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Impact of potentially inappropriate medications on emergency ambulance admissions in geriatric patients after discharge

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This study aimed to determine the risk of emergency admission by ambulance in patients taking potentially inappropriate medications (PIMs). We included 273,932 patients aged over 75 years of age admitted between January 1, 2019, and December 31, 2019, using the Japan Medical Data Center medical insurance database containing anonymized patient data. We excluded patients without a history of admission. In total, 22,017 patients were included in the analysis. The commonly prescribed PIMs were diuretics, benzodiazepines, non-benzodiazepines, H_2 receptor blockers, and nonsteroidal anti-inflammatory drugs. The primary endpoint, which was the incidence rate of emergency admission by ambulance after discharge, was 31.5/100,000 person-days in patients aged over 75 years. The secondary endpoints, which were risk factors for admission, included the use of PIMs, age over 85 years, male sex, history of congestive heart failure, history of chronic respiratory disease, and the number of medications at discharge. In contrast, body mass index was observed to have a negative trend in relation to admission. In conclusion, we observed 31.5/100,000 person-days of emergency admission by ambulance after discharge in patients aged over 75 years. Administration of PIMs upon discharge poses a risk for admission. To avoid emergency admissions via ambulances, it is important to discontinue or reduce the prescription of PIMs while considering the risks and benefits for each patient.

1. Introduction

A prolonged lifespan is accompanied by advances in medical care and the development of novel medicines. The proportion of geriatric patients is increasing, particularly in developed countries. In 2019, Japan had the highest proportion of older individuals globally (World Health Organization n.d.), with 29.1% of the population aged over 65 years and 16.1% aged over 75 years as of 2023 (Statistics Bureau of Japan n.d.).

Approximately 33% of patients with dementia are prescribed at least one potentially inappropriate medication (PIM) (Thorpe et al. 2012). Patients exposed to PIMs are reported at a higher risk of hospital admissions (Endres et al. 2016), unplanned admissions (Sato et al. 2018), and the number of drugs (Masumoto et al. 2018; Kojima et al. 2012a; Kojima et al. 2012b). In the United States (US), the most commonly identified PIMs inducing emergency hospitalizations for adverse drug events include warfarin, insulin, oral antiplatelet agents, and oral hypoglycemic agents (Budnitz et al. 2011). Other studies reported that the prevalence of PIMs is particularly high among geriatric patients taking antidiabetics and diuretics (Sato et al. 2018). The economic burden of the medical costs associated with PIMs in the US community-dwelling population was estimated to be approximately 7.2 billion dollars in 2001 (Fu et al. 2007). Similar findings were reported in Ireland, where the cost of PIMs was estimated to be approximately €45.6 million in 2007 (Cahir et al. 2010), representing 9% of the total pharmaceutical expenditure for individuals aged 70 years and above.

Several studies have revealed that polypharmacy, defined as the use of five or more medications, is closely related to PIM exposure and serves as an easily understood benchmark in clinical practice. This condition is associated with an increased risk of trauma (Farrell et al. 2023) and adverse events, including medication-related adverse events, in geriatric patients (Kojima et al. 2012a; Koh et al. 2005). Over the past two to three decades, the global prevalence of polypharmacy has increased significantly from 12.8% to 39.0% (Charlesworth et al. 2015). The prevalence tends to be higher in low-income countries such as Africa (47%), South America (46.9%), Asia (37.2%), Europe (35.0%), North America (29.0%), and Oceania (23.6%) (Tian et al. 2023). The increasing prevalence of polypharmacy is closely related to the use of PIMs, and the balance between the benefits and risks of medication use may be compromised, particularly in geriatric patients.

Half of the medication-related emergency admissions are reported avoidable (Leendertse et al. 2008; McDonnell and Jacobs 2002). Although interventions such as pharmacist involvement (Hashimoto et al. 2020), electronic prescribing systems (Ghibelli et al. 2013), and proper education (Bayliss et al. 2022), have been shown to reduce PIMs, which is one of the most important causes of emergency admission, their implementation can be challenging because of the necessity of substantial resources. Recently, the incidence of adverse events has shifted from hospital settings to home environments (Lazarou et al. 1998). This underscores the importance of monitoring patient health and enhancing regional healthcare systems. Furthermore, there is often a discrepancy in the recognition of the health of the patient between the medical staff and the patients themselves (Basch 2010). Half of the patients with nonspecific complaints require emergency department visits because of hidden severe symptoms (van Dam et al. 2023). Therefore, understanding the practical risk factors for PIMs and emergency admissions in geriatric patients is crucial. This study analyzed the risk of emergency admissions via ambulances after discharge, which is the largest burden on economic and human resources among geriatric patients in Japan.

