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Prevalence and risk factors of self-reported adverse drug events in elderly co-morbid patients in northeastern China: a cross-sectional study

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Abstract

Background Older adults are vulnerable to adverse drug events given the pharmacokinetic and pharmacodynamic changes that coming with ageing, as well as they often take multiple medications for their chronic health conditions, especially older co-morbidities. ADEs can cause unnecessary emergency department visits and hospitalization, which contribute to financial burden and decreased quality of life. This study aims to investigate the prevalence of adverse drug events in elderly co-morbid patients in Liaoning province and explore its risk factors, in order to ensure medication safety in elderly patients.

Methods This was a cross-sectional study that enrolled elderly patients with co-morbidities, and the data were collected by nurses using a structured interview method for elderly patients with multimorbidity. Risk factors for patient-reported adverse drug events were identified by univariate and logistic regression analyses.

Results A total of 329 elderly patients were enrolled, among whom 169 were females, with an age ranging from 61 to 90 years. 205 participants (62.3%) had 462 "possible-probable-certain" adverse drug events, and 156 (47.4%) experienced two or more self-reported adverse drug events concurrently. The logistic regression analysis included four variables: female (OR = 2.194, 95% confidence interval 1.281–3.760, $P = 0.004$), numbers of daily drugs > 12 (OR = 2.257, 95% confidence interval 1.254–4.061, $P = 0.007$), history of fall within 1 year (OR = 3.106, 95% confidence interval 1.112–8.674, $P = 0.031$), and medication noncompliance (OR = 3.768, 95% confidence interval 1.535–9.249, $P = 0.004$).

Conclusion Patient-reported adverse drug events are more prevalent in older co-morbid patients in Liaoning province. Female, numbers of daily drugs, fall history with 1 year and poor medication compliance were significantly and independently associated with adverse drug events. These findings may provide informative interventions for the medication management in elderly patients living with multimorbidity.

Keywords Co-morbidities, Adverse drug events, Medication safety, Risk factors, Prevalence

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Introduction

China has the largest elderly population in the world, and the proportion of the elderly population is still growing rapidly. Recent data of the 7th National Census Bulletin in 2020 [1] shows that the population aged 60 and above in China accounts for 18.7% of the total population, with Liaoning Province ranking the first in the country with this figure of 25.72%. The chronic health problems closely related to aging have become a hot issue. Older adults often suffer from multiple chronic diseases at the same time and rely on medications to control symptoms, so multiple medication use is common among older adults, which can significantly increase the risk of adverse drug events caused by drug interactions [2–4]. Additionally, the pharmacokinetic and pharmacokinetic changes that occur in the elderly with physiological aging, make the elderly more susceptible to adverse drug events (ADEs) [5, 6]. ADEs in older adults can lead to an increase in drug-related hospitalization [4, 7] and unnecessary emergency department visits [8, 9], which contribute to increased medical cost [10], as well as increase the risk of geriatric syndrome [11], induce adverse social outcome and adverse medication management outcome [12], reduce the quality of life [13], and even cause death [14], so medication safety in the elderly population should be given continuous attention.

An effective way to prevent ADEs is to use a well-organized risk assessment to identify populations to at high risk of ADEs so that additional medication management services can be delivered to this group. Studies conducted in different countries have assessed which factors are associated with a higher risk of ADEs in the ambulatory [15, 16], in hospitalized patients [11, 17], in older community-dwelling patients [11, 15, 16, 18, 19], and in nursing home [3]. What's more, Zhou and Rupa reviewed categorization of risk factors for ADE, and grouped them into five main categories: patient-related, disease-related, medication-related, health service related, and genetics-related [20]. However, based on the special cultural background of China, where older adults may take chemical drugs, traditional Chinese medicines (TCM), and health supplements concurrently, as well as health conditions specific to older adults, such as frailty, limited ability to perform activities of daily living, and polypharmacy, it is unclear about the impact on the prevalence of adverse drug events in older adults with co-morbidities in the northeastern China. The aims of this study are to investigate the prevalence of adverse drug events in elderly comorbid outpatients in Liaoning province and to explore its risk factors, in order to help healthcare professionals to identify the population at high risk of adverse drug events, and provide additional monitoring and early prevention measures to ensure medication safety in elderly patients.

Methods

Study design and population

In this study, a cross-sectional survey was conducted. Geriatric outpatients at the First Hospital of China Medical University from October 2019 to June 2020 were recruited for the study using a convenience sampling method. The inclusion criteria were as follows: (1) those aged 60 years or above, (2) those who voluntarily participated in this study, (3) those with at least two chronic non-communicable diseases, as diagnosed by a physician according to diagnostic criteria, (4) those with a regular medication taking (>4 weeks of continuous medication use) in community, and the medications used included prescribed, over-of-counter (OTC), traditional Chinese medicines and vitamin as well as supplements. The exclusion criteria were as follows: (1) those who could not participate in this study due to health status or other reasons, (2) tumor patients undergoing anticancer treatment, and (3) those with cognitive impairment or mental illness and those who were unable to communicate normally.

