Drugs & Aging
https://doi.org/10.1007/s40266-026-01282-0

ORIGINAL RESEARCH ARTICLE

Potentially Inappropriate Prescription and Its Association with Index Hospitalization: A Multicenter, Cross-Sectional Study Using TIME Criteria

Gulistan Bahat[1] · Serdar Ozkok[1] · Tugba Erdogan[1] · Birkan Ilhan[2] · Meryem Merve Oren[3] · Duygu Erbas Sacar[1] · Busra Can[4] · Bahar Tekin Cetin[5] · Timur Selcuk Akpinar[5] · Rana Tuna Dogrul[6] · Kamile Silay[6] · Suna Burkuk[7] · Meltem Halil[7] · Fatma Erol[8] · Sumru Savas[8] · Sevnaz Sahin[8] · Pinar Arman[9] · Deniz Suna Erdincler[9] · Emine Gemci[10] · Sevgi Aras[10] · Murat Varli[10] · Melike Yazici[11] · Suna Avci[11] · Asli Tufan[4] · Banu Ozulu Turkmen[12] · Betul Gulsum Yavuz Veizi[13] · Mehmet Ilkın Naharci[13] · Ilker Tasci[14] · Gozde Sengul Aycicek[15] · Zekeriya Ulger[15] · Funda Salgur[16] · Huseyin Doruk[17] · Umut Karabay[2] · Mehmet Akif Karan[1]

Received: 11 September 2025 / Accepted: 27 January 2026
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Abstract

Background and Objective To evaluate the prevalence and types of potentially inappropriate prescriptions (PIP) in hospitalized older adults and to study whether PIP was a causative factor for index hospitalization, using the Turkish Inappropriate Medication Use in oldEr adults (TIME) criteria.

Methods This multicenter, cross-sectional study included 405 inpatients aged ≥60 years from 13 tertiary hospital departments in Turkiye between January 2020 and April 2021. PIP were assessed using TIME criteria, which include both potentially inappropriate medications, PIM (TIME-to-STOP) and potential prescribing omissions, PPO (TIME-to-START). Following the completion of medical history taking, physical examination, and comprehensive geriatric assessment (CGA), managing physicians evaluated each criterion individually. Based on clinical adjudication, they determined whether any PIM or PPO predefined in the TIME criteria could plausibly have contributed to the hospitalization.

Results The prevalence of PIP was 82.5%, with 63.2% of patients meeting at least one TIME-to-STOP and 71.6% meeting one TIME-to-START criterion. The top-three most common PIM identified via TIME-to-STOP criteria were: *Long-term proton pump inhibitor (PPI) use without indication* with 7.2%, *PPI use for uncomplicated peptic ulcer disease, or erosive peptic esophagitis at full therapeutic dose for > 8–12 weeks* with 3.0%, and *diuretic use as first-line treatment of essential hypertension with concurrent urinary incontinence* with 3.0%. The top-three most common PPO identified via TIME-to-START criteria were: *Herpes zoster vaccination* with 73.6%, *Seasonal influenza vaccination annually* with 59.3%, and *Pneumococcal vaccination after age 65* with 57.3%. Among all participants, 34.1% had PIP causally related to hospitalization. *Overtreatment of hypertension in patients with frailty* was the most common PIM-related hospitalization factor (2.5%). *Lack of oral nutritional supplements in patients with malnutrition* was the leading PPO linked to hospitalization (11.6%).

Conclusions PIP were highly prevalent in hospitalized older adults and frequently contributed to hospital admission. TIME criteria provided a comprehensive and context-adapted tool for identifying both inappropriate medication use and missed treatment opportunities. Routine implementation of TIME criteria-guided medication reviews may represent a promising strategy to enhance medication safety and reduce avoidable hospitalizations in older populations, warranting further investigation.

1 Introduction

Potentially inappropriate prescriptions (PIP), encompassing both overprescribing and underprescribing, remain a leading contributor to adverse drug events, functional decline, and preventable hospitalizations in older adults [1–3]. The challenge of optimizing pharmacotherapy is heightened in this population owing to multimorbidity, polypharmacy, and age-related changes in pharmacokinetics and pharmacodynamics [2, 4].

Several explicit tools have been developed to identify potentially inappropriate medications (PIM) and potential prescribing omissions (PPO), including the American Geriatrics Society Beers Criteria [5] for the PIM, and the

Extended author information available on the last page of the article

Key Points

Turkish Inappropriate Medication use in oldEr adults (TIME) criteria set is an internationally validated explicit tool developed to identify potentially inappropriate prescriptions.

Both underprescribing and overprescribing were highly prevalent among older adults according to the TIME criteria, affecting approximately 72% and 63% of patients, respectively.

One-third of hospitalizations were associated with PIP with a potential contribution to the hospitalization.

Routine implementation of TIME criteria-guided medication reviews may represent a promising strategy to enhance medication safety and reduce avoidable hospitalizations.

Screening Tool of Older Persons' Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) [6] and the FORTA (Fit fOR The Aged) [7, 8] lists, for both PIM and PPO. These tools have proven effective in diverse settings and are widely endorsed in geriatric pharmacotherapy [9, 10]. Despite their appreciated utility in Central Europe, these criteria may fail to capture local prescribing patterns and cultural or system-level healthcare nuances in other regions. To address these limitations, the Turkish Inappropriate Medication use in oldEr adults (TIME) criteria were developed in 2020 to better reflect regional prescribing patterns and healthcare system characteristics [11]. TIME criteria were initially drafted on the basis of the STOPP/START and CRIME frameworks and were refined through adaptations and additional criteria [12]. The titles STOP and START were deliberately retained to align with the established STOPP/START framework, ensuring structural clarity and practical utility. Unlike prior tools developed primarily by geriatricians and pharmacologists, TIME criteria benefited from a multidisciplinary approach, incorporating insights from 27 experts across various medical specialties such as cardiology, neurology, and psychiatry. This collaborative effort aimed to improve the tool's relevance, reliability, and adoption in broader clinical settings. Through the refinement process, 43 new criteria were added, 17 were removed, and 60 were revised, resulting in an independent tool comprising a total of 153 criteria.

