Factors Associated with the Detection of Inappropriate Prescriptions in Older People: A Prospective Cohort

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Abstract: (1) Background: Ageing is associated with complex and dynamic changes leading to multimorbidity and, therefore, polypharmacy. The main objectives were to study an older community-dwelling cohort, to detect inappropriate prescriptions (IP) applying the Patient-Centred Prescription model, and to evaluate the most associated factors. (2) Methods: This was a prospective, descriptive, and observational study conducted from June 2019 to October 2020 on patients \( \geq 65 \) years with multimorbidity who lived in the community. Demographic, clinical and pharmacological data were assessed. Variables assessed were: degree of frailty, using the Frail-VIG index; therapeutical complexity and anticholinergic and sedative burden; and the number of chronic drugs to determine polypharmacy or excessive polypharmacy. Finally, a medication review was carried out through the application of the Patient-Centred Prescription model. We used univariate and multivariate regression to identify the factors associated with IP. (3) Results: We recruited 428 patients (66.6% women; mean age 85.5, SD 7.67). A total of 50.9% of them lived in a nursing home; the mean Barthel Index was 49.93 (SD 32.14), and 73.8% of patients suffered some degree of cognitive impairment. The prevalence of frailty was 92.5%. Up to 90% of patients had at least one IP. An increase in IP prevalence was detected when the Frail-VIG index increased \( (p < 0.05) \). With the multivariate model, the relationship of polypharmacy with IP detection stands out above all. (4) Conclusions: 90% of patients presented one IP or more, and this situation can be detected through the PCP model. Factors with higher association with IP were frailty and polypharmacy.

Keywords: frailty; polypharmacy; inappropriate prescription; multimorbidity; medication review; goal-oriented care

1. Introduction

High-income countries face significant population ageing [1,2], which is associated with complex and dynamic changes that lead to the appearance of one or more chronic diseases, giving rise to multimorbidity [3]. Older patients with multimorbidity often meet frailty criteria [3].

Frailty is defined as an increased vulnerability to stressors resulting from a decrease in the physiological reserves of different systems [4]. It has been determined by identifying a critical number of impairments in physical strength, physical activity, nutrition, and mobility [4]. It is known that frailty is associated with a higher need for healthcare resources and...
Epidemiological studies have associated multimorbidity and frailty with higher exposure to polypharmacy and the use of anticholinergic and sedative drugs. Polypharmacy is considered when the patient takes five or more medications continuously [6], and severe polypharmacy is when the number of chronic medications is ≥10 [7]. These facts have been associated with poorer outcomes, such as impaired cognitive and physical function, falls and hip fractures [8]. Furthermore, frailty and polypharmacy increase the risk of receiving inappropriate prescriptions (IP) [8–11]. This fact increases the risk of suffering adverse drug events (ADE) related to pharmacokinetics and pharmacodynamics changes by drug-drug interaction (DDI) associated with their multiple comorbidities [5,8–10,12,13]. Current evidence suggests that medication is often inappropriate in older patients [3,14], especially among frail individuals with polypharmacy and with a bad health self-assessment and comorbidities [11]

The use of several medications is the most documented independent risk factor to develop ADE, such as DDI, hospitalizations, cognitive and functional impairment, mortality, and healthcare expenditures, either in the overall population or, especially, in the older population [12,14]. Additionally, it is essential to remark that polypharmacy is also a risk factor for inappropriate pharmacological treatment adherence [15].

According to individual evolution, both concepts, appropriate and inappropriate prescription, are dynamic; thus, medications that previously could have been considered appropriate can become inappropriate depending on the progression of a chronic condition or the appearance of a new diagnosis that implies a change in the patient’s primary care goal. Consequently, depending on the patient’s characteristics and particular context, any medication can be potentially inappropriate [16].

There is agreement that constant vigilance and review are required when prescribing for these patients, considering the impact of every medication, the overall drug load, the presence of comorbidities, and function and care goals [8]. Pharmacological prescription in older patients has become a global concern because of a progressive, positive number of prescribed medications [6] and the increasing difficulties guaranteeing appropriate prescription to each patient profile [17].

Therefore, developing a specific tool to optimize prescription in older patients is crucial. This tool might consider the quality of life, functional status, main care goal, and life expectancy [18]. In this context, we propose a Patient-Centred Prescription (PCP) model as a methodology to optimize prescription in frail older patients. This approach combines clinical judgment and scientific evidence in a pragmatic and systematic process [19].

The objectives of the study were: (1) To determine the baseline situation and to calculate the frailty index (FI) of a cohort of older patients who lived in the community; (2) To assess the therapeutic plan through a PCP model and to analyse the prevalence of polypharmacy, number of IP, medication complexity and anticholinergic and sedative burden; and (3) To identify the variables that are potentially most related to IP.

2. Materials and Methods

2.1. Study Design and Subjects

This was a prospective, descriptive, and observational study on a cohort of older patients (from now on, the Community Older Patients cohort (COP cohort)) who lived in the community, either at home or in a nursing home. It was conducted from June 2019 to October 2020 in Osona, a semi-urban area in Catalonia (Spain).

Inclusion criteria: Patients 65 years of age or older, living in the community, either at home or in a nursing home with multimorbidity (two or more morbidities), that their primary care physician identified prescription management difficulties and requested a consultant team to review the pharmacological treatment.

Exclusion criteria: Patients who are probably living their last hours or days of life [20].
Ethics approval: We obtained verbal informed consent from patients or their main caregivers. Afterwards, we included the patient’s verbal informed consent in their electronic health record. The study was approved by the Scientific Ethics Committee, of each site: (1) FORES (Fundació d’Osona per la Recerca i l’Educació Sanitària), under reference number 2019-106/PR237; (2) IDIAP Jordi Gol, under reference number 19/206-P; (3) Fundació Catalana d’Hospitals, under reference number CEI 20/23.

2.2. Data Collected

Personal data: Age and gender.

Functional data: Dependence or independence for medication management and the Barthel Index (BI) to assess basic activities of daily living were graded [21].

Medical data: we collected morbidities (from the diagnostic clusters within the Johns Hopkins University ACG system) [22] and adjusted-age Charlson Index [23]; dementia diagnosis, as stated in patients’ medical records, and the degree of deterioration established following the GDS (Global Deterioration Scale) [24]; blood pressure available in the last year; and geriatric syndromes.

Analytical data: Full blood count, sodium, potassium, urea, and glycosylated haemoglobin (HbA1c) were collected if available during the last year.

Pharmacological data: Number of chronic medicines prescribed for at least six months before the Medication Review (MR). It was determined if the patient had moderate polypharmacy (between 5 and 9 medications) or excessive polypharmacy (10 or more medications) [7]. Type of medication (qualitative classification) was recorded by ATC (Anatomical Therapeutic Chemical) system. Detection of therapeutic complexity through the MRCI [25] and DBI [26].

Frailty Index (FI): This variable was measured by the Frail-VIG index (“VIG” is the Spanish/Catalan acronym for Comprehensive Geriatric Assessment), which contains 22 simple questions that assess 25 different deficits [27,28]. FI was categorised as (1) no frailty (FI < 0.20); (2) mild frailty (FI 0.20–0.35); (3) moderate frailty (FI 0.36–0.50); and (4) severe frailty (FI > 0.50).