Measures

Demographic & health status-related variables

Demographic data included gender, age, weight, height, BMI (body mass index, calculated from the formula weight/height^2); socioeconomic data included health insurance, marital status, living status, education level, pre-retirement occupation. Lifestyle data were also collected, such as smoking and alcohol consumption. Health status data were comprised of hospital admission within 3 months, function in activities of daily living, falls within 1 year, and frailty. Frailty was scored by the frailty questionnaire (FRAIL scale [21]); function in activities of daily living was assessed by the Barthel index. The disease diagnosis of each participant was obtained through a combination of interviews and review of medical records. The medical records included information on drug allergies, the patient's previous visits to the doctor, the repeat and acute prescriptions, the results of various examinations, and the doctors' instructions and ongoing medical conditions.

Data on medications

Medication list was used to collect data on medications taken in the past 4 weeks included prescribed, OTC, traditional Chinese medicine, vitamin and supplements. Names of drugs, dosage, frequency and length of use were also collected. The researcher explained the definition of medication adherence and outlined some common medication non-adherent behaviors to the participants during the interview, and the participants self-assessed their medication adherence based on their own medicine-taking behaviors, which were classified as poor, fair, and good.

Identifying and assessing the presence of ADE.

ADE was defined in this study as "an adverse outcome that occurs while a patient is taking a drug, but is not or not necessarily attributable to it" [22], includes harm caused by the drug (adverse drug reactions and overdoses) and harm from the use of the drug (including dose reductions and discontinuations of drug therapy) [23]. In this study, participants received a structured interview began with a general question "have you experience any side effects or any other problems from the drugs you were taking in the previous 4 weeks?" and then a questionnaire with a list of 42 patient-reported symptoms categorized by body system was used to detect potential ADE [24]. For any symptoms, if the participant reported yes, 8 additional questions followed to assess the symptoms, including (1) do you belief that the symptom was related to your drugs, (2) which drug or drugs do you think caused this symptom, (3) in the past 4 weeks, how often did you have the symptom—never / rarely / occasionally / frequently / almost consistently (4) how do you rate the severity of the symptoms at the worst—none / mild/ moderate / severe / very severe, (5) how much did the symptom interfere with your daily activities?--- not at all/ a little bit/ somewhat/ quite a bit / very much, (6) has this symptom gone away by now or improved, (7) what action did you take in relation to this symptom during the past 4 weeks, and (8) Do you think there are other reasons for your experiencing this symptom (other than your medication).

Patient-reported symptoms were reviewed by a physician with expertise in geriatric and a pharmacist independently to determine the symptom as an ADE or not according to World Health Organization Uppsala Monitoring Centre (WHO-UMC) [25], which is a causality criterion to gauge the causal link between the symptom to a drug in terms of 6 levels of certainty (certain, probable/ likely, possible, unlikely, conditional/ unclassified, assessable/unclassifiable). The symptom was classified as an ADE if it was determined as possible, probable or certain categories.

Procedure

This study was approved by the Medical Science Research Ethics Committee of the First Hospital of China Medical University (No. 2018 – 266), and the study subjects signed the informed consent form before the study started. Face-to-face structured interviews were used to collect information from elderly patients when they consulted at the geriatric outpatient. Standardized trained nurses interviewed the study subjects according to the questionnaire and completed the questionnaire based on the information provided by the elderly about their medication, their feelings and experiences during the medication taking period. The brown bag method was used to clarify the patients' medication list [6]. The elderly were asked to bring all of their current medications, including prescribed, OTC, herbal medications and supplementary to their health care visit. After information collection, a geriatrician and a pharmacist performed back-to-back to determine the causal relationship between the drug intake and the patient-reported ADE. For inconsistent results, a third clinical pharmacist was invited to determine the results.

Statistical analysis

IBM SPSS 21.0 was applied for statistical analysis, and the data were statistically described using means, standard deviations, medians, percentages, and rates. The data between two groups with and without adverse events were compared, and the t-test was used for measurement data obeying normal distribution and the rank sum test for those obeying non-normal distribution; the count data were analyzed by $\chi 2$ test or Fisher's exact test. Univariate analysis was applied to screen variables with $P < 0.2$, and further binary logistic regression analysis was applied to determine the risk factors for the occurrence of "probable and certain" adverse drug events in elderly co-morbid patients, and the OR values together with 95% confidence interval (CI) of each factor were counted. The Hosmer-Lemeshow goodness-of-fit test was used to evaluate the calibration of the model, and the area under the subject operating characteristic curve (AUROC) was used to evaluate the discrimination. Sensitivity and specificity, and Youden's Index were also calculated on the data.

Results

Characteristics of the subjects

A total of 340 questionnaires were distributed and data collection was interrupted by 11 people due to discomfort ($n = 6$) or the need for physical examination ($n = 5$). 329 elderly co-morbid patients with an age ranging from 61 to 90 years, (mean 72.67 ± 8.233 years), 169 (51.4%) were female, 156 (47.4%) had a BMI of ≥ 24 kg/m^2, 126 (38.3%) had been hospitalized within 3 months, and 26 (7.9%) had fall history within 1 year. Based on the Frail Scale and Barthel index assessment, 41.03% were in the frailty stage with a score of ≥ 3, and 21.28% had limited ability to perform daily activities. The characteristics were shown in Table 1. The analysis of the disease status of the study population revealed that the number of chronic conditions was 2–11 /subject (the median number was 4). The five most common chronic diseases were hypertension ($n = 234$, 71.1%), coronary heart disease ($n = 232$, 70.5%), hyperlipidemia ($n = 151$, 45.9%), diabetes mellites ($n = 127$, 38.6%) and stroke ($n = 117$, 35.6%).

