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ORIGINAL RESEARCH

Comparison of three criteria for potentially inappropriate medications in Chinese older adults

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Objectives: This study aimed to compare the prevalence of potentially inappropriate medications (PIMs) among Chinese aged patients using the Beers criteria of 2015, the Screening Tool of Older Persons' Prescriptions (STOPP) of 2014 and the criteria of PIMs for older adults in China (Chinese criteria), and to identify the correlates of the PIMs' use.

Methods: A retrospective, cross-sectional study was conducted among geriatric patients at Beijing Chao-Yang Hospital between January 2018 and March 2018. Three criteria (the Beers criteria of 2015, the STOPP criteria of 2014 and the Chinese criteria) were used to detect PIMs. A multivariate logistic regression analysis was carried out to determine factors associated with the use of PIMs. Leading PIMs for each set of criteria were also listed. The concordance among the three PIM criteria was calculated using kappa tests.

Results: Totally, 863 inpatients aged ≥65 years were included. The prevalence of patients receiving at least one PIM was 80.2%, 58.1% and 44.0% according to the Chinese criteria, 2015 Beers criteria and 2014 STOPP criteria, respectively. The Beers and the STOPP criteria indicated a moderate coherence, whereas the Chinese criteria showed poor concordance with the other two criteria. Proton-pump inhibitors in the Beers and STOPP criteria and clopidogrel in the PIM-Chinese accounted for most leading PIMs. The most important factor associated with PIM use by all three sets of criteria was the number of prescribed medications.

Conclusion: Data showed a high PIM prevalence among older adults in China, which was associated with the number of prescribed medications. The Chinese criteria had the highest detection rate but a poor concordance with the Beers and STOPP criteria ($P<0.001$).

Keywords: elderly, hospitalized, Beers criteria, STOPP criteria, Chinese criteria, polypharmacy

Introduction

The rapid growth of the aged population imposes heavy burdens on the Chinese government and health systems. As the elderly often experience polypharmacy[1–3] and have reductions in liver and kidney function, they suffer from more drug-related problems, such as adverse drug reactions, drug–drug interactions or drug–disease interactions.[4,5] Potentially inappropriate medication (PIM) is a term used to describe the use of a medication for which the associated risks outweigh the potential benefits, especially when more effective alternatives are available.[6] PIMs are associated with more adverse drugs events, longer hospital stays, increased resource utilization, higher hospital readmission rates and increased health care costs.[7–12]

There are different screening tools to assess the extent of PIMs in aged patients. The most widely used and cited tools for PIMs are the Beers criteria in the USA and the Screening Tool of Older Persons' Prescriptions (STOPP) in Europe. The Beers criteria devised by Beers et al in 1991, for use in nursing homes,[13] was subsequently

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expanded and revised in 1997, 2003, 2012 and 2015. Beers criteria of 2015 were divided into five groups: 1) PIMs to avoid in older adults, 2) PIMs to avoid in older adults with diseases and syndromes that the drugs can exacerbate, 3) medications to be used with caution, 4) drugs for which dose adjustment is required based on kidney function and 5) drug–drug interactions.[14]

The STOPP criteria version 1 was first launched by geriatricians from Cork University Hospital (Ireland) in 2008 and updated in 2014.[15,16] The new version included 80 STOPP criteria which classified the physiological system.[17] Several new STOPP categories were created in version 2, namely antiplatelet/anticoagulant drugs, drugs affecting, or affected by, renal function and drugs that increase anticholinergic burden.

Criteria of potentially inappropriate medications for older adults in China (the Chinese criteria) proposed by an expert panel was published in 2017, including medication risk and medication risk under morbid state. This country-specific criteria was divided into high risk and low risk medications according to experts' evaluation and divided into A and B categories according to defined daily doses.[18] The overlap between the Chinese criteria and the Beers criteria regarding medication risk irrespective of conditions was about 90%. The Chinese criteria contained clopidogrel, gatifloxacin, vancomycin, clindamycin, aminoglycosides, theophylline and warfarin that were not included in the Beers criteria (theophylline and warfarin were considered inappropriate only for potential interactions with specific medications in the Beers criteria). With regard to medication risk under morbid state, glucocorticoids with osteoporosis or diabetes, reserpine with hypertension or depression and phenylephrine or pemoline with insomnia were unique to China.