Patients in end-of-life (EOL) were identified according to the NECPAL CCOMS-ICO© tool criteria [29]. These patients are considered to be in the last months or the year of their life. The identification of EOL was based on: (a) the previous identification by the primary care team, (b) advanced disease criteria [29], or (c) Frail-VIG index >0.50.

Main therapeutic goal: According to the patients’ baseline situation, an individualized therapeutic goal was established: (i) survival when the patient’s baseline was optimal; (ii) functionality in patients in an intermediate situation; and (iii) symptomatic control in patients with a very vulnerable established baseline situation (patients in EOL situation were included).

2.3. Medication Review

Each patient’s pharmatherapeutic plan was reviewed through the application of the PCP model [19]. This model was a process with four systematic stages and a multidisciplinary team carried it out made up of the patient’s primary care physician and nurse, with a consulting team (a geriatrician and a clinical pharmacist). The model focused all therapeutic decisions on the individualized global assessment of each patient: comprehensive geriatric assessment (CGA), the frailty index calculation (Frail-VIG index) [30], and the resulting individual therapeutic goal (prolonging survival maintaining functionality or prioritizing symptomatic control) [31]. The decisions were taken together with the patient or with their main caregiver in case of incapacity (Figure 1).
2.4. Inappropriate Prescription (IP)

With the MR, different criteria were used to determine IP; for example, in patients at EOL, Type 2 Diabetes Mellitus, hypertension and cardiovascular therapy, dyslipidaemia, mental health and dementia, pain, and osteoporosis.

Patients at EOL (NECPAL CCOMS-ICO© tool criteria [29]): according to STOPPFrail criteria, medications aimed at prolonging survival and those for primary prevention were assessed for potential discontinuation. Medications for secondary prevention were individualised based on patient goals [31,32].

Type 2 Diabetes Mellitus (T2DM): Two main proposals were used to individualise hypoglycaemic treatment: (a) therapeutic intensity criteria, following the American Diabetes Association (ADA) recommendations [33–35]; (b) type of medication: sulphonylureas (SU) were considered inappropriate because of the high risk of hypoglycaemia [34,36]; metformin was considered inappropriate if there were non-adjusted doses in cases of renal failure [34]; glifozins (SGLT2 inhibitors) were considered inappropriate when it was prescribed in patients without heart failure and chronic renal failure (glomerular filtration rate (GFR) < 45 mL/min) [34,37]; and short-acting insulin or mixtures were also considered inappropriate, except when it could be justified [34]. Table 1 describes the therapeutic goals in T2DM according to the patient profile.

Table 1. Type 2 Diabetes Mellitus (T2DM) therapeutic goals considering patient profile.

| Target         | Healthy Older Adults * | Frail Older Adults † | Older Adults in a Probable EOL Situation ‡ |
|----------------|------------------------|----------------------|-------------------------------------------|
| Qualitative Glycaemic | Similar to those for diabetic young adults | Assess the decrease of therapeutic intensity | Quality of life preservation ** |
| Quantitative Hba1c ¶ | ≤7–7.5% | ≤8.0% | Avoid reliance on A1C ** |
| Therapeutic Goal †† | Prolong survival | Maintain functionality | Symptomatic treatment |

* Good functional and cognitive status, and long life expectancy. † With functional disability and dementia or moderately limited life expectancy. ‡ End-of-life (EOL) situation, understood as a period of 1–2 years. Hba1c ¶, glycated haemoglobin. ** Glucose control decisions should be based on avoiding hypoglycaemia and symptomatic hyperglycaemia episodes. †† Based on the Patient Centred Prescription (PCP) Model.
Hypertension (HT) and Cardiovascular Therapy: There is currently evidence suggesting less intensive monitoring in people with multimorbidity, particularly in cases of dementia or limited life expectancy [38]. Globally, blood pressure under 140/90 mmHg has been associated with a higher risk of falls and mortality [39–41]. We considered an antihypertensive medication as an IP in EOL patients when the patient’s mean systolic blood pressure has been lower than 130 mmHg over the last year [31].

Dyslipidaemia: Statins are not recommended in EOL patients [32], regardless of the indication, particularly in primary prevention cases. In secondary prevention, we can individualise decision-making based on each patient’s associated risks and benefits [31]. We considered a lipid-lowering drug as an IP when prescribed to a patient with a total cholesterol level under 150 mg/dL, because it is a malnutrition marker [41].

Mental Health and Dementia: The European Association of Palliative Care’s recommendations were used to make decisions; they propose a different therapeutic main goal in patients with dementia according to the stage of their pathology, based on evidence and consensus among experts [42]. We considered chronic antipsychotic drugs as an IP when prescribed to patients without behavioural disorders over the last 3–6 months or when prescribed to treat insomnia, as there is no evidence to support this indication [31,42,43].

Pain: Following Beers/STOPP criteria, the following proposals were made [36,44–46]: (a) Tricyclic antidepressants were considered an IP because of their anticholinergic effects; (b) non-steroidal anti-inflammatory drugs (NSAIDs) were considered inappropriate when they were not prescribed at the lowest dose or for the shortest time possible, because of their high risk of ADEs; (c) weak opioids such as tramadol and codeine were registered as IP unless prescribed at low doses, due to the risk of ADEs; (d) major opioids, such as morphine and oxycodone, were considered IP if they were not associated with a laxative; and (e) meperidine was considered an IP due to its anticholinergic potential.

Osteoporosis: We considered calcium supplements (except in cases of symptomatic hypocalcaemia), vitamin D, or anti-resorption drugs as inappropriate in EOL patients [32].

Other groups: Based on the PCP model, the medications that could not be considered a correct indication or the most optimised posology were recorded as IP.

2.5. Sample Size

IP prevalence in the frail older population was estimated at 71% to calculate sample size [47]. With a 95% confidence level and 5% accuracy, a minimum of 352 patients should be included.

2.6. Statistical Methods

IBM SPSS Statistics v27.0 statistical software was used to perform statistical analysis. The results for categorical variables were described as absolute and relative frequencies. Outcomes for continuous variables were expressed by means and standard deviations (SD). The statistical tests used to evaluate the relationship between two qualitative variables were the Chi-square test (or Fisher’s exact test in 2 × 2 tables where the expected frequencies were <5). The Student’s t-test was used to analyse the relationship between quantitative and qualitative variables. To identify the factors associated with IP, we used univariate and multivariate logistic regression. Statistical significance was established when the value of p was under 0.05.

3. Results

3.1. Subject Baseline Data

A total of 428 patients were enrolled (66.6% women). The mean age was 85.5 years (SD 7.67). Almost half of them lived in a nursing home (50.9%). Globally, they had moderate dependence for basic daily activities, with a mean Barthel Index of 49.93 (SD 32.14), a prevalence of frailty of 92.5%, with 73.8% of patients suffering some degree of cognitive impairment. Table 2 outlines the COP-cohort’s baseline demographic, clinical, functional, and
cognitive data, and Table 3 lists the baseline pharmacological data. Globally, a particularly high prevalence of IP was detected. Up to 90.0% of the patients had at least one IP.

Table 2. COP-cohort’s baseline data.

