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Evaluation of Potentially Inappropriate Prescription and Drug-Drug Interactions in the Critically Sick Elderly Patients in China

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Abstract

Background There is ongoing debate about the incidence and relationships of potentially inappropriate prescriptions and drug-drug interactions (DDIs) in elderly patients in China.

Objective This study aims to evaluate the prevalence of potentially inappropriate medications (PIMs) and DDIs in elderly patients in an intensive care unit (ICU).

Methods A total of 547 patients aged ≥ 65 years from the 30-bed ICU in a 3A (Class Three/Grade A) hospital in China over a 1-year period were included. The participant statistics and drugs prescribed were collected by the Hospital Information System (HIS). The study was limited to drugs ordered at and during ICU hospitalization. The drug list of every patient was reviewed to identify PIMs based on the 2012 Beers criteria, and the drugs implicated in PIMs were classified at five levels according to World Health Organization Anatomical Therapeutic Chemical classification.

Results In total, 94.3% of the patients had prescriptions for ≥ 10 drugs, and 61.4% of the patients were prescribed at least one PIM. DDIs were identified in 95.6% of the medication profiles evaluated.

Conclusions The results of this study conducted in an ICU setting that assessed the incidence and relationships of PIMs and pDDIs in elderly patients in China, providing baseline information and quantifying drug-related problems among critically ill elderly patients receiving PIMs. It is of clinical importance that better information must be provided to physicians and intensive care specialists regarding the risks and benefits of drug therapy, and patient compliance and inappropriate and unnecessary prescriptions must be addressed.

Key words intensive care unit; potentially inappropriate medication; drug-drug interactions; elderly patients

Introduction

According to research findings based on new features of China's population aging during the 14th five-year plan period, $>13\%$ (180 million) of Chinese citizens are expected to be over 65 years old [1], resulting in a major challenge to the health care system. With the increasing average life expectancy, the number of elderly patients admitted to hospitals is growing faster. Intensive care units (ICUs) are also confronted with a steadily growing proportion of critically

ill elderly patients [2, 3].

Elderly patients admitted to the ICU are in serious conditions and often receive multiple medications for various pharmacological classes because of life threatening illnesses. They are more vulnerable than their younger counterparts because they are a unique population with diverse disease processes, existing or impending co-morbidities, multiorgan failure and potentially altered pharmacokinetic and pharmacodynamic characteristics because of age-associated physiologic changes that may cause a reduction in functional reserve capacity. Therefore, drug therapy for critically ill elderly patients is complicated. The routine use of conventional drug dosage regimens may expose a significant portion of elderly patients in the ICU to drug-related problems, such as treatment failure, drug interactions, and a high risk of adverse drug reactions (ADRs). Complications include drug interactions, uncertainty in the part of the patients, or even serious adverse events resulting in the need for an extensive stay in the ICU.

These elderly patients may experience potentially inappropriate medications (PIMs) during ICU hospitalization and have a high risk of ADRs and potential drug-drug interactions (DDIs). These problems are commonly observed in patients in the ICU because it is difficult to treat patients in the ICU with multiple co-morbidities with few drugs. They require drugs for the treatment of specific conditions and for prophylaxis; however, it is essential to balance the number of drugs with effective pharmacotherapy [4]. Polypharmacy is always associated with PIMs, ADRs, drug interactions and increased costs of therapy. PIMs are defined as drugs that are ineffective or have a high risk-benefit ratio [5]. Despite evidence of poor efficacy for the use of PIMs in elderly adults, they are continued to be prescribed and used as a first-line treatment for the most vulnerable elderly adults [6, 7]. It was recently reported that 85% of elderly survivors in the ICU were discharged on at least one PIM, and half of all PIMs are first prescribed in the ICU [8]. In addition, the incidence of ADRs was 24.6% [9] among patients in the ICU, and the elderly were more susceptible to develop ADRs.

To the best of our knowledge, none of previous study has analyzed the prevalence of PIMs and DDIs among elderly patients in ICUs in China. The main purpose of this study was to evaluate the prevalence of PIMs and DDIs in elderly patients in the ICU, particularly focusing on whether age is related to PIMs or DDIs.