Up to now, no studies have reported the prevalence of PIMs according to updated version of the STOPP criteria and only one study investigated PIMs identified by the 2015 Beers criteria in China.[19] Besides, no studies have compared this country-specific and non-country-specific criteria to detect PIMs. The objectives of this study were: 1) to compare the prevalence of PIMs in Chinese aged inpatients based on the Beers criteria of 2015, the STOPP criteria of 2014 and the Chinese criteria; 2) to investigate related risk factors for PIMs; 3) to list the leading medications detected by three sets of criteria.

Methods

Setting and sample

From January to March 2018, a retrospective, cross-sectional study was conducted in the General Medicine Department and the Heart Center of the Beijing Chao-Yang Hospital, a 1,900 bed tertiary hospital. The Department of General Medicine mainly cares for chronic disease (such as cardiovascular diseases, cerebrovascular disease and respiratory disease) and the Heart Center cares for cardiovascular disease in which patients are mainly aged people.

Inclusion criteria: inpatients aged $\geq$65 years. Exclusion criteria: 1) length of stay $<$2 days or $>$30 days; 2) non-doctor's advice to leave hospital (death or discharge against medical advice); 3) more than one visit within the study period; 4) diagnosed as malignancy and 5) without any medications.

The study protocol was approved by the Ethics Committee of the Beijing Chao-Yang Hospital and was granted an exemption from patients' consents for the review of medical records. The study used secondary data and no contact was made with the participants. Anonymity and confidentiality was maintained by ensuring that patients' names did not appear in the research findings; the information collected from the patients' records was recorded anonymously and used purely for research purposes. Only the researcher had access to the patients' records.

Data collection

Data, including age, gender, principal diagnosis, comorbidities, prognosis (discharge or death), prescribed drugs and dosages, length of stay and serum creatinine, were extracted from patients' electronic medical records. The estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation.[20] Patients' performance of activities of daily living (ADL) was assessed by the Barthel Index.[22] Patients' current diagnosis for which they received medications was classified using the International Classification of Diseases-10 (ICD10). Comorbidity was quantified using the Charlson Comorbidity Index (CCI).[21]

Evaluation of PIMs

The PIMs were evaluated using the application of the Beers criteria of 2015, the STOPP criteria of 2014 (not including screening tool to alert to right treatment criteria) and the Chinese criteria. The patients' latest eGFR data were considered in evaluating PIMs due to kidney functions. Use of anticholinergic medications was defined in accordance with the 2015 Beers criteria.

Two authors (Zhuo Ma and Caixia Zhang) independently reviewed each patient's electronic records and assessed PIMs. Each reviewer was blinded to the other reviewer in the process of data extraction and PIMs' evaluation. Another author Xiangli Cui was consulted if there were any discrepancies.

Statistical analysis

The continuous variables were represented as mean ± SD, the nonparametric variables were represented as median ± IQR and the categorical data were represented as frequencies. The Student's *t*-test or non-parametric test was applied to compare continuous variables for the mean or median, respectively. The chi-squared test was used for between-group comparisons of categorical variables. The concordance among the three PIM criteria was calculated using kappa tests (values of kappa >0.75 indicate good to excellent agreement; values between 0.40 and 0.75 indicate moderate agreement; values <0.40 indicate poor agreement). The possible risk factors affecting PIM in elderly patients were analyzed by a logistic regression in which the enter method strategy and likelihood ratio method were used. A *P*-value of <0.05 was considered to be statistically significant. The statistical analysis was carried out using SPSS version 23.0 software.