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|--------------------------------------|
| **Baseline Data**                   |
| **Total N = 428**                   |
| **Demographic Data**                |
| Age, mean (SD)                      | 85.52 (7.67) |
| Gender, N (%)                       |               |
| Men                                  | 143 (33.4%)  |
| Women                                | 285 (66.6%)  |
| Origin, N (%)                       |               |
| Home                                 | 210 (49.1%)  |
| Nursing Home                         | 218 (50.9%)  |
| **Clinical, Functional and Cognitive Data** |
| Medication self-management *         | 58 (27.6%)   |
| Barthel Index (BI), mean (SD)        | 49.93 (32.14)|
| BI (degrees)                         |               |
| Independence (BI ≥ 95)               | 51 (11.9%)   |
| Mild dependence (BI 90–65)           | 120 (28.0%)  |
| Moderate dependence (BI 60–25)       | 129 (30.2%)  |
| Severe dependence (BI ≤ 20)          | 128 (29.9%)  |
| Cognitive status                     |               |
| No dementia                          | 112 (26.2%)  |
| Mild dementia                        | 62 (14.5%)   |
| Moderate dementia (GDS 5 to GDS 6B)  | 112 (26.2%)  |
| Advanced dementia (from G6C)         | 142 (33.1%)  |
| Geriatric Syndromes (GS), mean (SD)  | 2.92 (1.52)  |
| Falls                                | 144 (33.6%)  |
| Dysphagia                            | 84 (19.6%)   |
| Pain                                 | 99 (23.1%)   |
| Depressive syndrome                  | 198 (46.3%)  |
| Insomnia                             | 229 (53.5%)  |
| Morbidities, mean (SD)               | 4.91 (2.16)  |
| Morbidities (number)                 |               |
| 1–2                                  | 43 (10.0%)   |
| 3–4                                  | 168 (39.3%)  |
| 5 or more                            | 217 (50.7%)  |
| Morbidities (type)                   |               |
| Hypertension                         | 290 (67.8%)  |
| Chronic renal failure                | 186 (43.5%)  |
| Type 2 Diabetes                      | 110 (25.7%)  |
| Heart Failure                        | 88 (20.6%)   |
| Charlson Index, mean (SD)            | 3.26 (2.27)  |
| Frailty (Fl), mean (SD)              | 0.39 (0.13)  |
| Fl (degrees)                         |               |
| No frailty (0–0.19)                  | 32 (7.5%)    |
| Mild frailty (0.20–0.35)             | 113 (26.4%)  |
| Moderate frailty (0.36–0.50)         | 201 (47.0%)  |
| Severe frailty (0.51–1)              | 82 (19.1%)   |
| End-of-life patients                 | 155 (36.2%)  |
| Therapeutic aim                      |               |
| Survival                             | 41 (9.6%)    |
| Functionality                        | 223 (52.1%)  |
| Symptomatic                          | 164 (38.3%)  |

*Only patients living at home were assessed (N = 210).
Table 3. Baseline pharmacological data for the COP-cohort.

| Baseline Pharmacological Data | Total N = 428 |
|-------------------------------|---------------|
| Polypharmacy, mean (SD)       | 8.13 (3.88)   |
| Polypharmacy (degree)         |               |
| 0–4 medications              | 80 (18.7%)    |
| 5–9 medications              | 205 (47.9%)   |
| 10 or more medications       | 143 (33.4%)   |
| Medication Regimen Complexity Index (MRCI), mean (SD) | 30.74 (16.26) |
| MRCI (degree)                |               |
| Low complexity (0–19.99)      | 109 (25.5%)   |
| Moderate complexity (20–39.99)| 208 (48.6%)   |
| High complexity (40 or more)  | 111 (25.9%)   |
| Drug Burden Index (DBI), mean (SD) | 1.17 (0.84) |
| DBI (degree)                 |               |
| Low DBI (0–0.99)             | 70 (16.4%)    |
| Moderate DBI (1–1.99)        | 197 (46.0%)   |
| High DBI (2 or more)         | 161 (37.6%)   |
| Inappropriate prescriptions (IP), mean (SD) | 3.14 (2.27) |
| Number of IP                 |               |
| 0 IP                         | 43 (10.0%)    |
| 1 or more IP                 | 385 (90.0%)   |
| 2 or more IP                 | 322 (75.2%)   |
| 3 or more IP                 | 246 (57.5%)   |

Moreover, an increase in the prevalence of IP was detected when the Frail-VIG index increased \((p < 0.05)\) (Figure 2).

![Figure 2. Number of inappropriate prescriptions (IP) according to the frailty index (FI).](image)

3.2. Data of IPs

Table 4 shows the descriptive analysis of the baseline situation and the number of IPs. The clinical variables most associated with presenting at least one IP were BI and the number of morbidities. BI had a mean of 60.7 in patients without IP and 48.7 in patients with at least one IP \((p = 0.020)\). Regarding the morbidities, 6.9% of patients without IP presented five or more morbidities, and the percentage was 93.1% when they had at least one IP \((p = 0.011)\).
Table 4. Descriptive analysis at baseline and number of Inappropriate Prescriptions (IPs): 0 (n = 43, 10.0%), 0–1 (n = 385, 24.8%), ≥2 (n = 322, 75.2%), 0–1 (n = 182, 42.5%), and ≥3 (n = 246, 58.5%).

| Baseline Demographic Data | N = 428 | 0 | ≥1 | p | 0–1 | ≥2 | p | 0–2 | ≥3 | p |
|---------------------------|---------|---|----|---|-----|----|---|-----|----|---|---|
| Age, mean (SD)            | 85.5 (7.2) | 85.5 (7.7) | 0.990 | 85.20 (8.5) | 85.63 (7.4) | 0.618 | 86.0 (7.8) | 85.2 (7.6) | 0.273 |
| Gender                    |         |    |    |   |     |    |   |     |    |    |
| Men                       | 11 (7.7%) | 132 (92.3%) | 0.251 | 29 (20.3%) | 114 (79.7%) | 0.128 | 57 (39.9%) | 86 (60.1%) | 0.430 |
| Women                     | 32 (11.2%) | 253 (88.8%) |       | 77 (27.0%) | 208 (73.0%) |       | 125 (43.9%) | 160 (56.1%) |       |
| Origin                    |         |    |    |   |     |    |   |     |    |    |
| Home                      | 25 (11.9%) | 185 (88.1%) | 0.209 | 49 (23.3%) | 161 (76.7%) | 0.500 | 81 (38.6%) | 129 (61.4%) | 0.105 |
| NH                        | 18 (8.3%) | 200 (91.7%) |       | 57 (26.1%) | 161 (73.9%) |       | 101 (46.3%) | 117 (53.7%) |       |

