AMERICAN UNIVERSITY OF BEIRUT

INVESTIGATING PREDICTORS AND HEALTH OUTCOMES OF POLYPHARMACY AMONG OLDER ADULTS WITH TYPE 2 DIABETES MELLITUS AT A PRIMARY HEALTHCARE CENTER IN LEBANON

by
AHMED-RUFAI YAHAYA

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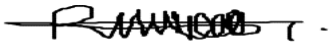

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ABSTRACT

OF THE THESIS OF

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Title: Investigating Predictors and Health Outcomes of Polypharmacy among Older Adults with Type 2 Diabetes Mellitus at a Primary Healthcare Center in Lebanon

Background: Globally, demographics have shifted in the past several decades, with a rise in the elderly population, and polypharmacy has emerged as a significant public health concern. Older adults over the age of 65 with T2DM may need multiple medications to treat their disease and any associated or unrelated comorbidities; a situation often resulting in polypharmacy. Thus, the goal of this research was to determine the proportion of polypharmacy, its predictors, and associated health outcomes in older adults with T2DM at a primary health care facility in Lebanon.

Aims/objectives/hypothesis: The research had three objectives: to determine the proportion of patients with polypharmacy in the sample, to identify polypharmacy predictors, and to determine the health consequences associated with polypharmacy. We hypothesized that, polypharmacy is positively associated with age, gender, BMI, smoking status, and the study-specific comorbidity index. Also, polypharmacy is associated with an increased risk of falls and hospitalization.

Methods: The research was a secondary analysis of deidentified data from a retrospective cohort study on older adults aged 65 years or older (with and without dementia) who were seen at a primary healthcare center in Lebanon; our sample consisted of all patients with T2DM (n=190) in the original dataset. We resorted to descriptive statistics. We also used logistic regression to examine possible predictors of polypharmacy, and to determine the association between polypharmacy and health outcomes (falls and hospitalization).

Results: Our study discovered that 81.6 % (n=155) of patients had polypharmacy. Patient ages varied from 65 to over 90 years old, with a mean of 77.48± 6.34 years . More than half of the sample (54.7%) were between 75 to 84 years of age. Female participants were the larger group of 58.5 % (n=111). The average number of medications used was 8.14 ± 4.285 drugs per patient. Age, gender, smoking status, BMI and number of comorbidity were not predictors of polypharmacy in our sample. There was no significant associations between polypharmacy and falls [OR 1.873, 95% CI 0.529-6.627, p =0.330], or between polypharmacy and hospitalizations [OR 2.077, 95% CI 0.989-4.363, p= 0.054]. BMI and the use of CNS active agents were associated with hospitalization in unadjusted models. An increase in number of comorbidities was associated with higher odds of hospitalization in both unadjusted [OR 1.430 95% CI 1.119-1.828, p= 0.004] and adjusted models [AOR 1.398 95% CI 1.075-1.818, p= 0.012].

Conclusion: Polypharmacy is more prevalent among patients 65 years and older, which may be related to the rising frequency of various chronic conditions in this demographic. In our research sample at a primary healthcare facility, we discovered a significant proportion of older patients with T2DM were on polypharmacy. Additional data on possible predictors may aid in the identification of factors associated with polypharmacy in Lebanese older adults with T2DM. In our sample, we found no relationship between polypharmacy and falls or hospitalizations. Further examination of the context-specific definition of polypharmacy and the relationship of polypharmacy with other complications may be informative.

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ABBREVIATIONS

BMI - Body Mass Index
ESCWA - Economic and Social Commission for Western Asia
T2DM - Type 2 Diabetes Mellitus
IDF - International Diabetes Federation
WHO - World Health Organization

CHAPTER 1

INTRODUCTION

1.1. Background of Study

Diabetes is a major public health concern that is attaining epidemic levels worldwide. Globally, diabetes affects around 463 million individuals (20-79 years), with 700 million expected by 2045. Type 2 diabetes mellitus (T2DM) is increasing in most nations with 79% living in low- and middle-income countries. T2DM accounts for about 90% of cases of diabetes globally. Diabetes affects 1 in every 5 adults over the age of 65years (International Diabetes Federation, 2019). Type 2 diabetes mellitus (T2DM) accounts for about 90% of cases of diabetes globally (International Diabetes Federation, 2019). According to Sibai et al. (2004), the Lebanese population transition has been characterized by rapid declines in fertility and mortality, with a greater proportion of people living into old age. By 2025, older adults are expected to account for 10.2% of the population in Lebanon. Generally, between 2015 and 2050, the number of persons aged 60 and above will double from 900 million to 2 billion (moving from 12 percent to 22 percent of the total global population). The population is aging more rapidly than in the past (World Health Organization, 2017). Specifically, the Lebanese population is currently made up approximately 8% of older adults aged 65years and above (World Bank, 2020). Furthermore, the population of Lebanon is aging at the fastest rate among Arab nations, with demographic projections showing that over a quarter of the country's population, or 23%, will be over the age of 65 by 2050 (ESCWA, 2021). In Lebanon, Costanian et al., (2014) reported the prevalence of T2DM to be 15.8%, and Nasrallah et al. (2017) found a T2DM prevalence of 15% in a

community-based sample of Lebanese adults (18 to 79 years). T2DM is a complicated metabolic disorder, which has significant health, social, and economic implications (Li et al, 2019).

Notably, in older adults, T2DM is often accompanied by a number of other chronic medical conditions. These medical conditions include hypertension, solid or hematologic cancers, and persistent heart failure, obesity, hyperlipidemia, kidney failure, as well as geriatric syndromes such as cognitive decline, anxiety, falls, and disability (Dardano et al., 2014; Dobrică et al., 2019; Kirkman et al., 2012). Multiple medications are necessary to manage diabetes and the various comorbidities (Emslie-Smith, Dowall & Morris, 2003), resulting in a phenomenon described as "polypharmacy", with patients taking five or more drugs simultaneously (Dorks et al., 2016; Turner et al., 2016; Jokanovic et al., 2015; Masnoon et al. 2017). Also, polypharmacy may lead physicians to misinterpret adverse drug reactions as the onset of a new medical condition, resulting in additional prescriptions based on such misdiagnoses that exacerbate the phenomenon of polypharmacy (Peron et al., 2015). Polypharmacy is increasing in prevalence as overall life expectancy increases, owing to the occurrence of multiple chronic conditions (Sakib et al., 2019). T2DM is a significant contributor to polypharmacy in older adults, with the need to prevent and treat related comorbidity clusters such as macrovascular and microvascular complications (Dobrică et al., 2019; Horii et al. 2019).

A number of studies have investigated factors associated with polypharmacy. Li et al. (2019) studied the prevalence and predictors of polypharmacy among T2DM in Ningbo, China. Their findings showed age, duration of T2DM, length of hospitalization, poor blood glucose level, and comorbidities as predictors of polypharmacy. Similarly, a

study by Assari, Wisseh, and Bazargan (2019) on obesity and polypharmacy revealed that older African American women who are obese have an increased risk of polypharmacy mainly due to comorbidities. Additionally, two other studies revealed that increasing age, low income, low level of education, higher Body Mass Index (BMI), long-term diabetes, excessive smoking, and cardiovascular disease are all predictors of polypharmacy in primary healthcare center (Slater et al., 2018; Oort et al. 2021).

Finally, dementia may be a significant risk factor for polypharmacy. It is also worth noting that polypharmacy is associated with an increased risk of dementia in older persons with T2DM, increasing the risk by 1.5–2.5 times (Strachan et al., 2011). Maust et al. (2021) showed that 13.9 % of older adults with dementia filled prescriptions in 2018 was associated with central nervous system (CNS)-active polypharmacy (prescriptions filled concurrently for three or more drugs from the following pharmacological classes: antidepressants, antipsychotics, antiepileptics, benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonist hypnotics, and opioids). The exposed older adults had a greater total burden of medical comorbidity and a considerably higher prevalence of all clinical variables of concern, including noncancer pain, sleeplessness, mental diagnoses, and seizure disorders (all $p < 0.001$). Similarly, Walsh et al. (2016) revealed that polypharmacy (five drugs) was associated with older dementia patients (≥70 years old) on hospital admission. Psychotropic polypharmacy (≥ 2 psychotropics) is more prevalent in persons with dementia than in those without dementia (p 0.001). Therefore, identifying predictors of polypharmacy helps clinicians address those factors in an effort to limit the number of prescribed medications.

1.2. Significance

Importantly, polypharmacy may be associated with adverse health outcomes. Previous studies revealed that polypharmacy among older adults with T2DM is associated with an increase in the likelihood of an undesirable drug incident, drug-drug interactions, treatment duplication, depression, mortality, myocardial infarction, falls, severe renal failure, hospitalization, and decrease adherence to diabetes medication (AL-Musawe et al. 2019; Bailey & Kodack, 2011; Dhalwani et al. 2017; Dorks et al., 2016; Golchin et al., 2015; Huang et al. 2010; Peron et al., 2015; Rodrigues & Oliveira, 2016; Vinik et al., 2015). Studying the association of polypharmacy with major outcomes (such as falls and hospitalizations) may provide crucial information, leading clinicians to prescribe drugs with caution, especially in vulnerable populations such as older adults with T2DM.

By 2050, the world's population of older adults will reach two billion (United Nations Population Fund, 2012).T2DM is one of the most prevalent chronic diseases in older adults aged 65 years, and the number of diabetic aged persons is increasing globally (Dardano et al., 2014; Noale et al. 2016). According to Kim et al. (2012), older adults aged 65 and above with diabetes are expected to make up the majority in the future, along with a variety of comorbidities including cognitive impairment, depression, muscle weaknesses, fractures associated with falls, and physical frailty. Therefore, they are a vulnerable population requiring special attention and care. Also, Khezrian et al. (2020) indicated that polypharmacy is one of the most serious public health problems facing older adults, and the burden is expected to grow as they suffer from more chronic conditions. Hence, priority needs to be placed on the immediate and

effective management of polypharmacy in order to reduce prescription risks and costs in older adults.