2. Investigations and results

2.1. Incidence rate of emergency admission by ambulance after discharge in patients aged over 75 years

We analyzed 22,017 patients (male/female: 9,767/12,250) with a follow-up period of 3,923,770 days. The primary endpoint, the incidence rate of emergency admission by ambulance after discharge, was 31.5/100,000 person-days among the study patients (n=1,236). In the group without emergency admission by ambulance after discharge, 20.5% (4,250/20,781) of the study patients had a history of admission after discharge without ambulance during the observation period (such as planned admission). The proportion of male patients (p=0.0003), patients aged over 85 years (p<0.0001), length of hospital stay prior to emergency admission (p=0.0002), number of medicines administered at the time of discharge (p<0.0001), and patients with PIMs (p<0.0001) was greater in the emergency admission by ambulance group (n=1,236) than in the ambulance group without emergency admission (n=20,781). The number of patients with congestive heart failure (p<0.0001), chronic respiratory disease (p<0.0001), and peripheral arterial disease (p=0.0361) hospitalized by ambulance was higher than that of patients not hospitalized by ambulance (Table 1). Conversely, body mass index (BMI) (p<0.0001) was lower in the group with emergency admissions by ambulance versus the group without emergency admissions. Commonly prescribed PIMs included diuretics (n=4,179), benzodiazepines (n=2,270), non-benzodiazepines (n=1,364), H_2 receptor blockers (n=1,214), and nonsteroidal anti-inflammatory drugs (n=1,161) (Fig. 1). At discharge from prior admissions, the use of medications, including magnesium oxide, diuretics, anticoagulants, benzodiazepines, anti-parkinsonian agents, steroids, and antiplatelet drugs, was significantly higher among patients with emergency admissions, whereas it was lower among users of biguanides, alpha-glucosidase inhibitors, and nonsteroidal anti-inflammatory drugs (Fig. 1).

2.2. Risk factors for emergency admission by ambulance after discharge

Kaplan–Meier curves from significant risk factors observed from univariable analysis are shown in Fig. 2. The Kaplan–Meier curve showed a higher proportion of patients with emergency admission by ambulance after discharge for patients with PIMs

Table 1: Risk factors for emergency admission by ambulance after discharge in geriatric patients aged over 75 years

	With emergency admission by ambulance after discharge (n=1,236)	Without emergency admission by ambulance after discharge (n=20,781)	p-value
Sex			
Female	626 (50.6%)	11,624 (55.9%)	
Male	610 (49.4%)	9,157 (44.1%)	0.0003
Age (years)			
75–84	565 (45.7%)	12,440 (59.9%)	
over 85	671 (54.3%)	8,341 (40.1%)	<0.0001
BMI, average (SD)	21.0 (4.1)	22.2 (4.0)	<0.0001
Length of hospital stay (SD)	27.9 (24.6)	27.2 (27.2)	0.0002
Number of medicines administered at discharge in the previous admission (SD)	5.8 (3.8)	5.1 (3.6)	<0.0001
With potentially inappropriate medications			
No	544 (44.0%)	11,088 (53.4%)	
Yes	692 (56.0%)	9,693 (46.6%)	<0.0001
Transient ischemic attack (G450–G453, G458–G459, I65–I66)			
No	1,217 (98.5%)	20,388 (98.1%)	
Yes	19 (1.5%)	393 (1.9%)	0.3723
Congestive heart failure (I50, I42-I43.8, I11.0, I13.0, I13.2, I25.5)			
No	838 (67.8%)	16,051 (77.2%)	
Yes	398 (32.2%)	4,730 (22.8%)	<0.0001
Stroke (I61, I63, I64)			
No	1,162 (94.0%)	19,241 (92.6%)	
Yes	74 (6.0%)	1,540 (7.4%)	0.0621
Chronic respiratory disease (J40–J47)			
No	1,082 (87.5%)	18,959 (91.2%)	
Yes	154 (12.5%)	1,822 (8.8%)	<0.0001
Peripheral arterial disease (I70, I73.9, I74, I77)			
No	1,187 (96.0%)	20,174 (97.1%)	
Yes	49 (4.0%)	607 (2.9%)	0.0361
Diabetes mellitus (E10–E14)			
No	925 (74.8%)	15,651 (75.3%)	
Yes	311 (25.2%)	5,130 (24.7%)	0.7064
Osteoporosis (M80–M82)			
No	1,123 (90.7%)	18,494 (89.0%)	
Yes	113 (9.1%)	2,287 (11.0%)	0.0412

