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Potentially inappropriate medications based on TIME criteria and risk of in-hospital mortality in COVID-19 patients

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SUMMARY

OBJECTIVE: This study aimed to evaluate the relationship between hospital admission potentially inappropriate medications use (PIM) and in-hospital mortality of COVID-19, considering other possible factors related to mortality.

METHODS: The Turkish inappropriate medication use in the elderly (TIME) criteria were used to define PIM. The primary outcome of this study was in-hospital mortality.

RESULTS: We included 201 older adults (mean age 73.1±9.4, 48.9% females). The in-hospital mortality rate and prevalence of PIM were 18.9% (n=38) and 96% (n=193), respectively. The most common PIM according to TIME to START was insufficient vitamin D and/or calcium intake per day. Proton-pump inhibitor use for multiple drug indications was the most prevalent PIM based on TIME to STOP findings. Mortality was related to PIM in univariate analysis (p=0.005) but not in multivariate analysis (p=0.599). Older age (hazards ratio (HR): 1.08; 95% confidence interval (CI): 1.02–1.13; p=0.005) and higher Nutritional Risk Screening 2002 (NRS-2002) scores were correlated with in-hospital mortality (HR: 1.29; 95%CI 1.00–1.65; p=0.042).

CONCLUSION: Mortality was not associated with PIM. Older age and malnutrition were related to in-hospital mortality in COVID-19.

KEYWORDS: COVID. Older adult. Potentially inappropriate medication use. Criteria.

INTRODUCTION

Coronavirus disease-2019 (COVID-19) started in China in December 2019 and it has caused mortality in approximately 6 million people and infected about 448 million people worldwide, as accessed at the time of writing this manuscript[1]. The predictors of poor outcomes in COVID-19 have been reported as male sex, older age, immunodeficiency, and having comorbidities (coronary artery disease, congestive heart failure [CHF], chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, hypertension, and/or obesity)[2-4].

Aging poses comorbidities and, accordingly, it is correlated with multiple drug use (polypharmacy). Potentially inappropriate medication (PIM), closely linked to polypharmacy, contributes to many problems such as falls, syncope, malnutrition, frailty, delirium, and also cost burden[5]. PIM is responsible for one-fifth of the mortality in the elderly; additionally, it is probably responsible for more deaths if unrecognized drug adverse effects are taken into account[6]. Globally, approximately 40% of outpatients over the age of 65 years have PIM at least once[5]. PIM is defined as having a safer alternative drug or drug dose, using drugs without an indication or any benefit, or not using the appropriate drug despite an indication[5,7]. There are many different screening tools for detecting PIM (e.g., the Beers criteria[8], the Screening Tool of Older Persons' potentially inappropriate Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) criteria[9], and country-specific criteria such as those seen in Austria[10], China[11], and the Turkish inappropriate medication use in the elderly (TIME) criteria[12]). The TIME criteria were published in 2019 and composed of 112 TIME to STOP criteria and 41 TIME to START criteria, with a total of 153 criteria[12]. Recently, the TIME criteria have also been internationally validated for use in European countries[7].

Previous research has shown that PIM is related to mortality. However, there is little known about PIM and COVID-19 mortality in hospitalized patients[13,14]. Mortality may be associated with PIM in elderly individuals; this situation is often ignored and not studied by physicians other than geriatricians. This study aimed to provide for this deficiency. To the best of our knowledge, no studies have been published on PIM and

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in-hospital mortality related to COVID-19. Therefore, we aimed to investigate the relationship between PIM and in-hospital mortality due to COVID-19 and other factors that predict in-hospital mortality.

METHODS

A single-center cross-sectional study was designed at the Marmara University Medical School Hospital, which is a referral hospital for patients with COVID-19, comprising patients admitted between February and June 2021. This research was conducted in accordance with the Helsinki World Medical Association Declaration. Written informed consent was obtained from patients or proxies. Those who did not give consent were excluded. The study was approved by the Local Ethics Committee of Marmara University (Marmara University Clinical Research Ethics Committee/Decision no: 09.2021/68).