Numerous studies on polypharmacy in older adults, including those with T2DM, have been conducted in developed countries such as the United States, Europe, Canada, Asia, and certain parts of the Middle East (Badawy et al. 2020; Huang et al 2010; Huang et al 2021; Li et al. 2019; Pijpers et al. 2012; Oort et al. 2021). Notably, relatively little research has been conducted in low and middle-income countries on polypharmacy and older adults with T2DM. Importantly, polypharmacy (the use of more than five medications) was assessed to be prevalent in the Lebanese population at 50.9 % of older adults aged 60 years not specifically T2DM (Rahi et al., 2020). Similarly, the demography of older adults is fast expanding in developed and developing nations, and as the population ages, more chronic diseases become prevalent (ESCWA, 2021; Shetty, 2012; World Bank, 2020,). In addition, few studies were done involving primary healthcare centers (Badawy et al. 2020; Oort et a. 2021; Slater et al. 2018). Furthermore, few studies have been conducted exclusively on older adults with T2DM, who are at a higher risk of developing hypertension, heart failure, kidney failure, and myocardial infarction due to their advanced age. The issues confronting this vulnerable group need attention, and this research is crucial (Dobrica et al., 2019, Huang et al. 2010; Huang et 2021; Horii et al. 2019). There has been no study to date on polypharmacy prescription among older adults with T2DM in a healthcare setting in Lebanon. As such, the goal of this research is to investigate the proportion of patients with polypharmacy, its predictors, and associated health outcomes in older adults with T2DM who attend a Lebanon primary health care facility. The insights gained will assist clinicians in designing therapies and interventions that will aid in decreasing the

dire consequences of polypharmacy in this vulnerable population accessing primary health care service.

1.3. Study Aims

The specific aims of this study are as follows, as specifically related to a sample of older adults with T2DM at a primary health care center in Lebanon:

1. To determine the proportion of patients with polypharmacy in the sample
2. To identify the predictors of polypharmacy
3. To examine the association between polypharmacy and health outcomes (falls and all-cause hospitalization)

The current study will test the following hypotheses.

1.4. Aim 2 and Aim 3

Ho: Age, gender, BMI, smoking status, and study-specific comorbidity index are not positively associated with polypharmacy

H_1: Age, gender, BMI, smoking status, and study-specific comorbidity index are positively associated with polypharmacy

Ho: Polypharmacy is not associated with falls and hospitalization

H_1: Polypharmacy is positively associated with falls and hospitalization

CHAPTER 2

LITERATURE REVIEW

2.1. Introduction

This chapter reviews the literature about polypharmacy and is divided into three sections as follows: Proportion of polypharmacy among older adults, factors associated with polypharmacy, and associated health outcomes (fall and hospitalization).

2.2. Prevalence of polypharmacy among older adults

In some countries, the rising proportion of concurrent medications' use has been thoroughly investigated and documented. The developing world is becoming greyer and by 2050, one in every five persons in developing countries will be beyond the age of 60 (Shetty, 2012). Even though the proportion of older adults in less-developed countries is significantly higher, there is scarce research on polypharmacy, which is a growing phenomenon with it attending consequences in the older adults population. By 2050, 80% of the world's two billion older adults would reside in developing countries (Shetty, 2012).

Polypharmacy is prevalent across all age groups; however, it is much higher and globally more common among older adults. A cross-sectional analysis of polypharmacy prevalence by Midão et al. (2018) in 17 European countries and Israel, revealed that the prevalence of polypharmacy (five or more drugs taken concurrently) among those aged 65 years and older ranges between 26.3% and 39.9%. The study revealed that Switzerland, Croatia, and Slovenia had a lower prevalence of polypharmacy, while

Portugal, Israel, and the Czech Republic had higher rates of polypharmacy. Also, in England, a study by Dhalwani et al. (2017) revealed that older adults over 60 years of age taking five or more drugs comprised 30.9% of the overall study population and had a 21% risk of fall over the two years period of the study. Salvi et al. (2017) conducted a study in the emergency department in Italy; the authors found that 30.3% of older adults (65 years and older) in the emergency department of a geriatric hospital in Italy had taken 6–9 medications simultaneously, indicating polypharmacy, and 17.8% had taken ten or more drugs, indicating excessive polypharmacy (defined as taking concurrently ten drugs). Moreover, Golchin et al. (2015) a cross-sectional study of polypharmacy in 59 older adults over the age of 65 years from three separate community centers in Cuyahoga county (USA), with a mean age of 76.9 years. The findings revealed that 24 (40.6%) used several pharmacies and 21 (35.6 %) patients were prescribed more than five drugs. Furthermore, Carmona-Torres et al. (2018) found that 21.9 % of community-dwelling older adults over 65 years in Spain had polypharmacy, 0.6 % had excessive polypharmacy, and 10.7 % had self-medication. Similarly, a French study conducted by Bongue et al. (2009) discovered that 30% of older adults had polypharmacy, while an Italian study conducted by Nobili et al. (2011) discovered that 51.9 % of hospitalized and 67.0 % of discharged older adults aged 65 and over, used more than five medications daily.

In Asia, the prevalence of polypharmacy among older adults is also reported. In China, over 72.2% of patients with T2DM were prescribed polypharmacy, with an average of eight medicines (Li et al., 2019). Also, the Korean situation reveals an estimated prevalence of polypharmacy of 86.4% among older adults 65 years and older who received six or more prescriptions daily (Kim et al, 2014). Similarly, in Japan

between 2010 and 2016, the prevalence of polypharmacy among older adults 65 and older rose from 85.2% to 93.8% per 1,000 persons per month, while excessive polypharmacy climbed from 13.6% to 14.0% per 1,000 persons per month (Onoue et al., 2018).

Finally, when it comes to polypharmacy in older adults, reports of research in the Middle East are also highlighted. A study by Alwhaibi et al. (2018) examined the prevalence of polypharmacy among patients with diabetes in Saudi Arabia. The authors found that overall polypharmacy (five or more drugs) was 77.9% in the sample and 81.7% of the women in the study with diabetes had polypharmacy as compared to men (71.6%). Additionally, the researchers discovered a considerably greater rate of polypharmacy among older adults (≥ 60 years) than among patients between the ages of 18 and 29, at 84.8 % and 37.4 % respectively. Abu Farha et al. (2021) conducted a cross-sectional study on 300 older adults ≥65 years old in Jordan and found that the majority of patients recruited (n=248, 82.7%) experienced polypharmacy (five or more medications); hypertension (n = 240, 80.0%) was the most prevalent medical condition, followed by diabetes (n = 185, 61.7%). In Lebanon, a recent study reported that an estimated 50.9% of older adults aged 60 years and above took at least five drugs daily, however, the study did not report polypharmacy among T2DM (Rahi et al., 2020). Overall, polypharmacy prevalence is observed to vary greatly between countries, yet prescribing rates continue to rise due to the aging population with comorbidities.

2.3. Factors associated with polypharmacy

Numerous studies have identified a variety of predictors of polypharmacy in older adults. Several factors associated with polypharmacy have been identified in

research such as age, gender, smoking status, comorbidities, BMI, and obesity. First, a study by Kim et al. (2014) examined the prevalence and predictor variables of polypharmacy among older adults, using data (2010-2011) from the Korea Health Insurance Review and Assessment Service. Data from 319,185 patients aged 65 years and above were analyzed using a multivariate ordinal logistic regression model. Kim et al. (Kim et al. 2014) also found having medical aid, comorbidity, gender (precisely male), and age group (those between 70 – 84 years) as predictors of polypharmacy among older adults. Moreover, in a study by Slater et al. (2018), lower income, obesity, aging, and chronic health conditions were all associated with polypharmacy (5-9 drugs) and hyperpolypharmacy (10 drugs or more) but smoking was not associated with polypharmacy. Similarly, other studies have shown the following factors to be associated with polypharmacy: older age, low educational level, smoking, longer duration of diabetes, obesity, female gender, malnutrition, comorbidities, numerous hospitalizations, patient's clinics' visits, cardiovascular disease, falls, and unbalance (Badawy et al., 2020; Castioni et al., 2017; Noale et al., 2016; Oort et al. 2021). Similarly, Carmona-Torres et al. (2018) conducted a cross-sectional study in Spain with community-dwelling older adults over the age of 65years. The authors utilized logistic regression to discover sex (females), age, being separated/divorced/widowed, lack of education, having a higher body mass index, being immobile for the previous two weeks, and self-medication were all associated with polypharmacy.

Also, Alwhaibi et al. (2018) conducted a cross-sectional study in Saudi Arabia, extracting data from electronic health records at a teaching hospital. Multivariable logistic regression was performed to study the association between polypharmacy and demographic and clinical factors. The results revealed that polypharmacy was

associated with age, gender, and coexisting chronic conditions. Polypharmacy was found to be significantly associated with cardiovascular conditions, mental illness, respiratory diseases, and musculoskeletal conditions. Similarly, Dobrică et al. (2019) conducted a retrospective case (T2DM)-control (no diabetes) study using the medical records of patients at Bucharest's Clinical Emergency Hospital. 63 T2DM patients (mean age 69.19 years, range 46–89 years) were included in the study group and 63 non-diabetic patients (mean age 67.05 years, range 42–93 years) were included in the control group. Results indicated that T2DM patients had more comorbidities and received more medications than non-T2DM patients. Also, Huang et al., (2021), conducted a longitudinal study in England to examine polypharmacy in older adults with and without diabetes. The authors deduced that patients with diabetes who had chronic conditions, were male, and were obese experienced polypharmacy and excessive polypharmacy more frequently than their counterparts without diabetes; interestingly, females with diabetes had a lower rate of polypharmacy compared to patients without diabetes in that study. However, age and smoking were not statistically significant with polypharmacy and excessive polypharmacy. On the other hand, Assari, Wisseh, and Bazargan (2019) found that obese African American older females had a higher risk of polypharmacy than African American males, owing mainly to comorbidities.

In a retrospective, cross-sectional study, Li et al. (2019) studied prescriptions in patients with T2DM in Ningbo, China; they used the medical records of patients with T2DM from a tertiary care department (2012 to 2017). The study results indicated that on average 8 medications were prescribed to patients with T2DM; approximately 75% of those patients with T2DM had polypharmacy. Moreover, increasing age, duration of

T2DM, length of hospitalization, poor blood glucose level, and comorbidities were predictors of polypharmacy. Similarly, Horii et al (2019) studied polypharmacy and oral antidiabetic treatment in T2DM in Japan. The study found that age, the total number of consultations, and body mass index (BMI) influenced polypharmacy. In contrast to the preceding, Abu Farha et al. (2021) a cross-sectional study in Jordan about the prevalence and predictors of polypharmacy among 300 hospitalized patients who agreed to participate in the study, females (45.3%) of the recruited sample (n = 139), and around 48.0% (n = 144) of the study sample were older adults (≥65 years old). The findings discovered that although age and monthly income were significant predictors of polypharmacy, gender, smoking, BMI, and education level were not. Abu Farha et al. highlighted that the inconsistency in the relationship between polypharmacy and gender among varied research suggests that gender may have a distinct effect on polypharmacy in different societies and that this relationship may be subjective and depending on social conventions. Again, smoking may not have been the primary cause of polypharmacy in this study, since non-smokers may have been exposed to other risk factors for polypharmacy that smokers were not exposed to. Similarly, Golchin et al. (2015) in a cross-sectional convenience sample of 59 older adults 65 years or more, found no correlation between polypharmacy and factors such as age, gender, educational level, or the number of comorbidities. Additionally, Golchin et al. noted that these discrepancies may be due to differences in the characteristics of the populations examined and/or sample size. Moreover, Bueno et al. (2016) conducted a cross-sectional study in Brazil with 190 older adults aged 65 years and above with hypertension to explore the relationship between physical activity (PA) in several domains (leisure, locomotion, and occupational) and polypharmacy in hypertensive

patients. The study's findings indicated that poorer PA during leisure and mobility, T2DM, and having three or more diseases were all related to polypharmacy in hypertensive individuals. However, there was no association between polypharmacy and the independent variables such as age, smoking, BMI, gender, alcohol use, educational level, and ethnicity.