Methods

Ethical Approval

This study was approved by the Institutional Ethics Committee. Confidentiality was maintained in this study. Informed consent was considered unnecessary by the Ethics Committee because this study was a survey involving the collection or study of existing data. The documents, records of diagnostics, and information were recorded by the investigators in such a manner that the subjects cannot be identified, directly or through identifiers linked to the subjects.

Study Subjects

A prospective observational study was conducted at Zhejiang Hospital, which is a 2000-bed tertiary integrating medical treatment, teaching, scientific research, prevention and health care hospital specializing in geriatric and intensive care, from June 1, 2013 to May 31, 2017. All patients aged ≥ 65 years admitted to the ICU during the study period were included in the study. The population aged ≥ 65 years were divided into three categories: young-old (65–74 years), middle-old (75–84 years), and oldest-old (≥ 85 years). The main exclusion criteria included (1) patients who died at the index admissions and (2) those who were not prescribed or discharged within 24 h.

Data Collection and Classification

The participant statistics and drugs prescribed were collected by the Hospital Information System (HIS). The study was limited to drugs ordered at and during ICU hospitalization. Each patient had a data sheet that lists all the drugs given to that patient. The drug list of every patient was reviewed to identify PIMs based on the 2012 Beers criteria [10]. Furthermore, the drugs implicated in PIMs were classified at five levels according to World Health Organization Anatomical Therapeutic Chemical classification [11].

On the first day of the study and with each new admission to the ICU, the entire participants' medication profile was screened for DDIs. Each subsequent day was considered a new patient evaluation, and newly added medications were evaluated for the presence of

DDIs based on the existing medication configurations. DDIs were checked through a commercial prescription screening system (Ipharmacare, Hangzhou, China). This prescription screening system runs on the Microsoft Windows platform and includes the national drug database of China and the Clinical Guide of Chinese Pharmacopoeia (2010 Edition) [12]. The prescription screening system ranked the severity of the potential DDIs as minor, moderate, major, or contraindicated (Table 1). The DDI identification used in this study was based on the specific substances of the medications administered.

Statistical Analysis

Statistical analyses were performed with statistical software (SPSS 22.0). Descriptive statistics were used to analyze most of the variables. The results were expressed as percentages, the mean $\pm$ standard deviation for continuous parametric variables, and the median and inter-quartile range (25-75%) for continuous, nonparametric variables.

The characteristics of the patients were compared by age group using a one-way ANOVA and Student's t-test, as appropriate. Un-adjusted and then multivariable, adjusted, logistic regression modeling was used to determine the association of covariates with the occurrence of PIMs and DDIs. Results of the regression models are reported as odds ratio and 95% confidence interval. Statistical significant is defined as p-values <0.05 .

Results

During the study period, 547 patients with 15,087 patient-days were enrolled (Table 1). The mean age of these 547 participants was 83.1 ± 6.3 years; the most common age group was the middle-old group (47.3%), followed by the oldest-old group (42.8%). The ratio of male-to-female was 2.4. The mean length of stay in the ICU was 27.6 ± 13.7 days. Among the 547 patients, common clinical diagnoses included sepsis, acute respiratory distress syndrome, pneumonia, myocardial infarction and congestive heart failure.

A total of 17,215 drugs were prescribed among the 547 patients during their stay in the ICU, with an average of 31.5 ± 13.1 drugs prescribed per patient. The mean number of drugs received by male and female patients was 32.1 ± 13.4 and 29.9 ± 12.5 , respectively. In total, 94.3% of the patients had prescriptions for ≥ 10 drugs. With the growth of age, there was a

significantly increase of drug consumption (Table 1). The oldest-old group received 37.2 ± 12.2 drugs, followed by the middle-old (29.1 ± 11.8) and young-old (18.3 ± 10.1) groups.

Among these 547 patients, 336 (61.4%) were prescribed at least one PIM: 182 (54.2%), 100 (29.8%), and 54 (16.1%) patients filled their prescriptions for a single PIM drug, two drugs of concern, and ≥ 3 PIMs, respectively. A total of 566 PIMs were prescribed to these 336 patients. Thus, the rates of prescribed PIMs were 101.6 per 100 admissions and 37.5 per 1000 patient-days. The young-old group experienced the least PIMs among the three age groups, which was approximately 0.8 PIMs per patient on average (Table 1). In terms of the prescribed PIMs, only a few comprised the maximum percentage of total prescriptions (Table 2). The prescribed frequencies of amiodarone (17.8%), diazepam (17.0%), and estazolam (13.4%) were the highest (48.2%) of all the PIMs.