All older adults aged ≥60 years who had a positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) of COVID-19 and/or positive radiologic involvement of COVID-19 were included in the study. The primary outcome of this study was in-hospital mortality.

Age, sex, weight (kg), height (cm), body mass index (BMI), smoking habits, comorbidities, the number of drugs, specific drugs or drug contents, admission to the intensive care unit (ICU), ICU stay time (days), and presence of in-hospital mortality were collected. The length of hospital stay or time until in-hospital mortality was used as the follow-up time. Medication use on admission was recorded from the electronic records of the Turkish Ministry of Health. In this study, polypharmacy is defined as the regular use of five or more drugs[5]. The TIME criteria were used to define PIM[12]. On admission, an experienced geriatrician checked the patients' drugs, determined PIM, and analyzed overprescribed and underprescribed drugs. The nutritional status of the participants was determined using the Nutritional Risk Screening 2002 (NRS-2002) screening tool[15]. Patients with ≥3 points were defined as at nutritional risk and those with <3 points were assessed as well-nourished.

The SARS-CoV-2 infection was detected using RT-PCR assay of samples collected with nasopharyngeal swabs. We included participants with probable and confirmed COVID-19[16]. Confirmed disease was described as a positive result of the COVID-19 RT-PCR. The severity of infection was categorized as mild, moderate, severe, and critical[17].

At the time of hospital admission, laboratory parameters were measured and assessed. Thorax CT was performed on participants who had polypnea (30 cycles per minute with 90% of blood oxygen saturation on room air) and/or hypoxia (oxygen saturation level ≤92). A specialist radiologist evaluated all the CT imaging. All patients were treated with favipiravir (first day: 1600 mg twice daily, 600 mg twice daily for 4 days), prophylactic enoxaparin (1 mg/kg), and proton-pump inhibitors (PPIs). If the patients had hypoxia (oxygen saturation level ≤92%), dexamethasone and oxygen-supportive treatment were started.

Statistical analysis

We determined the normality of the variables using visual (histograms and probability plots) and the Kolmogorov-Smirnov test. Categorical variables are shown as numbers and percentages (n, %). These analyses were compared using the chi-square test or Fisher's exact test, if appropriate. Normally distributed continuous variables are reported as a mean and standard deviation; group comparisons were performed using the independent sample t-test. When the distribution of continuous variables was normal, the data were expressed as median (minimum-maximum) and compared using the Mann-Whitney U test. The relationships between the variables and mortality were investigated using the Cox regression analysis. Multicollinearity was checked among independent variables. Results are shown as 95% confidence intervals (CI) and hazard ratios (HR). Statistical analyses were performed using the SPSS software package version 22.0 (IBM, Armonk, NY). p-values <0.05 were considered significant.

RESULTS

A total of 201 hospitalized participants (73.1±9.4, 48.3 female) were involved in the study. The medians and ranges for the numbers of drugs and numbers of PIM were 4.0 (1–11) and 2.0 (1–6), respectively. The in-hospital mortality rate was 18.9% (n=38). Table 1 presents the baseline characteristics and laboratory parameters of the 201 participants.

The prevalence of PIM, as determined using the TIME criteria, was 96% (n=193). Of note, 84% of PIM was categorized as TIME to START, and 29.4% was categorized as TIME to STOP. Table 2 shows the top five ranked PIMs.

Nonsurvivors were older (median age 80.5 vs. 70.0 years, p<0.001) and had more PIMs (p=0.005) compared with survivors of COVID-19. In addition, mortality was associated with the presence of CHF (p<0.001), dementia (p=0.040), admission to the ICU (p<0.001), long hospital stay (p=0.026), and the presence of malnutrition (p<0.001) (Table 1).