Since its release, the TIME criteria set has been validated via a Delphi panel to be used across Central and Eastern Europe and studies on its adaptation into different languages are ongoing [13, 14]. Given its international validation, the criteria included in the TIME Criteria set are anticipated to be valid in the aforementioned world regions as well. However, despite some ongoing efforts for its clinical validation in different countries and settings, real-world evidence on its use remains limited. Previous small-scale studies were conducted on specific populations (including patients with coronavirus disease-2019 (COVID-19) [15], emergency department admissions [16], or nursing home residents [17]), with no data describing TIME-defined prescribing patterns or criteria that may contribute to hospitalization in geriatric inpatient settings. Therefore, this study aimed to assess the prevalence and types of PIP in Turkish inpatients aged ≥ 60 years using TIME criteria and to identify the most frequent TIME-to-STOP and TIME-to-START criteria triggers contributing to hospitalization.

2 Methods

This study employed a multicenter, cross-sectional design, conducted in inpatient departments of geriatrics and internal medicine across 13 tertiary-care hospitals in Turkiye. The study period extended from January 2020 to April 2021. The study was designed to investigate PIP, using TIME criteria and to identify both PIM and PPO that may have contributed to hospitalization. TIME criteria were selected owing to their explicit structure, dual-component design (TIME-to-STOP and TIME-to-START), and well-recognized regional adaptability. The presence of any PIP was evaluated on the first day of hospitalization, prior to therapeutic modifications by the admitting clinical team, thus aiming to provide an accurate reflection of real-world prescribing practices at the time of admission.

2.1 Participants

Eligible participants were aged ≥60 years and admitted to internal medicine or geriatric medicine wards. Because age-related changes and the risk of PIP may become clinically relevant before 65 years—particularly in developing countries such as Turkiye—and in line with the international demographic frameworks, individuals aged ≥60 years were included [18–20]. The study was restricted to geriatrics and internal medicine wards, since mainly these two disciplines provide care for older adults with multimorbidity and multiple drug use, for whom the application of an explicit tool such as the TIME criteria is most relevant. In addition to admissions for acute illnesses, we included elective admissions because PIP may contribute to progressive clinical deterioration or suboptimal disease control, ultimately necessitating planned hospitalization for diagnostic or therapeutic purposes. Patients were enrolled within the first 24 h of admission to capture data on the baseline medication use. Exclusion criteria included refusal to participate and

hospitalization for surgical, psychiatric, palliative, or perioperative care, as these cases often involve prescribing patterns unrelated to internal medicine-based pharmacotherapy.

2.2 Data Collection

Upon enrollment, a structured comprehensive geriatric assessment (CGA) was conducted. In geriatric clinics, all current medications—including prescription drugs, over-the-counter (OTC) agents, supplements, and herbal products—were reviewed by at least one trained geriatrician, while in internal medicine clinics they were reviewed by at least one internist. All medications were recorded with their brand names, active ingredients, doses, routes of administration, and frequencies of use, on the basis of both medical records and direct patient and/or caregiver interviews. As vaccination-related recommendations are part of the TIME criteria, participants' vaccination status was also evaluated. Since no centralized official vaccination registry is available in Turkiye, vaccination status could not be verified through a single system. Although the national personal electronic health record system (e-Nabız) contains vaccination-related information, it mainly covers childhood vaccinations. Nevertheless, vaccinations formally prescribed were verified via e-Nabız prescription records, and when necessary, additional confirmation was obtained from medical records of patients' family physicians or geriatricians.

All managing physicians participating in the study were instructed to review and acquire a comprehensive understanding of the TIME criteria before study initiation. Evaluations in the geriatrics clinics were conducted by physicians who were expected to have prior familiarity with the TIME criteria through national congress presentations and webinars. Since 2019, at least one oral presentation on the TIME criteria has been delivered annually at national congresses, supporting widespread awareness of their application among geriatricians. Internists were not provided with formal training in the application of the TIME criteria, although they reviewed the criteria prior to the evaluations. Nevertheless, they received a 2-h training on CGA prior to study initiation, which included relevant aspects of medication use in older adults, aiming to facilitate accurate and standardized implementation of all assessments used in the study.

Medication appropriateness was assessed using the 2020 version of TIME criteria (first version), which includes 112 STOP and 41 START indicators [11]. Each medication was assessed in the context of the patient's medical conditions, functional status, and laboratory parameters. While explicit tools may perform comparably to simple medication counts in identifying potentially inappropriate medication use, the TIME criteria inherently include elements requiring implicit clinical judgment, such as the presence of dementia, frailty, falls, and osteoporosis. Therefore, medication reviews in this study integrated explicit criteria with patient-specific implicit clinical adjudication [21].

An additional assessment involved determining whether identified PIP had a clinically adjudicated association with the reason for hospitalization. This was determined by the clinical judgement of the attending physician, who knew all aspects of each individual patient and consequently could assess holistically. Physicians classified a case as a PIP–related hospitalization when it was judged to be **either a direct precipitating cause of admission** (e.g., selective serotonin reuptake inhibitor (SSRI) use in a patient presenting with hyponatremia, or metformin use in a patient with malnutrition/frailty), or **a contributing factor to hospitalization** (e.g., cognitive deterioration or delirium partially attributable to medications with high anticholinergic burden). PIP that were judged to be contributors to hospitalization were further classified into categories including: *PIM-related adverse drug events* (e.g., falls, bleeding, hypotension, etc.); *PPO-related deterioration* (e.g., stroke due to lack of anticoagulation, malnutrition due to absence of supplementation, etc.).

The moderator study center was Istanbul Medical Faculty; which hosts the primary investigator of the TIME criteria, the national senior author, and most of the academics involved in the development of the criteria. The affiliated centers were free to consult the moderator center regarding whether a specific medication could be considered a PIP in the individual patient context and whether it could be potentially associated with the cause of hospitalization. If there was any uncertainty, a consensus was reached through case discussion.

2.2.1 Parameters and Assessment Tools

Demographic data, comorbidities, and clinical variables were collected, encompassing age, sex, body mass index (BMI), cognitive, nutritional, and functional status, quality of life, and the presence of frailty, sarcopenia, falls, chronic pain, and polypharmacy.

Confusion Assessment Method (CAM) was used to identify delirium [22]. Cognitive assessment was performed using the standardized Mini-Mental State Examination (sMMSE). sMMSE consists of eleven items evaluating orientation, recording memory, attention and calculation, recall and language. The total score is 30 points, where scores below 24 suggest cognitive impairment [23].

