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Age- and gender-related differences in drug utilisation and adverse drug reaction patterns among patients in a coronary care unit

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INTRODUCTION This study aimed to examine age- and gender-related differences in the comorbidities, drug utilisation and adverse drug reaction (ADR) patterns of patients admitted to a coronary care unit (CCU).

METHODS The present study was a retrospective cohort study. Two trained physicians independently reviewed the case records of CCU patients over a period of one year (Jan–Dec 2008). The demographic, clinical, and drug prescription data of the patients were analysed according to age group (18–59 years vs ≥ 60 years) and gender.

RESULTS A total of 574 patients were admitted to the CCU during the study period. Of these 574 patients, 65.2% were male, and 48.4% were ≥ 60 years old. No significant gender-based differences were found for the prescription of cardiovascular and non-cardiovascular drugs, and ADR patterns ($p > 0.05$). Male patients aged ≥ 60 years were found to have a higher rate of polypharmacy than those aged 18–59 years ($p = 0.001$). The duration of hospital stay was longer in male than female patients ($p = 0.008$), and the duration of CCU stay was longer for male patients aged ≥ 60 years than males aged 18–59 years ($p = 0.013$). Compared to patients aged 18–59 years, a greater number of patients aged ≥ 60 years were prescribed cardiovascular ($p = 0.006$) and non-cardiovascular drugs ($p = 0.015$). Patients aged ≥ 60 years also had a higher rate of polypharmacy ($p = 0.001$) and ADRs ($p = 0.013$), and a longer duration of CCU stay ($p = 0.013$). Renal ($p = 0.047$) and cutaneous ($p = 0.003$) ADRs were found to be more common in patients aged ≥ 60 years.

CONCLUSION No major gender-related differences were observed in the prescription, drug utilisation and ADR patterns of our study cohort. Higher drug utilisation, ADR rates, and longer duration of CCU stay were noted in patients aged ≥ 60 years.

Keywords: adverse drug reactions, age, coronary care unit, drug utilisation, gender

INTRODUCTION

Cardiovascular diseases (CVDs) have emerged as the leading cause of deaths worldwide. Low- and middle-income countries account for more than 80% of the global burden of CVDs. By 2020, deaths from CVDs are predicted to rise to four million per year in China and almost five million per year in India.[1]

Women tend to be diagnosed at an older age and have more comorbidities, such as diabetes mellitus (DM) and obesity.[2] Although men are more likely to have episodes of myocardial infarction (MI), women who do suffer an episode of MI are more likely to have a second MI, develop heart failure, or suffer subsequent sudden cardiac death.[3] Increasing age, lipid abnormalities, high blood pressure, obesity, DM and smoking are major risk factors for CVDs in both genders.[4] Data from the INTERHEART study indicates that the lower prevalence of acute coronary syndrome (ACS) among women of younger ages (i.e. < 60 years) is largely explained by a lower risk factor burden.[5] Recent data from the National Health and Nutrition Examination Survey has shown that, over the past two decades, the prevalence of MI has increased in women aged 35–54 years, while declining in men of the same age group.[6]

Age and gender inequalities exist in the preventive pharmacotherapy of CVDs, particularly in cholesterol-lowering treatment.[7,8] Previous research has shown a 'treatment-risk' paradox for secondary prevention, whereby patients become less likely to receive appropriate treatment as they advance in age.[9,10] Compared to men, women have been found to be less frequently prescribed both antihypertensive and lipid-lowering drugs.[8,11]

Up to 5% of all hospital admissions are the result of adverse drug reactions (ADRs). It has been reported that patients with adverse drug events spend an average of 2.2 days longer in hospitals.[12] Among the known risk factors for ADRs (e.g. advanced age, polypharmacy, liver and renal disease), female gender has been shown to have a 1.5- to 1.7-fold increased risk of developing an ADR as compared to the male gender.[13,14] The reasons for the age- and gender-related differences observed in ADRs include pharmacokinetic, pharmacodynamic, immunological and hormonal factors, as well as differences in the use of medications in female and elderly (≥ 60 years) patients.