SD, standard deviation

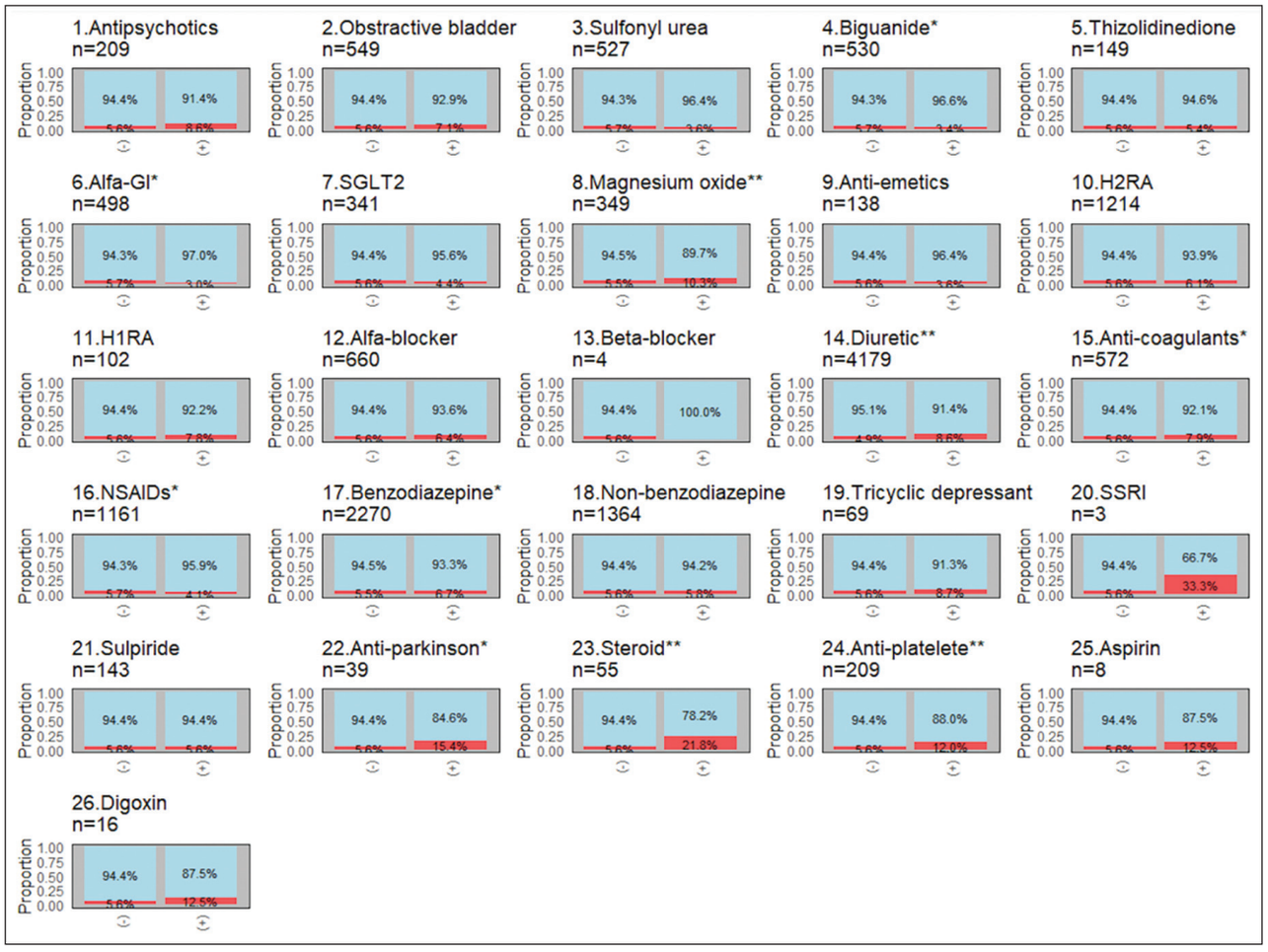


Fig. 1: Bar plot for the proportion of PIMs prescription at discharge in the prior admission in the groups between with and without emergency admission by ambulance in patients aged over 75 years. (+) and (–) show patients with and without emergency admission by ambulance in the study. *: p<0.05, **: p<0.01 vs. without focused PIMs.
GI – glucosidase inhibitor; SGLT2 – sodium-glucose co-transporter 2 inhibitor; H2RA -histamine H2 receptor antagonist; H1RA – histamine H1 receptor antagonist; NSAID – non-steroidal anti-inflammatory drugs; SSRI – selective serotonin reuptake inhibitor.