Table 1 Characteristics of ADEs in older comorbidity patients(*N* = 329)

Variable	min-max/*N*(%)	Variable	Min-max/*N*(%)
Age	61–90 Y	Use of alcohol	
60–69 Y	141(42.9)	No	282(85.7)
70–79 Y	108(32.8)	Drinking	47 (14.3)
≥ 80 Y	80 (24.3)	Smoking	
Gender		No smoker	273(83.0)
Female	169(51.4)	Smoker	56(17.0)
Male	160(48.6)	BMI	
Marital status		≤18.4	26(7.9)
Married	218(66.3)	18.5–23.9	147(44.7)
Divorced/widowed	111(33.7)	≥24	156(47.4)
Educational level		Fall within 1 year	
Primary school or less	158(48.0)	N	303 (92.1)
Junior high school	93(28.3)	Y	26 (7.9)
High school	35(10.6)	Admission in preceding 3 months	
College or above	43(13.1)	N	203(61.7)
Living status		Y	126(38.3)
With spouse	172(52.3)	ADL	
With daughter/son	64 (19.5)	No assistance	259(78.7)
With spouse and daughter/son	46(14.0)	Assistance with ≥ 1 ADL	70 (21.3)
		Frailty	
Alone	42 (12.8)	No	58(17.6)
With others	5 (1.5)	Pre-frailty (1–2)	136(41.3)
Medical payment		Frailty (≥3)	135(41.0)
Medical insurance	286(86.9)	Medication compliance	
Self-paying	5(1.5)	Poor	203(61.7)
Free	38(11.6)	Fair	67(20.4)
Pre-retirement occupation		Good	59(17.9)
Doctor/nurse	11 (3.3)	Use of TCM	
Teacher	37 (11.2)	No	104(31.6)
Worker	85 (25.8)		
Farmer	69(21.0)	Yes	225(68.4)
Other	127(38.6)	Types of daily drug	1–17
Family income, CNY		<5	82(24.9)
<5000	166(50.5)	5–10	210(63.8)
5000–9999	99(30.1)	>10	37(11.2)
10,000–14,999	48(14.6)	Numbers of daily drug	1–51
≥ 15,000	16(4.9)	≤12	162(49.2)
Numbers of chronic conditions	2–11	>12	167(50.8)
2–5	299(69,6)	Time interval	
6–9	94(28.6)	No	200(60.8)
≥ 10	6(1.8)	Yes	129(39.2)

Adverse drug events and related drugs

Polypharmacy is common among older persons, with up to 75% of older persons taking five or more medications. Older people have a complex medication regimen, taking prescription medications, as well as OTC, proprietary Chinese medicines and herbal remedies. The maximum number of pills taken per day was 51 (median 12.5), 60.8% of older people took multiple medications without time intervals, and 225 participants (68.4%) took TCM. Poor adherence to medication was reported by 206 subjects (61.7%).

One clinical pharmacist and one geriatrician determined that 205 participants (62.3%) had 462 "possible-probable-certain" adverse drug events, among which 167 were "probable-certain" adverse drug events. 156 participants experienced two or more symptomatic adverse drug events concurrently. As shown in Table 2, the most common patient-reported adverse drug events were dizziness/headache, fatigue, palpitations, dyspepsia, loss of appetite, nausea/vomiting and insomnia.

Risk factors for adverse drug events in the elderly

Univariate analysis of risk factors for ADEs shows that gender, BMI, health insurance, living status, pre-retirement occupation, family income per month, function in activity of daily living, numbers of comorbidities, numbers of daily drugs and medication compliance were associated with increased risk of ADEs, with *P*-value<0.05. Then, binary logistic regression analysis was performed with the presence of "certain and probable" ADE as the dependent variable and those variables with *P*-value<0.2 in univariate analyses as independent variables. The results showed that gender (female), number of daily drug (< 12), history of fall within 1 year, and medication noncompliance were independent risk factors for ADEs in elderly co-morbid patients (Fig. 1).

Hosmer-Lemeshow test was used to evaluate the goodness of fit of the model, with $X^2 = 6.276$, $P = 0.616$ ($P > 0.05$), indicating no evidence of statistically significant difference between the observed and expected values. As Fig. 2 showed, the apparent discrimination of the model was AUC 0.718 (95% CI 0.649 to 0.788). The Youden's index (YI), which is the cut-off point when (sensitivity + specificity-1) is maximum, was chosen as the cut-off value. By calculation, when the Youden's index was 0.431, the sensitivity and the specificity were 64.4% and 78.7% respectively.

