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# Prevalence of Potentially Inappropriate Medication and Frailty: A Comparison of Three Criteria in Older Turkish Adults

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ABSTRACT

**Objective:** The aim of this study is to determine the prevalence of potentially inappropriate medication (PIM) use in older Turkish adults on the basis of three criteria as well as to investigate its relationship with frailty.

**Materials and Methods:** This cross-sectional study was conducted in an outpatient clinic. The Turkish Inappropriate Medication Use in the Elderly (TIME), Beers 2019, and Screening Tool of Older Person's Prescriptions Version 2 (STOPPv2) criteria were used to detect PIM. Frailty was determined using the Fried Frailty Index categorized as 0 points, non-frail; 1, pre-frail; and ≥2, frail.

**Results:** Of the 382 patients, 179 (46.9%) were identified with at least one PIM according to the three sets of criteria. The prevalence rates of PIM based on the TIME, Beers 2019, and STOPPv2 criteria were 46.1%, 30.6%, and 26.2%, respectively. No association was found between PIM and frailty (p=0.593 for the TIME criteria, 0.562 for the Beers 2019 criteria, and 0.524 for the STOPPv2 criteria). The risk of PIM presence was higher when the TIME criteria were applied than when the other criteria were used (odds ratio [OR]: Beers 2019 vs. TIME, 0.5231 and STOPPv2 vs. TIME, 0.4072; p<0.001 for all). The number of prescribed medications and older age were associated with the use of any PIM (ORs, 1.3143 and 1.0301, respectively).

**Conclusion:** The TIME criteria showed the highest PIM frequency in older Turkish adults and had moderate-to-significant concordance with non-country-specific criteria. Further studies are needed to evaluate the relationship between frailty and PIM.

**Keywords:** Beers 2019, older adult, potentially inappropriate medications, STOPPv2, TIME

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## INTRODUCTION

In older adults, the prevalence of multiple drug use is higher than in the younger population because of the increasing burden of chronic diseases. The pharmacokinetics and pharmacodynamics of drugs change during the aging process owing to chronic disease-associated alterations in organ function, increasing the risk of adverse drug events (ADEs) (1). ADEs are important causes of hospitalization, morbidity, and mortality in older adults, leading to wasted health resources. Decreased inappropriate medication usage is vital for minimizing ADEs and ADE-related hospitalizations. Research has shown that most ADEs are preventable through drug-age checking and drug-specific guidelines (2).

A potentially inappropriate medication (PIM) use is defined as a drug prescription in which the attributed risk of adverse events is more likely than the clinical benefits, or a safer alternative exists, no cost-effectiveness is obtained, no clear scientific evidence for specific indications is found, and a clinically indicated medication is omitted (3). The Beers and Screening Tool of Older Person's Prescriptions/Screening Tool to Alert doctors to Right Treatment (STOPP/START) criteria have been established to reduce inappropriate drug use in older adults (4, 5). The Beers and STOPP/START criteria were revised in 2019 and 2015, respectively. The Turkish Inappropriate Medication Use in the Elderly (TIME) criteria, published in 2019, were developed on the basis of common medical conditions and frequently used drugs in Türkiye (6). PIM was identified in 25% to 75% of patients (7–9).

PIM can increase drug-drug interaction, risk of adverse events, and drug-disease interaction (10). The relationship between PIM and frailty, a significant geriatric syndrome in that increases vulnerability to stressors is increased owing to impairment of multiple body systems and is considered more prevalent with increasing age, is controversial. Some studies have shown this relationship and PIM as a risk factor of frailty but others have not (11–18). In one study, the risk of PIM increased by 2% in frail people (18). In another study, the combination of PIM and polypharmacy was associated with frailty, but after adjustment for polypharmacy, the relationship between PIM and frailty disappeared (16). In other studies, no such relationship was demonstrated (14, 17). This discrepancy