Nutritional status was screened with the Mini-Nutritional Assessment-Short Form (MNA-SF) [24]. A MNA-SF score of <12 is considered "undernutrition," and a score of 12 and above is considered "normal nutritional status." Functional

status was assessed by Katz Activities of Daily Living Scale-ADL (min 0, max 6 points) [25] and Lawton Instrumental Activities of Daily Living Scale-IADL (min 0, max 8 points) [26]. Each item in ADL and IADL scales is scored 0 if the patient is dependent and 1 if the patient is independent for the activity. Lower scores indicate functional dependency. Dependence in at least one item of the ADL or IADL scale was categorized as *impairment in ADL* or *impairment in IADL*, respectively [27].

Quality of life (QoL) was assessed by the EuroQoL five-dimensional questionnaire (EQ-5D). The five domains of EQ-5D include mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Higher scores indicate poor quality of life [28]. Frailty was evaluated using the FRAIL scale. The scale questions fatigue, resistance, ambulation, illnesses, and weight loss. Scores of 0, 1–2, and 3–5 were categorized as robust, prefrail, and frail, respectively [29].

Sarcopenia was defined according to the criteria recommended in the second consensus paper of the European Working Group on Sarcopenia in Older People (EWGSOP2) [30]. Low muscle strength measured via Jamar hydraulic hand-dynamometer was considered as probable sarcopenia. Handgrip strength was measured in the sitting position, with the elbow in 90° flexion, wrist in the neutral position. Patients were asked to apply maximum grip strength with both hands, three times for both sides. The maximum grip strength was recorded. Cut off points for low handgrip strength were 27 kg and 16 kg for males and females, respectively [30].

Participants were asked, through closed-ended questions, whether they had experienced a fall within the past year. For chronic pain assessment, patients were asked whether they have been experiencing pain ongoing ≥3 months. Polypharmacy was defined as the use of ≥5 medications, and excessive polypharmacy as ≥10 medications, based on established definitions [22].

All assessments and measurements were performed by geriatrics or internal medicine specialists. Data collection adhered to standardized procedures across all centers. Data were entered into a standardized electronic case form with predefined variables and instructions to promote consistency and data quality across participating centers. No patients were excluded due to missing data, and internal audits ensured the completeness and integrity of data entry.

2.3 Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY). Descriptive statistics were used to summarize the demographic and clinical characteristics. Normality was assessed using Kolmogorov–Smirnov test and visually by histograms. Categorical variables were presented as number and percentages, while continuous variables were expressed as means ± standard deviations (SD) or median and ranges as appropriate. Prevalence rates were calculated for all PIP categories (overall, PIM [TIME-to-STOP], PPO [TIME-to-START], and hospitalization-related). Chi-square tests and Fisher's exact tests were used to compare proportions, while independent sample *t*-test were used for continuous variables. Logistic regression analysis was performed to evaluate factors independently associated with overall PIP or PIP-related hospitalizations. Variables were selected on the basis of significance in univariate analysis ($p < 0.05$) or on established clinical relevance, including factors known to influence disease burden and medication use [e.g., age, sex, number of chronic diseases, number of regular drugs]). Models were constructed independently for each outcome (i.e., for overall PIP, PIP-related hospitalization, PIM-related hospitalizations according to TIME-to-STOP criteria, and PPO-related hospitalizations according to TIME-to-START criteria). Multicollinearity among the independent variables considered for the regression analyses was assessed using Pearson, Spearman, or Kendall's tau-b correlation analyses. The results of the regression analysis were presented as odds ratios (OR) with 95% confidence intervals. A two-tailed *p*-value <0.05 was considered statistically significant.

3 Results

A total of 405 inpatients met the inclusion criteria and were included in the analysis (Fig. 1). The mean age of the participants was 77.8 ± 8.8 years, and 55.3% ($n = 224$) were female. The mean number of chronic diseases was 4.2 ± 1.8 (median [interquartile range, IQR]: 4 [2–5]), and the mean number of medications used at admission was 7.3 ± 2.5 (median [IQR]: 6 [3–8]). A total of 63.7% of the patients met the criteria for polypharmacy and 13.3% met the criteria for excessive polypharmacy (Table 1).

3.1 The Prevalence and Types of Overall PIP According to the TIME Criteria

PIP defined as the presence of at least one TIME-to-STOP (PIM) or TIME-to-START (PPO) criterion- was detected in 82.5% ($n = 334$) of the patients. Specifically: TIME-to-STOP criteria were met in 63.2% ($n = 256$) and TIME-to-START omissions were identified in 71.6% ($n = 290$). The frequency of combined STOP + START (PIM+PPO) issues was also notable; 41.7% ($n = 169$) had both types concurrently.

The top-three most common TIME-to-STOP (PIM) criteria identified were (in descending order): *Long-term proton pump inhibitor (PPI) use without indication* with 7.2% (n = 29); *PPI use for uncomplicated peptic ulcer disease or erosive peptic esophagitis at full therapeutic dose for* >