(p<0.0001), male patients (p=0.00025), patients aged over 85 years (p<0.0001), more than five medicines administered at discharge in the previous admission (p<0.0001), patients with congestive heart failure (p<0.0001), and patients with chronic respiratory disease (p<0.0001) (Fig. 2). The secondary endpoint, which was a risk factor for emergency admission by ambulance after discharge assessed using a Cox-regression hazard model, was observed in patients with PIMs (p=0.0191), patients aged over 85 years (p<0.0001), male patients (p<0.0001), patients with a history of congestive heart failure (p<0.0001), chronic respiratory disease (p=0.0082) and the number of medicine at the timing of discharge (p=0.0006) (Fig. 3). In contrast, BMI was observed to have a negative trend with emergency admission by ambulance after discharge (P <0.0001).

3. Discussion

Using a hospital-based medical insurance database in Japan, this study revealed that emergency admission after discharge via ambulance occurred in 31.5/100,000 person-days of study patients aged over 75 years. Prescription of PIMs at discharge in the previous admission was identified as a risk factor for emergency admission after discharge by ambulance.Older adults account for 61.6% of all ambulance dispatches (Ministry of Internal Affairs and Communications. Fire and Disaster Management Agency 2023). In recent years, the increasing number of ambulance dispatches, with about 5% of these being inappropriate use, has become a societal issue (Yamashita et al. 2016). Moreover, older adults are more likely to call an ambulance than the young (Kawakami et al. 2007).

The population of individuals aged 75 and over constitutes 16.1% of Japan's total population as of 2023 (Statistics Bureau of Japan n.d.), positioning Japan as the country with the longest-living old adults population (World Health Organization n.d.). In Japan, healthcare expenditures of aged 75 and over is total 18.8 trillion yen, representing about 50% of total healthcare costs (Ministry of Health, Labour and Welfare. 2023). Addressing the continually rising national healthcare costs remains a significant challenge.
Medical costs associated with ambulance dispatches significantly exceed those for regular outpatient visits. For instance, in cardiology, these costs are 121% higher (Yasui et al. 2021), and for lower back pain, they are 114% higher (Coombs et al. 2021) compared to standard visits. Reducing the number of ambulance dispatches and encouraging more patients to seek hospital care through regular means is expected to help preserve medical resources and decrease healthcare expenses. Considering these factors, this study conducted a frequency analysis to predict the likelihood of old adults patients being readmitted. The result was 31.5 per 100,000 person-days, and based on this rate, the cost of ambulance dispatches alone at 45,000 yen per dispatch (Morimura et al. 2010) amounts to approximately 100 billion yen annually in Japan, underscoring the importance of minimizing these costs. Moreover, although it varies with underlying conditions, possessing information that can predict emergency visits by high-risk old adults patients after discharge is essential.
The analysis in this study is based on the JMDC Claims Database, which includes patients aged 75 years and older who were admitted and discharged between January 1, 2019, and December 31, 2019.