| Baseline Clinical, Functional and Cognitive Data | N = 428 | 0 | ≥1 | p | 0–1 | ≥2 | p | 0–2 | ≥3 | p |
|-----------------------------------------------|---------|---|----|---|-----|----|---|-----|----|---|---|
| Medication management                        | 44 (9.3%) | 54 (14.0%) | 0.391 | 14 (13.2%) | 44 (13.7%) | 0.905 | 26 (14.3%) | 32 (13.0%) | 0.703 |
| BI, mean (SD)                                | 60.7 (31.1) | 48.7 (32.0) | 0.020 * | 53.21 (32.4) | 48.85 (32.0) | 0.226 | 50.5 (31.9) | 49.5 (32.3) | 0.755 |
| BI (degree)                                  |         |    |    |   |     |    |   |     |    |    |
| IB ≥ 95                                     | 8 (15.7%) | 43 (84.3%) | 0.013 * | 15 (29.4%) | 36 (70.6%) | 0.192 | 22 (43.1%) | 29 (56.9%) |       |
| IB 90–65                                    | 16 (13.3%) | 104 (86.7%) |       | 32 (26.7%) | 88 (73.3%) |       | 52 (43.3%) | 68 (56.7%) |       |
| IB 60–25                                    | 12 (9.3%) | 117 (90.7%) |       | 32 (24.8%) | 97 (75.2%) |       | 52 (40.6%) | 76 (59.4%) |       |
| IB ≤ 20                                     | 7 (5.5%) | 121 (94.5%) |       | 27 (21.1%) | 101 (78.9%) |       | 7 (5.5%) | 121 (94.5%) |       |
| Cognitive Status (dementia)                  |         |    |    |   |     |    |   |     |    |    |
| No dementia                                 | 10 (8.9%) | 102 (91.1%) | 0.546 | 28 (25.0%) | 84 (75.0%) | 0.730 | 45 (40.2%) | 67 (59.8%) | 0.608 |
| Mild                                       | 2 (3.2%) | 60 (96.8%) |       | 11 (17.7%) | 51 (82.3%) |       | 26 (41.9%) | 36 (58.1%) |       |
| Moderate †                                 | 19 (17.0%) | 93 (83.0%) |       | 32 (28.6%) | 80 (71.4%) |       | 50 (44.6%) | 62 (55.4%) |       |
| Advanced ‡                                 | 12 (8.5%) | 130 (91.5%) |       | 35 (24.6%) | 107 (75.4%) |       | 61 (43.0%) | 81 (57.0%) |       |
| GS, mean (SD)                               | 2.7 (1.5) | 2.9 (1.5) | 0.400 | 2.6 (1.4) | 3.0 (1.5) | 0.020 * | 2.7 (1.4) | 3.1 (1.5) | 0.004 * |
| GS Type                                     |         |    |    |   |     |    |   |     |    |    |
| Fall                                       | 10 (23.3%) | 134 (76.7%) | 0.128 | 27 (25.5%) | 117 (74.5%) | 0.040 * | 54 (29.7%) | 90 (70.3%) | 0.134 |
| Dysphagia                                  | 5 (11.6%) | 79 (88.4%) | 0.164 | 16 (20.5%) | 68 (79.5%) | 0.176 | 29 (25.9%) | 55 (74.1%) | 0.098 * |
| Pain                                       | 13 (30.2%) | 86 (69.8%) | 0.244 | 24 (22.6%) | 75 (77.4%) | 0.890 | 36 (19.8%) | 63 (80.2%) | 0.157 |
| Depressive Syndrome                       | 16 (37.2%) | 28 (62.8%) | 0.209 | 41 (38.7%) | 157 (61.3%) | 0.071 | 68 (37.4%) | 130 (62.6%) | 0.001 * |
| Insomnia                                   | 24 (55.8%) | 205 (44.2%) | 0.749 | 51 (48.1%) | 178 (51.9%) | 0.199 | 89 (48.9%) | 140 (51.1%) | 0.101 |
| Morbidities, mean (SD)                     | 4.1 (2.1) | 5.0 (2.1) | 0.014 * | 4.2 (1.9) | 5.1 (2.2) | <0.001 * | 4.4 (2.0) | 5.3 (2.2) | <0.001 * |
| Morbidities (number)                       |         |    |    |   |     |    |   |     |    |    |
| 1–2                                       | 8 (18.6%) | 35 (81.4%) |       | 19 (44.2%) | 24 (55.8%) |       | 26 (60.5%) | 17 (39.5%) |       |
| 3–4                                       | 20 (11.9%) | 148 (88.1%) |       | 47 (28.0%) | 121 (72.0%) |       | 83 (49.4%) | 85 (50.6%) |       |
| 5 or more                                  | 15 (6.9%) | 202 (93.1%) |       | 40 (18.4%) | 177 (81.6%) |       | 73 (33.6%) | 144 (66.4%) |       |
Table 4. Cont.

| Morbidities (type) | N = 428 | 0 | $\geq 1$ | $p$ | 0–1 | $\geq 2$ | $p$ | 0–2 | $\geq 3$ | $p$ |
|--------------------|---------|---------|--------|----|------|--------|----|------|--------|----|
| Hypertension       |         | 22 (51.1%) | 268 (69.6%) | 0.003 * | 61 (57.5%) | 229 (77.1%) | 0.002 * | 107 (58.8%) | 183 (74.3%) | <0.001 * |
| Chronic renal failure | 15 (34.9%) | 171 (44.4%) | 0.232 | 40 (37.7%) | 146 (45.3%) | 0.171 | 71 (39.0%) | 115 (46.7%) | 0.110 |
| Type 2 Diabetes    | 2 (4.7%) | 84 (21.8%) | 0.008 * | 15 (14.2%) | 95 (29.5%) | 0.009 * | 33 (18.1%) | 77 (31.3%) | 0.010 * |
| Heart failure      | 6 (14.0%) | 82 (21.3%) | 0.258 | 17 (16.0%) | 71 (22.0%) | 0.184 | 34 (18.7%) | 54 (22.0%) | 0.408 |

| FI, mean (SD)      |         | 0.34 (0.1) | 0.39 (0.1) | 0.023 * | 0.36 (0.12) | 0.40 (0.13) | 0.013 * | 0.36 (0.1) | 0.40 (0.1) | 0.007 * |

| FI (degree)        |         |         |         |    |         |         |    |         |         |    |
| No FI              | 3 (9.4%) | 29 (90.6%) |          |    | 10 (31.3%) | 22 (68.8%) | 15 (46.9%) | 17 (53.1%) | 0.004 * |
| Mild FI            | 17 (15.0%) | 96 (85.0%) | 0.017 * |    | 33 (29.2%) | 80 (70.8%) | 52 (46.0%) | 61 (54.0%) | 0.004 * |
| Moderate FI        | 22 (10.9%) | 179 (89.1%) |          |    | 55 (27.4%) | 146 (72.6%) | 98 (48.8%) | 103 (51.2%) | 0.004 * |
| Severe FI          | 1 (1.2%) | 81 (98.8%) |          |    | 8 (9.8%) | 74 (90.2%) | 17 (20.7%) | 65 (79.3%) | 0.007 * |

| End-of-life patients |         | 11 (25.6%) | 144 (37.4%) | 0.126 | 34 (32.1%) | 121 (37.6%) | 0.307 | 64 (35.2%) | 91 (37.0%) | 0.697 |

| Therapeutic Aim    |         |         |         |    |         |         |    |         |         |    |
| Survival           | 3 (7.3%) | 38 (92.7%) |          |    | 11 (26.8%) | 30 (73.2%) | 18 (43.9%) | 23 (56.1%) | 0.754 |
| Functionality      | 28 (12.6%) | 195 (87.4%) | 0.198 |    | 58 (26.0%) | 165 (74.0%) | 98 (43.9%) | 125 (56.1%) | 0.754 |
| Symptomatic        | 12 (7.3%) | 152 (92.7%) |          |    | 37 (22.6%) | 127 (77.4%) | 66 (40.2%) | 98 (59.8%) | 0.754 |

* Statistically Significant. † Global Deterioration Scale (GSD) from 5 to 6B. ‡ Global Deterioration Scale (GSD) from 6C. Abbreviations: NH, Nursing Home; MD, mild dependence; BI, Barthel Index; GS, Geriatric Syndromes; FI, Frailty Index.
Regarding morbidities, 51.1% of patients without IP had HT and 69.6% of patients with at least one IP had HT \( (p = 0.003) \). 4.7% of patients without IP had T2DM and 21.8% of them had at least one IP had T2DM \( (p = 0.008) \). Concerning FI, there was also an association with IP. Patients with one or more IPs presented a higher mean of FI than those without IP \((0.39 \text{ (SD 0.1)} \) vs. \(0.34 \text{ (SD 0.1)} \) \( (p = 0.023) \)).