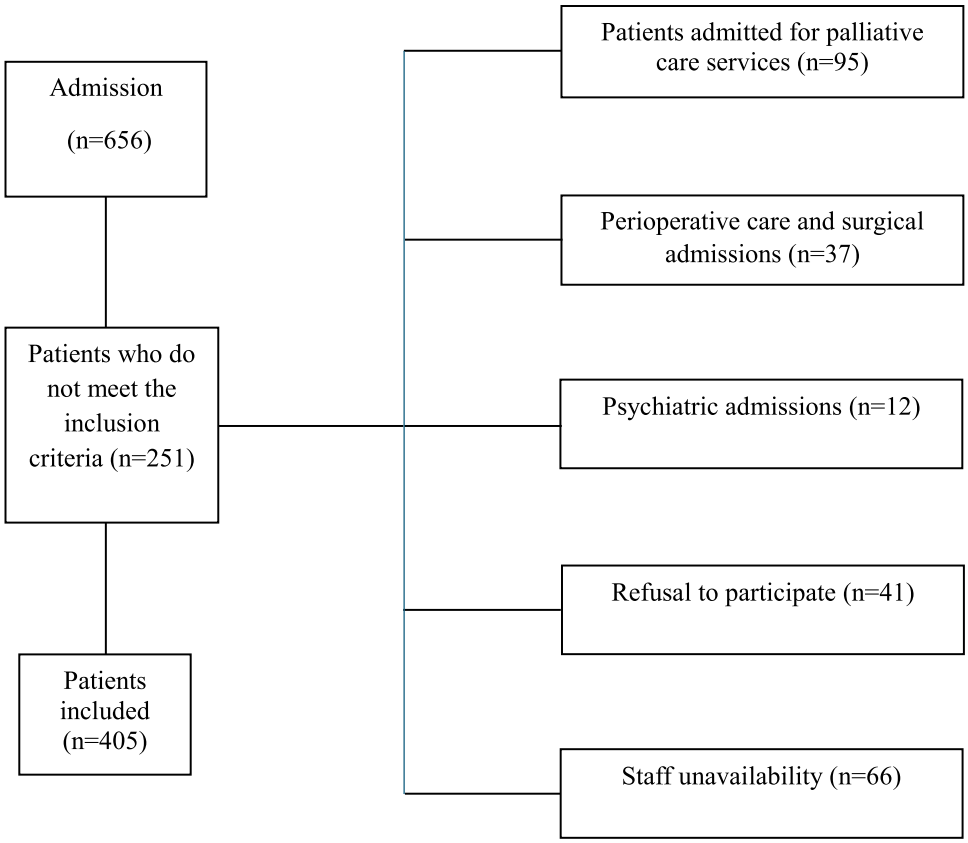


Fig. 1 Flowchart on the number of patients included in the study

8–12 weeks with 3.0% ($n = 12$), and *diuretic use as first-line treatment of essential hypertension with concurrent urinary incontinence* with 3.0% ($n = 12$).

The top-three most common TIME-to-START (PPO) included *Herpes zoster vaccination* with 73.6% ($n = 298$), *Seasonal influenza vaccination annually* with 59.3% ($n = 240$), and *Pneumococcal vaccination (each one dose for 13-valent conjugate and 23-valent polysaccharide) after age 65* with 57.3% ($n = 232$). The most common TIME-to-STOP and TIME-to-START criteria on admission were given in Table 2.

3.2 The Prevalence and Types of PIP-Related Hospitalizations

In 138 patients (34.1%), at least one case of PIP was associated with the cause of hospitalization. Two-thirds of PIP-related hospitalizations were associated with PPOs (83 [20.5%] were related to the TIME-to-START criteria, and 55 [13.6%] to the TIME-to-STOP criteria). The top-three most frequent causes of PIM-related hospitalizations associated with the TIME-to-STOP criteria (PIM, overtreatment) were: *strict blood pressure control (<140/90 mmHg) in frail patients* with 2.5% ($n = 10$), *metformin use in patients with malnutrition/frailty* with 2.2% ($n = 9$), and *use of high-potency anticholinergic drugs* with 1.5% ($n = 6$). On the other hand, the top-three most frequent PPO-related causes of hospitalization associated with the TIME-to-START omissions (undertreatment) were: *lack of oral nutritional supplements (ONS) in patients with malnutrition* with 11.6% ($n = 47$), *absence of pneumococcal vaccination after age 65* with 6.7% ($n = 27$), and *lack of vitamin D replacement when vitamin D intake <800–1000 IU per day and/or calcium replacement if elementary calcium intake <1000–1200 mg per day* with 4.4% ($n = 18$) (Table 3).

3.3 Factors Associated with Overall PIP According to TIME Criteria

According to the *univariate analysis*, male sex and the presence of chronic pain were associated with a higher prevalence of overall PIP (p values were 0.040 and <0.001, respectively) (Supplementary Table 1). *Multivariate analysis* showed that female sex and having chronic pain were independently associated with overall PIP (OR [95% CI] were 0.54 [0.31–0.94] and 2.62 [1.40–4.91], respectively) (Table 4).

3.4 Factors Associated with PIP-Related Hospitalizations

According to the *univariate analysis*, patients with frailty, undernutrition, and delirium demonstrated a higher

Table 1 Characteristics of study participants ($n = 405$)

Characteristics	Value
Age*	77.8 ±8.8
Sex (female)[a]	223 (55.2%)
Number of medications[b]	6 (3–8)
Number of chronic diseases[b]	4 (2–5)
Chronic diseases	
Hypertension[a]	276 (68.1%)
Type II diabetes mellitus[a]	134 (33.1%)
Ischemic heart disease[a]	79 (19.5%)
Chronic kidney disease[a]	82 (20.2%)
Chronic obstructive pulmonary disease[a]	67 (16.5%)
Geriatric syndromes	
Impairment in ADL (ADL < 6)[a]	268 (66.5%)
Impairment in IADL (IADL < 8)[a]	304 (75.6%)
Pre-frailty[a]	96 (23.8%)
Frailty[a]	279 (69.2%)
Polypharmacy[a]	258 (63.7%)
Excessive polypharmacy[a]	54 (13.3%)
Undernutrition (MNA-SF < 12)[a]	319 (79.2%)
Sarcopenia (probable)[a]	149 (65.6%)
Cognitive impairment[a]	185 (50.1%)
Delirium[a]	57 (14.4%)
Chronic pain[a]	146 (36.4%)
Falls in the past year[a]	165 (41.0%)

ADL, Activities of Daily Living; IADL, Instrumental Activities of Daily Living; MNA-SF, Mini Nutritional Assessment-Short Form

*Mean ± standard deviation

[a]Numbers (percentages)

[b]Median (interquartile range)

prevalence of PIP-related hospitalization compared with their counterparts (p-values were 0.011, 0.013, and < 0.001, respectively). Moreover, patients with PIP-related hospitalization had poorer quality of life ($p = 0.001$) (Supplementary Table 2). *Multivariate analysis* revealed that lower number of regular drugs and the presence of delirium were associated with the risk of PIP-related hospitalizations (OR[95% CI] were 0.89 [0.82–0.97] and 2.44 [1.29–4.59], respectively) (Table 5).