Therapies in critical care settings are challenging due to the coexistence of multiple comorbidities that warrant

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polypharmacy. The interplay of multiple comorbidities and polypharmacy in intensive care settings is a possible risk factor for ADRs, resulting in higher ADR rates than that in out- and inpatient settings.[15] A study by Mohebbi et al documented the rate of ADRs attributed to cardiovascular drugs alone in the coronary care unit (CCU) to be as high as 24%.[16] The authors also found that 22% of ADRs in the CCU were severe ADRs, and that 7% of ADRs were potentially preventable.[16]

In India, there is a paucity of data regarding the age- and gender-related aspects of drug utilisation and ADR patterns in critical care settings. Thus, the objective of the present study was to determine the age- and gender-related differences in the drug utilisation and ADR patterns of patients admitted to the CCU of a tertiary care hospital.

METHODS

The present study was a retrospective cohort study conducted in the CCU of St John's Medical College Hospital, Bangalore, India. The hospital is a 1,200-bedded multispecialty, charitable hospital. The study method employed and the preliminary results on the patterns, predictors and preventability of ADRs that occurred in the CCU of the hospital were reported in our earlier paper.[17] Study approval was obtained from the Institutional Ethical Review Board of St John's Medical College.

The case records of consecutive patients admitted to the CCU from 1 January to 31 December 2008 (i.e. a period of one year) were retrospectively reviewed. Two physicians independently reviewed and extracted relevant data from the case records. Data extracted included the patient's demographic data, existence of comorbid conditions, diagnosis at admission, investigations performed, treatments prescribed, duration of stay in the CCU and hospital, and information on observed ADRs (i.e. organ system involved, suspected drug, reaction time, management and outcome). Data was collected using standardised case record forms. For the purpose of standardisation, we used the established international terminologies of the Anatomical Therapeutic Classification (ATC) for medication,[18] the International Classification of Diseases version 10 for diagnoses[19] and the World Health Organization's definition for adverse drug reaction.[20] The differences observed in the prescription of cardiovascular and non-cardiovascular drugs were analysed. Drugs were classified into different pharmacological groups and subgroups, according to the third and fourth levels of the ATC. Further detailed analysis of the drug data focused on the cardiovascular drugs prescribed based on the ATC classification codes 'B' and 'C'.

Data was analysed according to age (18–59 years vs ≥ 60 years) and gender (male vs female), and stratified according to age in gender (male [18–59 years vs ≥ 60 years] and female [18–59 years vs ≥ 60 years]). Polypharmacy (i.e. ≥ 10 drugs per prescription), duration of CCU stay, and duration of hospital stay were analysed based on age and gender. Renal dysfunction was defined based on the estimated creatinine clearance values that were calculated using the Cockroft-Gault equation – values of 120 mL/min/1.73 m^2 and 100 mL/min/1.73 m^2 were considered normal for men and women, respectively. Descriptive data was presented as mean ± standard deviation (SD), median and interquartile range (IQR), and frequencies. Chi-square test and Mann-Whitney *U* test were appropriately used to compare characteristics between the two genders (male vs female), and between the two age groups (18–59 years vs ≥ 60 years). The Statistical Package for the Social Sciences version 16.0 software (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. A p-value of < 0.05 was considered statistically significant.

RESULTS

In all, 574 consecutive patients were admitted to the CCU of St John's Medical College from 1 January to 31 December 2008. Data on both gender and age were missing for two patients. Of the 572 patients, 373 (65.2%) were male. Among the male patients, 166 (44.5%) were aged ≥ 60 years. Among the 199 female patients, data on age was missing for 3 patients and 3 patients were aged < 18 years. Of the 193 female patients with available and relevant data on age, 108 (56.0%) were aged ≥ 60 years. Among the patients with relevant and complete gender and age data (i.e. 566 patients), 292 (51.6%) patients were aged 18–59 years and 274 (48.4%) were aged ≥ 60 years. A total of 3,832 cardiovascular drugs (mean ± SD = 6.7 ± 2.3) and 1,746 non-cardiovascular drugs (mean ± SD = 3.0 ± 1.9) were prescribed to the 574 patients admitted to the CCU. A total of 142 (24.7%) ADRs were reported, of which 32.4% were cardiovascular and 29.6% involved electrolyte imbalances.