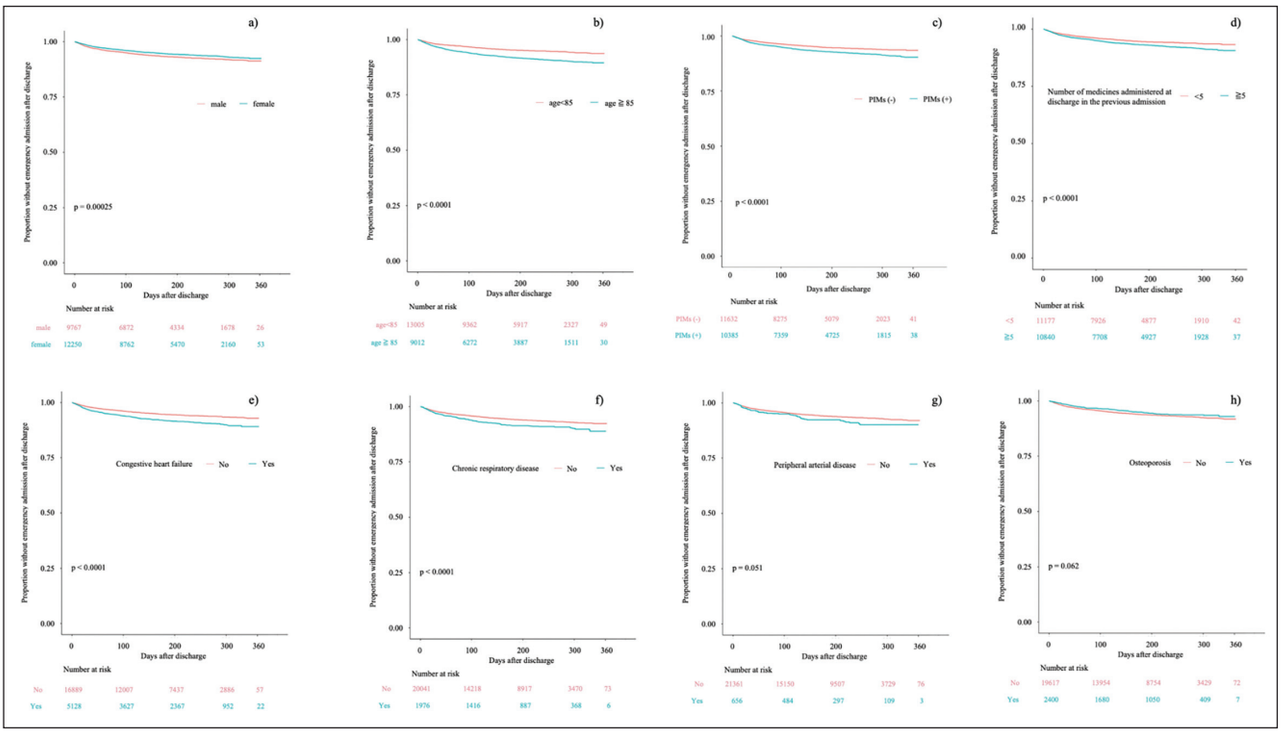


Fig. 2: Kaplan–Meier curve for emergency admission by ambulance after discharge in patients aged over 75 years by (a) sex, (b) age under and over 85 years, (c) with and without potentially inappropriate medications administered at discharge in the previous admission, (d) more than five and less than five medicines prescribed at discharge in the prior admission, (e) with and without congestive heart failure, (f) with and without chronic respiratory disease, (g) with and without peripheral arterial disease, and (h) with and without osteoporosis. PIM – Potentially Inappropriate Medication.

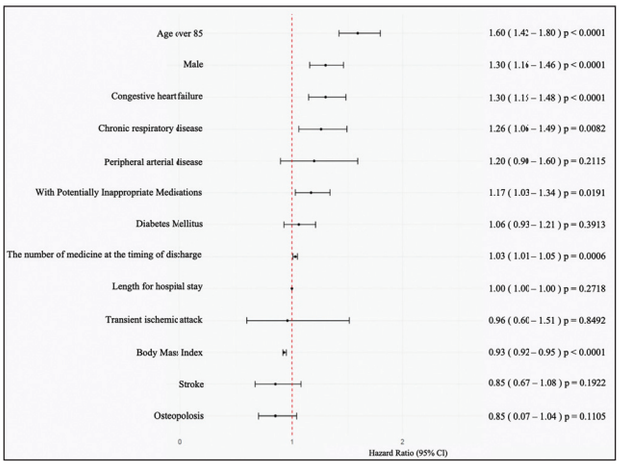


Fig. 3: Forest plot for adjusted hazard ratios for emergency admission by ambulance after discharge in patients aged over 75 years using the Cox-regression hazard model. CI – Confidence Interval.

Our data exhibit the following characteristics: (1) the follow-up period varies among patients who were included at the onset of the study period and those incorporated later, and (2) the number of patients analyzed increases as day 0 approaches the end of the study period. If these characteristics are considered to potentially introduce bias affecting the secondary endpoint, we have conducted a sub-analysis in patients who have been observed for over 60 days (n=18,689). The risk factor identified through Cox regression analysis remains consistent when compared to including all patients (n=22,017) (data not shown).

Additionally, winter seasons, characterized by low and fluctuating temperatures, contribute to higher mortality rates and increased hospital admissions among patients with influenza, cardiovascular diseases, and respiratory diseases (Achebak et al. 2023, 2024; Paget et al. 2023). There is also a reduced likelihood that emergency admissions will be captured in the data. Moreover, shorter follow-up periods during times of lower disease prevalence may lead to an underestimation of these diseases' impact on the risk of emergency ambulance admissions.