3.4.1 Factors Associated with PIM-Related Hospitalizations According to TIME-to-STOP Criteria

Univariate analysis regarding factors associated with PIM-related hospitalization meeting TIME-to-STOP criteria were presented in Supplementary Table 2. *Multivariate analysis* revealed that only the presence of chronic pain at admission was associated with higher risk of PIM-related hospitalization meeting TIME-to-STOP criteria (OR [95% CI = 2.04 [1.18–3.53]) (Table 6).

3.4.2 Factors Associated with PPO-Related Hospitalizations According to TIME-to-START Criteria

The findings of the *univariate analysis* examining the factors associated with PPO-related hospitalizations meeting TIME-to-START criteria were presented in Supplementary Table 2. *In multivariate analysis*, the presence of delirium, higher QoL scores (i.e., lower QoL), and undernutrition were associated with increased odds of PPO-related hospitalization meeting TIME-to-START criteria (OR [95% CI] were 2.58 [1.33–5.03], 1.13 [1.01–1.27], and 2.55 [1.05–6.22], respectively). On the other hand, female sex and number of regular drugs were associated with decreased odds of PPO-related hospitalization meeting TIME-to-START criteria (OR [95% CI] were 0.51 [0.30–0.87] and 0.88 [0.80–0.97], respectively) (Table 6).

4 Discussion

This multicenter study indicates a substantial burden of PIP among hospitalized older adults in Turkiye. Furthermore, in approximately one-third of cases, hospitalization was associated with PIP that may have contributed to the admission. Many of the contributing factors identified were modifiable prescribing issues, such as overtreatment of hypertension in individuals with frailty or omission of ONS in patients with malnutrition. These findings offer clinically relevant insights that may guide efforts to optimize medication use and improve outcomes in older adults.

The overall prevalence of PIP observed in this study (82.5%) exceeded estimate rates reported in studies of hospitalized older adults by using the Beers or STOPP/START criteria, where prevalence ranges between 30 and 60% [31]. While this difference could partially reflect local prescribing patterns and limited familiarity with geriatric pharmacotherapy, prior outpatient studies from Turkiye using the Beers and STOPP/START criteria have reported prevalence rates comparable to those from other countries, making this theory somewhat less likely for this much higher PIP prevalence among hospitalized older patients [32–36]. On the other hand, previous local studies applying TIME criteria have similarly reported high PIP prevalence. For example, a study conducted among older adults hospitalized with COVID-19 found PIPs in 96% of patients, predominantly due to PPO [15]. Likewise, a nursing home-based study reported at least one PIP in all participants [17]. A recently published study assessing PIM on the basis of the TIME-to-STOP criteria in older adults presenting to the emergency department reported a PIM prevalence of 61.5% [16]. Furthermore, in a comparative study assessing TIME criteria, Beers 2019, and STOPP/START v2 criteria in older outpatients, PIP prevalence rates were 46.1%, 30.6%, and 26.2%, respectively

Table 2 The most frequent (top five) overall TIME criteria on admission

TIME-to-STOP criterion	% (*n*)
1. PPIs for multiple drug use indication (no benefit, potential harm)	7.2% (29)
2. PPIs for uncomplicated peptic ulcer disease or erosive peptic esophagitis at full therapeutic dose for > 8–12 weeks (dose reduction or earlier discontinuation indicated)	3.0% (12)
2. Diuretics as first-line treatment of essential hypertension with concurrent urinary incontinence (may exacerbate urgency and incontinence, impair quality of life and increase falls)	3.0% (12)
3. Metformin in malnourished/frail patients (due to GIS side effects and loss of appetite)	2.7% (11)
4. Aspirin, clopidogrel, NSAIDs or corticosteroids in patients with peptic ulcer history/dyspepsia-gastroesophageal reflux symptoms or with concurrent antiplatelet/anticoagulant/corticosteroid treatment(s) without PPI prophylaxis	2.5% (10)
4. High potency anticholinergic drugs [e.g., tricyclic antidepressants, chlorpromazine, thioridazine, clozapine, olanzapine, hyoscine, oral oxybutynin, first generation antihistamines (pheniramine, chlorpheniramine, hydroxyzine, cyproheptadine, dimenhydrinate, diphenhydramine, meclizine etc.), paroxetine] in patients with falls/constipation/narrow angle glaucoma/delirium/dementia/urinary retention/obstructive LUTS symptoms/concurrent use of anticholinergic drugs	2.5% (10)
5. Continuous and long-term use of betahistine, trimetazidine, dimenhydrinate in the treatment of vertigo (no evidence-based beneficial effect)	2.2% (9)
TIME-to-START criterion	
1. Vaccination for herpes zoster (reduction in risk of shingles infection and post-herpetic neuralgia)	73.6% (298)
2. Seasonal influenza vaccination annually	59.3% (240)
3. Pneumococcal vaccination (each one dose for 13-valent conjugate and 23-valent polysaccharide) after age 65	57.3% (232)
4. Vaccination with Td (tetanus-diphtheria toxoid) every 10 years	55.8 % (226)
5. Vitamin D if vitamin D intake <800–1000 IU per day and/or calcium if elementary calcium intake <1000–1200 mg per day	28.1% (114)

GIS, gastrointestinal system; LUTS, lower urinary tract symptoms; NSAID, Non-steroidal anti-inflammatory drug; PPI, proton-pump inhibitor

[37]. This supports the notion that locally adapted tools tend to be more sensitive in detecting inappropriate prescribing [38, 39]. However, in the context of TIME, this increased sensitivity may be explained not only by their adaptation to regional prescribing practices, but also by their broader scope in addressing both PIM and PPO. Unlike the Beers criteria, which does not systematically include PPO, TIME explicitly targets underuse of therapies such as anticoagulants, nutritional supplements, and vaccinations—areas often overlooked but critically important in geriatric care. Even when compared with the FORTA, the number of PIP evaluated (both over and under treatment) is substantially higher, likely resulting in a higher prevalence.

One particularly important contributor to the high prevalence of PIP was the integration of nutritional treatment via ONS as a PPO [40]. Nutritional treatment is well-recognized as having paramount importance in older adults with acute problems adversely affecting their adequate nutrient intake, directly related to morbidity, need for hospitalization, and mortality [40–42]. To our knowledge, TIME stands forward as the only PIP evaluation tool where nutritional treatment is included among PPO.