Results

Demographic characteristics of the patients

A total of 1,029 participants aged ≥65 years were included in the present study. One hundred sixty-six patients were excluded from the study due to length of stay <2 days (n=72), length of stay >30 days (n=5), non-doctor's advice to leave hospital (n=20), more than one visit within the study period (n=12), diagnosed as malignancy (ICD10: C00-C97; n=52) and non-medication prescribed during hospitalization (n=5). Finally, there were 466 female (54.0%) and 397 male (46.0%) patients who were included in the study. Age ranged between 65 and 98 years with an average of 75.4±7.4 years. A total of 207 (24.0%) patients had a Barthel Index ≤60, which indicated moderate-to-severe physical impairment.[19] The median (IQR) CCI points, prescribed medications, length of hospital stay were 2 (1–3), 10 (8–12.5) and 7 (5–9), respectively. The prevalence of elderly patients who were regularly prescribed ≥5 drugs was 91.9% and ≥10 drugs was 43.7%. The most common principal diagnosis included unstable angina pectoris (ICD10: I20.001, 30.6%), acute non-ST-segment elevation myocardial infarction (ICD10: I21.401, 7.0%), coronary atherosclerotic heart disease (ICD10: I25.105, 5.0%), paroxysmal tachycardia (ICD10: I47.901, 4.5%) and lacunar infarction (ICD10: I63.801, 2.4%).

PIM use and leading medications in three sets of PIM criteria

Of the 863 patients, 780 patients (90.4%) were identified with at least one PIM based on three sets of PIM criteria. The prevalence rate of PIMs identified was highest in the Chinese criteria (80.2%), followed by the Beers criteria (58.1%) and the STOPP criteria (44.0%). The median number of PIMs per person identified was 1 (1–2), 1 (1–1) and 1 (1–2) using the Beers criteria, the STOPP criteria and the Chinese criteria, respectively (Table 1).

The kappa statistic for the Beers criteria and STOPP criteria was 0.575, indicating a moderate coherence; whereas the Chinese criteria showed poor concordance with the Beers criteria and the STOPP criteria (κ=0.114 and 0.079, respectively) (Table 2).

Table 3 lists the top ten PIMs recognized by the three criteria. In the Beers and STOPP criteria, proton-pump inhibitors (PPIs) accounted for the most frequent PIMs. In contrast, the most frequent PIM according to the Chinese criteria was clopidogrel (Table 3). Benzodiazepines were ranked in the top three, and NSAIDs and amiodarone in the top ten by all the three sets of criteria.

Factors associated with PIM

Using the univariate analysis, patients having a higher number of prescribed medications were at high risk of being prescribed PIMs (*P*<0.05), while there were no associations between PIM use and sex according to all three criteria (*P*>0.05). Patients identified with PIMs were found to have a higher age, a longer length of hospital stay and a higher grade of dependency for ADL (Barthel score ≤60) (*P*<0.05), except when using the Chinese criteria (Table 1).

The results of the multivariate analysis are displayed in Table 4. All variables presented in Table 1 were entered into a logistic regression model to analyze their association with the use of PIM. Patients who were prescribed more medications were more likely to have PIMs across all three sets of criteria (*P*<0.001). For the Beers criteria only, PIM patients exhibited significant differences regarding a Barthel Index ≤60 (*P*=0.016) and length of stay (*P*=0.004) compared to the non-PIM patients. Similarly, CCI was associated with PIM use only when the PIM-Chinese criteria were applied (*P*=0.028) (Table 4).

Discussion

In the present study, we have four major findings: 1) The prevalence of PIMs use was highest with the Chinese criteria (80.2%), followed by the Beers criteria (58.1%) and the STOPP criteria (44.0%). 2) PPIs were the most frequent PIMs according to the Beers 2015 criteria and the STOPP 2014 criteria, while clopidogrel occurred the most frequently in the Chinese criteria. 3) Factors associated with PIMs varied and the number of medications was the only common risk factor

Table 1 Demographic and clinical characteristics of the aged Chinese people and prevalence of PIMs (n=863)