Discussion

In this descriptive study, the prevalence of patient-reported adverse drug events in older co-morbidity patients was 62.3%, which is higher than the report issued by the National Adverse Drug Reaction Monitoring Center. The National Adverse Drug Reaction

Table 2 The common patient-reported ADEs in the last 4 weeks

ADE	*N* (%)	Main Therapeutic drug associated with ADE
Dizzy, headache	54 (16.41)	Calcium channel blockers (e.g., nifedipine) Beta-blocking agents (e.g., bisoprolol, atenolol, metoprolol) Psycholeptics (e.g., benzodiazepine derivatives) Antianginal agent (e.g., trimetazidine, isosorbide mononitrate)
Fatigue, tiredness	40 (12.16)	Beta-blocking agents (e.g., bisoprolol, atenolol, metoprolol) ARBs (e.g., valsartan)
Loss of appetite, indigestion or heartburn	30 (9.12)	Antithrombotic agents (e.g., aspirin, warfarin) Anti-inflammatory and antirheumatic products (e.g., ibuprofen) Anti-diabetes agents (e.g., acarbose, metformin)
Nausea, vomiting,	25 (7.60)	Diuretics (e.g., furosemide) Magnesium supplementation Alkaloid (e.g., colchicine) Anti-diabetes agents (e.g., metformin)
Unstable blood sugar level	21 (6.38)	Anti-diabetes agents (e.g., insulin)
Bruise easily	18 (5.47)	Antithrombotic agents (e.g., aspirin, warfarin)
Low blood pressure	17 (5.17)	Antihypertensives
Dry mouth	17 (5.17)	Diuretics (e.g., furosemide)

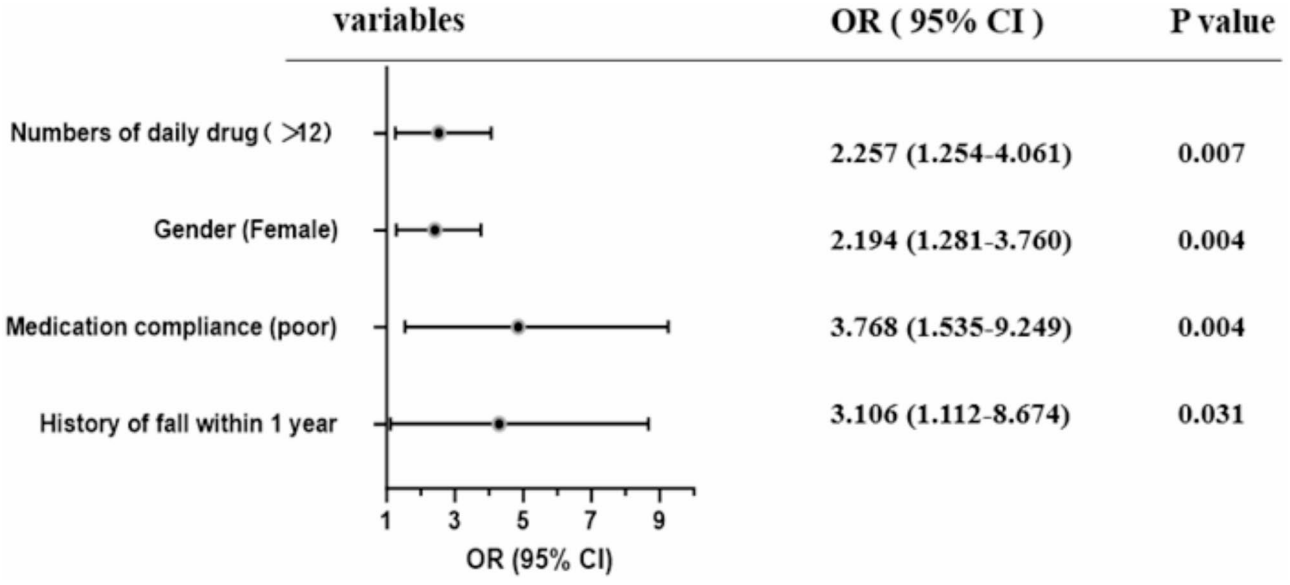

Fig. 1 Forest plot for binary logistic regression of risk factors for ADE

Monitoring Annual Report (2020) showed that in 2020, 30.3% of the reports were related to the elderly in the national ADR monitoring network [26]. Additionally, in this study, nearly a half of the elderly patients had two or more potential adverse drug events concurrently and the most common patient-reported adverse drug events were subjective symptoms, such as dizziness/headache, fatigue, palpitations, dyspepsia, loss of appetite, nausea/vomiting and insomnia. Adverse drug events experienced by patients, especially subjective symptomatic adverse drug events, are often underestimated or underreported [27]. Healthcare professionals tend to pay more attention to serious adverse drug events; however, "non-alarming" adverse drug events often have greater impacts on patients' daily lives [28] and may lead to poor medication adherence and discontinuation of their medications, which can seriously affect the safety of medication and therapeutic outcomes [16, 29]. Therefore, it is essential for patients to participate in the monitoring and reporting the adverse drug events, which not only enables healthcare professionals to be more well-informed about their patients' medication use, but also improves patients' medication literacy.

Further investigation was performed to identify risk factors associated with patient-reported ADEs in comorbidity elder patients, and found that the main risk factors were numbers of chronic medical conditions, numbers of daily drugs, female, medication noncompliance, and history of fall within 1 year. These risk factors consisted of sociodemographic-related factor, medication-related