In the United Kingdom, there are 420 emergency admissions per 1,000 registrants aged 85 years and above, highlighting the importance of emergency admissions in the older adult population (Chenore et al. 2013). It is estimated that the utilization rate of emergency departments in Australia will increase until 2050, with a particularly notable rise observed in the older adult population (Burkett et al. 2017). Given that Japan has the largest aging population in the world, understanding and identifying risk factors for emergency admissions by ambulance may significantly reduce future healthcare resources.

We also found that polypharmacy, indicated by an increased number of medications, pose a risk for emergency admissions by ambulance after discharge (Figs, 2, 3). In addition, PIMs acted as risk factors for emergency admissions post-discharge via ambulance (Figs. 1 and 2). A nationwide survey in Italy reported a high frequency of low-quality prescriptions in individuals aged 85 years and above (Onder et al. 2014). The prescription of PIMs in older patients has been reported to be associated with mortality in Europe (Endres et al. 2016; Counter et al. 2018). However, it has also been reported that over 60% of older adults in China are exposed to PIMs, which increases the risk of admission after discharge but does not necessarily increase the risk of overall mortality (Wang et al. 2019). The usage of PIMs varies between countries, and in Japan, it has been associated with unplanned hospitalizations in individuals aged 65 years and above (Sato et al. 2018). Previous surveys in Japan reported that 57% of older patients admitted via the emergency department had received PIM prescriptions with high frequencies of benzodiazepines, proton pump inhibitors, and nonsteroidal anti-inflammatory drugs (Aida et al.2022). These reports clearly indicate that PIMs, and closely related poly pharmacy pose harm to older individuals. Given that trends may vary by region and over time, longitudinal evaluation is essential.

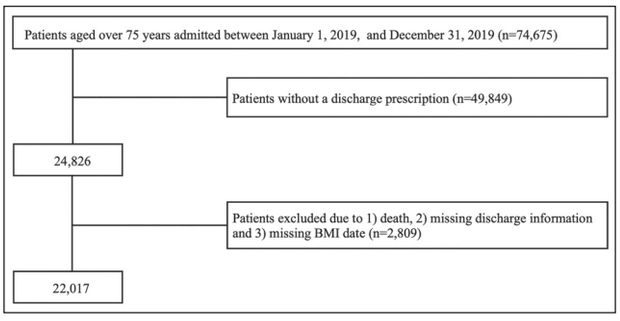


Fig. 4: Patient identification flowchart. BMI – Body Mass Index.

Among PIMs, benzodiazepines and non-benzodiazepines are characteristic medications that distinguish Japan from other countries. Although most advanced countries recommend limiting the duration for prescribing benzodiazepines to between 2–12 weeks (Panes et al. 2020; Kaiser Permanente; Aslett and Huckerby 2017), the recommended duration in Japan is overwhelmingly longer for these medications, which is set at 12 months (Saitoh and Suzuki 2020). Furthermore, the use of sedative drugs in older adults has clear risks. Therefore, in Japan, where restrictions on the use of benzodiazepines and non-benzodiazepines are not as stringent as those in other countries, special attention is warranted. In addition to PIM prescriptions, a low BMI was identified as a factor predicting emergency admissions by ambulance after discharge among older adults (Fig. 3). There have been consistent reports on the occurrence of adverse outcomes and a U-shaped relationship between BMI and adverse outcomes, known as the obesity paradox, which is particularly prominent in patients with heart failure (Fusco et al. 2023), and this trend has been well-documented (Sud et al. 2017; Nishikido et al. 2019; Khaled and Matahen 2017). This study confirmed that a low BMI in older individuals contributed to the risk of admission via ambulance. Our study identified the risks associated with ambulance admission; future efforts should focus on developing prediction tools for emergency admissions via ambulances, which would be socioeconomically significant.

This study has some limitations. The data obtained were limited to hospital information, potentially leading to missing information. The use of the diagnosis procedure combination (DPC) data indicated that the description of the medical records could not be captured.

In conclusion, this study provided insights into emergency admissions by ambulance after discharge among individuals aged over 75 years, revealing an incidence rate of 31.5/100,000 person-days. Furthermore, the administration of PIMs upon discharge poses a clear risk to older patients. To avoid emergency admissions via ambulances, it is important to discontinue or reduce the prescription of PIMs while considering the risks and benefits for each patient.

4. Experimental

4.1. Data source

The Japan Medical Data Center (JMDC) medical insurance database contains anonymized patient data. The cumulative dataset contains approximately 9.4 million subjects (inpatients, outpatients, and DPC data) as of October 2019 (Nagai et al. 2020; Nagai et al.2021).