Finally, it is worth mentioning that the majority of the studies reviewed discovered an association between polypharmacy and a variety of demographic (age, gender, socioeconomic status) and clinical variables (obesity, comorbidities) characteristics in older adults, including those with T2DM.

2.4. Polypharmacy and associated health outcomes

Polypharmacy has been linked to a variety of negative health outcomes in the literature, including frailty, mortality, cognitive impairment, and adverse drug reaction. In this paper, there will be particular emphasis on falls and hospitalizations as possible health outcomes of polypharmacy in the study sample.

2.4.1. Falls

Falls, particularly in older adults, can result in serious injuries and are associated with a high rate of morbidity and mortality. According to Kannus et al. (2005), 5% of falls resulted in fractures, and fall-related injuries were the 5th leading cause of mortality in older adults, which accounted for more than 80% of injury-related hospitalizations in people over the age of 65years. The risk of falling varies according to the kind of medicine used; central nervous system medications, such as

antipsychotics, antiparkinsonian medications, and narcotic analgesia, are thought to be the most significantly connected with falls (Shuto et al., 2010).

Dhalwani et al. (2017) in a longitudinal study assessed the association between polypharmacy and falls; a sample of 5213 older adults (60 years and above) was studied over two years. The authors reported that approximately one-third of the general population that used five or more drugs had a 21% increased risk of falling over a 2-year period. Participants using ≥ 4 medications had an 18% fall rate, while those with ≥ 10 medications had a 50% fall rate. Similarly, Pijpers et al. (2012) examined whether older adults (65 years) with or without diabetes had an increased risk of recurrent falls: an analysis of potential mediating factors from the Amsterdam Longitudinal Ageing Study. After a 139-week follow-up period using Poisson regression, the study found that 30.6 % of older adults with diabetes and 19.4 % of older adults without diabetes fell recurrently [incidence rate of 129.7 versus 77.4 per 1,000 persons-years, respectively, HR = 1.67 (95 % CI:1.11–2.51). Adjustments for possible confounding variables had no effect on the increased risk of diabetes [HR = 1.63 (1.06–2.52)]. Additionally, the authors noted that the following factors contributed to the increased risk of falls: increased number of diabetes-related medication use (≥4), increased pain levels, decrease self-perceived health, decrease physical activity and grip strength, increased limitations in ADLs, lower-extremity physical performance, and cognitive impairment. Considered collectively, these factors explained 47% of the increased risk of recurrent falls associated with diabetes [adjusted HR = 1.30 (0.79–2.11)].

In a systematic review, Zia, Kamaruzzaman, and Tan (2015) in a systematic review study found that using ≥ 4 medications is associated with an increased risk of falls, repeated falls, and injurious falls in older adults. However, Zia et al. (2015)

observed that polypharmacy the risk of falls remains high regardless of whether the term "polypharmacy" was ≥ 4 or ≥ 5 drugs according to their research. Inappropriate polypharmacy is linked to severe drug responses in older adults. Moreover, the study done by Huang et al. (2010), found that adults with T2DM prescribed ≥ 4 drugs had an increased risk of falling. The authors found female gender, increasing age, Non-Hispanic white had a higher increased incidence of falls. The authors found that none of the glucose-lowering drugs they studied increased the incidence of falls in patients.

2.4.2. Hospitalization

Over the last two decades, there has been a significant increase in hospitalizations resulting from adverse drug events (due to polypharmacy); this phenomenon is prominent in older adults above the age of 80 years, thus, an important health consequence for older adults (Hilmer & Gnjidic, 2009).

AL-Musawe et al. (2019) in a systematic review analyzed the literature from four databases on polypharmacy and its associated health consequences for T2DM in older adults. The results showed that polypharmacy was associated with all-cause mortality ($p<0.001$) and myocardial infarction ($p <0.001$). Additionally, a non-significant relationship between polypharmacy and stroke ($p = 0.538$) and hospitalization ($p = 0.057$) was discovered. However, Using categorical criteria, pooled risk estimates indicate that polypharmacy is related to an increased risk of all-cause mortality, and macrovascular complications.

Akshar et al. (2012) conducted a retrospective chart review at a tertiary medical institution to examine polypharmacy and its effects on 324 older people over the age of 65 years. Participants were divided into three groups based on their medication burden:

those with a low medication burden (≤ 5 drugs, n=60), those with a medium medication burden (between 5 and ≤ 10 drugs, n=159), and those with a high medication burden (more than > 10 drugs, n=105). A multivariate logistic regression analysis revealed that patients with a high medication burden (> 10 medications) had a greater burden of hospitalization than the other two groups.

Also, a prospective cohort study conducted by Sganga et al. (2015), examined 480 older adults in geriatric and internal medicine acute care hospitals in Italy. Participants were divided into two groups according to the number of drugs prescribed at hospital discharge: those with no polypharmacy (< 8drugs) and those with polypharmacy (≥ 8 drugs). The findings indicated that 253 (52.7%) were female and that 238 (49.6 percent) used multiple drugs (≥ 8 drugs). The study also revealed that 39.1% of participants in the polypharmacy group and 26.9% of participants in the no polypharmacy group were readmitted ($p < 0.004$). The polypharmacy group had a significantly higher risk of one-year rehospitalization than the non-polypharmacy group (RR = 1.81, 95 % CI = 1.18–2.75). Polypharmacy (≥8) was significantly associated with a higher prevalence of diabetes ($p < 0.01$), ischemic heart disease ($p < 0.01$), and heart failure ($p < 0.01$), as well as a significantly higher Charlson Comorbidity Index ($p < 0.01$) when compared to those with no polypharmacy. Similarly, a 5-year nationwide Korean longitudinal cohort study (Chang et al., 2020) examined polypharmacy, hospitalization, and mortality risk in 3,007,620 older adults (≥ 65 years) who received at least one routinely prescribed drug but had no previous hospitalization within a year. During the 5-year follow-up period, 2,028,062 (67.4 %) patients were hospitalized, and polypharmacy (≥ 5 prescription drugs per day) was associated with an increased risk of

hospitalization and mortality, with adjusted HRs (95 % confidence intervals) of 1.18 (1.18–1.19) and 1.25 (1.24–1.25), respectively.

Additionally, taking multiple medications simultaneously can increase the risk of adverse drug reactions, which are estimated to account for 6.5% of hospital admissions and are preventable in 70% of cases (Cantlay et al., 2016). Furthermore, according to a systematic review conducted by Howard et al. (2007), the nine research papers most frequently used medicine classes collectively represent more than 50% of all drug classes involved with avoidable drug-related hospitalizations: antiplatelets (16%), diuretics (15.9%), non-steroidal anti-inflammatory drugs (11%) and anticoagulants (8.3%). Similarly, a systematic review of literature from 1966 to September 2012, conducted using the PubMed search engine by Salvi et al. (2012) identified warfarin, oral antiplatelet medicines, insulin and oral hypoglycemic medications, and central nervous system agents as the most frequently used drugs in older adults, accounting for most of the emergency hospitalizations.

Several gaps have been found in the aforementioned literature evaluation. First, there are no studies that we are aware of that examined the predictors and health outcomes of polypharmacy in older people with T2DM in Lebanon. Second, the majority of prior research was done in high-income countries. Also, most of the studies were not done at the primary health care centers. Finally, most of the studies' reviews focused on the prevalence, determinants, and consequences of polypharmacy on older adults. Also, the studies that looked at T2DM mostly examined the prevalence of polypharmacy and associated factors. There were few studies on the predictors and adverse health consequences of polypharmacy in older adults over 65 or more years with T2DM. The current study will address the above-mentioned gaps by conducting a

thorough assessment of the predictors and health outcomes (falls and hospitalization) of polypharmacy in older adults with T2DM at a primary healthcare center in a low and middle-income country.

2.5. Conceptual framework

The conceptual framework for this study was adapted from the model by Khezrian et al (2020). The Khezrian model was developed after a comprehensive narrative literature review that was aimed to appraise and summarize recent studies published about polypharmacy. The model identifies the factors that contribute to the determinants and prevalence of polypharmacy as reported in various research. Additionally, the model demonstrates the complex relationship between polypharmacy and health outcomes. Most adverse events related to polypharmacy occur irrespective of pre-existing multimorbidity conditions of the patient according to the authors. Finally, it summarized some of the research on the relationship between polypharmacy and health outcomes in older adults, with a specific focus on frailty, hospitalization, and mortality. Therefore, health outcomes may aggravate the incidence of polypharmacy, implying a bidirectional association. For instance, individuals with polypharmacy have a much greater likelihood of adverse drug reactions (ADR). Contrary to popular belief, patients may need additional medicine to alleviate or manage these unpleasant effects. This model will direct our investigation on predictors and health outcomes of polypharmacy in older adults with T2DM. We elaborate on selected concepts we used in the model, specifically age and older adults, comorbidities, polypharmacy, and falls. The conceptual framework for this study was adapted from the model by Khezrian et al (2020). The Khezrian model was developed after comprehensive narrative literature

review that was aimed to appraise and to summarise recent studies published about polypharmacy.

2.5.1. Definition of key concepts

2.5.1.1 Aging and Older Adults

The term "aging" has been variously defined in the biomedical literature. Comfort (1979) defined aging as "a progressive increase throughout life, or after a given stadium, in the likelihood that a given individual will die, during the next succeeding unit of time, from randomly distributed causes." According to Rose (1991), "Aging is a persistent decline in the age-specific fitness components of an organism due to internal physiological deterioration." Aging has also been defined from a biological, psychological, and social perspective. According to Adams & White (2004), the deterioration in a living organism's physiological capabilities to match requirements over the period is referred to as biological aging. Psychological aging occurs due to an individual's changing mental functions, while social aging refers to the changes in an individual's responsibilities and variations in a person's family and societal ties. Lee et al. (2018) classified the population of older adults (65 years and older) into three distinct groups: the youngest-old, aged 65 to 74 years; the middle-old, aged 75 to 84 years; and the oldest-old, over 85 years.