DDIs were identified in 95.6% (523/547) of the evaluated medication profiles. Upon evaluation of the total number of DDIs, 4,532 total DDIs were being given (300.4 DDIs/100 patient-days), 339 of which were the unique drug pairs. A unique drug pair is a specific combination of interacting medications. Regardless of how many times this interaction is identified, it is counted as one unique drug pair. Of the 4,532 DDIs identified, 6.9% (311/4532) and 54.9% (2486/4532) were considered to be a major and moderate DDIs by database, respectively. The 10 most common DDIs are listed in Table 3.

The number of drugs, PIMs and DDIs were all significantly correlated with each other in all three groups (Figure 1). In the young-old group, the correlation factors between the number of drugs given and PIMs, the number of drugs given and DDIs, and PIMs and DDIs were 0.422 ($p=0.001$), 0.627 ($p<0.001$), and 0.561 ($p<0.001$), respectively; whereas the correlation factors were 0.112 ($p=0.071$), 0.623 ($p<0.001$), and 0.374 ($p<0.001$) in the middle-old group; and 0.264 ($p<0.001$), 0.572 ($p<0.001$), and 0.499 ($p<0.001$) in the oldest-old group, respectively.

In an unadjusted logistic regression model, older age was associated with number of drugs prescribed (odds ratio [OR]=8.931 per increase in age group, $p<0.001$). After the factors of LOS, PIMs, and DDIs were included, age was still associated with an increased number of prescribed drugs (OR=6.146, $p<0.001$). LOS and DDIs were associated with the occurrence of PIMs (Table 4), number of prescribed drugs and PIMs were associated with DDIs (Table

5).

Discussion

To our knowledge, this is the first prospective observational study conducted in an intensive care unit setting to assess the incidence and relationship between potentially inappropriate prescriptions and drug-drug interactions in elderly Chinese patients.

Intensive care units are often affected by polypharmacy, inappropriate medication and drug-drug interactions. In this setting, patients who frequently require the most acute care are likely to be treated with multiple pharmacological agents and multiple health-care providers at the same time. More seriously, elderly patients admitted to the ICU often have diseases and acute/chronic organ dysfunction that can affect physiologic responses to pharmaceuticals and drug metabolism. However, in China, few studies have assessed the quality of prescribed medications in elderly populations in the ICU.

We applied the Beers criteria to determine whether medication prescribed to the elderly in the ICU were appropriate. The explicit Beers criteria were established in the US by panels of expert geriatricians and pharmacologists in 1991, and they have been updated three times since then [13]. These recommendations include avoiding medications with a high potential for harm and regarding alternatives with a low risk. No such criteria have been developed in China; however, PIMs were defined by the 2012 Beers criteria [10] in this study. Of the 547 patient evaluations, 58.8% of the evaluations involved at least one PIM. Compared with other reports of ICU elderly patients, the rate of PIMs appeared to be lower than that reported in the US (85%) [14] but higher than that in Japan (50.7%) [15]. In addition, our results revealed that the most commonly prescribed potentially inappropriate drug was amiodarone, followed by diazepam and estazolam. This result corresponds to the report that one-quarter of elderly patients received a drug that may be inappropriate considering their age, and the most commonly prescribed potentially inappropriate drugs were amiodarone and diazepam [16]. Age was associated with PIMs. Overall, there was a statistically significant frequency of PIMs prescribed in the three age groups ($F=7.325$, $p=0.001$). Given the high prevalence of PIMs in elderly patients with critical illnesses, physicians practicing in the ICU should adequately understand the dangers of individual medications in the high-risk elderly

population and be more attentive to the appropriateness of medication therapy.