Of all the patients admitted to the CCU during the study period, the incidence of hypertension, DM, renal dysfunction, acute heart failure, chronic obstructive pulmonary disease (COPD) and unstable angina were higher in patients aged ≥ 60 years and in male patients aged ≥ 60 years. Patients aged ≥ 60 years and female patients aged ≥ 60 years had significantly higher rates of non-ST elevation myocardial infarction (NSTEMI). The distribution of the study cohort's comorbidities, based on age and gender, is presented in Table I.

We did not find any gender difference in the number of cardiovascular and non-cardiovascular drugs prescribed. However, male patients aged ≥ 60 years were prescribed significantly more cardiovascular drugs than male patients aged 18–59 years ($p = 0.012$), and female patients aged ≥ 60 years were prescribed significantly more non-cardiovascular drugs than those aged 18–59 years ($p = 0.040$). Prescription of cardiovascular ($p = 0.006$) and non-cardiovascular ($p = 0.015$) drugs were significantly higher in patients aged ≥ 60 years than in patients aged 18–59 years (Table II).

Table III shows the utilisation of cardiovascular drugs in the CCU. A significantly higher number of male patients

Table I. Distribution of comorbidities among patients admitted to the coronary care unit, according to gender and age.

Comorbidity	Gender*		Age*		Male		Female*	
	Male 373 (65.2)	Female 199 (34.8)	18–59 yrs 292 (51.6)	≥ 60 yrs 274 (48.4)	18–59 yrs 207 (55.5)	≥ 60 yrs 166 (44.5)	18–59 yrs 85 (44.0)	≥ 60 yrs 108 (56.0)
Significant† variables								
Hypertension	201 (53.9)	125 (62.8)‡	144 (49.3)	176 (64.2)‡	96 (46.4)	105 (63.3)‡	48 (56.5)	71 (65.7)
Diabetes mellitus	152 (40.8)	96 (48.2)	114 (39.0)	131 (47.8)‡	72 (34.8)	80 (48.2)‡	42 (49.4)	51 (47.2)
Renal dysfunction	74 (19.8)	27 (13.6)	29 (9.9)	71 (25.9)‡	23 (11.1)	51 (30.7)‡	6 (7.1)	20 (18.5)‡
Acute heart failure	73 (19.6)	48 (24.1)	40 (13.7)	79 (28.8)‡	28 (13.5)	45 (27.1)‡	12 (14.1)	34 (31.5)‡
NSTEMI	67 (18.0)	34 (17.1)	39 (13.4)	59 (21.5)‡	32 (15.5)	35 (21.1)	7 (8.2)	24 (22.2)‡
COPD	39 (10.5)	16 (8.0)	18 (6.2)	37 (13.5)‡	12 (5.8)	27 (16.3)‡	6 (7.1)	10 (9.3)
LRTI	38 (10.2)	22 (11.1)	23 (7.9)	36 (13.1)	14 (6.8)	24 (14.5)‡	9 (10.6)	12 (11.1)
Cardiomyopathy	24 (6.4)	10 (5.0)	23 (7.9)	11 (4.0)	15 (7.2)	19 (11.4)	8 (9.4)	2 (1.9)‡
Unstable angina	23 (6.2)	17 (8.5)	14 (4.8)	26 (9.5)	8 (3.9)	15 (9.0)‡	6 (7.1)	11 (10.2)
Hypothyroidism	17 (4.6)	37 (18.6)‡	17 (5.8)	35 (12.8)‡	5 (2.4)	12 (7.2)	12 (14.1)	23 (21.3)
Nonsignificant variables								
STEMI	108 (29.0)	52 (26.1)	84 (28.8)	73 (26.6)	62 (30.0)	46 (27.7)	22 (25.9)	27 (25.0)
Dyslipidaemia	91 (24.4)	45 (22.6)	77 (26.4)	56 (20.4)	54 (26.1)	37 (22.3)	23 (27.1)	19 (17.6)
IHD/Stable angina	65 (17.4)	36 (18.1)	46 (15.8)	55 (20.1)	30 (14.5)	35 (21.1)	16 (18.8)	20 (18.5)
Arrhythmias	40 (10.7)	21 (10.6)	27 (9.2)	34 (12.4)	20 (9.7)	20 (12.0)	7 (8.2)	14 (13.0)
CVA/Old CVA	21 (5.6)	8 (4.0)	15 (5.1)	14 (5.1)	11 (5.3)	10 (6.0)	4 (4.7)	4 (3.7)
Valvular disease	11 (2.9)	9 (4.5)	10 (3.4)	10 (3.6)	5 (2.4)	6 (3.6)	5 (5.9)	4 (3.7)
PTE	8 (2.1)	7 (3.5)	9 (3.1)	6 (2.2)	4 (1.9)	4 (2.4)	5 (5.9)	2 (1.9)