2.5.1.2. Comorbidity

The coexistence of two or more chronic conditions is referred to as comorbidity. As death rates have decrease and there are more older adults living with comorbidities, it has become more common among older adults (Salive, 2013).

2.5.1.3. Dementia

Dementia is a leading cause of disability and dependency among the world's older adults. Dementia is a progressive syndrome in which the ability to process thoughts deteriorates beyond normal aging. Memory, cognition, orientation, comprehension, calculation, learning capacity, language, and judgment are all impacted. Cognitive impairment is typically accompanied, and in certain situations mainly characterized by a loss of emotional control, social behavior, or motivation (WHO, 2020).

2.5.1.4. Polypharmacy

Polypharmacy is a broad term that refers to the usage of several drugs by the same person simultaneously; however, there is no standard definition among researchers, medical practitioners, and global health organizations or regulators (Bushardt, 2008). Polypharmacy has been studied widely across the world using a variety of definitions. Polypharmacy is defined numerically and descriptively. Masnoon et al. (2017) in their comprehensive systematic literature review of the definition of polypharmacy reveal that the most common polypharmacy definition was referred to as the concurrent use of five or more medications. The second most widely used polypharmacy definition was six or more drugs. A further numerical definition of the term pegs the threshold at the concomitant use of 5 to 9 medicines, often referred to as "polypharmacy." A higher dimension of the definitions by other scholars considers using 10 or more drugs, which is referred to as excessive polypharmacy. According to Masnoon et al (2017) polypharmacy is defined descriptively as "co-prescribing

numerous medicines" and "simultaneous and long-term usage of various medicines by the same person" and "concurrent use of multiple medications". Polypharmacy is defined by the World Health Organization (WHO) as "the administration of many drugs at the same time or the administration of an excessive number of drugs" (WHO, 2004). Similarly, Oort et al. (2021) classified polypharmacy as follows: none (0–4 medications), moderate (5–9 medications), and severe (≥10 medications).

2.5.1.5. Falls

According to Kenny et al. (2017), there is no universally accepted definition of falls; however, the frequently accepted definition is the one used by the American Geriatrics Society (AGS) and the British Geriatrics Society (BGS) falls prevention recommendations, which says "*a fall is an unexpected event in which the participant comes to rest on the ground, floor or lower level without known loss of consciousness.*

2.6. Conceptual Model

Demographic and clinical variables Health Outcomes

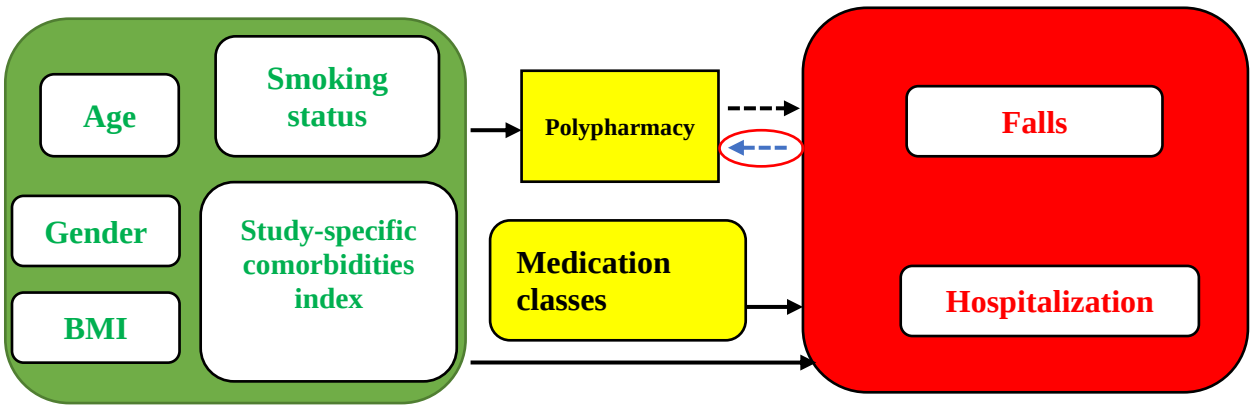

Figure 1. The adapted version of Khezrian et al. (2020) with demographic and clinical variables; and health Outcomes of Polypharmacy.

In reference to the adapted version of the Khezrian model in figure 1, polypharmacy is hypothesized to be predicted by many factors including age, gender, specific-study comorbidity index, and other modifiable variables (smoking status, BMI). Similarly, the adapted model seeks to show the direct relationship between the (demographic and clinical variables) and the health outcomes (falls and hospitalization). Importantly, the model will be used to examine the association between medication classes and health outcomes of interest (falls and hospitalization).

Additionally, the Khezrian model demonstrated the complex relationship between polypharmacy and health outcomes. The authors showed that health outcomes that were associated with polypharmacy are independent of pre-existing multiple health conditions of the patient. Therefore, health outcomes may aggravate the incidence of polypharmacy, implying a bidirectional association as shown in the red circle. Particularly, individuals who take several medications have a substantially greater risk of falls and hospitalizations. Contrary to expectations, these patients may need additional medicines to prevent or manage falls and hospitalization. However, in our current study, we examined the association between polypharmacy and health outcomes (falls and hospitalization) and not the bidirectional relationship. We examined the association of the following medication classes (CNS active agents, antidiabetic drugs, cardiovascular medications, and antihyperlipidemic) and health outcomes in older adults with T2DM.

2.7. Study research questions

1. What is the proportion of polypharmacy among older adults with T2DM?
2. What are the predictors of polypharmacy among older adult with T2DM?
3. What is the association between polypharmacy and health outcomes (falls and all-cause hospitalization)?

CHAPTER 3

METHODOLOGY

The study was a secondary analysis of de-identified data from the following study at the Department of Family Medicine, American University of Beirut Medical Center (AUBMC) " The association between polypharmacy and dementia in primary care: a case-control study". The investigators of the original study used a retrospective cohort design to examine polypharmacy and prescription of potentially inappropriate medications in community-dwelling older adults ≥65 with dementia and a control group of patients without dementia (Dementia cases to controls ratio was set at 1:3) in a primary health care center. Data was collected in 2017 prior to the COVID-19 pandemic.

3.1. Sample and sample size

The study participants were based on a subset from the main dementia cohort dataset. The subset consisted of all patients with T2DM (n=190), in the above-mentioned primary healthcare cohort of older adults ≥ 65 years of age. In this particular subsample, there were 45 older adults who were selected as cases and 145 older adults selected as controls. Of note, the original study purposefully included older adults ≥ 65 years with dementia. In addressing our study aims that are different from those of the original study, we integrated the dementia variable in a study-specific comorbidity index that was developed. The sample size calculation was done based on study aim 2 with polypharmacy as an outcome and the proportion of polypharmacy estimated at 50.9% of older adults aged 60 years and above in the Lebanese population in the previous study (Rahi et al. 2020). For a logistic regression with 9 predictors (age,

gender, Body Mass Index (BMI), smoking status, and study-specific comorbidity index), assuming 10 cases per predictor and a 50% proportion of polypharmacy in older adults in Lebanon (Rahi et al. 2020) a minimum sample size of 180 is required. Thus, the sample size of 190 is adequate for the analysis.

3.2. Research design

The current study is based on the original study that used a retrospective cohort design. To examine the predictors of polypharmacy, we used "baseline data" consisting of data at reference or selected date. Reference date indicates the date of diagnosis of the cases with dementia, and selection date refers to the date of selection of controls in the original study. In investigating the association between polypharmacy and outcomes (falls and hospitalizations), data on events was used as captured in the dataset, namely within three years from the reference dates in cases (date of diagnosis of dementia) and controls (clinic visit date at selection time) who utilize outpatient services at least once.

3.3. Study variables

3.3.1. Polypharmacy:

The main study variable was polypharmacy, which serves as the outcome variable for aim 2 and as the main predictor for aim 3 in the study. Masnoon et al. (2017) defined polypharmacy as the concurrent use of five or more medications (≥5) per day, while excessive polypharmacy was defined as the cumulative use of more than ten medications (>10) per day. The prevalence of polypharmacy is defined as the percentage of people who take five or more medications daily. In our study, we defined polypharmacy as the use of five or more medications by patients (YES) and no polypharmacy as the use of fewer than five drugs ((NO).

3.3.2. Predictors:

The predictors in the study were age, gender, BMI, smoking, and study-specific comorbidity index.

- **Age:** The older adults were defined (65 years or older), and "age" was categorized into 3 groups as the youngest-old, aged 65 to 74 years; the middle-old, aged 75 to 84 years; and the oldest-old, over 85 years (Lee et al., 2018). For the purposes of this research, we considered age (65–90+ years) as a continuous variable and further divide it into three categories for statistical analysis: 65–75 years, 75–84 years, and over 85 years.
- **Gender:** Participants were categorized as males and females.
- **Smoking status:** The study examined the smoking status of participants and group them as current smokers, ex-smokers, and non-smokers.
- **Body Mass Index** (**BMI):** BMI was determined by dividing weight in kilograms by height in meters squared. According to the World Health Organization (2021), overweight is a BMI of 25 kg/m² or more in adults, while obesity is defined as a BMI of 30 kg/m² or greater in adults. Also, the Centers for Disease Control and Prevention (2021), BMI less than 18.5 kg/m² indicates underweight, 18.5 kg/m² to < 25 indicates normal, 25.0 to < 30 kg/m² indicates overweight, and >30.0 kg/m² indicates obesity). In our study, we used the classification of BMI by the Center for Disease Control and Prevention (2021).
- **Dementia:** Dementia was be included in the study-specific comorbidity index.
- **Study-specific comorbidity index:** The comorbidities included in the index were history of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident, hemiplegia, dementia, chronic pulmonary

disease, connective tissue disease, peptic ulcer disease, liver disease, moderate to chronic renal disease, malignancy/Tumor leukemia, and lymphoma. We developed a study-specific comorbidity index to concentrate on particular comorbidities associated with polypharmacy, falls, and hospitalization, based on the literature [Charlson et al. (1987), Sganga et al. (2015), and Vrettos et al. (2017)] and the dataset. The index was created by counting the number of comorbidities experienced by each patient and adding them up to create a study-specific comorbidity index.

- **Medications classes:** In the original study, medication classifications were based on the 2018 Anatomical Therapeutic Chemical (ATC) classification system devised by the WHO Collaborating Centre for Drug Statistics Methodology (WHO, 2018). Drug classes were taken into consideration until the 5th level of the ATC classification. We considered medication classes that may relate to falls and hospitalizations, such as CNS active agents, antidiabetic drugs, antihyperlipidemic drugs, and cardiovascular drugs. Last prescription preceding reference date cases and selection date for controls (medications/classes, as in source dataset). Our research was based on the last prescription before reference and selection date for analysis.