In the present study, the number of drugs given during the ICU hospitality increased significantly along with age ($p < 0.001$). Several factors are postulated to be responsible for polypharmacy in the elderly [17, 18]. Firstly, the incidence of chronic diseases gradually increases with the age of patients, and >90% of patients aged >65 years have at least one chronic disease and approximately 30% of patients have more than one chronic medical diagnosis [19]. A number of different alternative medications may be used to treat these chronic health conditions. Although patients were admitted to the ICU because of acute or critical medical conditions, physicians have to treat the specific condition and any comorbidities that may arise. Secondly, current medical practice guidelines often require multiple medications to treat each disease state for optimal clinical benefit [20]. To further compound the problem, critically ill elderly patients with multiple drugs were predisposed to drug-drug interactions, leading to toxicity that may affect the patients' safety or diminish therapeutic benefit, and may increase the incidence of ADRs while resulting in extra treatment or medications for avoidable medical complications [21-22].

Our findings demonstrated that a total of 4,532 DDIs were identified, corresponding to a rate of 300.4 DDIs per 100 patient days. The most common types of drugs were antiplatelet or anticoagulant and antibiotics for systemic use. One study of DDIs frequency in 400 cardiac and cardiothoracic ICU patients showed a rate of 287.5 DDIs per 100 patient days [23]. The mean age of the study population was 62.15.7 years, much younger than our study participants, which may have led to the lower DDI rate. However, as the author states, their results cannot be generalized to the general ICU population because most DDIs involved anticoagulants and antiplatelet agents. Another study, which included 9,644 admissions (median age, 63 years) to the adult ICU in the Netherlands between 2002 and 2009, reported a potential DDIs rate of 167.2 per 100 patient days in critical care unit [24]. Additionally, the most frequently encountered drug classes were antithrombotic agents and antibiotics. These findings are in concordance with ours.

There are relatively few literatures on the relationship between age, PIMs, DDIs, and the length of ICU hospitalization among critically ill elderly patients in China. We found a statistically significant correlation between age and a cumulative index of the drugs

prescribed. Few studies have investigated the correlation between increasing age and the number of drugs prescribed, PIMs, DDIs and LOS (length of stay) in various settings and in different populations. Gokce Kutsal et al. [25] demonstrated that polypharmacy was correlated with various factors, including age, in elderly outpatients. In Brazil, a study reported that the rate of potential DDIs was significantly associated with an in-patient age of 55 years (OR=1.5, p=0.0008) [26]. It has also shown that polypharmacy and advanced age are important risk factors for potential drug interactions [16].

Unfortunately, there are many negative consequences associated with polypharmacy, PIMs and DDIs. Specifically, the burden of taking multiple medications is associated with greater healthcare costs and an increased risk of ADRs [9, 27]. Recognizing the potential for unexpected outcomes in the critically ill elderly patients, various groups have attempted to intervene to improve the appropriateness of medication prescribing. Most interventions hinge upon pharmacy intervention, the use of inappropriate drug lists, such as the Beers or the STOPP/START criteria [28]. Computer feedback using the Beers criteria in a large cohort of elderly patients in a pharmacy benefit plan resulted in a significant change to more appropriate medications [29-31].

However, this study has some limitations. Firstly, it was performed in a single central ICU. Thus, the prescribing behaviors of physicians might have been identified in this study. The single-center nature of this study limits the generalizability of the results to populations similar to the one studied. Secondly, PIMs was based on the 2012 Beers Criteria, but some of these medications were appropriately prescribed to individuals with complicated health statuses who may benefited from these medications. Thus, a more useful clinical approach is to measure the prevalence of actual inappropriate medications in the critically ill elderly patients. Thirdly, the clinical outcome was not further corroborated by PIMs and DDIs. Investigating the DDIs samples to assess individual patient factors and determine the rate of ADRs caused by these factors is a subject for future research.

Conclusions

The results of the current study revealed that PIMs and DDIs are significant issues, and few studies have been conducted regarding the elderly population in intensive care units to assess

the quality of prescribed medications in China. Age was significantly associated with PIMs, DDIs, and the length of ICU hospitalization. The rational prescription of drugs or better patient care is essential. Interventions to improve the optimal use of medication must target critically ill elderly patients. Better information must be provided to physicians and intensive care specialists regarding the risks and benefits of drug therapy, and patient compliance and inappropriate and unnecessary prescriptions must be addressed.