In multivariate Cox regression analysis, we investigated variables that were associated with mortality in univariate

Table 1. Characteristics and laboratory parameters of participants (n=201) and univariate analysis of survivors and nonsurvivors.

	All participants (total n=201) n (%)	Survivors (total n=163) n (%)	Nonsurvivors (total n=38) n (%)	p-value
Sex				
Female	97 (48.3%)	81 (49.7)	16 (42.1)	0.399
Male	104 (51.7%)	82 (50.3)	22 (57.9)	
Age*	73.0 (60–96)	70.0 (60–95)	80.5 (61–96)	**<0.001†**
BMI*	27.5 (16.3–44.1)	27.8 (16.3–44.8)	26.9 (18.4–40.0)	0.109
Smoking	62 (30.8%)	53 (32.5)	9 (23.7)	0.279
HT	131 (65.2%)	107 (65.6)	24 (63.2)	0.772
DM	87 (43.3%)	71 (43.6)	16 (42.19)	0.871
CAD	54 (26.9%)	44 (27)	10 (26.3)	0.932
COPD	36 (17.9%)	28 (17.2)	8 (21.1)	0.581
Malignancy	25 (12.4%)	23 (14.1)	2 (5.3)	0.105
CKD	24 (11.9%)	17 (10.4)	7 (18.4)	0.193
Dementia	22 (10.9%)	14 (8.6)	8 (21.1)	**0.040†**
CHF	19 (9.5%)	8 (4.9)	11 (28.9)	**<0.001†**
COVID severity				
Mild	9 (4.5%)	9 (5.5)	0 (0.0)	0.077
Moderate	48 (23.9%)	39 (23.9)	9 (23.7)	
Severe	135 (67.2%)	110 (67.5)	25 (65.8)	
Critical	9 (4.5%)	5 (3.1)	4 (10.5)	
COVID severity				
Mild+moderate	57 (28.4)	48 (29.4)	9 (23.7)	0.478
Severe+critical	144 (71.6)	115 (70.6)	29 (76.3)	
Number of chronic diseases*	3.0±1.5 (1–7)	2.9±1.5 (1–7)	3.4±1.7 (1–7)	0.174
Number of drugs*	4.0 (1–11)	4.0 (1–11)	4.0 (1–10)	0.663
Polypharmacy	76 (37.8%)	63 (38.7)	15 (39.5)	0.814
Number of PIM*,†	2.0 (1–6)	2.0 (1–6)	2.5 (1–6)	**0.005†**
PIM†	193 (96)	155 (95.1)	38 (100)	0.064
TIME to START	180 (89.6)	142 (91.6)	38 (100)	**0.015†**
TIME to STOP	59 (29.4)	47 (30.5)	12 (31.6)	0.549
Length of hospital stay (days)*	14.0 (3–68)	13.0 (3–68)	22.0 (4–67)	**0.026†**
ICU stay	47 (23.4%)	19 (11.7)	28 (73.7)	**<0.001†**
ICU stay (days)*	5.0 (1–28)	5.0 (2–27)	6.0 (1–28)	0.924
Score of NRS-2002*	3.4±1.5 (0–7)	3.2±1.5 (0–7)	4.3±1.2 (2–7)	**<0.001†**
NRS-2002				
Nonmalnutrition	62 (30.8%)	60 (36.8)	2 (5.3)	**<0.001†**
Malnutrition risk	139 (69.2%)	103 (63.2)	36 (94.7)	
White blood cell (×10³/µL)*	7.2 (1.4–23.7)	7.1 (1.4–23.7)	7.3 (1.6–17.8)	0.856
Lymphocyte (×10³/µL)*	1.1 (0.1–11.0)	1.1 (0.1–3.9)	1.0 (0.2–11.0)	0.445
Neutrophil (×10³/µL)*	5.5 (0.7–23)	5.5 (0.7–23.0)	5.6 (0.2–13.2)	0.924
Hemoglobin (g/dL)	12.5 (4.1–16.9)	12.5 (4.1–16.9)	12.1 (8–16.6)	0.600
Thrombocyte (x10³/µL)*	201 (27–588)	204.0 (35–538)	162.0 (27–414)	0.007

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Table 1. Continuation.