The high prevalence of PIP may also be explained by the combined use of explicit criteria and implicit clinical judgment. A key strength of implicit assessment lies in its capacity to reveal conditions that are not captured by standardized screening tests, but can be recognized through the clinician's evaluation. The clinician's judgment, informed by a comprehensive evaluation of the patient—including past and present medical history, physical examination, laboratory findings, and CGA data—may have contributed to the higher detection rate of PIP in this study.

Although both PIM and PPO were highly prevalent in our study, the finding of PPO slightly exceeding PIM was particularly noteworthy (71.6% versus 63.2%). This finding emphasizes that optimizing prescribing in older adults requires more than deprescribing; it requires proactive identification and treatment of unmet clinical needs [43]. The most frequent PPO identified was herpes zoster vaccination, absent in 73.6% of eligible patients. A previous Turkish study also reported a 97.5% rate of Herpes zoster vaccine omission in older outpatients [44]. In Turkiye, the unavailability of the vaccine until recently and its current lack of reimbursement have likely contributed to low vaccination rates [45]. However, even though the pneumococcal and annual influenza vaccines were both available and reimbursed in Turkiye, their coverage remained far below the target in our study (42.7% and 40.7%, respectively). The main reasons for the undervaccination on the patients' side may be vaccine hesitancy (often caused by misinformation through television and internet or distrust toward pharmaceutical companies) and low awareness [46]. On the physicians' side, the lack of adequate knowledge, limited promotion of vaccination due to heavy workload, and time constraints can be listed as potential contributors [47]. The most frequently encountered PIM was *long-term use of PPIs*

Table 3 The most frequent (top five) TIME criteria associated with potentially inappropriate prescription-related hospitalizations

TIME-to-STOP criterion	% (*n*)
1. Strict blood pressure control (<140/90 mmHg) in patients with orthostatic hypotension/ cognitive impairment (e.g., dementia)/ functional limitation/ low life expectancy (<2 years)/ high risk of falling.	2.5% (10)
2. Metformin in malnourished/frail patients (due to GIS side effects and loss of appetite)	2.2% (9)
3. High potency anticholinergic drugs [e.g., tricyclic antidepressants, chlorpromazine, thioridazine, clozapine, olanzapine, hyoscine, oral oxybutynin, first generation antihistamines (pheniramine, chlorpheniramine, hydroxyzine, cyproheptadine, dimenhydrinate, diphenhydramine, meclizine etc.), paroxetine] in patients with falls/constipation/narrow angle glaucoma/delirium/dementia/urinary retention/obstructive LUTS symptoms/concurrent use of anticholinergic drugs	1.5% (6)
4. Potassium-sparing drugs (aldosterone antagonists, triamterene, amiloride, ACEI, ARB) in patients with eGFR <30 ml/min/1.73 m^2 and whose serum potassium level cannot be closely monitored (risk of hyperkalemia)	1.2% (6)
4. Neuroleptics/antipsychotics for hypnotic purpose (increased confusion, hypotension, extrapyramidal side effects, risk of fall)	1.2% (6)
4. NSAIDs if eGFR <50 ml/min/1.73 m^2 (risk of deterioration in renal function)	1.2% (6)
5. Thiazide diuretic with concurrent significant hypokalemia (i.e. serum K <3.0 mEq/L), hyponatremia (i.e. serum Na <130 mEq/L), hypercalcemia (i.e., corrected serum Ca >10.6 mg/dL) or with a history of gout (hypokalemia, hyponatremia, hypercalcemia and gout can be precipitated by thiazide diuretic)	1.0% (4)
5. High anticholinergic drugs in patients with delirium or dementia (amitriptyline, paroxetine, dicyclomine, l-hyoscyamine, thioridazine, chlorpromazine, clozapine, olanzapine, urinary antimuscarinics, H1 receptor blockers esp. 1st generation H1 receptor blockers (diphenhydramine, cyproheptadine, pheniramine), H2 receptor blockers (risk of cognitive deterioration)	1.0% (4)
5. Neuroleptics/antipsyhotics (may cause gait dyspraxia, parkinsonism), benzodiazepines (sedative, may cause reduced sensorium, impair balance) and Z-type hypnotic (e.g., zopiclone, zolpidem, zaleplon) (may cause protracted daytime sedation, ataxia) in patients with high fall risk	1.0% (4)
TIME-to-START criterion	
1. Oral nutritional supplements in patients with malnutrition or malnutrition risk if nutritional counseling/dietary supplementation are not sufficient to achieve nutritional goals	11.6% (47)
2. Pneumococcal vaccination (each one dose for 13-valent conjugate and 23-valent polysaccharide) after age 65	6.7% (27)
3. Vitamin D if vitamin D intake <800–1000 IU per day and/or calcium if elementary calcium intake <1000–1200 mg per day	4.4 % (18)
4. Seasonal influenza vaccination annually	3.0% (12)
5. Acetylcholinesterase inhibitors for mild-moderate Alzheimer's disease	2.5% (10)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; Ca, calcium; eGFR, estimated glomerular filtration rate; GIS, gastrointestinal system; K, potassium; LUTS, lower urinary tract symptoms; Na, sodium; NSAID, Nonsteroidal antiinflammatory drug

Table 4 Multivariate analysis on the factors associated with overall potentially inappropriate prescriptions in older inpatients

Parameters	OR (95% confidence interval)	*p* value
Age	0.99 (0.96–1.02)	0.369
Female sex	**0.54 (0.31–0.94)**	**0.028**
Number of chronic diseases	1.09 (0.92–1.29)	0.333
Number of regular drugs	0.93 (0.84–1.03)	0.160
Chronic pain	**2.62 (1.40–4.91)**	**0.003**

Values in bold denote statistical significance

Table 5 Multivariate analysis on the factors associated with potentially inappropriate prescription-related hospitalizations

Parameters	OR (95% confidence interval)	*p* value
Age	0.99 (0.96–1.01)	0.262
Female sex	0.78 (0.50–1.23)	0.288
Number of chronic diseases	1.14 (0.99–1.31)	0.054
Number of regular drugs	**0.89 (0.82–0.97)**	**0.009**
Undernutrition	1.37 (0.73–2.56)	0.333
Frailty	1.13 (0.62–2.09)	0.687
Delirium	**2.44 (1.29–4.59)**	**0.006**
Quality of life	1.07 (0.97–1.18)	0.171

Values in bold denote statistical significance

without a valid indication; consistent with previous findings where up to 50% of older PPI users lack appropriate indications, leading to unnecessary risk of adverse outcomes such as osteoporosis, Clostridioides difficile infection, and chronic kidney disease [17, 48, 49].