**Table 1.** Indicators of fried frailty index

| Frailty criteria | Parameters | |
|---|---|---|
| | Male | Female |
| Low handgrip strength | BMI <24.0, <29.0 kg,<br>BMI 24.1–26.0, <30.0 kg,<br>BMI 26.1–28.0, <30.0 kg,<br>BMI >28.0, <32.0 kg | BMI <23.0, <17.0 kg,<br>BMI 23.1–26.0, <17.3 kg,<br>BMI 26.1–29.0, <18.0 kg,<br>BMI >29.0, <21.0 kg |
| Slow gait speed (4 m) | Height <173 cm, 0.65 m/sec,<br>Height >173 cm, 0.76 m/sec | Height <159 cm, 0.65 m/sec,<br>Height >159 cm, 0.65 m/sec |
| Low physical activity | 3 Mets or more <270 kcal/week | 3 Mets or more <383 kcal/week |
| Weight loss | Unintentional weight loss of >%10% kg in 12 months or >5% in follow-up | |
| Exhaustion | Response to the question "Do you feel full of energy" (yes=1, no=0) which is found in the Geriatric Depression Scale (GDS) | |

0 points is categorized as non-frail, 1 as pre-frail, and 2 and above as frail. BMI: Body mass index

may be due to the use of different tools to determine frailty and PIM and the differences in the age, outpatient-inpatient-nursing home status, and race of the participants.

To our knowledge, no published study has reported the frequency of PIMs by comparing the TIME, Beers 2019, and STOPPv2 criteria in Türkiye. Moreover, no study has investigated the relationship between PIM, as determined using three different assessment tools, and frailty, which leads to functional decline and increased hospitalization, institutionalization, and mortality. The objectives of this study were to identify the prevalence of PIM according to the TIME, STOPPv2, and Beers 2019 criteria older adult outpatients in Türkiye and to determine the most frequently used PIMs. Furthermore, we aimed to investigate the relationship between frailty and PIM according to the three sets of criteria.

## MATERIALS and METHODS

### Study Design

This cross-sectional study was conducted in the geriatric outpatient clinic of Erciyes University between September 2020 and March 2021. The research conforms to the ethical standards stipulated in the World Medical Association Declaration of Helsinki. Written informed consent was obtained from patients or caregivers of patients with cognitive impairment (dementia or delirium). The study was approved by the local ethics committee of Erciyes University (Erciyes University Ethics Committee/Decision No. 2019/136).

### Data Collection

In this study, polypharmacy was defined as receiving five or more medications, and hyper polypharmacy was defined as receiving 10 or more medications. A total of 382 older adults who underwent comprehensive geriatric assessments were included in the study. All individuals aged >60 years who were using one or more drugs were included in the study. Their sociodemographic data (age, sex, marital status, educational status, and economic situation) and number and types of medications were recorded. The Charlson Comorbidity Index (CCI) was used to determine the presence of comorbidities (19). The functionality level was measured using a modified Katz Activities of Daily Living (ADL) scale and the Lawton Instrumental ADL (IADL) scale (20, 21). PIM was assessed using the TIME (6), Beers 2019 (4), and STOPPv2 criteria (5). The Fried Frailty Index (FFI) was used to determine the degree of frailty in accordance with five criteria (Table 1): self-reported exhaustion, low physical activity, weight loss, slow walking speed, and weakness (22). The scores were categorized as follows: 0, non-frail; 1, pre-frail; and ≥2, frail. A 4-meter walking test was used to determine the walking speed.

### Statistical Analysis

The data were analyzed using the R programming language (version 3.6.0) (Auckland, New Zealand). Numerical variables were summarized as mean and standard deviation for normally distributed data or median and quartile for non-normally distributed data. The normality of data was evaluated using graphical (e.g., Q-Q plot) and analytical approaches (e.g., Shapiro-Wilk normality test). Demographic variables were compared between the PIM users and the non-PIM users within each criterion set by using either the Student t-test or the Mann-Whitney U test. We also considered the three sets of criteria as repeated measurements by ordering TIME, Beers 2019, and STOPPv2. The relationships between the criteria were modeled using generalized estimating equations with a logit link and adjusted for possible confounders. We included risk factors that were either clinically important or found to be statistically significant in univariate logistic models. Furthermore, the kappa statistics was used to measure the concordance between the three sets of criteria. We set the level of significance at 0.05.