	All participants (total n=201) n (%)	Survivors (total n=163) n (%)	Nonsurvivors (total n=38) n (%)	p-value
LDH (U/L)*	383.0 (105–1329)	474.0 (149–1192)	425.0 (105–1329)	0.315
Glucose (mg/dL)*	127.0 (59–538)	128.0 (59–538)	108.5 (76–303)	**0.042**†
GFR (mL/m)*	72.1 (4.2–159.6)	76.8 (4.2–159.6)	48.8 (11.7–112)	**<0.001**†
C-reactive protein (mg/L)*	85.0 (0.6–342.0)	81.4 (0.6–342.0)	102.5 (3.3–300)	0.242
Prothrombin time (s)*	14.6 (10.6–85.2)	14.5 (10.6–47.1)	15.4 (11.6–85.2)	0.071
INR*	1.1 (0.9–6.9)	1.1 (1.02–1.21)	1.2 (0.94–6.94)	0.090
aPTT (s)*	30.6 (19.9–75.1)	30.4 (0.9–3.7)	31.8 (21.8–74.1)	**0.049**†
Fibrinogen (mg/dL)*	544.0 (198–999)	547 (19.8–75.1)	533.5 (198–792)	0.376
D-dimer (mg/dL)*	0.99 (0.05–20)	0.91 (0.1–20.0)	1.5 (0.05–5.3)	0.230
Ferritin (µg/L)*	413.0 (14–3484)	397 (29.0–3484.0)	441.0 (14.0–1754.0)	0.946
Procalcitonin (µg/L)*	0.14 (0.02–31.4)	0.1 (0.1–29.9)	0.3 (0.1–31.4)	**<0.001**†

BMI: body mass index; HT: hypertension; DM: diabetes mellitus; CAD: coronary artery disease; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; CHF: congestive heart failure; PIM: potentially inappropriate medications; TIME: Turkish Inappropriate Medication use in the Elderly; ICU: intensive care unit; LDH: lactate dehydrogenase; GFR: glomerular filtration rate; INR: international normalized ratio; aPTT: activated partial thromboplastin time. *Numeric variables were presented as median (minimum-maximum) or mean±SD. †PIM was determined based on TIME criteria; †significant p-value.

Table 2. Top five ranked potentially inappropriate medications of participants based on TIME criteria.

Participants with PIM n (%)	TIME to START n (%)	TIME to STOP n (%)
	193 (96.0)	59 (37.6)
1	E1. n=170 (84.6%) Vitamin D if vitamin D intake <800–1000 IU per day and/or calcium if elementary calcium intake <1000–1200 mg per day	C4. n=10 (6.4%) PPIs for multiple drug use indication (no benefit, potential harm)
2	I1. n=127 (63.2%) ONS with MN or MNR if nutritional counseling/ dietary supplementation are not sufficient to achieve nutritional goals	C2. n=10 (6.4%) 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
3	A2. n=29 (14.4%) Statin therapy for secondary prevention in patients with documented atherosclerotic coronary artery disease (previous acute coronary syndrome/coronary artery angioplasty or stenting/coronary artery bypass grafting/ abdominal aortic aneurysm), documented atherosclerotic cerebrovascular disease (presence of ischemic stroke/ TIA/previous carotid endarterectomy or stenting) or peripheral arterial disease	H1. n=9 (5.7%) 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
4	A1. n=21 (10.4%) Antiplatelet therapy (aspirin or clopidogrel) for secondary prevention in patients with documented atherosclerotic coronary artery disease (previous acute coronary syndrome/ coronary artery angioplasty or stenting/coronary artery bypass grafting/abdominal aortic aneurysm), documented atherosclerotic cerebrovascular disease (presence of ischemic stroke (TIA/previous carotid endarterectomy or stenting) or symptomatic lower extremity artery disease	E1. n=7 (4.5%) Long-term use of NSAIDs (>3 months) in the presence of alternative treatment
5	A6. n=20 (10.0%) Beta-blocker with ischemic heart disease (antianginal effect in chronic ischemic heart disease/mortality reduction effect in post-MI era) or systolic heart failure (EF≤40%) (bisoprolol/ prolonged release metoprolol succinate/carvedilol/nebivolol in systolic heart failure; any beta blocker in ischemic heart disease)	B18. n=7 (4.5%) Piracetam except for myoclonic convulsion therapy (with no proven clinical efficacy, cost burden, and side effect potential)