In our study, 34.1% of hospitalizations were related to at least one PIP. The clinical relevance of PPO is underscored by the observation that almost two-thirds of PIP-related hospitalizations involved PPO. The proportion observed in our study exceeds global estimates reporting that up to 25% of hospitalizations in older adults are medication-related [50], possibly because underprescribing was not consistently captured in many previous studies. PPO with the highest

Table 6 Multivariate analysis on the factors associated with PIM-related hospitalizations meeting the TIME-to-STOP criteria and PPO-related hospitalizations meeting the TIME-to-START criteria

PIM-related hospitalization meeting the TIME-to-STOP criteria		
Parameters	OR (95% confidence interval)	*p* value
Age	1.01 (0.97–1.04)	0.745
Female sex	0.92 (0.53–1.60)	0.757
Number of chronic diseases	1.15 (0.98–1.34)	0.088
Number of regular drugs	1.01 (0.92–1.12)	0.788
Chronic pain	**2.04 (1.18–3.53)**	**0.011**
PPO-related hospitalization meeting the TIME-to-START criteria		
Age	1.00 (0.97–1.03)	0.842
Female sex	**0.51 (0.30–0.87)**	**0.013**
Number of chronic diseases	1.03 (0.88–1.20)	0.736
Number of regular drugs	**0.88 (0.80–0.97)**	**0.014**
Impaired IADL	1.09 (0.46–2.59)	0.842
Frailty	0.81 (0.36–1.79)	0.596
Undernutrition	**2.55 (1.05–6.22)**	**0.039**
Delirium	**2.58 (1.33–5.03)**	**0.005**
Quality of life	**1.13 (1.0 –1.27)**	**0.038**

Values in bold denote statistical significance

IADL, instrumental activities of daily living; PIM, potential inappropriate medication use; PPO, potential prescription omissions

impact on PIP-related hospitalizations was the underutilization of ONS in patients with malnutrition (~12%). Despite coverage by the Turkish social security system, ONS remain underprescribed, which may be a reflection of a broader underrecognition of malnutrition and probably its consequences such as sarcopenia, frailty, cachexia and consequent need for hospitalization [51]. Equally noteworthy was the contribution of overtreatment to hospitalization risk. For instance, *strict blood pressure control in frail patients with orthostatic hypotension or dementia* was the most common PIM-related to hospitalization. This finding aligns with prior evidence, showing increased hospitalizations and mortality in vulnerable older adults receiving intensive antihypertensive treatment [52–54]. As such, recommending relaxed blood pressure targets in vulnerable subgroups such as older adults with frailty is in accordance with the latest hypertension guidelines [55–59].

Our study has its own limitations. First, the cross-sectional design limits causal inference. However, evaluations based on standardized CGA and detailed clinical context may have partially mitigated this limitation. In addition, the study findings may not be fully representative of the entire hospitalized older adult population nationwide. Nevertheless, the inclusion of cities from three different geographical regions, together accounting for approximately 35% of Turkiye's total population, may have partially alleviated concerns regarding representativeness. While the evaluators were knowledgeable on TIME criteria, we lack inter-rater reliability measures or a pilot study objectively assessing their capacity, leaving room for potential variability in evaluations. Moreover, the internists' expertise in geriatric medicine may not have been comparable to that of geriatricians, and their relative unfamiliarity with PIP criteria may have resulted in some cases being overlooked. Although the coordinating center provided educational session on how to perform CGA and offered consultation support for every patient, some evaluators—particularly internists—may have been unaware of gaps in their evaluations and therefore might not have fully communicated these issues to the geriatrics team or the coordinating center. Consequently, reliance on individual assessments without case-by-case central consensus discussions may have favored underdetection of PIP. Furthermore, as this was not a blinded study, physician assessments may have been influenced by awareness of the study objectives, introducing further potential observer bias and possibly resulting in higher reported rates of PIP and PIP-related hospitalizations. Nevertheless, given the observational nature of the study, the primary aim was not to establish definitive causality but to identify clinically meaningful associations while minimizing the risk of missing relevant contributors. In addition, owing to the absence of a centralized adult vaccination registry in Turkiye, vaccination history was primarily based on patient or caregiver reports, and recall bias cannot be entirely excluded. Finally, as data were collected during the COVID-19 pandemic (2020–2021), temporal changes in prescribing practices during this period may limit the generalizability of the findings.

On the other hand, several strengths are also present. First, although studies reporting the prevalence of PIP are abundant in the literature, to the best of our knowledge, this is the first study conducted in Turkish older inpatients using a context-adapted tool, to evaluate PIP prevalence and its association with hospitalizations. Beyond describing prevalence, our study provides specific, locally relevant PIM and PPO that may represent actionable targets for intervention, particularly in relation to potentially preventable hospitalizations. A key strength of this study is the use of a dual approach that integrates explicit tool-based evaluation with implicit clinical assessment—widely regarded as the reference standard for identifying inappropriate prescribing—to examine the association between PIP and hospitalization.

Evidence from comparative studies suggests that locally adapted tools tend to perform better in identifying PIP [37–39]. However, whether systematic implementation of such tools improves clinical outcomes remains uncertain. The lack of benefit observed in trials such as OPERAM (OPtimising thERapy to prevent Avoidable hospital admissions in Multimorbid older people) highlights that explicit

tools alone may not be sufficient; effectiveness can also depend on implementation fidelity, clinician engagement, and continuity of care [60]. Nevertheless, the true clinical impact of TIME requires confirmation through real-world prospective and/or pharmacoepidemiological studies. Ongoing interventional comparative trials evaluating the effect of TIME-based medication review on outcomes such as hospitalization and mortality are expected to provide more definitive evidence of its role in real-world clinical practice.