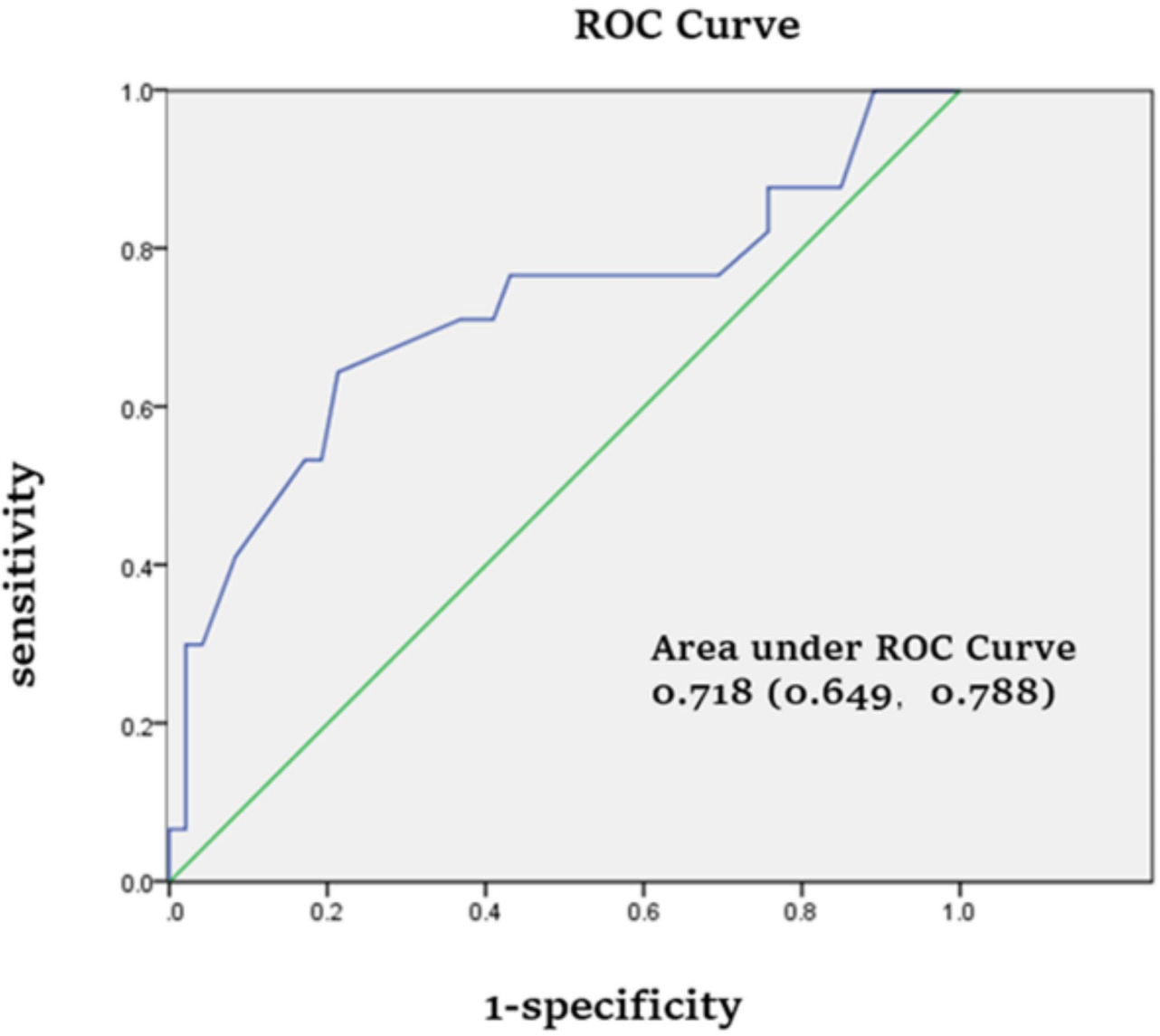

Fig. 2 Receiver operating characteristic (ROC) curve for logistic regression

factors and health condition factor, which manifested that the complexity of the adverse drug events in the elderly population. In spite of the fact that it is impossible to change socio-demographic characteristics (e.g., gender), patient-related factors (e.g., numbers of medication taken, medication compliance, and fall) can be intervened to prevent the risk of adverse drug events and to protect medication safety in elderly patients.

Both pharmacokinetics and pharmacodynamics undergo significant changes with advancing age. Pharmacokinetic changes include decreased renal excretion and hepatic clearance as well as an increase in the volume of distribution of fat-soluble drugs (and therefore a prolongation of the elimination half-life), while pharmacodynamic changes involve changes in sensitivity to several classes of drugs, such as anticoagulants, cardiovascular medications, and psychotropic medications [5]. At the same time, the pharmacokinetics and pharmacodynamics of drugs likewise show gender differences [30]. Compared to males, females have greater risk of adverse events, which is consistent with many studies [15, 20, 31–33]. Biological differences between males and females affect the pharmacodynamics and pharmacokinetics of drugs, especially for the latter [32]. Gender can affect the bioavailability, distribution, metabolism and excretion of drug through different mechanisms, resulting in gender differences in pharmacokinetics [30]. Therefore, for older adults on long-term medications, especially at the initial stages of the treatment and drugs with narrow therapeutic index, sex-related differences should be fully considered to improve the effectiveness and safety of the medications.

The number of daily drug was a risk factor for reported ADE in older co-morbid patients, as supported by previous studies worldwide [20, 34, 35]. Older people are taking multiple medications for several chronic conditions, thereby increasing the risk of adverse drug interactions that lead to adverse drug events. Studies showed that participants with potentially inappropriate prescribing were more likely to have an ADE [3, 14, 36]. To reduce potentially inappropriate prescribing, healthcare providers were recommended to monitor patients' current medication lists and eliminate unnecessary medications to reduce the risks of adverse drug events, as well as the financial hardship [6, 37]. Registered nurses (RNs) were not only drug distributors, but also "vigilant intermediaries" in drug therapy [38]. In other words, RNs may prompt conversations with patients and their families to clarify medication lists and assess potential adverse events, with the aim of encouraging patients to participate in medication safety [6, 39]. Furthermore, effective communication with other healthcare workers could promote information sharing within multidisciplinary team members to deprescribe and ensure medication safety [6].