Note: Data is presented as no. (%). *Data on gender and age was missing for 2 patients. Data on age was not available for 3 female patients and 3 female patients were aged < 18 years. †Significant in any one parameter assessed. ‡Statistically significant ($p < 0.05$).
COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident; IHD: ischaemic heart disease; LRTI: lower respiratory tract infection; NSTEMI: non-ST elevation myocardial infraction; PTE: pulmonary thromboembolism; STEMI: ST elevation myocardial infraction

Table II. Differences in the prescription of cardiovascular and non-cardiovascular drugs, according to gender and age.

Parameter	Cardiovascular drugs		p-value*	Non-cardiovascular drugs		p-value*
	Mean ± SD	Median (IQR)		Mean ± SD	Median (IQR)	
Gender			0.772			0.119
Male	6.7 ± 2.3	7 (5,8)		2.9 ± 1.9	3 (2,4)	
Female	6.6 ± 2.4	7 (5,8)		3.1 ± 1.8	3 (2,4)	
Age (yrs)			0.006†			0.015†
18–59	6.4 ± 2.5	6 (5,8)		2.9 ± 1.9	3 (2,4)	
≥ 60	7.0 ± 2.1	7 (6,8)		3.2 ± 1.9	3 (2,4)	
Gender by age						
Male (yrs)			0.012†			0.105
18–59	6.4 ± 2.4	6 (5,8)		2.8 ± 1.9	2 (1,4)	
≥ 60	7.1 ± 2.1	7 (6,8)		3.3 ± 2.0	3 (2,4)	
Female (yrs)			0.154			0.040†
18–59	6.3 ± 2.7	6 (4.5,8)		2.9 ± 1.4	3 (2,4)	
≥ 60	6.8 ± 2.1	7 (5,8)		3.4 ± 1.5	3 (2,4)	

*Mann-Whitney *U* test was used for analysis. †Statistically significant ($p < 0.05$). IQR: interquartile range; SD: standard deviation

were prescribed antiplatelets as compared to female patients ($p = 0.023$). When compared with male patients aged 18–59 years, the prescriptions of antiplatelets ($p = 0.014$), lipid-lowering drugs ($p = 0.01$), and diuretics ($p = 0.001$) were significantly higher among male patients aged ≥ 60 years. Similar results were found when female patients aged 18–59 years were compared with those aged ≥ 60 years; the prescriptions of antiplatelets ($p = 0.007$), lipid-lowering drugs ($p = 0.003$), and diuretics ($p = 0.003$) were significantly higher in the latter. Utilisation of calcium channel blockers (CCBs) was significantly higher in male patients aged ≥ 60 years than in those aged 18–59 years ($p = 0.005$). Female patients aged ≥ 60 years were prescribed significantly more antiarrhythmics than those aged 18–59 years ($p = 0.008$). When compared with patients aged 18–59 years, patients aged ≥ 60 years were prescribed significantly more antiplatelets ($p = 0.001$), diuretics ($p = 0.0001$), and antiarrhythmics ($p = 0.034$). Lipid-lowering drugs ($p = 0.0001$) and beta blockers ($p = 0.015$) were used more frequently in patients aged 18–59 years than in patients aged ≥ 60 years.