3.4. Health Outcomes

3.4.1. Falls:

In our study, we looked at the number of visits per patient to the emergency room with falls as a reason and the number of hospital admissions with falls as the reason for admission within three years after the selection or reference date. We combined the

emergency room visit with fall as reason and hospital admission with fall as the reason to form the fall variable in our study. Therefore, the fall variable represented at least one fall for a recorded emergency room visit with fall, or hospital admission with fall and was classified as "YES" for falls (at least one fall), while the absence of any fall was classified as "NO" for falls.

3.4.2. Hospitalization:

We account for the hospitalization rate based on the number of hospital admissions per patient within three years after the selection or reference date. The hospitalization was categorized into at least one hospitalization and no hospitalization (1=Yes for all-cause hospitalization) and (0= No hospitalization).

3.5. Ethical considerations

Prior to the start of the original study, approval was obtained from the American University of Beirut's Institutional Review Board (IRB) and the American University of Beirut Medical Center (AUBMC) administration for retrieval and ethical usage of the database. We obtained exempt approval from IRB for the current study (secondary data analysis) which was based on a de-identified dataset.

3.6. Data management

The original dataset was stored in an Excel file and then imported into IBM SPSS; we performed data cleaning, addressed missing data and created new variables. To begin, we assigned a unique research ID to our 190 T2DM patients. Additionally, we searched for missing values for all of our variables of interest and discovered that smoking status had one missing data (.5%), fall variable had one missing data (.5%),

and hospitalization had one missing data (.5%), all of which were less than 5%. However, the BMI variable had 33 missing data totaling more than 5% within a single variable, which we addressed using the "Impute missing values using Mean/Median" technique [i.e., the BMI variable had 33 missing values more than 5%, which were imputed using the mean approach (age group and gender specific)]. Variables on "polypharmacy", "study-specific comorbidity index", "falls" and "hospitalizations" were created as described above (in Methodology). Moreover, the variable on "total number of drugs per patient" was created by counting the number of medications for each patient, and the variables on classes of medications used in the analysis were created with "yes" denoting the patient using at least one drug belonging to each of the class of central nervous system active agents, cardiovascular drugs, antihyperlipidemic and antidiabetics.

3.7. Data Analysis

Dataset was obtained, data cleaning and management were performed for the purposes of our study. Data analysis was conducted using the IBM SPSS version 28. Descriptive statistics were conducted on demographic and clinical variables to examine the distribution of individual variables, and minimum and maximum values (to identify outliers). Means and standard deviations were calculated for continuous variables, frequencies and percentages were reported for categorical variables. Bivariate analysis (using Chi square test and independent sample t-test) was performed to study the association between individual independent variables and polypharmacy as a dependent variable. Descriptive statistics were used to address **aim 1** of the study. Further analyses

were conducted as such: **Aim 2:** Logistic regression was used to calculate the odds ratios (ORs) and 95% confidence intervals (CI) to investigate predictors of polypharmacy at reference or selected date. The dependent variable **(aim 2)** was polypharmacy. We consider independent variables such as age, gender, Body Mass Index (BMI), smoking status, and study-specific comorbidity index (including dementia, as mentioned in the section on "study variables"). **Aim 3:** Logistic regression analysis was used to examine the association between polypharmacy (independent variable) and health outcomes (dependent variables: falls and all-cause hospitalizations). We considered covariates such as age, gender, smoking status, BMI, study-specific comorbidity index. Also, relevant medication classes were included in the models with falls and hospitalizations as outcomes. The statistical significance level was set at $p < 0.05$.

CHAPTER 4

RESULTS

4.1. Sample Characteristics

The sample consisted of 190 older adults with T2DM. The demographic and clinical characteristics of the sample (at selection date or date of diagnosis of dementia as per original dataset) are listed in Tables 1 and 2. The data analysis encompassed data on 100% of the selected participants. Patients' ages ranged from 65 to 90+ years, with a mean of 77.48 ± 6.347 years. Thirty-three percent (n = 64) of the patients were between the ages of 65 and 74 years, 54.7 % (n = 104) were between the ages of 75 and 84 years, and 11.6 % (n = 22) were over the age of 80 years. Furthermore, more than half of the sample (58.4 percent, n=111) were female.

4.2. Polypharmacy

We found that 81.6 % (n=155) had polypharmacy, whereas 18.4 % (n=35) did not (Fig. 2). The mean number of medications per patient was 8.14 ± 4.285. The number of medications prescribed ranged from 1 to 19 with a median of 8 and an interquartile range (IQR) of 6, in the sample. In the “Polypharmacy” group, there were a greater number of females 58.7% (n=91), compared to males 41.3% (n= 64).

4.3. Falls and hospitalizations

The overall fall was presented in 21.7% (n=41) of the sample; 13.8 % (n=26) of falls resulted in emergency room visit, 7.9 % (n=15) resulted in hospital admission. Those who had at least one fall were 13.8 % (n=26) of the sample, as presented with an

emergency room visit or hospital admission. Similarly, 63.0 % (n=119) of patients required hospitalization regardless of the reason for hospitalization (Fig. 3 and 4).

4.4. Medication classes

In our sample, cardiovascular drugs (blood pressure-lowering drugs/other CV Drugs) were the most frequently utilized medication class with the majority of the patients (n=171; 90%) using these medications. Not all patients were on antidiabetic medications (n=141; 74.2%). Other commonly used medications included antihyperlipidemic drugs 60.0% (n=114; 60%) and central nervous system active drugs (n=71; 37.4%).

4.5. Comorbidities

Summarized study's findings on comorbidities are presented in (Table 2). Our findings indicated that moderate to chronic renal disease was the most prevalent comorbidity, accounting for 26.3 % (n=50) of the sample, dementia accounted for 23.2 % (n=44), chronic pulmonary disease accounted for 20.5 % (n=39), and malignancy/tumor accounted for 18.4 % (n=35), congestive heart failure constituted 17.9% (n=34), cerebrovascular accident was 15.8% (n=30), peripheral vascular disease 12.6% (n=24), while the least prevalent comorbidities at almost 10% or less were connective tissue diseases with a prevalence of 10.5% (n=20), history of myocardial infarction 6.3% (n=12), peptic ulcer disease and liver disease with a 5.8 % (n=11) each, leukemia and lymphoma constituted 0.50% (n=1) and 2.1% (n=4), respectively. The comorbidities were further classified into groups, no comorbidity constituted 21.1% (n=40), 1-3 comorbidities accounting for the majority of research participants 68.9%

(n=131) and the least was ≥4 comorbidities, accounting for 10% (Fig 5). Mean and standard deviation of study-specific comorbidity index is stated in the table.

Table 1. Sample characteristics

Variables	**Mean ± SD/ n (%) (N= 190)**
Age (65-90+ years)	77.48 ± 6.347
Age (years)	64 (33.7)
65 to 74 years	104 (54.7)
75 to 84 years	22 (11.6)
Over 85 years	
Gender	
Male	79 (41.6)
Female	111 (58.4)
Smoking status	
Non-smoker	121 (64.0)
Smoker	31 (16.4)
Ex-smoker	37 (19.6)
Body Mass Index (kg/m^2)	30.64 ± 5.294
Normal 18.5 kg/m² to < 25	23 (12.1)
Overweight 25.0 to < 30 kg/m²	67(35.3)
Obesity >30.0 kg/m²	100 (52.6)
Fasting Plasma Glucose (FPG) mg/dl	134.48 ± 47.511
Systolic Blood Pressure (SBP) mmHg	134.28 ± 18.096
Diastolic Blood Pressure (DBP) mmHg	69.52 ± 12.249
Lipid profile	
Total cholesterol mg/dl	170.12 ± 38.987
High Density Lipoprotein (HDL) mg/dl	44.63 ± 13.342
Low Density Lipoprotein (LDL) mg/dl	97.10 ± 30.287
No Polypharmacy (<5 drugs)	35 (18.4)
Polypharmacy (≥5 drugs)	155 (81.6)
Total Number of drugs per patient	8.14 ± 4.285
Fall as a reason of emergency room (ER) visit	26(13.8)
Fall as a reason of hospital admission	15(7.9)
Total falls	41(21.7)
Falls (ER visit or hospital admission) at least one fall	26(13.8)
Hospitalization	119 (63.0)

Medication classes	
Central nervous system drugs	71(37.4)
Cardiovascular (Blood pressure-lowering drugs /other CV Drugs)	171(90.0)
Antihyperlipidemic	114(60.0)
Antidiabetics drugs	141(74.2)

Table 2. Comorbidity in the study sample (n=190)

Comorbidities	**Mean ± SD/ n(%)**
History of myocardial infarction	12(6.3)
Congestive heart failure	34(17.9)
Peripheral vascular disease	24(12.6)
Cerebrovascular accident	30(15.8)
Hemiplegia	3(1.6)
Dementia	44 (23.2)
Chronic Pulmonary Disease	39(20.5)
Connective Tissue Disease	20(10.5)
Peptic Ulcer Disease	11(5.8)
Liver disease	11(5.8)
Moderate to chronic renal disease	50(26.3)
Malignancy/Tumor	35(18.4)
Leukemia	1(0.50)
Lymphoma	4(2.1)
Number of Comorbidities	
None	40(21.1)
1-3	131(68.9)
≥4	19(10.0)
Study-specific comorbidity index	1.66± 1.354

4.6. Bivariate analysis on demographic and polypharmacy

The bivariate associations of all the independent variables (age, gender, smoking status, BMI, number of comorbidities, and study-specific comorbidity index) with polypharmacy were non-significant, with a p-value greater than 0.05 (Table 3). Despite insignificant findings, we then proceed with the whole model analysis in Aim 1, as per preset conceptual model.

Table 3. Bivariate association between demographic and clinical variables, and polypharmacy

Variables	**Polypharmacy <5 NO (N=35) Mean ±SD/ n(%)**	**Polypharmacy ≥5 Yes (N=155) Mean ±SD/ n(%)**	**Chi-square/ T-test statistic**	***p*-value**
Age group (65-90+years)	77.4026±5.805	77.4927±6.481	-.076	.940
Gender				
Male	15(42.9)	64(41.3)	.029	.865
Female	20(57.1)	91(58.7)		
Smoking status				
Non-smoker	22(62.9)	99(64.3)	.478	
Smoker	7(20.0)	24(15.6)		.767
Ex-smoker	6(17.1)	31(20.1)		
Body Mass Index (kg/m^2)	29.743±4.405	30.844±5.466	-1.112	.267
Number of Comorbidities				
None	6(17.1)	34(21.9)	.489	.798
1-3	25(71.4)	106(68.4)		
≥4	4(11.4)	15(9.7)		
Study-specific comorbidity index	1.74±1.314	1.65±1.366	.385	.701

Bivariate analysis using chi-square for categorical variables and independent t-test for continuous variable.