Medication noncompliance can increase the risk of adverse drug events, which is matched with previous studies [20, 40, 41]. To improve medication adherence in older adults, several studies have been conducted to examine the effects of behavioral interventions, including reminder devices, large-print labels, and individual or group education sessions [42]. Additionally, medication compliance was associated with medication knowledge [40, 43]. Previous qualitative studies indicated that both the elderly and their families lacked knowledge about drug indicators, actions and potential adverse events, which impeded their ability to recognize adverse drug events during medication use and engage in shared decision-making processes regarding their treatment [44–46]. RNs could build effective communication with patients and their families, for hearing their needs and providing education on medication knowledge, which may promote understanding of and compliance to medications.

The presence of fall history may increase the risk of adverse drug events for elder patients, which agreed with the findings of other studies [11, 47]. In this study, fall history is an independent risk factor for the occurrence of adverse drug events, and fall is also one of the items in the list of the patient-reported symptomatic ADE questionnaire. Published literatures have shown a significant association between the risk of fall and fall risk increasing drugs (FRIDs) [48–51], which are commonly used in the elderly, such as hypnotics, antipsychotics, antiparkinsonian medications, antidepression, antihypertensive drugs, antiarrhythmic drugs and glucose control medications. Additionally, a previous fall is also recognized as one of predictors of falls [47, 52, 53]. Nurses play important roles in implementing fall prevention programs [39, 51, 52, 54, 55], which include patient assessment, communicating with interdisciplinary team of healthcare workers, conducting fall preventing education to promote fall risk awareness and knowledge for the older individuals and their families, instructing older adults in exercise and vitamin D supplementation, and enhancing monitoring for the patients taking FRIDs, to secure a safer environment for the older adults and achieve fall prevention goals.

This study had some limitations. Firstly, the sample size was relatively small and from one single medical center, which may have resulted in selection bias that limits the generalizability of the findings. Further investigations will be conducted at different regions in Liaoning Province. Additionally, patient-reported ADE relies on patients' accurate recall of events and patients' knowledge on medication use, which will help them to self-monitor for the potential ADEs and to discriminate effectively between ADEs and their medical conditions. Healthcare professional should educate the patients on their medications use and identifying ADEs, to improve the awareness of patient participation in medication safety monitoring.

Conclusions

Patient-reported adverse drug events are more prevalent in older co-morbid patients in Liaoning province. Female, numbers of daily drugs, fall history with 1 year and poor medication compliance were significantly and independently associated with adverse drug events. These findings may provide informative interventions for nurses who work with interdisciplinary team to secure medication safety for elderly patients living with multimorbidity.

Abbreviations

ADE	Adverse Drug Event
TCM	Traditional Chinese Medicine
OTC	Over-the-counter Medications
BMI	Body Mass Index
WHO-UMC	World Health Organization Uppsala Monitoring Centre
AUROC	The Area Under the Receiver Operating Characteristic Curve
AUC	Area Under the Curve
RN	Registered Nurse
FRIDs	Fall Risk Increasing Drugs
OR	Odds Ratio
95%CI	95% Confidential Intervals
YI	The Youden's Index

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-025-05732-z.

Supplementary Material 1

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Author contributions
DQ Wang and AP Wang, conceptualized and designed the study. DQ Wang and X Meng, performed the data collection and analysis. DQ Wang drafted the manuscript. DQ Wang, L Liu and AP Wang read and revised the manuscript. All authors approved the final manuscript as submitted.

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Data availability
The datasets generated and analyzed during the current study are not publicly available due to privacy protection and ethical considerations. But they are available from the corresponding author upon reasonable request.

Declarations

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Ethic approval and consent to participate
This study was approved by the Medical Science Research Ethics Committee of the First Hospital of China Medical University (No. 2018 – 266), and carried out in accordance with the relevant guidelines and regulations of Declaration of Helsinki. All the study subjects signed the informed consent form before the study started.