## RESULTS

In the present study, among the 382 enrolled older adults, 259 (67.8%) participants were female, with a mean age of 72.4±7.39 years and an age range of 60–98 years. Of all the participants, 4.2%, 47.6%, and 48.2% were non-frail, pre-frail, and frail, respectively. Eighty-nine (50.5%), 61 (52.1%), and 52 participants (53.1%) were frail according to the TIME, Beers 2019, and STOPPv2 criteria, respectively. A statistically significant difference in age was found between the PIM and non-PIM groups based on

**Table 2.** Demographic and clinical characteristics of patients based on the three sets of criteria

| | TIME | | | | p | Beers 2019 | | | | p | STOPPv2 | | | | p |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | PIM n=176 | | Non-PIM n=206 | | | PIM n=117 | | Non-PIM n=265 | | | PIM n=98 | | Non-PIM n=284 | | |
| | n | % | n | % | | n | % | n | % | | n | % | n | % | |
| Gender | | | | | | | | | | | | | | | |
| Male | 50 | 28.4 | 73 | 35.4 | 0.143 | 31 | 326.5 | 92 | 37.4 | 0.113 | 26 | 26.5 | 97 | 34.2 | 0.164 |
| Age (mean±SD) | 73.34+7.9 | | 71.59+6.82 | | 0.021 | 72.77+7.79 | | 72.23+7.22 | | 0.512 | 72.55+7.54 | | 72.34+7.35 | | 0.809 |
| HT | 131 | 74.4 | 155 | 75.2 | 0.855 | 83 | 70.9 | 203 | 76.6 | 0.239 | 70 | 71.4 | 216 | 76 | 0.362 |
| DM | 74 | 42 | 108 | 52.4 | 0.043 | 50 | 42.7 | 132 | 49.8 | 0.202 | 43 | 43.8 | 139 | 48.9 | 0.387 |
| Number of comorbidities (mean±SD) | 2.71+1.35 | | 2.70+1.34 | | 0.964 | 2.72+1.45 | | 2.7+1.3 | | 0.915 | 2.68+1.46 | | 2.71+1.3 | | 0.844 |
| Number of medication (mean±SD) | 5.09+2.65 | | 3.80+2.39 | | <0.001 | 5.24+2.89 | | 4.02+2.37 | | <0.001 | 5.21+2.94 | | 4.11+2.4 | | <0.001 |
| Katz-ADL (25-75 quantiles)* | 17.000-18.000 | | 18.000-18.000 | | 0.077 | 18.000-18.000 | | 18.000-18.000 | | 0.277 | 18.000-18.000 | | 18.000-18.000 | | 0.858 |
| IADL (25–75 quantiles)* | 17.000-24.000 | | 19.000-24.000 | | 0.246 | 16.750-24.000 | | 18.000-24.000 | | 0.570 | 17.000-24.000 | | 18.000-24.000 | | 0.978 |
| FFI | | | | | | | | | | | | | | | |
| Non-frail | 6 | 3.4 | 10 | 4.8 | 0.593 | 4 | 3.4 | 12 | 4.5 | 0.562 | 4 | 4.1 | 12 | 4.2 | 0.524 |
| Pre-frail | 81 | 46 | 101 | 49 | | 52 | 44.4 | 130 | 49 | | 42 | 42.9 | 140 | 49.2 | |
| Frail | 89 | 50.5 | 95 | 46.1 | | 61 | 52.1 | 123 | 46.4 | | 52 | 53.1 | 132 | 46.4 | |
| CCI total score (mean±SD) | 4.28+1.75 | | 4.14+1.6 | | 0.389 | 4.19+1.83 | | 4.21+1.6 | | 0.900 | 4.22+1.89 | | 4.2+1.59 | | 0.898 |

*: As the Katz ADL and IADL distributions were extremely skewed and significantly deviated from normality, the use of nonparametric tests (Mann-Whitney U) was considered appropriate. TIME: Turkish Inappropriate Medication Use in the Elderly; STOPP: Screening Tool of Older Person's Prescriptions; PIM: Potentially inappropriate medicine; SD: Standard deviation; HT: Hypertension; DM: Diabetes mellitus; ADL: Activities of daily living; IADL: Instrumental Activities of Daily Living; FFI: Fried frailty index; CCI: Charlson comorbidity index