Overall, the proportion of patients receiving polypharmacy was significantly higher in patients aged ≥ 60 years than in those aged 18–59 years ($p = 0.001$). Male patients aged ≥ 60 years also had higher rates of polypharmacy than male patients aged 18–59 years ($p = 0.001$) (Table IV).

We did not observe any significant gender differences with regard to the occurrence of ADRs ($p = 0.262$). The frequency of ADRs was significantly higher in patients aged ≥ 60 years than in those aged 18–59 years ($p = 0.013$). ADRs related to electrolyte imbalances were more common in female patients than male patients ($p = 0.001$). Compared to patients aged 18–59 years, those aged ≥ 60 years had significantly more ADRs related to the renal system ($p = 0.047$) and skin ($p = 0.003$) (Table V).

Table III. Utilisation patterns of cardiovascular drugs in the coronary care unit, according to gender and age.

Drug prescribed	Gender*		Age*		Male		Female*	
	Male 373 (65.2)	Female 199 (34.8)	18–59 yrs 292 (51.6)	≥ 60 yrs 274 (48.4)	18–59 yrs 207 (55.5)	≥ 60 yrs 166 (44.5)	18–59 yrs 85 (44.0)	≥ 60 yrs 108 (56.0)
Significant† variables								
Antiplatelets	340 (91.2)	169 (84.9)‡	247 (84.6)	256 (93.4)‡	182 (87.9)	158 (95.2)‡	65 (76.5)	98 (90.7)‡
Lipid-lowering	294 (78.8)	144 (72.4)	228 (78.1)	205 (74.8)‡	153 (73.9)	141 (84.9)‡	52 (61.2)	87 (80.6)‡
Beta blockers	218 (58.4)	115 (57.8)	183 (62.7)	144 (52.6)‡	131 (63.3)	87 (52.4)	52 (61.2)	57 (52.8)
Diuretics	163 (43.7)	100 (50.3)	96 (32.9)	163 (59.5)‡	64 (30.9)	99 (59.6)‡	32 (37.6)	64 (59.3)‡
CCBs	95 (25.5)	66 (33.2)	72 (24.7)	87 (31.8)	41 (19.8)	54 (32.5)‡	31 (36.5)	33 (30.6)
Antiarrhythmics	37 (9.9)	16 (8.0)	20 (6.8)	33 (12.0)‡	18 (8.7)	19 (11.4)	2 (2.4)	14 (13.0)‡
Nonsignificant variables								
ACE-i/ARBs	266 (71.3)	140 (70.4)	203 (69.5)	197 (71.9)	144 (69.6)	122 (73.5)	59 (69.4)	79 (73.1)
Heparin, vitamin K antagonist, antithrombotics	238 (63.8)	136 (68.3)	191 (65.4)	177 (64.6)	135 (65.2)	103 (62.0)	56 (65.9)	74 (68.5)
Vasodilators	164 (44.0)	94 (47.2)	122 (41.8)	133 (48.5)	82 (39.6)	82 (49.4)	40 (47.1)	51 (47.2)
Other cardiac preparations	58 (15.5)	28 (14.1)	43 (14.7)	39 (14.2)	29 (14.0)	29 (17.5)	10 (11.8)	14 (13.0)
Cardiac glycosides	44 (11.8)	16 (8.0)	29 (9.9)	31 (11.3)	19 (9.2)	25 (15.1)	10 (11.8)	6 (5.6)
Enzymes (fibrinolytics)	32 (8.6)	15 (7.5)	25 (8.6)	20 (7.3)	19 (9.2)	13 (7.8)	6 (7.1)	7 (6.5)
Cardiac stimulants	19 (5.1)	13 (6.5)	17 (5.8)	15 (5.5)	14 (6.8)	5 (3.0)	3 (3.5)	10 (9.3)
α-blockers and centrally-acting antihypertensives	16 (4.3)	8 (4.0)	12 (4.1)	12 (4.4)	7 (3.4)	9 (5.4)	5 (5.9)	3 (2.8)