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References

1. Seventh Population Census Leading Group Office of the State Council. Major Figures on 2020 Population Census of China.
2. Ahmed B, Nanji K, Mujeeb R, Patel MJ. Effects of Polypharmacy on adverse drug reactions among geriatric outpatients at a Tertiary Care Hospital in Karachi: a prospective cohort study. PLoS ONE. 2014;9:e112133.
3. Lao CK, Ho SC, Chan KK, Tou CF, Tong HHY, Chan A. Potentially inappropriate prescribing and drug–drug interactions among elderly Chinese nursing home residents in Macao. Int J Clin Pharm. 2013;35:805–12.
4. Crescioli G, Bettiol A, Bonaiuti R, Tuccori M, Rossi M, Capuano A, et al. Risk of Hospitalization Associated with Cardiovascular medications in the Elderly Italian Population: a Nationwide Multicenter Study in Emergency Departments. Front Pharmacol. 2021;11:611102.
5. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Brit J Clin Pharma. 2004;57:6–14.
6. Kim J, Parish AL. Polypharmacy and Medication Management in older adults. Nurs Clin North Am. 2017;52:457–68.
7. Oscanoa TJ, Lizaraso F, Carvajal A. Hospital admissions due to adverse drug reactions in the elderly. A meta-analysis. Eur J Clin Pharmacol. 2017;73:759–70.
8. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US Emergency Department visits for outpatient adverse drug events, 2013–2014. JAMA. 2016;316:2115.
9. Phoemlap P, Vadcharavivad S, Musikatavorn K, Areepium N. Prevalence and factors associated with preventable drug-related emergency department visits (DREDp) in elderly patients. BMC Emerg Med. 2024;24:197.
10. Gyllensten H, Rehnberg C, Jönsson AK, Petzold M, Carlsten A, Andersson Sundell K. Cost of illness of patient-reported adverse drug events: a population-based cross-sectional survey. BMJ Open. 2013;3:e002574.
11. Lattanzio F, Laino I, Pedone C, Corica F, Maltese G, Salerno G, et al. Geriatric conditions and adverse drug reactions in Elderly hospitalized patients. J Am Med Dir Assoc. 2012;13:96–9.
12. Adverse Outcomes of Polypharmacy in Older People. Systematic review of reviews. J Am Med Dir Assoc. 2020;21:181–7.
13. Mhatre SK, Sansgiry SS. Assessing a conceptual model of over-the-counter medication misuse, adverse drug events and health-related quality of life in an elderly population. Geriatr Gerontol Int. 2016;16:103–10.
14. Cahir C, Bennett K, Teljeur C, Fahey T. Potentially inappropriate prescribing and adverse health outcomes in community dwelling older patients. Br J Clin Pharmacol. 2014;77:201–10.
15. Field TS, Gurwitz JH, Harrold LR, Rothschild J, DeBellis KR, Seger AC, et al. Risk factors for adverse drug events among older adults in the ambulatory setting. J Am Geriatr Soc. 2004;52:1349–54.
16. Pedrós C, Formiga F, Corbella X, Arnau JM. Adverse drug reactions leading to urgent hospital admission in an elderly population: prevalence and main features. Eur J Clin Pharmacol. 2016;72:219–26.
17. Amanda Lavan J, Eustace D, Dahly E, Flanagan P, Gallagher S, Cullinane et al. Incident adverse drug reactions in geriatric inpatients: a multicentred observational study. Therapeutic Adv Drug Saf. 2018;9.
18. Ye L, Yang-Huang J, Franse CB, Rukavina T, Vasiljev V, Mattace-Raso F, et al. Factors associated with polypharmacy and the high risk of medication-related problems among older community-dwelling adults in European countries: a longitudinal study. BMC Geriatr. 2022;22:841.
19. Hanlon JT, Perera S, Newman AB, Thorpe JM, Donohue JM, Simonsick EM, et al. Potential drug-drug and drug-disease interactions in well-functioning community-dwelling older adults. J Clin Pharm Ther. 2017;42:228–33.
20. Zhou L, Rupa AP. Categorization and association analysis of risk factors for adverse drug events. Eur J Clin Pharmacol. 2018;74:389–404.
21. Morley JE, Vellas B, Van Abellan G, Anker SD, Bauer JM, Bernabei R, et al. Frailty Consensus: a call to action. J Am Med Dir Assoc. 2013;14:392–7.
22. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356:1255–9.
23. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. Ann Intern Med. 2004;140:795.
24. Cahir C, Wallace E, Cummins A, Teljeur C, Byrne C, Bennett K, et al. Identifying adverse drug events in Older Community-Dwelling patients. Ann Fam Med. 2019;17:133–40.
25. World Health Organization (WHO). Uppsala Monitoring Centre. The use of the WHO-UMC system for standardized case causality assessment.
26. National Center for Adverse Drug Reaction Monitoring (NCADRM). National Adverse Drug Reaction Monitoring Annual Report. (2020).
27. Basch E, Jia X, Heller G, Barz A, Sit L, Fruscione M, et al. Adverse symptom event reporting by patients vs clinicians: relationships with clinical outcomes. J Natl Cancer Inst. 2009;101:1624–32.
28. Schoenmakers TWA, Teichert M, Wensing M, De Smet PAGM. Evaluation of potentially drug-related patient-reported common symptoms assessed during clinical medication reviews: a cross-sectional observational study. Drug Saf. 2017;40:419–30.
29. Thomsen LA, Winterstein AG, Søndergaard B, Haugbølle LS, Melander A. Systematic review of the incidence and characteristics of preventable adverse drug events in ambulatory care. Ann Pharmacother. 2007;41:1411–26.
30. Farkouh A, Riedl T, Gottardi R, Czejka M, Kautzky-Willer A. Sex-related differences in Pharmacokinetics and Pharmacodynamics of frequently prescribed drugs: a review of the literature. Adv Ther. 2020;37:644–55.
31. O'Mahony Denis O'ConnorM, Noelle E, Joseph B, Stephen P, Mirko G. Paul. The adverse drug reaction risk in older persons (ADRROP) prediction scale: derivation and prospective validation of an ADR risk assessment tool in older multi-morbid patients. Eur Geriatr Med. 2018;9.
32. Schwartz JB. The influence of sex on pharmacokinetics. Clin Pharmacokinet. 2003;42:107–21.
33. Zopf Y, Rabe C, Neubert A, Gaßmann KG, Rascher W, Hahn EG, et al. Women encounter ADRs more often than do men. Eur J Clin Pharmacol. 2008;64:999–1004.
34. Green JL, Hawley JN, Rask KJ. Is the number of prescribing physicians an independent risk factor for adverse drug events in an elderly outpatient population? Am J Geriatr Pharmacother. 2007;5:31–9.
35. Lee JS, Yang J, Stockl KM, Lew H, Solow BK. Evaluation of eligibility Criteria used to Identify Patients for Medication Therapy Management Services: a retrospective cohort study in a Medicare advantage part D Population. JMCP. 2016;22:22–30.
36. Lu W-H, Wen Y-W, Chen L-K, Hsiao F-Y. Effect of polypharmacy, potentially inappropriate medications and anticholinergic burden on clinical outcomes: a retrospective cohort study. CMAJ. 2015;187:E130–7.
37. Halli-Tierney AD, Scarbrough C, Carroll D. Polypharmacy: evaluating risks and Deprescribing. Am Fam Physician. 2019;100:32–8.