**Table 3.** Number of PIMs and top 5 PIMs based on the three sets of PIM criteria

| | TIME | | Beers 2019 | | STOPPv2 | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Number of PIMs (mean±SD) | 1.31+0.61 | | 1.23+0.52 | | 1.12+0.32 | |
| Number of PIMs | | | | | | |
| 1 PIM | 135 | 76.7 | 91 | 77.7 | 86 | 87.8 |
| 2 PIMs | 29 | 16.4 | 18 | 15.3 | 12 | 12.2 |
| 3 PIMs | 11 | 6.2 | 3 | 2.5 | 0 | 0 |
| 4 PIMs | 1 | 0.5 | 0 | 0 | 0 | 0 |
| Drugs and items | | | | | | |
| NSAID | 45 | 36.5 | 45 | 25.5 | 43 | 41.3 |
| ASA | 44 | 25 | * | * | * | * |
| PPI | 27 | 21.9 | 44 | 25 | 38 | 36.5 |
| Antipsychotics | 16 | 13 | 38 | 21.5 | 13 | 12.5 |
| Muscle relaxants | 7 | 5.6 | 21 | 11.9 | 3 | 2.8 |

*: The use of ASA is not included in the criteria. TIME: Turkish Inappropriate Medication Use in the Elderly; STOPP: Screening Tool of Older Person's Prescriptions; PIM: potentially inappropriate medicine; SD: standard deviation; NSAID: Nonsteroidal anti-inflammatory drug; ASA: Acetylsalicylic acid; PPI: Proton pump inhibitor

**Table 4.** Concordance between the three sets of criteria

| STOPPv2 listed PIM | Beers 2019 listed PIM | | κ | p |
|---|---|---|---|---|
| | Yes | No | | |
| Yes | 97 | 1 | 0.864 | <0.001[a] |
| No | 20 | 264 | | <0.001[b] |
| **TIME listed PIM** | **Beers 2019 listed PIM** | | | |
| | Yes | No | | |
| Yes | 117 | 59 | 0.681 | <0.001[a] |
| No | 0 | 206 | | <0.001[b] |
| **TIME listed PIM** | **STOPPv2 listed PIM** | | | |
| | Yes | No | | |
| Yes | 97 | 79 | 0.564 | <0.001[a] |
| No | 1 | 205 | | <0.001[b] |

a: Based on the kappa test; b: Based on the chi-square test. STOPP: Screening Tool of Older Person's Prescriptions; PIM: Potentially inappropriate medication; TIME: Turkish Inappropriate Medication Use in the Elderly

the TIME criteria, and the participants in the PIM group were 1.75 years older (73 years vs. 72 years, p=0.021). No significant relationship was found between PIM and age according to the Beers 2019 and STOPPv2 criteria (p=0.512 and 0.809, respectively). In each set of three criteria, the number of medications was related to PIM (p<0.001 for all). No association was found between PIM, according to the three sets of criteria, and frailty (p>0.050 for all). The demographic variables of patients based on the three criteria are presented in Table 2. According to the three sets of criteria, 179 (46.9%) of the 382 participants received at least one PIM. The prevalence rate of PIM use according to the TIME criteria was the highest (46.1%). The prevalence of PIM according to the Beers 2019 and the STOPPv2 criteria were 30.6% and 25.7%, respectively (Table 3). The TIME criteria showed significant concordance with the Beers 2019 criteria and moderate coherence with the STOPPv2 criteria (kappa statistical values of 0.681 and 0.564, respectively; Table 4). According to the TIME, Beers 2019, and STOPPv2 criteria, the most frequent PIMs were nonsteroidal anti-inflammatory drugs (NSAIDs). Acetylsalicylic acid (ASA) was the second most frequent PIM according to the TIME criteria. Proton pump inhibitors (PPIs) and antipsychotics ranked in the top five according to the three sets of criteria. Table 3 lists the top five PIMs based on the three sets of criteria.