Figures 3 and 4 show the prevalence of each polypharmacy degree and the prevalence of MRCI degree considering the number of IPs. In both, all comparisons showed statistically significant differences \( (p < 0.001) \). Remarkably, patients with no IPs presented the lowest polypharmacy and MRCI rates. Moreover, on the contrary, those patients with more IPs had increased polypharmacy and MRCI rates \( (p < 0.001) \). Figure 5 shows the prevalence of the DBI degree considering the number of IPs, and differences were statistically significant in all groups, except when IPs were 0 versus \( \geq 1 \).

**Figure 3.** Prevalence of polypharmacy degree considering number of Inappropriate Prescriptions (IPs).

**Figure 4.** Prevalence of MRCI degree considering number of Inappropriate Prescriptions (IPs).
Table 5 outlines the types of IP analysed according to the Anatomical, Therapeutic, Chemical (ATC) classification. It is essential to highlight that the groups most frequently prescribed inappropriately were ATC A (alimentary tract and metabolism), B (blood and blood-forming organs), C (cardiovascular system), and N (nervous system), with a percentage of 24.72%, 9.29%, 30.85%, and 24.62%, respectively.

Table 5. Inappropriate prescriptions identified considering the ATC (Anatomical, Therapeutic, and Chemical) classification system.

| ATC Group                                      | Total |
|------------------------------------------------|-------|
| A–Alimentary tract and metabolism              | 330 (24.7%) |
| B–Blood and blood-forming organs               | 124 (9.3%)  |
| C–Cardiovascular system                        | 412 (30.8%) |
| D–Dermatological                               | 0     |
| G–Genitourinary system and hormones            | 26 (1.9%)   |
| H–Systemic hormonal preparations (excluding sex hormones and insulin) | 7 (0.5%)   |
| J–Anti-infective for systemic use              | 1 (0.1%)  |
| L–Antineoplastic and immunomodulation agents   | 2 (0.2%)   |
| M–Musculoskeletal system                       | 28 (2.3%)  |
| N–Nervous system                               | 329 (24.6%) |
| R–Respiratory system                           | 69 (5.1%)   |
| S–Sensory organs                               | 6 (0.4%)   |
| V–Various                                      | 0     |

3.3. Univariate Analysis and Multivariate Analysis

Table 6 shows the univariate analysis, which highlights the relationship of the detection of IP with the following variables: T2DM, number of morbidities (especially if they were ≥5), the Frail-VIG index (severe frailty), polypharmacy (both moderate as well as excessive), therapeutic complexity (high complexity), and DBI (high DBI).

With the multivariate model, the relationship of polypharmacy with IP detection stands out above all, both moderate and excessive. The frailty index was a significant predictor factor in the univariate model for those with a high IPs presence (≥2 or, or ≥3), but this did not remain significant in the multivariate analysis.
Table 6. Univariate and multivariate analysis.

| Patient Characteristics | Inappropriate Prescriptions 0 vs. ≥1 | Inappropriate Prescriptions 0–1 vs. ≥2 | Inappropriate Prescriptions 0–2 vs. ≥3 |
|-------------------------|--------------------------------------|----------------------------------------|----------------------------------------|
|                         | Univariate | Multivariate | Univariate | Multivariate | Univariate | Multivariate | Univariate | Multivariate | Univariate | Multivariate |
| OR                      |            |              |            |              |            |              |            |              |            |              |
| Barthel Index (BI), mean (SD) | 0.99 (0.98–0.99) | 1 | - | - | - | - | - | - | - | - |
| BI (degree)             |            |              |            |              |            |              |            |              |            |              |
| Indep.: ≥95             | 1.20 (0.48–3.03) | - | - | - | - | - | - | - | - | - |
| Mild: 90–65             | 1.81 (0.69–4.74) | - | - | - | - | - | - | - | - | - |
| Mod.: 60–25             | 3.2 (1.10–9.40) | - | - | - | - | - | - | - | - | - |
| Severe: ≤20             | - | - | - | - | - | - | - | - | - | - |
| Geriatric Syndrome (GS), mean (SD) | 1.19 (1.03–1.39) | 1.21 (1.06–1.37) | 1.19 (1.03–1.39) | 1.21 (1.06–1.37) | 1.19 (1.03–1.39) | 1.21 (1.06–1.37) | 1.19 (1.03–1.39) | 1.21 (1.06–1.37) | 1.19 (1.03–1.39) | 1.21 (1.06–1.37) |
| GS (degree)             |            |              |            |              |            |              |            |              |            |              |
| 0                       | - | - | - | - | - | - | - | - | - | - |
| 1–2                     | - | - | 1.69 (0.6–4.6) | - | 0.99 (0.37–2.62) | - | - | - | - | - |
| ≥3                      | - | - | 2.24 (0.8–6.0) | - | 1.69 (0.65–4.41) | - | - | - | - | - |
| Fall                    |            |              |            |              |            |              |            |              |            |              |
| Not                     | - | - | - | - | - | - | - | - | - | - |
| Yes                     | - | - | 1.67 (1.0–2.7) | - | - | - | - | - | - | - |
| Depressive Syndrome     |            |              |            |              |            |              |            |              |            |              |
| Not                     | - | - | - | - | - | - | - | - | - | - |
| Yes                     | - | - | 1.88 (1.27–2.78) | - | - | - | - | - | - | - |
| T2DM                    |            |              |            |              |            |              |            |              |            |              |
| Not                     | 5.7 (1.3–24.1) | 1 | - | 2.3 (1.2–4.5) | - | 1.9 (1.2–3.2) | - | - | - | - |
| Yes                     | - | - | - | - | - | - | - | - | - | - |
| Morbidities, mean (SD)  |            |              |            |              |            |              |            |              |            |              |
| 1–2                     | 1.69 (0.68–4.15) | - | - | 2.04 (1.0–4.0) | - | 1.57 (0.79–3.10) | - | - | - | - |
| 3–4                     | 3.08 (1.21–7.80) | - | - | 3.5 (1.8–7.0) | - | 3.02 (1.54–5.91) | - | - | - | - |
| ≥5                      | - | - | - | - | - | - | - | - | - | - |
| Frailty Index (FI), mean (SD) | 15.09 (1.43–159.6) | - | - | 8.27 (1.5–44.5) | - | 7.63 (1.70–34.23) | - | - | - | - |
| FI (degree)             |            |              |            |              |            |              |            |              |            |              |
| None: 0–0.19            | 0.58 (0.16–2.13) | 1 | - | 1.10 (0.5–2.5) | 1 | 1.04 (0.47–2.27) | 1 | 0.80 (0.54–1.89) | 1 | 1.04 (0.47–2.27) | 1 | 0.80 (0.54–1.89) |
| Mild: 0.20–0.35         | 0.84 (0.53–2.99) | - | - | 1.21 (0.7–2.7) | - | 0.93 (0.44–1.96) | - | 0.82 (0.62–1.84) | - | 0.93 (0.44–1.96) | - | 0.82 (0.62–1.84) |
| Mod.: 0.36–0.50         | 8.38 (0.93–83.79) | - | - | 2.62 (0.87–7.86) | 1 | 3.37 (1.41–8.10) | 1 | 2.13 (0.96–5.50) | 1 | 3.37 (1.41–8.10) | 1 | 2.13 (0.96–5.50) |
| Severe: 0.51–1          | - | - | - | - | - | - | - | - | - | - |
| Polypharmacy, mean (SD) |            |              |            |              |            |              |            |              |            |              |
| 0–4                     | 1.21 (1.09–1.34) | - | - | 1.26 (1.17–1.36) | - | 1.26 (1.19–1.35) | - | - | - | - |
| 5–9                     | 2.80 (1.36–5.77) | - | - | 3.3 (1.9–5.6) | - | 3.52 (1.99–6.22) | - | 3.17 (1.77–5.68) | - | 3.52 (1.99–6.22) | - | 3.17 (1.77–5.68) |
| ≥10                     | 4.55 (1.87–11.11) | - | - | 6.9 (3.6–13.4) | - | 9.75 (5.17–18.38) | - | 8.65 (4.53–16.51) | - | 9.75 (5.17–18.38) | - | 8.65 (4.53–16.51) |
Table 6. Cont.