4.7. Factors associated with polypharmacy

We proceeded with analyses, based on our conceptual model. Our findings showed that there were no significant associations between the independent variables (age, gender, smoking status, BMI, number of comorbidities, and study-specific comorbidity index) and polypharmacy, in unadjusted models (Table 4). As age increases, the odd of patients having polypharmacy increases by 1.002 times in our sample [OR 1.002, 95% CI 0.946-1.062], p =0.939]; a non-significant finding. Of note, females were more likely than men to be in the polypharmacy group (58.7 percent vs. 41.3 percent, respectively); $\chi 2$ [1] = 0.029; p= 0. 865, and the odds of having

polypharmacy in the female gender is 1.066 times higher than male gender as reference was [OR 1.066, 95% CI [0.508-2.239]; not a significant finding. Furthermore, when smoking status was analyzed, non-smokers had greater polypharmacy within the polypharmacy group compared to ex-smokers and smokers (64.3% vs 20.1% vs 15.6% respectively; $\chi 2$ [2] =0.478; p=.787) and the odd of polypharmacy in the ex-smokers is 1.148 times higher compared to the non-smoker's. Similarly, the odd of polypharmacy increases by 1.043 times as BMI increases [OR 1.043 95% CI 0.969-1.122, p =0.267]. Additionally, 68.4% of patients with polypharmacy had 1-3 comorbidities group had polypharmacy, those with no comorbidity accounted for 21.9% of the polypharmacy group, and the least was patients with comorbidity ≥4 accounted for 9.7%: $\chi 2$ [2] =0.437, p=0.798. Moreover, as the study-specific comorbidity index increases the odd of polypharmacy is 0.949 times lower, but comorbidity index was not a statistically significant predictor of polypharmacy [OR 0.949, 95% CI 0.726-1.240].

Table 4. Logistic regression analysis to identify predictors of polypharmacy

Variables	**B**	**Unadjusted OR 95 % CI EX(B)**	***p*-value**
Age group (65-90+years)	.002	1.002 [0.946-1.062]	.939
Gender			
Male		Reference	.865
Female	.064	1.066 [0.508-2.239]	
Smoking status			
Non-smoker		Reference	
Smoker	-.272	0.762 [0.292-1.991]	.579
Ex-smoker	.138	1.148 [0.427-3.086]	.784
Body Mass Index (kg/m^2)	.042	1.043 [0.969-1.122]	.267
Study-specific comorbidity index	-.053	0.949 [0.726-1.240]	.699

4.8. Association between polypharmacy and health outcomes

4.8.1. Falls

In examining the association between polypharmacy and falls (emergency room visit with fall as the reason or hospitalization with fall as the reason) in older adults with T2DM within three years (of selection or reference date), our findings showed that taking five or more medications was not associated significantly with falls [OR 1.873, 95% CI 0.529-6.627, p =0.330], (Table 5). The odds of presenting with a fall is almost 1.9 times greater in patients in the polypharmacy (≥5 drugs) group compared to those in the "no polypharmacy" group, with no statistical significance. We present additional findings on covariates (in our model) that did not exhibit significant relationships with the outcome of Fall. Of note, the odds of presenting with falls is 1.048 times higher with a one unit increase in age. Also, the odds of having a falls in females is 1.422 times higher compared to males. Similarly, current smokers had 1.575 times higher odds of presenting with fall compared to non-smokers, and the odds of presenting with a fall being an ex-smoker is 20% lower compared to non-smoker. Moreover, the odds of presenting with fall in patients who were on central nervous system active agents, cardiovascular drugs, antihyperlipidemic drugs, and antidiabetic drugs was 1.552, 1.397, 1.570, and 1.194 times higher compared to patients who were not prescribed those drugs. In summary, age, gender, smoking status, study-specific comorbidity index, and medication classes were not significantly associated with falls in our study.

4.8.2. Hospitalization

In examining the association between polypharmacy and hospitalization outcomes, our findings showed that patients in the polypharmacy (≥5 drugs) group had 2.08 times higher odds of being hospitalized than patients in the "no polypharmacy"

group [OR 2.077, 95% CI 0.989-4.363, p= 0.054 and an adjusted odds ratio (AOR) 2.127, 95% CI 0.627-7.215, p=0.23], (Table 6). Also, the odds of being hospitalized was 1.044 times higher with increasing age [OR 1.044, 95% CI 0.995-1.095, p=0.080]; the latter was not statistically significant. Furthermore, having female gender is 1.8 times the odds of being hospitalized than being male, but the association was not statistically significant [OR 1.816, 95% CI 0.982-3.360, p=.057]. Importantly, as patient BMI increases by one unit, there will be a 5.7% reduction in the odds of hospitalization [OR 0.943 95% CI 0.891-0.998, p= 0.043], which is statistically significant at the univariate model; however, in multiple logistic regression, the association was not significant [AOR 0.945 95% CI 0.888-1.007, p= 0.08]. Similarly, a unit increase in study-specific comorbidities index, the odds of being hospitalized is 1.430 times higher, which is statistically significant in both the univariate and multivariate models [OR 1.430 95% CI 1.119-1.828, p= 0.004] and [AOR 1.398 95% CI 1.075-1.818, p= 0.012]. Moreover, in univariate model, the odds of being hospitalized is 2.242 times higher (significant association) in patients who are on central nervous system active agents compared to patients who were not on central nervous system active agents [OR 2.242, 95% CI 1.174-4.282, p= 0.014]. The latter significant association was not sustained in the adjusted model. Patients who were on cardiovascular medication had 2.037 times higher odds for presenting for hospitalization compared to patients not on cardiovascular drugs, but the association was not statistically significant [OR 2.037 95% CI 0.785-5.288, p= 0.144] in a univariate model. Finally, the odds of being hospitalized were 1.233 and 1.105 times higher in patients who were on antidiabetic and antihyperlipidemic drugs compared to those who were not on those drugs, in univariate

models. There were no significant associations between the latter 3 classes of drugs and hospitalization in the adjusted model as well.

Table 5. Logistic regression to examine association between polypharmacy and falls (Emergency visit with fall or Hospital admission with fall) in older adults with T2DM.

Study variables	**Fall [at least 1] Mean ±SD/ n(%)**	**Unadjusted OR 95% CI EX(B)**	***p*-value**
No Polypharmacy (<5 drugs	3(8.6)	Reference	
Polypharmacy (≥5 drugs)	23(88.5)	1.873 [0.529-6.627]	.330
Age	78.9942 ±1.15202	1.048 [0.980-1.121]	.170
Gender			
Male	9(34.6)	Reference	
Female	17(65.4)	1.422 [0.598-3.378]	.425
Smoking status			
Non-smoker	16(61.5)	Reference	
Smoker	6(23.1)	1.575 [0.560-4.432]	.390
Ex-smoker	4(15.4)	0.795 [0.249-2.546]	.700
Body Mass Index (kg/m^2)	29.642 ±0.8722	0.957 [0.880-1.040]	.300
Study-specific comorbidities index	1.38 ±0.242	0.828 [0.594-1.154]	.264
Medication classes			
Central nervous system drugs	12(46.2)	1.552 [0.673-3.577]	.302
Cardiovascular	24(92.3)	1.397 [0.303-6.436]	.668
Antihyperlipidemic	18(69.2)	1.570 [0.645-3.821]	.320
Antidiabetics drugs	20(76.9)	1.194 [0.450-3.172]	.721

Table 6. Logistic regression to examine association between polypharmacy and hospitalizations in older adults with T2DM.

Study variables	**Hospitalization regardless of reason (at least 1) Mean ±SD/n(%)**	**Unadjusted OR 95 % CI**	***p*-value**	**Adjusted OR 95 % CI**	***p*-value**
No Polypharmacy(<5 drugs)	17(48.6)	Reference			
Polypharmacy (≥5drugs)	102(85.7)	2.077 [0.989-4.363]	**.054**	2.127 [0.627-7.215]	0.23
Age	78.0299 ±0.61	1.044 [0.995-1.095]	.080	1.032 [0.976-1.090]	0.27
Gender	9(34.6)				0.383
Male	17(65.4)	Reference		Reference	
Female		1.816 [0.982-3.360]	**.057**	0.733 [0.364-1.475]	
Smoking status					
Non-smoker	71(59.7)	Reference		Reference	0.515
Smoker	22(18.5)	1.721 [0.732-4.051]	.214	1.546 [0.614-3.889]	0.355
Ex-smoker	26(21.8)	1.665 [0.754-3.676]	.208	1.508 [0.606-3.753]	0.377
Body Mass Index (kg/m^2)	30.038 ±0.46	0.943 [0.891-0.998]	**.043**	0.945 [0.888-1.007]	0.08
Study-specific comorbidity index.	1.88 ±0.13	1.430 [1.119-1.828]	**.004**	1.398 [1.075-1.818]	**0.012**
Medication classes					
CNS drugs	52(43.7)	2.242 [1.174-4.282]	**.014**	1.504 [0.713-3.174]	0.28
Cardiovascular drugs	110(92.4)	2.037 [0.785-5.288]	.144	1.426 [0.385-5.279]	0.59
Antidiabetics	89(74.8)	1.233 [0.676-2.250]	.494	0.802 [0.379-1.698]	0.56
Antihyperlipidemic	74(62.2)	1.105 [0.566-2.160]	.770	0.961 [0.397-2.328]	0.93

CNS: Central Nervous System drugs

CHAPTER 5

DISCUSSION

Polypharmacy is a common phenomenon in older adults and has been linked with dire health outcomes. We investigated the proportion of patients with polypharmacy, and predictors and health outcomes of polypharmacy among older adults with T2DM, in a primary healthcare center in Lebanon. Our findings showed that, in a primary healthcare center , an overwhelming 81.6% of older adults with T2DM (between the ages of 65 or more to 90+ years) had polypharmacy. We did not find an association between age, gender, smoking status, BMI, and study-specific comorbidity and polypharmacy in our sample. Moreover, polypharmacy did not predict falls or hospitalizations.

5.1. Main Findings Compared to the Literature

5.1.1. Proportion of polypharmacy and its Predictors in older adults with T2DM

Polypharmacy prevalence in older adults is on an increasing trend across the globe in both developed and developing countries; various programs have been initiated to reduce these trends in older adults with various disease conditions such as dementia, diabetes, and heart failure. This study focused on older adults with T2DM. Our study found that 81.6% of older adults (65-90+ years) had polypharmacy, a rate similar to those in previous studies on the diabetes population (Alwhaibi et al. 2018; Abu Farha et al. 2021; Kim et al, 2014; & Li et al. 2019). The proportion of patients with polypharmacy in our study was higher compared to those in previous studies on older adults (Badawy et al. 2020; Dhalwani et al. 2017; Golchin et al. 2015; Huang et al. 2021; Noale et al., 2016; Midão et al. 2018; Oort et al. 2021; & Rahi et al. 2020; Slater

et al. 2018; Salvi et al. 2017). Of note, only few studies (Alwhaibi et al; Li et al; Noale et al & Oort et al) focused on older adults with diabetes.

