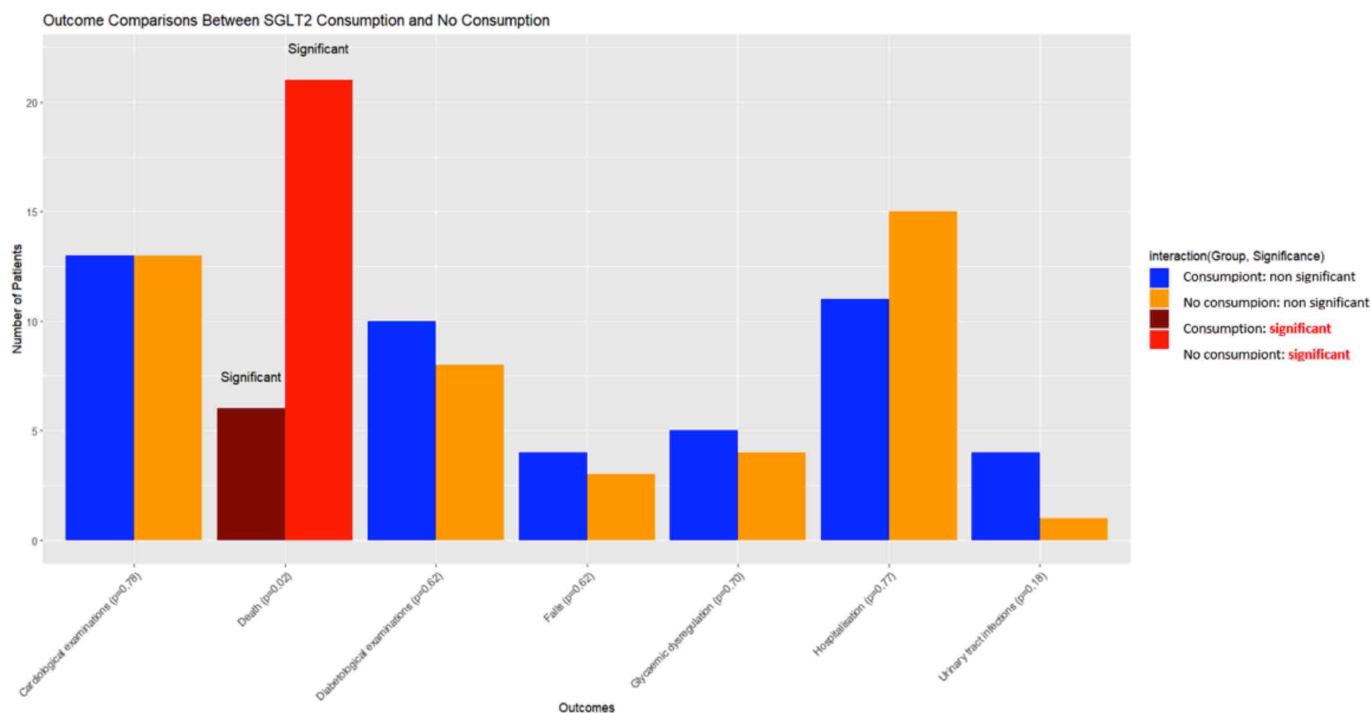


Fig. (2). Outcomes after discharge (1 year of follow-up). SGLT2i: sodium-glucose co-transporter 2 inhibitors. (A higher resolution/colour version of this figure is available in the electronic copy of the article).