| Patient Characteristics | 0 vs. ≥1 | Inappropriate Prescriptions | 0–1 vs. ≥2 | 0–2 vs. ≥3 |
|-------------------------|---------|-----------------------------|---------|---------|
|                         | OR      | Univariate | Multivariate | Univariate | Multivariate | Univariate | Multivariate |
| MRCI, mean (SD)         | 1.03 (1.01–1.06) | - | 1.05 (1.3–1.07) | - | 1.05 (1.04–1.07) | - | - |
| MRCI (degree)           |         |         |         |         |         |         |         |
| Low: 0–19.99            | 1       | - | 1       | - | 1       | - | - |
| Mod.: 20–39.99          | 3.6 (1.7–7.3) | - | 2.76 (1.68–4.54) | - | 2.80 (1.73–4.53) | - | - |
| High: ≥40               | 3.6 (1.4–8.8) | - | 6.87 (3.31–14.24) | - | 7.11 (3.87–13.06) | - | - |
| DBI, mean (SD)          |         |         |         |         |         |         |         |
| DBI (degree)            |         |         |         |         |         |         |         |
| Low: 0–0.99             |         |         |         |         |         |         |         |
| Mod.: 1–1.99            |         |         |         |         |         |         |         |
| High: ≥2                |         |         |         |         |         |         |         |

Abbreviations: Indep., independence; Mod., moderate; OR, Odds ratio; MRCI, Medication Regimen Complexity Index; DBI, Drug Burden Index.

4. Discussion

In this study describing a sample of older patients recruited at the community level, we detected a high prevalence of functional and cognitive impairment and frailty in a specific health region with semi-urban characteristics. Similarly, high rates of moderate and excessive polypharmacy, therapeutic complexity, and anticholinergic and sedative burden with the pharmacological data were observed. These results are higher than might be expected in a standard cohort with patients aged 65 or older [14,48]. This fact could be explained by the inclusion criteria that selected patients according to one objective criterion (presenting multimorbidity), as well as one subjective criterion (patients with multimorbidity whose primary care physician identified prescription management difficulties).

The application of the PCP model detected a prevalence of IPs of up to 90%. This result is a much higher proportion of IPs than those detected in other studies using explicit criteria (Beers and STOPP-START criteria) [49]. This data is probably due to two main reasons: (i) inclusion criteria with patients with multimorbidity [50,51] and (ii) the PCP model allows the optimisation of individualised medication, thus resulting in a more thorough analysis of the prescription.

Thus, PCP should generally be considered an advanced MR (based on medication history, patient information, and clinical information) that optimises the prescription process [52].

Regarding ATC groups, we found that four of the 13 groups included in this classification accounted for almost 90% of IPs (alimentary tract and metabolism, blood and blood-forming organs, and cardiovascular and nervous system). Once again, this shows that IP is usually concentrated in a small number of pharmacological groups [53,54]. According to the multivariate analysis, it is remarkable that polypharmacy is the variable most commonly associated with the IP presence.

Notably, the positive relationship between frailty and IP was detected in this descriptive study. Furthermore, in the univariate model, a relationship between the FI and IP was observed. Nevertheless, in the multivariate model, this relationship disappeared. This fact could be due to FI being the result of summarising all the other data analysed. Indeed, this study could help open a path towards new studies to investigate the relationship between frailty and IP.

The current study has some limitations, such as the lack of a larger sample of non-frail patients, which would allow us to conduct a more accurate statistical analysis.

As a future goal, it would be interesting to assess clinical and pharmacological outcomes after applying different proposals to individualise the therapeutic approach through a longitudinal follow-up study.

5. Conclusions

The application of the PCP model in older adults with multimorbidity enabled to identify up to 90% of them presenting at least one IP. Frailty had a positive association with IP detection, and polypharmacy was the most involved factor in IP detection.

However, more studies should be performed with frail and non-frail patients to validate the potential of this tool.

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**References**

1. European Commission Directorate-General for Economic and Financial Affairs. The 2015 Ageing Report: Economic and budgetary projections for the 28 EU Member States (2013–2060). *Econ. Financ. Afff*. 2015, 399. [CrossRef]

2. Global Health and Aging, National Institutes of Health, U.S. Department of Health and Human Services; World Health Organization: Bethesda, MD, USA, 2011.

3. Medicines Optimisation: The Safe and Effective Use of Medicines to Enable the Best Possible Outcomes; NICE Guideline: London, UK, 2015.

4. Fried, L.P.; Tangen, C.M.; Walston, J.; Newman, A.B.; Hirsch, C.; Grotti, J.; Seeman, T.; Tracy, R.; Kop, W.J.; Burke, G.; et al. Frailty in Older Adults: Evidence for a Phenotype. *J. Gerontol. Ser. A Biol. Sco. Med. Sci*. 2001, 56, M146–M157. [CrossRef] [PubMed]

5. Herr, M.; Sirven, N.; Grondin, H.; Pichetti, S.; Sermet, C. Frailty, polypharmacy, and potentially inappropriate medications in old people: Findings in a representative sample of the French population. *Eur. J. Clin. Pharmacol.* 2017, 73, 1165–1172. [CrossRef]

6. Duerden, M.; Avery, T.; Payne, R. *Polypharmacy and Medicines Optimisation. Making It Safe and Sound*; Authors; The King’s Fund: London, UK, 2013.