These differences in polypharmacy rates may be due to variations in factors such as sample size and geographical location. Also, there is no standard definition of polypharmacy that is agreed-upon by researchers, medical practitioners, global health organizations and regulators (Bushardt, 2008). Hence, different studies rely on different polypharmacy cutoffs ranging from 2 or more (Nguyen et al. 2006), to five or more (Alwhaibi et al. 2018; Abu Farha et al. 2021; Dhalwani et al. 2017; Masnoon et al. 2017 & Rahi et al. 2020). Sganga et al. (2015) used a cutoff ≥8 as the definition of polypharmacy in their sample. Some studies categorized polypharmacy into three such categories: no polypharmacy (<5), polypharmacy as ≥5 drugs, and excessive polypharmacy as ≥10 drugs (Carmona-Torres et al. 2018; Slater et al. 2018, & Oort et al. 2021).

5.1.2. Factors associated with polypharmacy

The findings of our study have similarity with a number of research investigations undertaken in various populations. Similar to our study, some previous studies found no association between factors such as age, gender, smoking, BMI, the number of comorbidities, other factors (educational level, ethnic group, alcohol consumption), and polypharmacy (Abu Farha et al. 2021; Bueno et al. 2016; Golchin et al. 2015; Huang et al. 2021 & Slater et al. 2018). Also, Castioni et al.(2017) found no association between polypharmacy and gender, marital status or country of birth. Of note, in our sample and within the polypharmacy group, there were more females than males. In fact, a number of previous studies found female gender to predict

polypharmacy (Alwhaibi et al. 2018; Assari et al. 2019; Carmona-Torres et al. 2018; Oort et al. 2021; & Noale et al., 2016). Given the above findings, we could not reject the null hypothesis that age, gender, BMI, smoking status, and study-specific comorbidity index are not associated with polypharmacy.

On the other hand, several studies contradict our findings; those studies had been conducted in different patient populations and settings. The following studies found an association between polypharmacy and increasing age, gender, higher BMI, number of comorbidities, increased number of hospital admission, low education (Alwhaibi et al. 2018; Horii et al 2019; Kim et al. 2014; Li et al. 2019; Noale et al., 2016 & Slater et al. 2018). Similarly, Castioni et al. (2017) found that increasing age, BMI, being a former-smoker, and lower education were associated with polypharmacy

Finally, the inconsistencies in results may be explained by the limited availability of potential variables that could influence polypharmacy in the secondary dataset, variations in population characteristics investigated, and the use of different polypharmacy cutoffs across various studies.

5.1.3. Polypharmacy and associated health outcomes

In the literature, polypharmacy has been related to a number of adverse health outcomes, including frailty, mortality, cognitive impairment, and adverse drug reactions. The focus of our research was on falls and hospitalizations as potential health consequences of polypharmacy.

5.1.3.1. Falls

We found that taking five or more drugs exhibits a higher odds of presenting with a fall compared with those who took less than five drugs, however the results were not statistically significant. Previous studies found taking 4 or more drugs was associated with a high risk for falls (Dhalwani et al. 2017; Huang et al. 2010; Pijpers et al. 2012; Zia et al. 2015) and those taking more than 10 drugs had the highest risk for fall (Dhalwani et al. 2017). However, Zia et al. 2015 indicated in their study that regardless of the definition of polypharmacy being ≥ 4 or ≥5 they observed a high risk for falls in patients. Our results are inconsistent with previous studies possibly due to methodologic differences such as differences in polypharmacy cutoffs. In contrast, a review by Al-Musawe et al. (2019) with a polypharmacy cutoff of ≥5 meditations found no correlation between polypharmacy and fall or risk of falling. This was consistent with our results.

Although we found higher odds of falls by age and female gender, the results were not statistically significant. However, other studies found age and female gender to be significant predictors of falls (Huang et al. 2010; Horii et al 2019). We found that smoking increases the odds of a patient presenting with falls compared to non-smokers, but these results were not statistically significant; previous studies did not examine the effect of smoking on falls. Furthermore, our results showed that an increase in BMI and study-specific comorbidity index lowers the odds of patients presenting with a fall but our results were not statistically significant. Moreover, the most frequently prescribed medication in our sample was cardiovascular drugs which was consistent with a study by Dhalwani et al. (2017) whose study was in the older adult population. The explanation here is that the majority of our sample had cardiovascular conditions as

comorbidities. On the other hand, in Alwhaibi et al. (2018), antidiabetics were the most prescribed medication in their sample.

Additionally, our study further found that patients had an increased odds of presenting with falls if they were on central nervous system active agents, cardiovascular drugs, antihyperlipidemic drugs, and antidiabetic drugs compared to patients who were not prescribed those drugs; these results were not statistically significant, even in the unadjusted model. Considering the absence of statistical significance of predictors of falls in our study, the explanation could be that additional variables being used in other studies compared to our study may account for the disparity.

5.1.3.2. Hospitalization

Polypharmacy is associated with a significant rise in adverse drug events in older adults, resulting in a detrimental health outcome of hospitalization (Hilmer & Gnjidic, 2009). We examined the association of polypharmacy and hospitalization in older adults with T2DM. The covariates in our analysis were age, gender, smoking status, BMI, study-specific comorbidity index, and medication classes.

Our results showed that patients who were prescribed more than five drugs had greater odds of being hospitalized (than those prescribed less than five drugs) with a p-value of 0.054 which was on the borderline , however this was not a significant finding. Few studies have found significant associations between polypharmacy and hospitalization (Chang et al., 2020; Sganga et al. 2015). However, AL-Musawe et al. (2019) found non-significant relationship between polypharmacy and hospitalization. Of note, Sganga et al. (2015) used a polypharmacy cutoff of ≥8 drugs per day in their

study sample while we used a cutoff of ≥5 drugs per day. Akshar et al. (2012) in retrospective chart-review study at a tertiary medical center found that the high (> 10) medication burden group was associated with a greater burden of hospitalization. Our study defined "no polypharmacy" as less than 5 drugs and "polypharmacy" as "5 or more" drugs as this may explain the lack of significance in findings.

We found that in unadjusted model, being female gender is associated with increase odds of hospitalization and higher BMI is significantly associated with lower odds of being hospitalized in the unadjusted model; in both unadjusted and adjusted models, higher study-specific comorbidity index significantly increased the odds of patients being hospitalized.

Furthermore, the results on the medication classes showed that a patient on central nervous system active agents had a higher risk for hospitalization than patients who were not prescribed central nervous system active agents; this association was statically significant in an unadjusted model. Moreover, in unadjusted models, being prescribed cardiovascular drugs, antihyperglycemics and antidiabetics increased the odds of hospitalization, however these results were not statistically significant. In other studies (Howard et al. 2007; Salvi et al. 2012), the use of central nervous system active agents, cardiovascular drugs, antihyperglycemics and antidiabetics of drugs has been shown to be associated with emergency hospitalizations of older adults.

Notably, the original dataset was set for an investigation on polypharmacy and outcomes in patients with and without dementia (a case-control study) . We included the dementia variable in our study-specific comorbidity index, rather than using it as a stand-alone predictor.

Given the lack of significant findings, we performed a sensitivity analysis on the polypharmacy cutoff value of ≥4 medications. The latter modification resulted in a larger number of individuals in the "polypharmacy" group (n=165), while the non-polypharmacy group consisted of only 24 people; there was no association between set predictors and polypharmacy.

Finally, we could not reject our null hypothesis that stated polypharmacy is not associated with falls and hospitalization because our findings did not achieve statistical significance. The reason may be that T2DM was a predictor of polypharmacy in previous studies, or we may need to resort to a different polypharmacy cutoff as seen in another study with a different patient population where the cutoff was set at greater than or equal to 8 drugs per day (Sganga et al. 2015). Importantly, patients may have other drug-related events such as adverse medication reactions that cannot be accounted for because adverse drug response data were not captured. Therefore, it will be critical to monitor adverse medication occurrences in patients on polypharmacy, in the future.

5.3. Strengths of the Study

There are a number of strengths in this study. Our study was sufficiently powered for identifying the predictors of polypharmacy. Importantly, outcome data was available in the original dataset. The diagnosis of T2DM was based on documentation in the electronic health records rather than self-report. Upon data cleaning and management, variables in the dataset were double-checked (and cross-checked) with the original research team, as needed; therefore, the data are deemed reliable for our study. Importantly, our study, was the first to examine polypharmacy among older adults with T2DM in a primary healthcare center in Lebanon, providing new insight into this

vulnerable population, and allowing us to assess the effect of polypharmacy on adverse health outcomes. Finally, our study contributes to the body of knowledge about the proportion of polypharmacy among vulnerable older adults with T2DM (and comorbidities) who are at high-risk for drug-related issues and other major adverse outcomes (like falls and hospitalizations).

5.4. Limitations of our study

Despite the strengths of our study, we acknowledge several limitations. To begin with, the dataset consisted of data gathered from one primary healthcare center only so our finding cannot be generalized. Additionally, since the dataset was designed for examining polypharmacy in a dementia case-control (1 case:3 controls) study with a different purpose than our investigation, and because 44 individuals (in our sample of 190 patients with T2DM) had dementia, the results are limited to the T2DM patients in our sample and cannot be extrapolated to other patients with T2DM . Furthermore, polypharmacy was defined as the daily usage of five or more drugs concurrently. Even though this is the most often used definition, the cutoff is determined by the characteristics of the patient population and the context, since there is no standard definition. Also, some over-the-counter medications may not have been captured in the dataset; this could lead to underestimation of the polypharmacy rate in our sample. Furthermore, as the study was a secondary analysis, the existing dataset did not include additional variables that could have an influence on polypharmacy in our sample, such as diabetes duration, HbA1c, Estimated Glomerular Filtration Rate Test (eGFR), diabetes complications, income level, marital status, alcohol use, geographic location (rural or urban), education level, health status, employment, number of visits to

different health care centers, physical inactivity, number of limitations with activities of daily living, and self-medication. In addition, due to the fact that this is a secondary dataset derived from electronic health record data, we cannot rule out the possibility of bias such as due to erroneous entry of data or missing data. That said, we mentioned on data cleaning and the handling of missing data. Moreover, in terms of health outcomes, we could not determine whether emergency visit with fall led to hospital admission (with fall) since the dataset did not capture the dates (of emergency and hospital admission); therefore, it was unclear whether the latter two components could be counted as distinct fall incidences. We, thus, were restricted to the use of logistic regression as the statistical analysis approach and could not resort to other methods like Poisson regression where individual count would be needed.