In the univariate analysis, the number of medications was a significant risk factor for PIM according to all three sets of criteria (Table 5). All three sets of criteria indicated no relationship between PIM use and frailty (estimate=0.2637, standard error [SE]=0.060, p=0.261 for the STOPPv2 criteria; estimate=0.2292, SE=0.2223, p=0.303 for the Beers 2019 criteria; and estimate=0.1784, SE=0.2056, p=0.356 for the TIME criteria). Older age, diabetes mellitus, and lower Katz ADL were associated only with PIM according to the TIME criteria. However, the relationship between older age and PIM according to the TIME criteria disappeared in the multivariate analysis (Table 6). The number of prescribed medications was associated with the use of any PIM (odds ratio [OR] for the number of medications, 1.31; 95% confidence interval [CI], 1.19–1.44; p<0.001). The risk of PIM use was 2.45 times higher when the TIME and STOPPv2 criteria were compared. The same risk decreased to 1.91 compared with the TIME and Beers 2019 criteria.

## DISCUSSION

In the present study, we found that according to the TIME criteria, PIM had the highest prevalence rate (46.9%), followed by PIM according to the Beers 2019 (39.3%), and STOPPv2 criteria (36.9%). NSAIDs were the most frequent PIMs based on the three sets of criteria. Most recently published set of criteria originating from Eastern Europe had good concordance with non-country-specific criteria. In addition, no relationship was found between frailty and PIM, according to all three sets of criteria.

Some studies compared the Beers, STOPPv2, and country-specific criteria. Different results were obtained in these studies. In Portugal, the percentage of patients receiving one or more PIMs was 30.6% according to the Beers criteria, 16.7% according to the Portuguese PIM criteria, and 75.4% according to STOPPv2 (23). In a study that compared three sets of criteria, PIM was found in 80.2%, 58.1%, and 44.0% of patients by using the Chinese, Beers 2019, and STOPPv2 criteria, respectively (7). Moderate concordance was found between the Beers and STOPPv2 cri-

**Table 5.** Univariate analysis risk factors associated with PIM

| | STOPPv2 | | Beers 2019 | | TIME | |
|---|---|---|---|---|---|---|
| | **Estimate (SE)** | **p** | **Estimate (SE)** | **p** | **Estimate (SE)** | **p** |
| Age | 0.0038 (0.0158) | 0.809 | 0.0098 (0.0149) | 0.511 | 0.0324 (0.0141) | **0.022** |
| Gender (female) | 0.3622 (0.2608) | 0.165 | 0.3889 (0.2460) | 0.114 | 0.3244 (0.2217) | 0.144 |
| Number of comorbidity | -0.0172 (0.0873) | 0.844 | 0.0088 (0.0823) | 0.914 | 0.0035 (0.0762) | 0.963 |
| Comorbidities (yes) | | | | | | |
| HT | -0.2395 (0.2633) | 0.363 | -0.2936 (0.250) | 0.240 | -0.0431 (0.2365) | 0.855 |
| DM | -0.2039 (0.2356) | 0.387 | -0.2851 (0.2237) | 0.202 | -0.4181 (0.2068) | **0.043** |
| Number of medications | 0.1577 (0.0446) | **<0.001** | 0.1794 (0.0439) | **<0.001** | 0.2056 (0.0442) | **<0.001** |
| Katz ADL | -0.0310 (0.0660) | 0.639 | -0.0762 (0.0617) | 0.217 | -0.1639 (0.0680) | **0.016** |
| IADL | -0.0209 (0.0262) | 0.424 | -0.0284 (0.0248) | 0.252 | -0.0362 (0.0237) | 0.127 |
| CCI (high) | -0.2964 (0.3351) | 0.376 | -0.2234 (0.3232) | 0.490 | 0.1429 (0.3089) | 0.644 |
| FFI (frail) | 0.2637 (0.2348) | 0.261 | 0.2292 (0.2223) | 0.303 | 0.1784 (0.2056) | 0.386 |

PIM: Potentially inappropriate medication; STOPP: Screening Tool of Older Person's Prescriptions; TIME: Turkish Inappropriate Medication Use in the Elderly; SE: Standard error; HT: Hypertension; DM: Diabetes mellitus; IADL: Instrumental Activities of Daily Living; CCI: Charlson Comorbidity Index; FFI: Fried Frailty Index