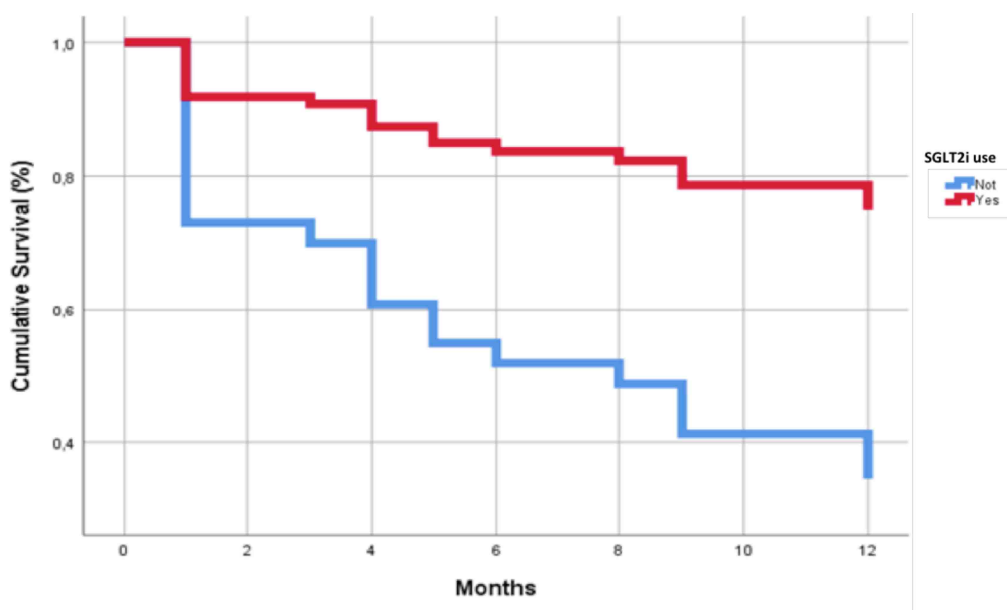


Fig. (3). Survival after 12 months by use of SGLT2i. SGLT2i: sodium-glucose co-transporter 2 inhibitors. (A higher resolution/colour version of this figure is available in the electronic copy of the article).

The participants in the study had an average age of 79.5 years and 50% were women. As reported in previous literature, SGLT2i revealed positive effects on patients with T2D and cirrhosis [26, 27]; in fact, in our study patients using these medications showed a higher prevalence of T2D and cirrhosis compared to the counter-

parts. The higher frequency of diabetes and cirrhosis in the SGLT2i group can be clearly explained: SGLT2i are typically prescribed to patients with diabetes, especially those who have cardiovascular or kidney complications [28]. Since these drugs are recommended to help manage blood sugar and lower cardiovascular risk,

it's logical that more patients in the SGLT2i group would have diabetes. This finding is consistent with previous studies showing that SGLT2i offer additional benefits beyond glucose control, such as reducing mortality and cardiovascular events [29], which is particularly valuable for frail older individuals with diabetes.

The higher prevalence of cirrhosis in the SGLT2i group may be due to increasing evidence that these medications benefit patients with liver conditions [30]. A Chinese systematic review and meta-analysis of eight articles and 686 patients showed positive effects of SGLT2i on hepatic fibrosis and steatosis, presented as liver stiffness measurement and controlled attenuation parameter, compared to other antihyperglycemic drugs [31].

SGLT2i plays a significant role in promoting diuresis by blocking glucose reabsorption in the kidneys, which leads to increased urinary glucose excretion. This process creates an osmotic diuretic effect, resulting in fluid loss and potential volume depletion [32], with beneficial effects even in patients with liver conditions like ascites. In a study on diabetic rats, SGLT2i caused sustained osmotic diuresis, prompting compensatory increases in vasopressin-induced solute-free water reabsorption to preserve body fluid volume. This was accompanied by an increase in renal aquaporin 2 expression in the collecting duct [33].

Another reason for the higher survival of these patients is that one of the effects of SGLT2i is the reduction of mitochondrial reactive oxygen species production and the decrease in Ca^{2+} overload within mitochondria, which plays a crucial role in improving vascular function in the diabetic environment [34]. This reduction in oxidative stress leads to an improvement in endothelial function, which is often impaired in diabetes. By enhancing endothelial function, SGLT2i helps to mitigate microvascular complications in the myocardium, thereby protecting the heart from the adverse effects commonly associated with diabetes.