5 Conclusions

This multicenter study showed that PIP were highly prevalent among hospitalized older adults in Turkiye, and that one-third of hospitalizations were clinically judged to be related to PIP. PPO, particularly related to nutrition and vaccination and PIM, such as intensive antihypertensive therapy in patients with frailty emerged as prominent and potentially preventable problems. By combining an explicit, context-adapted tool with implicit judgment, TIME criteria enabled the identification of locally relevant prescribing patterns that may have direct implications for inpatient clinical practice. These findings highlight the need for medication review that addresses not only deprescribing, but also proactive initiation of evidence-based treatments in older adults.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40266-026-01282-0.

Funding Open access funding provided by the Scientific and Technological Research Council of Türkiye (TÜBİTAK). No external funding was used in the preparation of this manuscript.

Declarations

Authors' contributions GB: Conceptualization, Methodology, Writing- Original draft preparation, Writing- Reviewing and Editing, Supervision; SO: Formal analysis and investigation, Writing- Original draft preparation, Writing- Reviewing and Editing; TE: Methodology, Formal analysis and investigation; BI: Methodology, Formal analysis and investigation, Supervision; MMO: Formal analysis and investigation; DES: Formal analysis and investigation; BC: Formal analysis and investigation, Writing- Original draft preparation; BTC: Formal analysis and investigation; TSA: Formal analysis and investigation, Supervision; RTD: Formal analysis and investigation; KS: Formal analysis and investigation, Supervision; SB: Formal analysis and investigation; MH: Formal analysis and investigation, Supervision; FE: Formal analysis and investigation; Sumru Savas: Formal analysis and investigation, Supervision; Sevnaz Sahin: Formal analysis and investigation, Supervision; PA: Formal analysis and investigation; DSE: Formal analysis and investigation, Supervision; EG: Formal analysis and investigation; SA: Formal analysis and investigation, Supervision; MV: Formal analysis and investigation, Supervision; MY: Formal analysis and investigation; SA: Formal analysis and investigation, Supervision; AT: Formal analysis and investigation, Supervision; BOT: Formal analysis and investigation, Supervision; BGYV: Formal analysis and investigation; MIN: Formal analysis and investigation, Supervision; IT: Formal analysis and investigation, Supervision; GSA: Formal analysis and investigation; ZU: Formal analysis and investigation, Supervision; FS: Formal analysis and investigation; HD: Formal analysis and investigation, Supervision; UK: Formal analysis and investigation; MAK: Resources, Supervision.

Availability of data and material Data supporting the findings of this study are available from the corresponding author upon reasonable request.

Code availability Not applicable

Conflict of interest Gulistan Bahat is an Editorial Board member of Drugs & Aging. Gulistan Bahat was not involved in the selection of peer-reviewers for the manuscript nor any of the subsequent editorial decisions. The other authors declare that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

Consent to participate Informed consent was obtained from all individual participants or their legal representatives included in the study.

Consent for publication Not applicable

Ethics approval This study was approved by the Istanbul University Istanbul Medical Faculty Ethics Committee (reference: 2020/1269).

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Authors and Affiliations

Gulistan Bahat[1] · Serdar Ozkok[1] · Tugba Erdogan[1] · Birkan Ilhan[2] · Meryem Merve Oren[3] · Duygu Erbas Sacar[1] · Busra Can[4] · Bahar Tekin Cetin[5] · Timur Selcuk Akpinar[5] · Rana Tuna Dogrul[6] · Kamile Silay[6] · Suna Burkuk[7] · Meltem Halil[7] · Fatma Erol[8] · Sumru Savas[8] · Sevnaz Sahin[8] · Pinar Arman[9] · Deniz Suna Erdincler[9] · Emine Gemci[10] · Sevgi Aras[10] · Murat Varli[10] · Melike Yazici[11] · Suna Avci[11] · Asli Tufan[4] · Banu Ozulu Turkmen[12] · Betul Gulsum Yavuz Veizi[13] · Mehmet Ilkın Naharci[13] · Ilker Tasci[14] · Gozde Sengul Aycicek[15] · Zekeriya Ulger[15] · Funda Salgur[16] · Huseyin Doruk[17] · Umut Karabay[2] · Mehmet Akif Karan[1]

✉ Gulistan Bahat
gbahatozturk@yahoo.com

[1] Division of Geriatrics, Department of Internal Medicine, Istanbul Medical Faculty, Istanbul University, Capa, 34390 Istanbul, Turkey

[2] Division of Geriatrics, Department of Internal Medicine, Sisli Hamidiye Etfal Training And Research Hospital, Istanbul, Turkey

[3] Department of Public Health, Istanbul Medical Faculty, Istanbul University, Istanbul, Turkey

[4] Division of Geriatrics, Department of Internal Medicine, Marmara University Pendik Training And Research Hospital, Istanbul, Turkey

[5] Department of Internal Medicine, Faculty of Medicine, Koc University, Istanbul, Turkey

[6] Division of Geriatrics, Department of Internal Medicine, Ankara Bilkent City Hospital, Istanbul, Turkey

[7] Division of Geriatrics, Department of Internal Medicine, Faculty of Medicine, Hacettepe University, Istanbul, Turkey

[8] Division of Geriatrics, Department of Internal Medicine, Faculty of Medicine, Ege University, Istanbul, Turkey

[9] Division of Geriatrics, Department of Internal Medicine, Cerrahpasa Faculty of Medicine, Istanbul University-Cerrahpasa, Istanbul, Turkey

[10] Division of Geriatrics, Department of Internal Medicine, Faculty of Medicine, Ankara University, Istanbul, Turkey

[11] Division of Geriatrics, Department of Internal Medicine, University of Health Sciences, Bursa Yuksek Ihtisas Training And Research Hospital, Istanbul, Turkey

[12] Division of Geriatrics, Department of Internal Medicine, Istanbul Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey

[13] Division of Geriatrics, Department of Internal Medicine, University of Health Sciences, Gulhane Training and Research Hospital, Istanbul, Turkey

[14] Department of Internal Medicine, Gulhane Training and Research Hospital, University of Health Sciences, Istanbul, Turkey

[15] Division of Geriatrics, Department of Internal Medicine, Faculty of Medicine, Kırıkkale University, Istanbul, Turkey

[16] Department of Family Medicine, Faculty of Medicine, Baskent University, Istanbul, Turkey

[17] Division of Geriatrics, Department of Internal Medicine, Faculty of Medicine, Başkent University, Istanbul, Turkey