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Declarations

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Conflicts of interest The authors declare no conflict of interest.

Ethics approval This study design was approved by Zhejiang Hospital Institutional Ethics Committee and conducted in accordance with the Declaration of Helsinki.

Data availability The authors can confirm that all relevant data are included in the article.

Authors' contributions YHY and FJZ directed the study. XHY, WL and FJZ designed the study and analyzed data. XHY developed the first manuscript draft. XHY, YHY, FJZ and OJO edited the manuscript. All authors critically revised the manuscript, and all authors contributed to the final version.

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Figure and tables

Figure 1 Correlation among the three factors, number of drugs prescribed, potentially inappropriate medications (PIMs) and potential drug–drug interactions (pDDIs), at each age group. In the young-old group, the correlation factors between the number of drugs given and PIMs, the number of drugs given, PIMs, and pDDIs were 0.422 ($p=0.001$), 0.627 ($p<0.001$), and 0.561 ($p<0.001$), respectively; whereas the correlation factors were 0.112 ($p=0.071$), 0.623 ($p<0.001$), and 0.374 ($p<0.001$) in the middle-old group; and 0.264 ($p<0.001$), 0.572 ($p<0.001$), and 0.499 ($p<0.001$) in the oldest-old group, respectively.

Table 1 Demographic and Clinical Characteristics of Elderly Patients in the Intensive Care Unit (N=547)

Age group (y)				
Description	Young-old (65-74)	Middle-old (75-84)	Oldest-old (≥ 85)	<i>p</i> value
Patient, No. (%)	54 (9.9)	259 (47.3)	234 (42.8)	-
Female, No. (% of each group)	9 (16.7)	62 (23.9)	92 (39.3)	-
ICU length of stay, days, mean (IQR)	21.3 (17.6 - 24.9)	28.1 (26.2 - 29.9)	28.5 (27.0 - 30.)	.001
Main reason for ICU admission, No. (% of each group)				
Sepsis or acute respiratory distress syndrome with infection	10 (18.5)	64 (24.7)	99 (42.3)	
Acute respiratory distress syndrome without infection	7 (13.0)	87 (33.6)	49 (20.9)	
Cardiogenic shock, myocardial infarction, congestive heart failure	18 (33.3)	65 (25.1)	44 (18.8)	
Cerebral infarction	13 (24.1)	12 (4.6)	9 (3.8)	
Surgery ^a	1 (1.9)	8 (3.1)	6 (2.6)	
CPR	1(1.9)	7 (2.7)	8 (3.4)	
Other ^b	4 (7.4)	16 (6.2)	19 (8.1)	
No. of drugs given, mean (IQR)	18.3 (15.5-21.1)	29.1 (27.6-30.5)	37.2 (35.6-38.7)	< .001
PIMs, mean (IQR)	0.8 (0.6-1.0)	0.9 (0.8-1.0)	1.3 (1.1-1.4)	.001
pDDIs, mean (IQR) ^c	5.1 (3.7-6.6)	7.3 (6.5-8.1)	10.1 (9.1-11.2)	< .001
Major of contraindicated	0.2 (0.1-0.4)	0.4 (0.3-0.5)	0.8 (0.7-1.0)	< .001
Moderate	2.9 (1.9-3.9)	4.2 (3.7-4.7)	5.3 (4.7-6.0)	< .001
Minor	2.0 (1.4-2.6)	2.7 (2.4-3.0)	4.0 (3.5-4.5)	< .001

Note: IQR=interquartile range, ^aabdominal; urological; cardiovascular; orthopedic; eye, ^bcancer; cirrhosis; hepatic failure; hemorrhagic shock; arrhythmia; gastrointestinal bleeding;

renal failure. °Description of major or contraindicated pDDI: The interaction was found to be life-threatening, and/or the concomitant use of the interacting agents was contraindicated or required medical intervention to minimize or prevent serious adverse effects. Moderate pDDI: The interaction resulted in an exacerbation of the patient's condition and/or required an alteration in therapy. Minor pDDI: The interaction had limited clinical effects and did not require a major alteration in therapy