The SGLT2 proteins are located in the proximal convoluted tubules of the kidneys and function by reabsorbing glucose from the filtered fluid in the tubules. All four types of SGLT2i work by blocking this glucose reabsorption, which lowers the renal threshold for glucose and triggers glucose excretion in the urine [32]. Research has shown that empagliflozin can lower mean arterial pressure and reduce arterial stiffness during daily activities [35]. Pre-clinical studies indicate that dapagliflozin promotes vasodilation, improves endothelial function and arterial stiffness, and has overall positive effects on the vascular system by decreasing oxidative stress [36]. SGLT2i reduces afterload *via* arterial vasodilation and preload through natriuresis and diuresis, and they also lower uric acid levels [37]. Canagliflozin has been shown to slow the increase in serum N terminal-proB-type natriuretic peptide [NT-proBNP] and troponin-I levels in patients with T2D [38].

In older adults, SGLT2i can cause several adverse effects, such as volume depletion resulting from increased diuresis, which heightens the risk of dehydration and low blood pressure [39]. Older individuals may also be more prone to urinary tract infections due to higher glucose levels in the urine. Additionally, there is concern about a greater risk of falls, especially among frail patients. Despite these risks, SGLT2i are typically well-tolerated when prescribed carefully and monitored closely in elderly populations [40]. In our study, we found that after adjusting for confounding factors, such as age, sex and MPI, patients taking SGLT2i had a 47% lower risk of death over a 12-month follow-up period compared to those who did not take these medications. These findings were also confirmed by a systematic review and meta-analysis of 20 studies and 77,083 patients, wherein older or frail patients with T2D and heart failure, SGLT2i were consistently linked with a decrease in total mortality and the overall burden of CV events, including hospitali-

sation for heart failure events and cardiac death [41]. The absence of significant differences during follow-up in secondary outcomes like falls, hospitalizations, glycemic dysregulation, urinary tract infections, and diabetological or cardiological evaluations between the groups may be due to several factors. One possibility is that the relatively small sample size reduced the ability to detect differences in these outcomes. Moreover, these outcomes are shaped by various factors beyond SGLT2i use, including the severity of patients' underlying conditions, differences in healthcare practices, and adherence to treatment. Although we accounted for important confounders such as age, sex, and frailty, other unmeasured factors, like baseline functional capacity or medication compliance, may have affected these results. Larger studies with more comprehensive data are needed to further investigate these secondary outcomes.

When stratified for the presence or absence of multidimensional frailty, SGLT2i use was significantly associated with a 73% lower risk of mortality in frailer patients. Previous research has validated our findings: an Italian study of 405 frail participants reported that empagliflozin reduced frailty in diabetic and hypertensive patients, most likely by decreasing the mitochondrial generation of reactive oxygen species in endothelial cells [42], defining frailty with Fried criteria; another Dutch study of 4304 participants, showed that the use of SGLT2i was associated with benefit in terms of a kidney composite outcome, CV endpoint and all-cause mortality in frail patients [43], defining frailty with Frailty index.