38. Johansson-Pajala R-M, Jorsäter Blomgren K, Bastholm-Rahmner P, Fastbom J, Martin L. Nurses in municipal care of the elderly act as pharmacovigilant intermediaries: a qualitative study of medication management. Scand J Prim Health Care. 2016;34:37–45.
39. Kaufman G. Polypharmacy: the challenge for nurses. Nurs Stand. 2016;30:52–60.
40. Lai X, Zhu H, Huo X, Li Z. Polypharmacy in the oldest old (≥ 80 years of age) patients in China: a cross-sectional study. BMC Geriatr. 2018;18:64.
41. Hsu KL, Fink JC, Ginsberg JS, Yoffe M, Zhan M, Fink W, et al. Self-reported medication adherence and adverse patient safety events in CKD. Am J Kidney Dis. 2015;66:621–9.
42. Cross AJ, Elliott RA, Petrie K, Kuruvilla L, George J. Interventions for improving medication-taking ability and adherence in older adults prescribed multiple medications. Cochrane Database Syst Rev. 2020;5:CD012419.
43. Pasina L, Brucato AL, Falcone C, Cucchi E, Bresciani A, Sottocorno M, et al. Medication non-adherence among elderly patients newly discharged and receiving polypharmacy. Drugs Aging. 2014;31:283–9.
44. Palagyi A, Keay L, Harper J, Potter J, Lindley RI. Barricades and brickwalls–a qualitative study exploring perceptions of medication use and deprescribing in long-term care. BMC Geriatr. 2016;16:15.
45. Gillespie R, Mullan J, Harrison L. Factors which influence the deprescribing decisions of community-living older adults and GPs in Australia. Health Social Care Comm. 2022;30.
46. Wang D, Meng X, Liu L, Wang A. Views on suspected adverse drug events in older adults with chronic conditions: a qualitative study. Patient Prefer Adherence. 2023;17:2051–61.
47. Dorj G, Nair NP, Bereznicki L, Kelly T-L, Pratt N, Kalisch-Ellett L, et al. Risk factors predictive of adverse drug events and drug-related falls in aged care residents: secondary analysis from the ReMInDAR trial. Drugs Aging. 2023;40:49–58.
48. Seppala LJ, Wermelink AMAT, de Vries M, Ploegmakers KJ, van de Glind EMM, Daams JG, et al. Fall-risk-increasing drugs: a systematic review and Meta-analysis: II. Psychotropics. J Am Med Dir Assoc. 2018;19:e37111–7.
49. de Vries M, Seppala LJ, Daams JG, van de Glind EMM, Masud T, van der Velde N, et al. Fall-risk-increasing drugs: a systematic review and Meta-analysis: I. Cardiovascular drugs. J Am Med Dir Assoc. 2018;19:e3711–9.
50. Seppala LJ, van de Glind EMM, Daams JG, Ploegmakers KJ, de Vries M, Wermelink AMAT, et al. Fall-risk-increasing drugs: a systematic review and Meta-analysis: III. Others. J Am Med Dir Assoc. 2018;19:e3721–8.
51. Just KS, Schneider KL, Schurig M, Stingl JC, Brockmöller J. Falls: the adverse drug reaction of the elderly and the impact of pharmacogenetics. Pharmacogenomics. 2017;18:1281–97.
52. Manirajan P, Sivanandy P, Ingle PV. Enhancing knowledge, attitude, and perceptions towards fall prevention among older adults: a pharmacist-led intervention in a primary healthcare clinic, Gemas, Malaysia. BMC Geriatr. 2024;24:309.
53. Moncada LVV, Mire LG. Preventing falls in older persons. Am Fam Physician. 2017;96:240–7.
54. Ong MF, Soh KL, Saimon R, Wai MW, Mortell M, Soh KG. Fall prevention education to reduce fall risk among community-dwelling older persons: a systematic review. J Nurs Manag. 2021;29:2674–88.
55. Wilson DS, Montie M, Conlon P, Reynolds M, Ripley R, Titler MG. Nurses' perceptions of implementing fall Prevention interventions to mitigate patient-specific fall risk factors. West J Nurs Res. 2016;38:1012–34.

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