5.5. Relevance of polypharmacy to nursing practice

Based on our study, polypharmacy is a prevalent phenomenon in older adults with T2DM. Therefore, in caring for this population, clinicians would need to recognize the importance of predictors of polypharmacy to be able to address them. Furthermore, they need to conduct periodic evaluation of medication lists, together with the patient, to ensure appropriate prescription, avoid and reduce potentially problematic polypharmacy, in preventing adverse effects or events such as medication errors, drug reactions or drug-drug interactions, and other outcomes.

Moreover, as nurses are frontliners in the delivery of patient care, it is vital that they recognize the significant burden that administering several drugs places on patients. Also, nurses must educate caregivers and family members on proper medication handling in order to minimize medication errors and to report adverse drug

reactions. In addition, nurses must educate patients on lifestyle improvement such as smoking cessation, exercising, proper diet consumption that may help limit the need for medication use.

5.6. Recommendation for future studies

Given our findings on high rate of polypharmacy in our sample, while suggested set of predictors were not associated with polypharmacy, it will be important to conduct further investigation on the topic. Therefore, we recommend the following for future studies:

1. Primary research needs to be conducted in this population, thus collecting all necessary variables that have the potential to predict polypharmacy, taking into consideration the cutoff of the polypharmacy, and comparing T2DM patients with those without T2DM on polypharmacy
2. Further studies could look at polypharmacy in hospitalized older adults with T2DM, and additional complications such as adverse drug reactions.
3. Finally, given an older adult population, it will be important to investigate effects of polypharmacy among older adults with T2DM, with or without dementia.

5.7. Conclusion

Patients aged 65 years and older are known to have a greater incidence of polypharmacy, which may be related to the increasing prevalence of several chronic diseases in this population. We found a high proportion of polypharmacy in our study sample, at a primary healthcare center. Additional data on potential predictors may help identify factors associated with polypharmacy in older adults with T2DM in the Lebanese. We did not find an association between polypharmacy and falls or

hospitalizations in our sample. Further scrutiny on the definition of polypharmacy in context, and on the association of polypharmacy with other complications may be informative.

APPENDIX

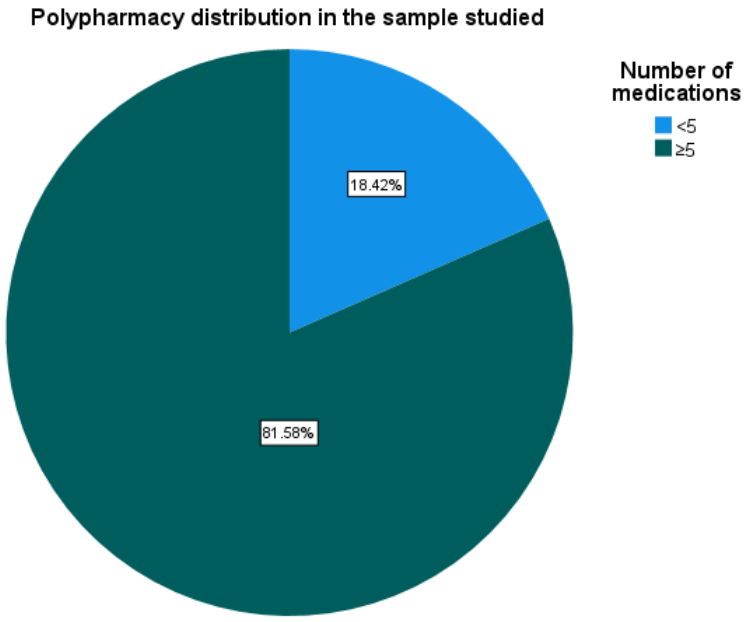

Figure 2. Polypharmacy distribution in the sample studied.

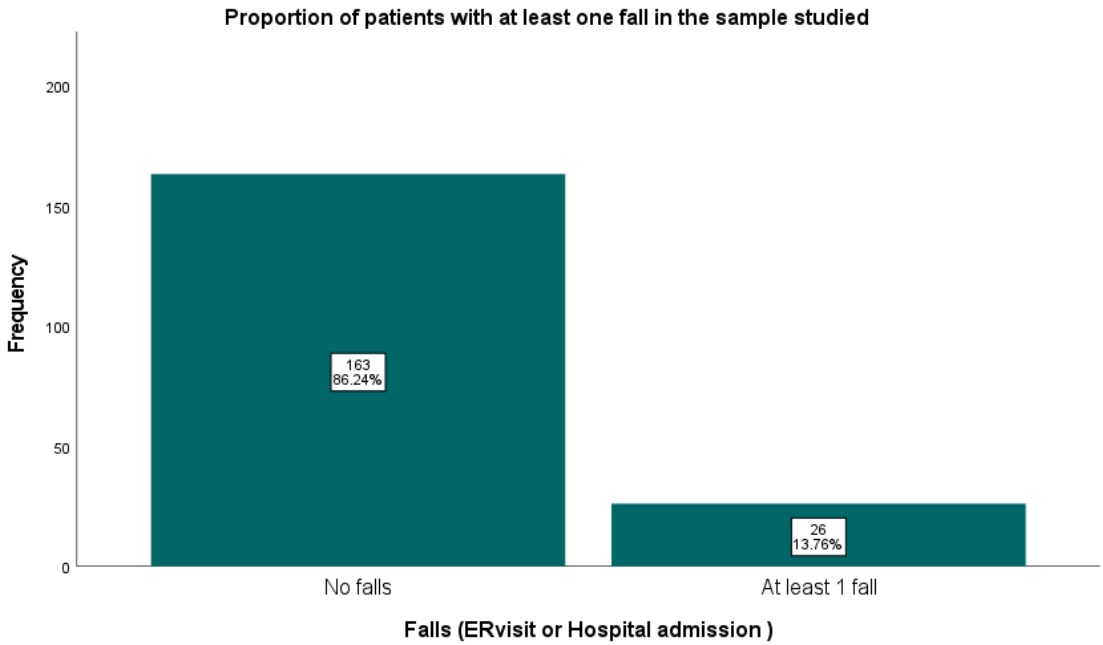

Figure 3. Proportion of patients with at least one fall in the sample studied

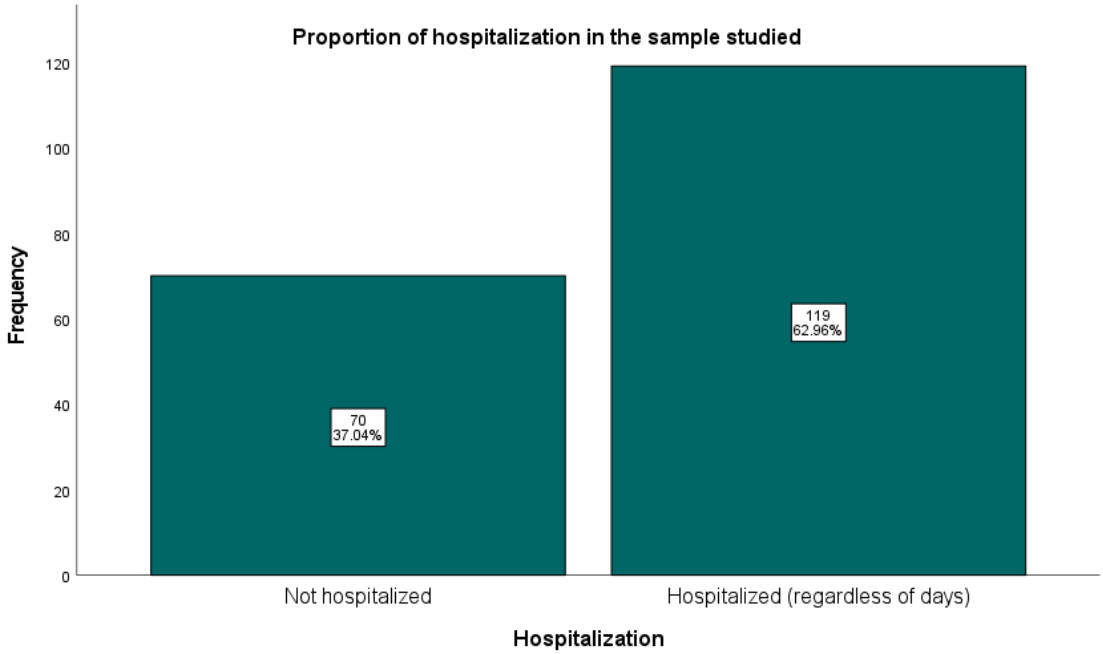

Figure 4. Proportion of hospitalization in the sample studied

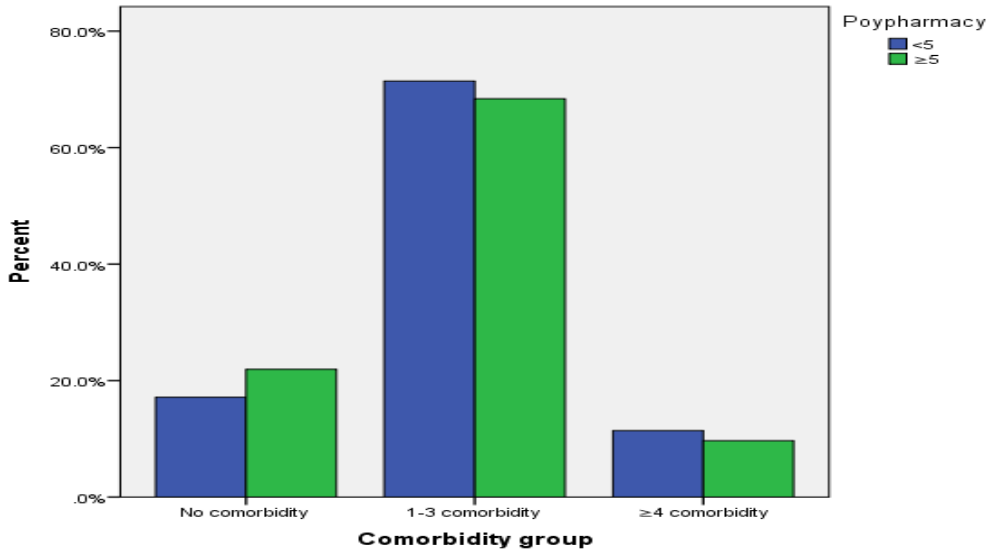

Figure 5. Relation between the proportion of polypharmacy and number of comorbidities.

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