**Table 6.** Fitted model for PIM status – GEE with logit link

| | | | | Odds ratio | | |
|---|---|---|---|---|---|---|
| **Coefficients** | **Estimate** | **SE** | **Sig.** | **Estimate** | **Lower** | **Upper** |
| Within effects | | | | | | |
| Beers | -0.6479 | 0.0805 | **<0.001** | 0.5231 | 0.4468 | 0.6126 |
| STOPPv2 | -0.8985 | 0.0968 | **<0.001** | 0.4072 | 0.3368 | 0.4922 |
| Between effects | | | | | | |
| Age | 0.0297 | 0.0167 | 0.076 | 1.0301 | 0.9969 | 1.0644 |
| Number of comorbidities | -0.2610 | 0.0955 | 0.006 | 0.7703 | 0.6388 | 0.9289 |
| Number of medications | 0.2733 | 0.0487 | **<0.001** | 1.3143 | 1.1946 | 1.4461 |
| IADL | 0.0023 | 0.0257 | 0.929 | 1.0023 | 0.9530 | 1.0542 |
| Gender (female) | 0.4073 | 0.2207 | 0.065 | 1.5028 | 0.9751 | 2.3159 |
| CCI (high) | -0.6927 | 0.3312 | 0.037 | 0.5002 | 0.2614 | 0.9574 |
| FFI (frail) | -0.0923 | 0.5057 | 0.855 | 0.9118 | 0.3384 | 2.4567 |

PIM: Potentially inappropriate medication; GEE: Generalized estimating equations; SE: Standard error; Sig.: Significance; STOPP: Screening Tool of Older Person's Prescriptions: IADL: Instrumental Activities of Daily Living; CCI: Charlson Comorbidity Index; FFI: Fried Frailty Index

teria, and the Chinese criteria showed weak coherence with the other criteria. A study that compared the STOPPv2, Beers, and Assessing Care of Vulnerable Elders (ACOVE) criteria found that STOPPv2 identified more PIM than the others sets of criteria (24). Binary comparisons of PIM use between the STOPPv2 and Beers criteria and between the STOPPv2 and ACOVE indicators showed low agreements, whereas the ACOVE and Beers criteria showed moderate agreement. In our research, the TIME criteria (46.1%) more successfully detected PIM in Türkiye as compared with the Beers 2019 criteria (30.6%) and STOPPv2 criteria (26.2%). Moreover, the kappa statistics analysis revealed a significant coherence between the TIME and Beers 2019 criteria and a moderate concordance between the TIME and STOPPv2 criteria. Thus, the TIME criteria were useful and effective, resembling non-country-specific criteria. Considering these results, physicians can determine PIM at least as much or better than using non-country-specific criteria when they create PIM criteria specific to their own country by considering drugs that are frequently used, inappropriately prescribed, or abused in society.

The drugs most commonly used as PIM in studies are PPI, clopidogrel, NSAIDs, selective serotonin reuptake inhibitors, ASA, and antipsychotics (7, 25). In two studies in Türkiye, NSAIDs, ASA, antipsychotics, and PPIs were the drugs most commonly used as PIM (26, 27). In the present study, the prevalence of PIM use according to the TIME, Beers 2019, and STOPPv2 criteria was ranked from highest to lowest in this order. Here, the most common PIMs were NSAIDs, ASA, PPIs, piracetam, and antipsychotics in patients as-

sessed using the TIME criteria. NSAIDs, PPIs, and antipsychotics were the most common PIMs in the patients assessed using the STOPPv2 and Beers 2019 criteria. In Türkiye, the restriction for prescribing benzodiazepine-derived drugs by the Ministry of Health has reduced the inappropriate use of these drugs in patients. Physicians often prefer to prescribe NSAIDs for pain. They also add a PPI to each NSAID prescription because of the risk of gastrointestinal bleeding, which is a side effect of NSAIDs. The use of ASA in primary prophylaxis is also widely prescribed by cardiologists, family physicians, endocrinologists, and other physicians in Türkiye. Moreover, the fact that ASA and NSAID derivatives are available without a prescription has caused these drugs to be the most frequently used inappropriate drugs according to research. Hence, NSAID, PPI, and ASA were the most commonly used PIM in this study. We hope that physicians and patients will be more informed about PIM and that more geriatricians will be trained for the aging Turkish population. Moreover, as in other countries, in Türkiye, antipsychotics are frequently used in patients with sleep problems.