Table 2 Top 10 Drugs Prescribed in the Beers Criteria for potentially Inappropriate Medication Use Among Elderly Patients in the Intensive Care Unit (N=566)

Sl. No.	Drug	ATC code	Organ System	QE	No. of prescription
1	Amiodarone	C01BD01	Cardiovascular	High	101 (17.8)
2	Diazepam	N05BA01	Central Nervous System	High	96 (17.0)
3	Estazolam	N05CD04	Central Nervous System	High	76 (13.4)
4	Indometacin	M01AB01	Pain Medications	Moderate	57 (10.1)
5	Metoclopramide	A03FA01	Gastrointestinal	Moderate	31 (5.1)
6	Growth Hormone	H01AC01	Endocrine	High	26 (4.6)
7	Olanzapine	N05AH03	Central Nervous System	Moderate	23 (4.1)
8	Propafenone	C01BC03	Cardiovascular	High	22 (3.9)
9	Clonidine	C02AC01	Cardiovascular	Low	19 (3.4)
10	Zolpidem	N05CF02	Central Nervous System	Moderate	17 (1.8)

Note: ATC=Anatomical Therapeutic Chemical classification system; QE=Quality of evidence

Table 3 The 10 Most Frequently Occurring Potential Drug-Drug Interactions among the Elderly Patients in the Intensive Care Unit

Interacting drug pair	Frequency ^a	Severity rating	Mechanism of pDDIs
Heparin+Cefoperazone/Sulbactam	113	Moderate	Heparin due to hypoprothrombinemia with an increase in prothrombin time.
Furosemide+Methylprednisolone	112	Moderate	The concomitant use of corticosteroids and agents that deplete potassium may result in an increased risk of hypokalemia.
Cilastatin/Imipenem+Theophylline	97	Moderate	Imipenem may enhance theophylline toxicity.
Aspirin+Furosemide	85	Minor	Salicylates may diminish the effects of loop diuretics.
Heparin+Piperacillin/Tazobactam	72	Minor	Intravenous penicillin may intensify the effect of heparin by the inhibition of platelet aggregation.
Diazepam+Furosemide	62	Moderate	Coadministration of diazepam with antihypertensive agents may result in additive effects on blood pressure and orthostasis.
Aspirin+Methylprednisolone	61	Moderate	Corticosteroids may decrease the serum concentrations and therapeutic effects of salicylates.
Digoxin+Furosemide	59	Moderate	Diuretic-induced hypokalemia and hypomagnesemia may predispose patients on digitalis to arrhythmias.
Aminophylline+Quinolones	45	Moderate	Quinolones may reduce the clearance of aminophylline.
Aspirin+clopidogrel	42	Moderate	Clopidogrel may enhance the adverse/toxic effects of the salicylates; an increased risk of bleeding may result.

Note: DDIs=potential drug-drug interactions, ^aNumber of occurrences during the study period

Table 4 Unadjusted and multivariable logistic regression modeling for characteristics associated with PIMs

Potential Risk Factors	Unadjusted		Adjusted Model	
	OR (95% CI)	P	OR (95% CI)	P
Age	.100 (-.039, .239)	.157		
LOS	.010 (.004, .016)	.001	.009 (.003, .015)	.003
No. of drugs prescribed	-.647 (-1.460, .167)	.119		
pDDIs	.079 (.065,.093)	< .001	.073 (.062,.085)	< .001

Note: LOS=length of stay; PIMs=potentially inappropriate medications; pDDIs=potential drug-drug interactions; OR=odds ratio; CI=confidence interval

Table 5 Unadjusted and multivariable logistic regression modeling for characteristics associated with DDIs

Potential Factors	Risk	Unadjusted		Adjusted Model	
		OR (95% CI)	P	OR (95% CI)	P
Age		-.715 (-1.463, .032)	.061		
LOS		-.007 (-.041, .027)	.706		
No. of drugs prescribed		.306 (.267, .346)	< .001	.289 (.254, .324)	< .001
PIMs		2.297 (1.884, 2.710)	< .001	2.276 (1.867, 2.685)	< .001

Note: DDIs=potential drug-drug interactions; LOS=length of stay; PIMs=potentially inappropriate medications; OR=odds ratio; CI=confidence interval