Characteristics	Total	Beers criteria			STOPP criteria			Chinese criteria		
		PIM	Non-PIM	*P*-value	PIM	Non-PIM	*P*-value	PIM	Non-PIM	*P*-value
	863	**501 (58.1%)**	**362**		**380 (44.0%)**	**483**		**692 (80.2%)**	**171**	
Number of PIMs per person (IQR)		1 (1–2)			1 (1–1)			1 (1–2)		
Age, years (mean ± SD)	75.4±7.4	76.3±7.3	74.2±7.3	*P*<0.001	76.1±7.1	74.8±7.6	0.011	75.3±7.3	75.9±7.7	0.312
Gender				0.444						0.568
Male (%)	466 (54.0)	265 (56.9)	201 (43.1)		196 (42.1)	270 (57.9)		377 (80.9)	89 (19.1)	
Female (%)	397 (46.0)	236 (59.5)	161 (40.6)		184 (46.4)	213 (53.7)	0.206	315 (79.4)	82 (20.7)	
Barthel index				*P*<0.001			*P*<0.001			*P*<0.001
Barthel score ≤60 (%)	207 (24.0)	154 (74.4)	53 (25.6)		109 (52.7)	98 (47.3)		163 (78.7)	44 (21.3)	
Barthel score >60 (%)	656 (76.0)	347 (52.9)	309 (47.1)		271 (41.3)	385 (58.7)		529 (80.6)	127 (19.4)	
CCI (IQR)	2 (1–3)	3 (2–4)	2 (1–3)	*P*<0.001	2 (1–4)	2 (1–3)	0.264	2 (1–3)	2 (1–3)	0.061
No prescribed medications (IQR)	10 (8–12.5)	11 (9–14)	8 (6–11)	*P*<0.001	11 (9–13)	9 (7–12)	*P*<0.001	10 (8–13)	8 (6–11)	*P*<0.001
Length of stay, days (IQR)	7 (5–9)	7 (5–10)	6 (4–7)	*P*<0.001	7 (5–9)	6 (4–8)	0.023	6.5 (5–9)	7 (5–9)	0.234

Abbreviations: CCI, Charlson Comorbidity Index; PIM, potentially inappropriate medication; STOPP, Screening Tool of Older Persons' Prescriptions.

according to three sets of criteria. 4) Region-specific criteria had a low concordance with non-region-specific criteria.

The incidence rate of PIMs in our study was higher than that reported in other countries. In Europe, the frequency of PIM is around 20% (identified by the Beers and McLeod),[23] while it ranges from 14% to 27% in the USA.[24] A study from Japan revealed PIM frequencies was 42.1%.[25] However, the frequency of PIMs reported in our population was close to or lower than those in previous studies in China. A retrospective observational study conducted at Peking University First Hospital in China based on the Beers 2015 reported a prevalence of PIMs of 53.5%, which was consistent with our results.[19] One study that evaluated 6,337 hospitalized Chinese elderly patients reported that the prevalence of PIMs detected by the Beers 2012 and STOPP 2008 were 72.48% and 51.37%, respectively.[26] Several factors may be responsible for the relatively high prevalence in our study. First, reliable knowledge of polypharmacy among the elderly in China is lacking.[27] Second, in Chinese culture, physicians and patients sometimes hold the belief that drugs provides a quicker and more complete relief even when non-drug methods could be effective. Third, the latest version of the Beers and the STOPP criteria added more medications as PIMs, such as PPIs and benzodiazepines regardless of their half-life. Fourth, our study lacks effective interventions, such as pharmacists' intervention and a computer-based warning.[25,28]

Our study showed that the order of PIMs prevalence identified from high to low was the Chinese, the Beers and the STOPP criteria. First, the highest detection of PIM by the Chinese criteria might come from clopidogrel which was listed only on this criterion. It accounted for 55.7% of all PIMs detected by this country-specific PIM criteria. It is worth noting that the statement "use of clopidogrel as first-line antiplatelet therapy where there is no contraindication to aspirin for treatment of stable coronary, cerebral or peripheral vascular disease" was removed from the STOPP list because consensus could not be reached following expert questionnaire.[15] Some panelists commented that use of clopidogrel in this instance was an issue of cost, not of safety. Clopidogrel was listed on the Chinese criteria for its hematologic toxicity and neurotoxicity.[18] Furthermore, the Chinese and the Beers criteria included the listing of PIM independent of the diagnoses/conditions. In contrast, all PIM listed by the STOPP criteria were the medications and classes to avoid in older adults with certain diagnoses/conditions. Third, some drugs listed on the Beers criteria and the STOPP criteria are not available in China, but all drugs

Table 2 Concordance between the three criteria

STOPP-listed PIM	Beers-listed PIM		κ	*P*-value
	Yes	**No**		
Yes	347	33	0.575	$P<0.001$[a]
No	154	329		$P<0.001$[b]
Chinese-listed PIM	**Beers-listed PIM**			
	Yes	**No**		
Yes	424	268	0.114	$P<0.001$[a]
No	77	94		$P<0.001$[b]
Chinese-listed PIM	**STOPP-listed PIM**	**STOPP-listed non-PIM**		
	Yes	**No**		
Yes	323	369	0.079	$P<0.001$[a]
No	57	114		$P<0.001$[b]