TIME: Turkish Inappropriate Medication use in the Elderly; PIM: potentially inappropriate medications; IU: international unit; PPI: proton-pump inhibitors; ONS: oral nutritional supplements; MN: malnutrition; MNR: malnutrition risk; NSAID: non-steroidal anti-inflammatory drug; TIA: transient ischemic attack; LUTS: lower urinary tract symptoms; MI: myocardial infarction; EF: ejection fraction.

analysis. Older age (HR: 1.07; 95%CI 1.03–1.11; p<0.001) and higher NRS-2002 scores (HR: 1.20, 95%CI 1.01–1.68; p=0.045) were related to in-hospital mortality. Different models were analyzed for assessing the relationship between PIM and mortality, as shown in Table 3.

DISCUSSION

In this study, older age and malnutrition were independently associated with in-hospital mortality in geriatric patients with COVID-19. Although the number of PIMs was statistically significantly higher in nonsurvivors compared with survivors, there was no longer a significant relationship with mortality after adjustment for confounders in multivariate analysis. To the best of our knowledge, this is the first study to analyze the relationships between PIM and in-hospital mortality of older adults with COVID-19.

In previous studies, the in-hospital mortality rate of COVID-19 in older adults was reported to be higher than in our study (30–50% vs. 18.9%)[18,19]. A possible explanation for these differences is that the mean age of our population was younger than those in other studies[18,19]. The other explanation is that the hypoxic patients received oxygen supplement treatment but not steroids in previous studies[18,19]. As in the report of the RECOVERY group[20], death rates were lower in patients with hypoxia who received dexamethasone treatment. In this study, all patients with hypoxia were treated with dexamethasone. In addition, experienced geriatricians were involved in the follow-up and treatment of all patients in this study. This may have resulted in better care for older patients during hospitalization, and a decrease in drug interactions and PIM, thus reducing the mortality rates. In this study, we recognized and discontinued PIM drugs during hospital admission time. There are different nutritional risk screening tools in clinical practice. In this study, we assessed malnutrition using the NRS-2002. A study, which compared four different nutritional risk screening tools, found that the NRS-2002 was more successful than others in recognizing malnutrition in COVID-19[21]. Although the number of studies evaluating the relationship between COVID-19 and malnutrition is small, most of these studies found that malnutrition was an important risk factor for COVID-19-related mortality[2]. Early implementation of nutritional support may have reduced the mortality rate of our patients.

In a study in Italy[22], 95% of participants had at least one PIM based on the Beers Criteria at admission. Cattaneo et al.[22] evaluated the drug-drug interactions (DDIs) and included them in PIM, so its prevalence was very high. However, the TIME criteria do not include DDIs. The prevalence of PIM in this study was slightly higher than in other studies[13]. This may be because the PIM prevalence was only considered deprescribing and not underprescribing in these studies. An important advantage of the TIME criteria is that PIM use should not only be limited to overuse of medications but also include a lack of use of beneficial medications. In our study, most of the participants who had untreated malnutrition were captured in the underprescribing group, and one of three in the overtreatment group based on the TIME criteria. The relationship between the

Table 3. Cox regression model for mortality with potentially inappropriate medications.