The pathophysiological link between T2D and frailty may be explicated by sarcopenia, defined as a reduction in muscle mass and function (strength or performance) [44] and considered a key component of frailty. Research reviewed by various authors indicates a close relationship between T2D, insulin resistance, chronic low-grade inflammation (characteristic of T2D), and sarcopenia or muscle deterioration [45, 46]. Numerous studies have shown that muscle strength and quality decline in patients with T2D, with this decline becoming more pronounced the longer the patient has T2D and the poorer their glycemic control. Insulin resistance is linked to decreased muscle strength, likely due to reduced protein synthesis, increased degradation, and subsequent loss of muscle mass [47, 48]. Additionally, insulin resistance in aging patients can cause mitochondrial alterations, leading to a decrease in the production of the energy needed for muscle contraction and an increase in oxidative stress [49]. These results showed how SGLT2i use should be crucial for frail patients with T2D, heart failure, or CKD, but unfortunately, this is often not the case, as shown by a Danish study of 119,390 people with T2D and CV disease, where frailty was associated with a significantly lower probability of SGLT2i initiation, despite their benefits [50]. One of the most common reasons for this delay in SGLT2i prescription is well explained by a study from Hong-Kong of 17 primary care doctors, in which most interviewees, to varying extents, were aware of the cardio-renal advantages and safety profile of SGLT2i but were reluctant to prescribe or change their patients to SGLT2i because of their knowledge gap that the cardio-renal benefits of these drugs were independent of glycemic efficacy [51].

Our study must be interpreted with some limitations. Firstly, a phone call questionnaire was used to research the outcomes of clinical interest and all data were self-reported by patients or their relatives. Self-reported data on chronic medical conditions are known to introduce significant biases, particularly when patients may fail to accurately recall or report their health status. This can lead to the underestimation of the actual prevalence or severity of certain conditions, as patients may overlook symptoms or misinterpret medical diagnoses. Moreover, self-reports are subject to social desirability bias, where individuals may downplay certain health issues or

overstate positive behaviors [52]. Secondly, the small number of recruited patients of our study and its retrospective design, which may introduce recall bias and limit the ability to establish causality. Thirdly, the study's inclusion criteria, which targeted older, frail patients admitted to a single geriatric ward, could introduce selection bias. Healthier individuals or those who did not meet the frailty criteria may have been excluded, which could limit how well the results apply to a wider population. The study may overrepresent patients with more severe conditions or comorbidities, potentially distorting the sample. To reduce this selection bias, we adjusted the association between baseline use of SGLT2i and mortality, for potential confounders, such as age, sex and MPI. Lastly, as reported in the methods, these analyses were adjusted for confounding factors, including age, sex, and MPI. Although we recognize that adjusting for more specific conditions, like cardiovascular or renal health, could offer further insights, the small sample size limited our ability to incorporate additional variables without risking overfitting the model.

CONCLUSION

In conclusion, our study demonstrated how in older frail patients the use of SGLT2i was associated with reduced mortality after 12 months of follow-up, while secondary outcomes, such as diabetological and cardiological examinations, falls, glycaemic dysregulation, hospitalisations did not differ between the two groups. Caution may be necessary for the use of SGLT2i in older frail patients, particularly those at a higher risk of volume depletion. Further large studies are needed to evaluate the role of these medications in older adults.

AUTHORS' CONTRIBUTIONS

NV was involved in the conceptualization, data collection was contributed by DA, CC, SC, CE, MCG, CG, SML, ALN, GP, GS, RC, AD and PT, data analysis was presented by FSR, SC and NV, supervision was provided by MB, NV and LJD, writing-original draft was contributed by FSR and NV and writing-review and editing were presented by LJD, DA, CC, SC, CE, MCG, CG, SML, ALN, GP, GS, PT and MB.

LIST OF ABBREVIATIONS

ADL	=	Activities of Daily Living
CIRS	=	Cumulative Illness Rating Scale
MNA	=	Mini Nutritional Assessment
NHCS	=	National Health Care System
SF	=	Short Form
SGLT2i	=	Sodium-glucose Co-transporter 2 inhibitors
SPMSQ	=	Short Portable Mental Status Questionnaire
T2D	=	Type 2 Diabetes

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institution's Ethical Committee (Comitato Etico Palermo 1 A.O.U.P. 'P. Giaccone', protocol #0031682) on 04 July 2024, according to the most recent Italian law.

HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional

and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

All patients were made to sign consent to participate in the study upon admission in the medical record; for patients who were unable to do so due to cognitive problems, relatives were asked to sign for them.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The authors confirm that the data supporting the findings of this research are available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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