7. Gnijdic, D.; Hilmer, S.; Blyth, F.M.; Naganathan, V.; Waite, L.; Seibel, M.; McLachlan, A.; Cumming, R.; Handelsman, D.J.; Le Couteur, D. Polypharmacy cutoff and outcomes: Five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. *J. Clin. Epidemiol.* 2012, 65, 989–995. [CrossRef]

8. Hilmer, S.; Gnijdic, D. Prescribing for frail older people. *Aust. Prescr.* 2017, 40, 174–178. [CrossRef]

9. Spinewine, A.; Schmader, K.E.; Barber, N.; Hughes, C.; Lapane, K.L.; Swine, C.; Hanlon, J.T. Appropriate prescribing in elderly people: How well can it be measured and optimised? *Lancet* 2007, 370, 173–184. [CrossRef]

10. Scott, I.A.; Hilmer, S.N.; Reeve, E.; Potter, K.; Le Couteur, D.; Rigby, D.; Gnijdic, D.; Del Mar, C.B.; Roughhead, E.E.; Page, A.; et al. Reducing Inappropiate Polypharmacy. *JAMA Intern. Med.* 2015, 175, 827. [CrossRef]

11. Fernández, A.; Gómez, F.; Curiño, C.L.; Pineda, E.; de Souza, J.F. Prevalence and impact of potentially inappropriate medication on community dwelling older adults. *Biomedica* 2020, 41, 1–30.

12. Reallón, E.; Chavent, B.; Gervais, F.; Dauphinot, V.; Vernaudon, J.; Krolak-Salmon, P.; Mouchoux, C.; Novais, T. Medication exposure and frailty in older community-dwelling patients: A cross-sectional study. *Int. J. Clin. Pharm.* 2020, 42, 508–514. [CrossRef] [PubMed]

13. Sevilla-Sánchez, D.; Molist-Brunet, N.; Amblas-Novellas, J.; Roura-Poch, P.; Espaulella-Panicot, J.; Codina-Jané, C. Adverse drug events in patients with advanced chronic conditions who have a prognosis of limited life expectancy at hospital admission. *Eur. J. Clin. Pharmacol.* 2017, 73, 79–89. [CrossRef]

14. Hernández-Rodríguez, M.A.; Sempere-Verdú, E.; Vicens, C.; González-Rubío, F.; Miguel-García, F.; Palop-Larrea, V.; Orueta-Sánchez, R.; Esteban-Jiménez, Ó.; Sempere-Manuel, M.; Arroyo-Aniés, M.P.; et al. Evolution of polypharmacy in a spanish population (2005–2015): A database study. *Pharmacoeconom. Drug Saf.* 2020, 29, 433–443. [CrossRef] [PubMed]

15. Yap, A.F.; Thirumoorthy, T.; Kwan, Y.H. Systematic review of the barriers affecting medication adherence in older adults. *Geriatr. Gerontol. Int.* 2015, 16, 1093–1101. [CrossRef]

16. Woodford, H.J.; Fisher, J. New horizons in deprescribing for older people. *Age Ageing* 2019, 48, 768–775. [CrossRef]

17. Hanlon, J.T.; Artz, M.B.; Pieper, C.F.; Lindblad, C.I.; Sloane, R.J.; Ruby, C.M.; Schmader, K.E. Inappropriate Medication Use Among Frail Elderly Inpatients. *Ann. Pharmacother.* 2004, 38, 9–14. [CrossRef]

18. Poudel, A.; Peel, N.; Mitchell, C.; Nissen, L.; Hubbard, R. A systematic review of prescribing criteria to evaluate appropriateness of medications in frail older people. *Rev. Clin. Gerontol.* 2014, 24, 304–318. [CrossRef]