Some studies published so far have shown a significant relationship between PIM and frailty (12, 15, 16). Thiruchelvam et al. (18) found that the risk of PIM increased by 2% in frail people. In a study in France, PIM and polypharmacy were associated with frailty, but after adjustment for polypharmacy, the relationship between PIM and frailty disappeared (16). As in our study, Muhlack and Porter determined frailty using FFI and found no relationship between PIM and frailty (14, 17). Many reasons can explain the differences between the studies, such as the different tools used for determining the level of frailty (electronic frailty index, FRAIL, FFI, etc.) and PIM detection (Beers, TIME, STOPP, ACOVE, etc.), and the differences in sample characteristics (community dwelling, outpatient-inpatient-nursing home resident status, race, characteristic variables of the participants, etc.). Martinot et al. (15) concluded that the use of NSAIDs, benzodiazepines, antithrombotic drugs, and loop diuretics was a risk factor of frailty. As no relationship was found between frailty and PIM in the present study, the relationships between the drug groups and frailty were not analyzed.

Several parameters have a direct relationship with PIM. In some studies, polypharmacy (7, 25, 28, 29), female sex, total dependence on basal ADL (28), >85 years of age (7, 25), increasing number of diseases, and high comorbidity (CCI > 3) (25) were directly related to PIM. In the present study, as in previous studies, the number of medications was associated with PIM. The detection rate for the risk of PIM was higher with the TIME criteria than with the Beers 2019 and STOPPv2 criteria. When a new drug is started, its probability of becoming a PIM is 31%.

This study has some limitations. First, the sample size was somewhat limited; however, many previous studies had fewer participants (9, 25, 30). In this study, we did not find any significant association of PIM with parameters such as frailty, older age, and CCI because of the small sample size. These parameters will be more meaningful in a research study with a higher number of patients. We could not compare our data with those of previous studies because no other study applied the TIME criteria. We did not include the neglect of necessary drug use in the study because our main objectives were to detect excessive drug use and to show the compatibility of three sets of criteria in determining PIM. The detection rate of PIM is greatly affected by the sample population's characteristics such as older age, number of comorbidities, resident status (community dwelling, outpatient, hospital inpatient, nursing home resident, etc.), and the methodology used (Beers, STOPP/START criteria, etc.). More research is needed to improve the available information about the concordance of the TIME criteria with the STOPPv2 and Beers 2019 criteria.

The significance of this research is that PIM was determined using three sets of criteria. In addition, this study is the first to investigate the relationship between frailty and PIM according to three sets of criteria. Although different sets of PIM criteria were used, we did not find a relationship between PIM and frailty in outpatients. However, some studies (14, 15) have reported a relationship between some PIM drug groups and frailty. All things considered, the relationship between vulnerability and PIM must be examined in greater detail. The present study is also the first to apply the TIME criteria. Our results suggest that different tools may be useful for detecting PIM.

## CONCLUSION

According to this study, the prevalence of PIM was approximately 40%, similar to that reported in Türkiye. The prevalence of PIM in older adults was highest when the TIME criteria were used and showed moderate-to-significant concordance with that assessed using non-country-specific criteria. PIM was related to the number of prescribed medications and female sex, but not frailty. Further studies are needed to evaluate the relationship between frailty and PIM. As shown in studies in other countries, the types of drugs used by patients, available in pharmacies, produced in countries, and preferred by physicians vary between countries. Therefore, owing to these differences, we believe that countries must establish their own PIM criteria to increase the detection rate of PIM.

**Ethics Committee Approval:** The Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 20.02.2019, number: 2019/136).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – NŞD, SA; Design – SA; Supervision – SA; Resource – SA; Materials – SA; Data Collection and/or Processing – NŞD, SA, DG; Analysis and/or Interpretation – NŞD, SA, DG; Literature Search – NŞD, SA; Writing – NŞD, SA, DG; Critical Reviews – NŞD, SA, DG.

**Conflict of Interest:** The authors have no conflict of interest to declare.

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