Notes: [a]Based on kappa test; [b]Based on chi-squared test.
Abbreviations: PIM, potentially inappropriate medication; STOPP, Screening Tool of Older Persons' Prescriptions.

in the PIM-Chinese criteria are available. Drug availability is one of the possible determinants of PIM prevalence.[29]

PPIs were the most frequent PIMs according to the Beers 2015 criteria and STOPP 2014 criteria which were not listed on PIM-Chinese criteria. PPIs are a class of important drugs for treating acid-related diseases, such as gastroesophageal reflux diseases, peptic ulcer, Zollinger–Ellison syndrome and upper gastrointestinal bleeding. Short-term use of PPIs is generally well tolerated but long-term use of PPIs can cause a series of safety issues, such as fractures,[30] *Clostridium difficile*-associated diarrhea,[31] increased risk of pneumonia,[32] vitamin B12 deficiency caused by the lack of nutrients,[33] hypomagnesemia,[34] interstitial nephritis,[35] increased risk of serious skin allergy[36] and so on. Inappropriate use

Table 3 Top ten PIMs based on the three sets of PIM criteria

Beers criteria (N=763)		STOPP criteria (N=477)		Chinese criteria (N=945)	
Drugs and items	**N (%)**	**Drugs and items**	**N (%)**	**Drugs and items**	**N (%)**
PPIs	260 (34.1)	PPIs	260 (54.5)	Clopidogrel	526 (55.7)
Diuretics	208 (27.3)	Beta-blocker for bradycardia, type II atrioventricular block or complete atrioventricular block	40 (8.4)	Benzodiazepines, nonbenzodiazepine, benzodiazepine receptor agonist hypnotics	121 (12.8)
Benzodiazepines, nonbenzodiazepine, benzodiazepine receptor agonist hypnotics	133 (17.4)	Benzodiazepines for ≥4 weeks	32 (6.7)	Insulin	47 (5.0)
Insulin	47 (6.2)	Aspirin, dipyridamole, Vitamin K antagonist, direct thrombin inhibitor or factor Xa inhibitors for patients with hemorrhagic diseases	20 (4.2)	Warfarin	46 (4.9)
Peripheral alpha-1 blockers	28 (3.7)	Benzodiazepines with history of falls	16 (3.4)	Amiodarone	40 (4.2)
NSAIDs, nondihydropyridine CCBs and thiazolidinediones with heart failure	14 (1.8)	Beta-blocker in combination with verapamil or diltiazem	14 (2.9)	Spirolactone (>25 mg/day)	26 (2.8)
Digoxin	13 (1.7)	Amiodarone for supraventricular arrhythmia as the first line drug	13 (2.7)	First-generation antihistamines	29 (3.1)
Amiodarone	13 (1.7)	NSAIDs with severe hypertension or severe heart failure	13 (2.7)	NSAIDs with cruor disorder, hypertension, renal insufficiency or heart failure	22 (2.3)
Antipsychotics, first (conventional) and second (atypical) generation	8 (1.1)	Verapamil or diltiazem with NYHA class III or IV heart failure	12 (2.5)	Narcotic and adjuvant drugs	14 (1.5)

Abbreviations: NYHA, New York Heart Association; PIM, potentially inappropriate medication; PPIs, proton-pump inhibitors.

Table 4 Multivariate analysis of risk factors associated with PIM use

Characteristics	Beers criteria		STOPP criteria		Chinese criteria	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age	1.013 (0.991–1.036)	0.245	1.014 (0.994–1.035)	0.174	0.974 (0.949–0.999)	0.039
Sex	1.257 (0.929–1.699)	0.138	1.232 (0.931–1.630)	0.144	1.050 (0.740–1.491)	0.784
Barthel score ≤60	1.624 (1.094–2.410)	0.016	1.320 (0.935–1.862)	0.115	0.509 (0.309–0.840)	0.008
CCI	0.900 (0.808–1.001)	0.053	0.913 (0.828–1.007)	0.069	1.165 (1.016–1.335)	0.028
No prescribed medications	1.249 (1.185–1.317)	<0.001	1.117 (1.070–1.165)	<0.001	1.200 (1.137–1.268)	<0.001
Length of stay	1.070 (1.022–1.121)	0.004	0.989 (0.954–1.026)	0.555	0.972 (0.935–1.011)	0.153