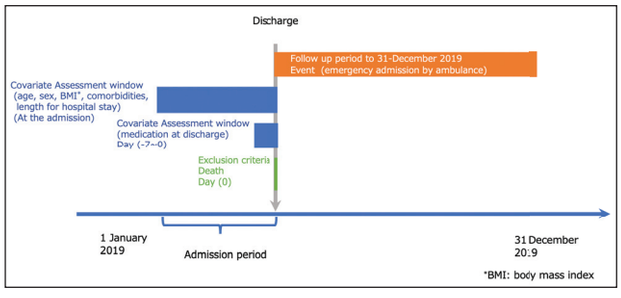
The DPC data is a comprehensive evaluation system for assessing medical fees for acute inpatient care in Japan. It was used to calculate medical expenses by classifying patients according to their diseases and treatments and defining the daily hospitalization cost for each classification (Yasunaga 2019).

4.2. Patient identification and data collection

The hospitalization history was obtained (n=74,675) (Fig. 4) from 273,932 patients aged over 75 years. We excluded patients without medication at the time of discharge and those lacking data such as that on BMI. Specifically, we sampled the patients included in this study and conducted a review of their medications with the clinical pharmacists. Consequently, we discovered that among patients without discharge prescriptions, some did not require these prescriptions because they were regularly attending clinics, while others genuinely lacked prescriptions. To enhance the quality of this study, we excluded patients without discharge prescriptions from the analysis. We analyzed data from 22,017 patients aged over 75 years who were admitted and discharged between January 1, 2019, and December 31, 2019. We defined day 0 as the date of discharge from the prior admission. During the study period, we considered emergency admissions by ambulance that occurred after day 0 as an event. Patients without such events were observed until censoring was performed. We collected the following information from prior admission in each patient: age (over/ under 85 years), sex (male/female), BMI, PIMs administered at the time of discharge, length of hospital stay, and number of medications administered at the time of discharge (Supplementary Table 1, Supplementary Fig. 1) (Wang et al. 2021).

Supplementary Table 1: Definition and categorization of study covariates

Characteristic	Definition/category
Demographic characteristic	
Age	75–85/over 85 years
Sex	Male/female
Body mass index	kg/m^2
Length of hospital stay	Days
Medication	
Number of medicines administered at discharge	Medications administered within 1 week before discharge
With or without potentially inappropriate medicine	Assessed medication at discharge
Comorbidity	***International Classification of Diseases-10 code***
Osteoporosis	M80, M81, M82
Congestive heart failure	I50, I42–143.8, I11.0, I13.0, I13.2 I50, I25.5
Chronic respiratory disease	J40–J47
Diabetes mellitus	E10–E14
Malignancy	C00–C97
Peripheral arterial disease	I70, I73.9, I74, I77
Stroke	I61, I63, I64
Transient ischemic attack	G45.0, G45.1, G45.2, G45.3, G45.8, G45.9, I65, I66



Supplementary Fig. 1: Study design diagram.

4.3. Primary and secondary endpoints

The primary endpoint was the incidence of emergency admission by ambulance after discharge in patients over 75 years, and the secondary endpoint was the identification of risk factors for emergency admission by ambulance.

4.4. Study definition and statistical analysis

Potentially inappropriate medications were defined according to "A list of drugs requiring particularly cautious administration" from The Japan Geriatrics Society (Supplementary Table 2) (The Japan Geriatrics Society n.d.).

Univariable (Mann–Whitney U-test and chi-square test) and multivariable analyses (Cox hazard model) of the data of patients with and without emergency admission by ambulance after discharge were performed. In this study, the date of discharge at prior admission was set as the index date (baseline). The risk factors for the emergency admission by ambulance after discharge were assessed using the baseline age of patients (older population were at a higher risk), sex (males were at a higher risk), BMI (lower BMI indicated a higher risk), comorbidities, PIMs at the time of discharge