	Model 1		Model 2		Model 3		Model 4	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Age	1.07 (1.03–1.11)	**<0.001†**	1.07 (1.03–1.12)	**0.001†**	1.07 (1.03–1.12)	**0.001†**	1.07 (1.02–1.13)	**0.005†**
Sex: male	1.40 (0.71–2.76)	0.329	1.28 (0.64–2.56)	0.483	1.46 (0.72–2.98)	0.293	1.32 (0.67–2.85)	0.383
Number of PIM*	1.02 (0.79–1.32)	0.869	0.99 (0.75–1.30)	0.914	0.91 (0.67–1.23)	0.543	0.92 (0.68–1.25)	0.929
CHF			0.47 (0.21–1.08)	0.074	0.51 (0.22–1.19)	0.118	0.46 (0.17–1.20)	0.112
Dementia			1.05 (0.42–2.61)	0.922	1.23 (0.48–3.12)	0.669	1.11 (0.42–2.92)	0.834
Score of NRS-2002					1.26 (0.99–1.60)	0.056	1.20 (1.011–1.68)	**0.045†**
Glucose (mg/dL)							1.00 (0.99–1.01)	0.895
Procalcitonin (μg/L)							1.04 (0.97–1.11)	0.294
GFR (mL/m)							1.01 (0.99–1.02)	0.487
aPTT (s)							1.02 (0.98–1.06)	0.375

Model 1: adjusted by sex, age, and PIM (based on TIME criteria); Model 2: adds CHF and dementia to Model 1; Model 3: adds score of NRS-2002 to Model 2; Model 4: adds 4 laboratory values to Model 3. HR: hazard ratio; CI: confidence interval; PIM: potentially inappropriate medications; CHF: congestive heart failure; GFR: glomerular filtration rate; aPTT: activated partial thromboplastin time; TIME: Turkish Inappropriate Medication use in the Elderly. *PIM was determined based on TIME criteria; †significant p-value.

number of PIMs that was significant in the univariate analysis but did not show significance in the multivariate analysis in this study, and mortality may be better explained with long-term follow-up studies, but due to the nature of the evolving pandemic, we wanted to publish our results as soon as possible for wide availability. In addition, although the effects of drug cessation are seen in a shorter period, longer follow-up is required to see the effect on mortality when drugs/support products are started.

Many studies reported that older age was the main risk factor for COVID-19 mortality[2,3]. With aging, the immune system is more prone to infections, impaired cell-mediated and humoral immunity, and pro-inflammation.

The other factor related to in-hospital mortality was malnutrition in the present study. Studies in Turkey[2], China[21], and other countries showed that malnutrition was related to in-hospital mortality in patients with COVID-19. In this study with the NRS-2002, 7 out of 10 patients were diagnosed as having malnutrition, and malnutrition increased the in-hospital mortality rate by 29%. Therefore, older patients with COVID-19 should receive nutrition screening.

This study has some limitations. This is a single-centered study performed at a referral COVID-19 center with a short follow-up period, which restrains the generalization of our results. With long-term mortality, drug effects can be observed better in patients with undertreatment. We only included hospitalized patients in this study, and most of the participants had severe COVID-19. Therefore, the results do not reflect the real effect of PIM on patients with COVID-19.

CONCLUSION

Older age and malnutrition were related to in-hospital mortality in COVID-19 in this study. Mortality is more common in older individuals with higher numbers of PIM; however, we could not show its effect on mortality in the early period, and the effect of PIM on mortality may be better revealed in long-term studies. The TIME criteria recommend diagnosing malnutrition and initiating treatment. Early intervention may have an impact on mortality in COVID-19 patients.

AUTHORS' CONTRIBUTIONS

NŞD: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **AT:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **BC:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **ŞO, DK:** Data curation, Investigation. **Bİ:** Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **GB:** Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing.

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