Abbreviations: CCI, Charlson Comorbidity Index; PIM, potentially inappropriate medication; STOPP, Screening Tool of Older Persons' Prescriptions.

and off-label use of PPIs, and even abuse of PPIs, are very common worldwide.[37] However, one study reported that underprescribing of PPIs was characterized by older age and greater burden of comorbidity and polypharmacy.[38] In our study, only medications data during hospitalization (≤30 days) were analyzed. So, PIM use of PPIs was defined as using PPIs in the hospital and recommendations to continue use after discharge from the hospital without specific indications.[19] This may be a possible reason for the high prevalence of PIM use of PPIs. Even so, clinical rational use of PPIs should be emphasized among the relevant clinical departments, clinicians and pharmacists. The difference of the most commonly encountered PIM between the Chinese criteria (clopidogrel) and the other two criteria (PPIs) may be a reason for the low concordance.

The use of benzodiazepines was listed in the top three by all three sets of criteria even with different definitions of PIM use. In the updated STOPP criteria of 2014, benzodiazepines prescribed for ≥4 weeks or prescribed for patients who were at high risk for falls were categorized as PIMs. In the updated Beers criteria of 2015, the use of all benzodiazepines, nonbenzodiazepine, benzodiazepine receptor agonist hypnotics were categorized as PIMs. The definition in the Chinese criteria was the same as in the Beers criteria except for zopiclone. Benzodiazepines were also frequent PIMs detected by the Beers and the STOPP criteria in previous studies.[25,26,39,40] The use of benzodiazepines has been reported to be associated with increased risks of prolonged sedation, confusion, impaired balance, falls and road traffic accidents in the elderly.[41–43] Various psychological/behavioral therapies have been used successfully to treat older adults with insomnia and were suggested as the initial treatment intervention.[44] If unavoidable, pharmacologic treatment of insomnia in the elderly requires joint decision-making between the health care provider and patient, balancing benefits vs risks, optimizing dosing and scheduling of drugs and monitoring for efficacy and side effects.

PIM-associated factors varied among the three sets of criteria. Generally, the results of multivariate analysis showed that the number of drugs taken was the most strongly associated independent risk factor for prescribing PIM according to all three criteria, which was consistent with most previous studies.[45–51] Usually, polypharmacy was defined as taking ≥5 drugs and extreme polypharmacy ≥10 drugs.[19] The median (IQR) number prescribed medications in this study was as high as 10 (8–12.5). What's more, the proportion of patients with polypharmacy and extreme polypharmacy were 91.9% and 43.7%, respectively, which were higher than those of previous studies.[19,52] Polypharmacy has become a major problem in the elderly leading to adverse drug events, compliance issues and higher costs.[53,54] We suggested using explicit criteria to reduce unnecessary medications and performing medication reconciliation carefully for elderly patients taking multiple medications by the geriatrician or the pharmacist.

Several limitations of this study should be noted. First, it was a retrospective observational study conducted at a single tertiary hospital in China in specific departments. Therefore, our results may not be applicable to other countries. Second, explicit criteria had some controversial issues,[55] and outcomes resulting from PIMs such as adverse drug reactions, readmissions and mortality detected by three sets of criteria were not compared. So we cannot figure out which tool is best to measure prescription quality. Third, we did not measure omission of necessary drugs. Fourth, the application of the STOPP criteria version 1 in the elderly has been reported to improve prescribing quality, clinical, humanistic and economic outcomes.[45,56] Whether interventions based on the Chinese criteria, the Beers criteria and STOPP criteria version 2 resulted in clinically significant improvements needs further research.

Conclusion

The outcomes from the present study showed a high occurrence of polypharmacy and PIM use in elderly inpatients in China. The number of prescribed medications was the most associated independent risk factor for PIM use by all three criteria. The Chinese criteria had the highest detection rate for assessing PIM of older adults in China but a poor concordance with non-region-specific criteria. Country-specific and non-country-specific criteria should be used in complementary ways.

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Author contributions

This study was conceived and designed by XC and LL. The data acquisition, statistical analysis, article drafting and revising were performed by ZM and CZ. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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