19. Espaulella-Panicot, J.; Molist-Brunet, N.; Sevilla-Sánchez, D.; González-Bueno, J.; Amblas-Novellas, J.; Solà-Bonada, N.; Codina, J. Patient-centred prescription model to improve adequate prescription and therapeutic adherence in patients with multiple disorders. *Rev. Esp. Geriatr. Gerontol.* 2017, 52, 278–281. [CrossRef]
20. Boyd, K.; A Murray, S. Recognising and managing key transitions in end of life care. BMJ 2010, 341, c4863. [CrossRef] [PubMed]
21. Granger, C.V.; Albretch, G.L.H. Outcome of comprehensive medical rehabilitation: Measurement by PULSES profile and the Barthel index. Arch. Phys. Med. Rehabil. 1979, 60, 145–154. [PubMed]
22. Salisbury, C.; Johnson, L.; Purdy, S.; Valderas, J.M.; Montgomery, A. Epidemiology and impact of multimorbidity in primary care: A retrospective cohort study. Br. J. Gen. Pr. 2011, 61, e12–e21. [CrossRef] [PubMed]
23. Charlson, M.E.; Pompei, P.; Ales, K.L.; Mackenzie, R. A New Method of Classifying Prognostic in Longitudinal Studies: Development. J. Chronic Dis. 1987, 40, 373–383. [CrossRef]
24. Reisberg, B.; Ferris, S.; de Leon, M.; Crook, T. The Global Deterioration Scale for assessment of primary degenerative dementia. Am. J. Psychiatry 1982, 139, 1136–1139. [CrossRef]
25. George, J.; Phun, Y.-T.; Bailey, M.J.; Kong, D.C.; Stewart, K. Development and Validation of the Medication Regimen Complexity Index. Ann. Pharmacother. 2004, 38, 1369–1376. [CrossRef] [PubMed]
26. Hilmer, S.N.; Mager, D.E.; Simonsick, E.M.; Cao, Y.; Windham, B.G.; Harris, T.B.; Rubin, S.M.; Shorr, R.I.; et al. A Drug Burden Index to Define the Functional Burden of Medications in Older People. Arch. Intern. Med. 2007, 167, 781–787. [CrossRef]
27. Amblás-Novellas, J.; Martori, J.C.; Espauelle, J.; Oller, R.; Molist-Brunet, N.; Inzitari, M.; Romero-Ortuno, R. Frail-VIG index: A concise frailty evaluation tool for rapid geriatric assessment. BMC Geriatr. 2018, 18, 1–12. [CrossRef] [PubMed]
28. Amblás-Novellas, J.; Martori, J.C.; Molist-Brunet, N.; Oller, R.; Gómez-Batiste, X. Frail-VIG index: Design and evaluation of a new frailty index based on the Comprehensive Geriatric Assessment. Rev. Esp. Geriatr. Gerontol. 2016, 52, 119–127. [CrossRef]
29. Gómez-Batiste, X.; Martinez-Muñoz, M.; Blay, C.; Amblás, J.; Vila, L.; Costa, X.; Espauelle, J.; Espinosa, J.; Constante, C.; Mitchell, G.K. Prevalence and characteristics of patients with advanced chronic conditions in need of palliative care in the general population: A cross-sectional study. Palliat. Med. 2014, 28, 302–311. [CrossRef] [PubMed]
30. Lee, S.J.; Kim, C.M. Individualizing Prevention for Older Adults. J. Am. Geriatr. Soc. 2018, 66, 229–234. [CrossRef] [PubMed]
31. O’Mahony, D.; O’Connor, M.N. Pharmacotherapy at the end-of-life. Age Ageing 2011, 40, 419–422. [CrossRef] [PubMed]
32. Curtin, D.; Gallagher, P; O’Mahony, D. Deprescribing in older people approaching end-of-life: Development and validation of STOPP frail version. Age Ageing 2021, 50, 465–471. [CrossRef] [PubMed]
33. American Diabetes Association. 12-Older Adults: Standards of Medical Care in Diabetes-2021. Am. Diabetes Assoc. Diabetes Care 2021, 44, S168–S179. [CrossRef] [PubMed]
34. Gómez-Huelgas, R.; Peralta, F.G.; Mañas, L.R.; Formiga, F.; Domingo, M.P.; Bravo, J.M.; Miranda, C.; Ena, J. Treatment of type 2 diabetes mellitus in elderly patients. Rev. Clin. Española 2018, 218, 74–88. [CrossRef] [PubMed]
35. Hamblin, C.E.; Khunti, K.; Cos, X.; Wens, J.; Martínez, L.; Topsever, P.; Del Prato, S.; Sinclair, A.; Schernthaner, G.; Rutten, G.; et al. Factors influencing safe glucose-lowering in older adults with type 2 diabetes: A PeRsOn-centred ApproaCh To IndiviDually-adaptEd (PROACTIVE) Glycemic Goals for older people. Prim. Care Diabetes 2019, 13, 330–352. [CrossRef] [PubMed]
36. O’Mahony, D.; O’Sullivan, D.; Byrne, S.; O’Connor, M.N.; Ryan, C.; Gallagher, P. STOPP/START criteria for potentially inappropriate prescribing in older people: Version. Age Ageing 2014, 44, 213–218. [CrossRef] [PubMed]
37. Gomez-Peralta, F.; Abreu, C.; Lecube, A.; Bellido, D.; Soto, A.; Morales, C.; Brito-Sanfiel, M.; Umpierrez, G. Practical Approach to Initiating SGLT2 Inhibitors in Type 2 Diabetes. Diabetes Ther. 2017, 8, 953–962. [CrossRef] [PubMed]
38. National Institute for Health and Care Excellence (NICE). Hypertension in Adults: Diagnosis and Management; NICE: London, UK, 2016.
39. Morley, J.E. Inappropriate Drug Prescribing and Polypharmacy Are Major Causes of Poor Outcomes in Long-Term Care. J. Am. Med. Dir. Assoc. 2014, 15, 780–782. [CrossRef] [PubMed]
40. Boockvar, K.S.; Song, W.; Lee, S.; Intrator, O. Hypertension Treatment in US Long-Term Nursing Home Residents with and Without Dementia. J. Am. Geriatr. Soc. 2016, 65, 2048–2064. [CrossRef] [PubMed]
41. Onder, G.; Vetrano, D.L.; Marengoni, A.; Bell, J.S.; Johnell, K.; Palmer, K. Accounting for frailty when treating chronic diseases. Eur. J. Intern. Med. 2018, 56, 49–52. [CrossRef]
42. Van der Steen, J.T.; Radbruch, L.; Hertogh, C.M.; de Boer, M.E.; Hughes, J.C.; Larkin, P.; Francke, A.L.; Jünger, S.; Gove, D.; Firth, P.; et al. White paper defining optimal palliative care in older adults with type 2 diabetes: A PeRsOn-centred ApproaCh To IndiviDually-adaptEd (PROACTIVE) Glycemic Goals for older people. Prim. Care Diabetes 2019, 13, 330–352. [CrossRef] [PubMed]
43. Gomez-Peralta, F.; Abreu, C.; Lecube, A.; Bellido, D.; Soto, A.; Morales, C.; Brito-Sanfiel, M.; Umpierrez, G. Practical Approach to Initiating SGLT2 Inhibitors in Type 2 Diabetes. Diabetes Ther. 2017, 8, 953–962. [CrossRef] [PubMed]
44. Fick, D.M.; Semla, T.P.; Steinman, M.; Beizer, J.; Brandt, N.; Dombrowski, R.; DuBeau, C.E.; Epplin, J.J.; Flanagan, N. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J. Am. Geriatr. Soc. 2019, 67, 674–694. [CrossRef] [PubMed]
45. Gokula, M.; Holmes, H.M. Tools to Reduce Polypharmacy. Clin. Geriatr. Med. 2012, 28, 323–341. [CrossRef] [PubMed]
46. Scottish Intercollegiate Guidelines Network (SIGN). Management of Chronic Pain. A National Clinical Guideline; Healthcare Improvement Scotland: Scotland, UK, 2019.
47. Récohé, I.; Lebady, C.; Cool, C.; Sourdet, S.; Piau, A.; Lapeyre-Mestre, M.; Vellas, B.; Cestac, P. Potentially inappropriate prescribing in a popula-lation of frail elderly people. Int. J. Clin. Pharm. 2017, 39, 113–119. [CrossRef] [PubMed]
48. Castell Alcalá, M.V.; Otero Puime, Á.; Sánchez Santos, M.T.; Garrido Barral, A.; González Montalvo, J.I.; Zurunegui, M.V. Prevalencia de fragilidad en una población urbana de mayores de 65 años y su relación con comorbilidad y discapacidad. *Atención Primaria*. **2010**, 42, 520–527. [CrossRef]

49. Liew, T.M.; Lee, C.S.; Goh, S.K.L.; Chang, Z.Y. The prevalence and impact of potentially inappropriate prescribing among older persons in primary care settings: Multilevel meta-analysis. *Age Ageing* **2020**, 49, 570–579. [CrossRef]

50. Poudel, A.; Peel, N.M.; Nissen, L.M.; Mitchell, C.A.; Gray, L.C.; Hubbard, R.E. Adverse Outcomes in Relation to Polypharmacy in Robust and Frail Older Hospital Patients. *J. Am. Med. Dir. Assoc.* **2016**, 17, 767.e9–767.e13. [CrossRef]

51. Bonaga, B.; Sánchez-Jurado, P.M.; Martínez-Reig, M.; Ariza, G.; Rodríguez-Mañas, L.; Gnjidic, D.; Salvador, T.; Abizanda, P. Frailty, Polypharmacy, and Health Outcomes in Older Adults: The Frailty and Dependence in Albacete Study. *J. Am. Med. Dir. Assoc.* **2018**, 19, 46–52. [CrossRef]

52. Griese-Mammen, N.; Hersberger, K.E.; Messerli, M.; Leikola, S.; Horvat, N.; Van Mil, J.W.F.; Kos, M. PCNE definition of medication review: Reaching agreement. *Int. J. Clin. Pharm.* **2018**, 40, 1199–1208. [CrossRef]

53. Molist Brunet, N.; Espaulella Panicot, J.; Sevilla-Sánchez, D.; Amblas Novellas, J.; Codina Jané, C.; Altimiras Roset, J.; et al. A patient-centered prescription model assessing the appropriateness of chronic drug therapy in older patients at the end of life. *Eur. Geriatr. Med.* **2015**, 6, 565–569. [CrossRef]

54. Budnitz, D.S.; Lovegrove, M.C.; Shehab, N.; Richards, C.L. Emergency Hospitalizations for Adverse Drug Events in Older Americans. *N. Engl. J. Med.* **2011**, 365, 2002–2012. [CrossRef]