Supplementary Table 2: Definition of potentially inappropriate medicine

No.	Category	Definition
1	Antipsychotics in patients with dementia	ATC code: N05 ICD 10 code: F00–F04
2	Medicine for overactive bladder	ATC code: G04BD04, G04BD, G04BD08, G04BD07, G04BD11, G04BD06
3	Sulfonylurea (including combination drug)	ATC code: A10BB31, A10BB09, A10BB, A10BB01, A10BB12, A10BB02, A10BB03, A10BD06
4	Biguanide (including combination drug)	ATC code: A10BA03, A10BA02, A10BD13, A10BD08, A10BD05
5	Thiazolidinedione (including combination drug)	ATC code: A10BG03, A10BD09, A10BD06, A10BD05
6	Alfa-glucosidase inhibitors (including combination drug)	ATC code: A10BF01, A10BF03, A10BF02
7	Sodium-glucose co-transporter 2 inhibitors	ATC code: A10BK, A10BK03, A10BK02, A10BK01, A10BK, A10BK
8	Magnesium oxide in patients with renal dysfunction	ATC code: A02AA02, A06AD02 ICD 10 code: N17–19
9	Antiemetics	ATC code: A03FA01, R06AD02, N05AB04
10	Histamine H_2 receptor antagonists	ATC code: A02BA
11	First-generation histamine H_1 receptor antagonists	ATC code: R06AA, R06AB, R06AD, R06AX, N05BB
12	Alpha-blockers	ATC code: C02CA06, G04CA03, C02CA04, C02CA, C02CA01
13	Beta-blocker in patients with chronic obstructive pulmonary disease or asthma	ATC code: C07AA ICD 10 code: J44-46
14	Diuretic medicines	ATC: C03CA, C03DA
15	Combination therapy for antiplatelet and anticoagulant medicines (including combination drug)	ATC code: B01AC06, N02BA01, B01AC04, B01AC05, B01AC22, B01AC23, B01AC24 B01AF02, B01AF03, B01AE07, B01AF01, B01AA03
16	Non-steroidal anti-inflammatory drugs	ATC code: M01AB, M01AC, M01AE, M01AG, M01AX, M01BG
17	Benzodiazepines	ATC code: N05CD, N05BA
18	Non-benzodiazepines	ATC code: N05CF
19	Tricyclic anti-depressants	ATC code: N06AA
20	Selective serotonin reuptake inhibitors in patients with gastrointestinal bleeding	ATC code: N06AB ICD 10 code: K92.1, K92.2
21	Sulpirides	ATC code: N05AL01
22	Antiparkinsonian medicines	ATC code: N04AA, R06AD
23	Oral steroids in patients with chronic obstructive pulmonary disease	ATC code: H02AB Component name: Betamethasone and d-chlorpheniramine maleate ICD 10 code: J44
24	Antiplatelet medicines in patients with arterial filiation	ATC code: B01AC06, N02BA01, B01AC04, B01AC05, B01AC22, B01AC23, B01AC24 ICD 10 code: I48.0, I48.1, I48.2
25	Aspirin in patients with bleeding from upper gastrointestinal	ATC code: B01AC06, N02BA01 Standard disease name for “bleeding from stomach” or “upper gastrointestinal bleeding” from ICD 10 code for K92.2
26	High dose of digoxin	Daily dose over 0.125 mg in ATC code for C01AA04, C01AA05, and 0.175 mg in ATC code for C01AA08.

We used potentially inappropriate medications according to a list provided by the Japan Geriatrics Society (The Japan Geriatrics Society. “A list of drugs requiring particularly cautious Administration: Tools in Elderly Care.”)
ATC, Anatomical Therapeutic Chemical Classification; ICD, International Classification of Diseases

Reference

The Japan Geriatrics Society. “A list of drugs requiring particularly cautious Administration: Tools in Elderly Care.” n.d.: <https://www.jpn-geriat-soc.or.jp/tool/>, accessed 18 Jun 2024.

of prior admission, number of medicines administered at the time of discharge of prior admission, and length of hospital stay of prior admission (Supplementary Tables 1, 2, and Fig. 4).

Data management and analysis were performed using JMP 17® (SAS Institute Inc., Cary, NC, USA) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p<0.05$.

4.5. Ethics approval

The commercially available JMDC database used in this study contains anonymized information processed according to Japan’s Personal Information Protection Law. Individual informed consent was not required for the provision or use of this information. In addition, according to the ethical guidelines for medical and biological research involving human subjects in Japan, an ethics committee review was not required for this study because of the use of anonymized information. Therefore, no informed consent was obtained for this study because the patient data were anonymized before access.

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Conflicts of Interest: KM received honorarium fees for presentations from JMDC, Inc. KM received travel reimbursements from Abbvie to attend the conferences. The

Department of Hospital Pharmaceuticals, School of Pharmacy, Showa University, receiving funding in other research project from Ono with a contract research project according to a collaborative research agreement.

As a potential conflict of interest, KM received honorarium fees from Nippon Kayaku, Abbvie, and Sawai. Hospital Pharmaceutics received a research grant from Daiichi Sankyo, Mochida Pharmaceutical, Shionogi, Ono Pharmaceutical, Taiho Pharmaceutical, Bayer, and Nippon-kayaku. The other authors have no conflicts of interest to declare.

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