Note: Data is presented as no. (%). *Data on gender and age was missing for 2 patients. Data on age was not available for 3 female patients and 3 female patients were aged < 18 years. †Significant in any one parameter assessed. ‡Statistically significant ($p < 0.05$).
ACE-i: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; CCBs: calcium channel blockers

Table IV. Differences in polypharmacy, according to gender and age.

Parameter	All	< 10 drugs	≥ 10 drugs	p-value†
Gender*				0.064
Male	373 (65.2)	180 (48.3)	193 (51.7)	
Female	199 (34.8)	92 (46.2)	107 (53.8)	
Age* (yrs)				0.001‡
18–59	292 (51.6)	159 (54.5)	133 (45.5)	
≥ 60	274 (48.4)	113 (41.2)	161 (58.8)	
Gender by age				
Male (yrs)				0.001‡
18–59	207 (55.5)	116 (56.0)	91 (44.0)	
≥ 60	166 (44.5)	64 (38.6)	102 (61.4)	
Female* (yrs)				0.471
18–59	85 (44.0)	43 (50.6)	42 (49.4)	
≥ 60	108 (56.0)	49 (45.4)	59 (54.6)	

Note: Data is presented as no. (%). *Data on gender and age was missing for 2 patients. Data on age was not available for 3 female patients and 3 female patients were aged < 18 years. †Mann-Whitney *U* test was used for analysis. ‡Statistically significant ($p < 0.05$).

Although the median duration of CCU stay was the same in both male and female patients, the median duration of hospital stay was significantly longer in the male patients when compared to the female patients ($p = 0.008$). CCU stay was found to be longer in patients aged ≥ 60 years ($p = 0.013$) and in male patients aged ≥ 60 years ($p = 0.013$) (Table VI).

DISCUSSION

In the present study we found that the incidence of hypertension was significantly higher in female patients than in male patients ($p = 0.040$) (Table I). Previous studies have also reported an increased likelihood of women having a history of hypertension.[21,22] Systolic blood pressure rises more steeply in ageing women than in ageing men.

We also observed a significant difference in the occurrence of NSTEMI in female patients aged ≥ 60 years when compared to its occurrence in female patients aged 18–59 years ($p = 0.009$). It has been hypothesised that the progression of atheroma into more vulnerable plaques develops at a slower rate in middle-aged women, with a more diffuse pattern of atherosclerosis occurring after menopause and outward remodelling.[23] Women have more inflammation in the coronary arteries than men, and classical patterns of plaque rupture and subsequent thrombus formation is more common in older women than in younger women.[24]

Patients aged ≥ 60 years had more prescriptions of cardiovascular ($p = 0.006$) and non-cardiovascular drugs ($p = 0.015$). Cardiovascular drug prescription was significantly higher in male patients aged ≥ 60 years than in male patients aged 18–59 years, while female patients aged ≥ 60 years were prescribed more non-cardiovascular drugs than those aged 18–59 years. This could be due to the greater number of

Table V. Adverse drug reactions that occurred in patients admitted to the coronary care unit, according to gender and age.

Adverse drug reaction	Gender		Age	
	Male (n = 373)	Female (n = 199)	18–59 yrs (n = 292)	≥ 60 yrs (n = 274)
Overall	87 (23.3)	55 (27.6)	57 (19.5)	82 (29.9)†
Significant* variables				
Renal complications	17 (4.6)	8 (4.0)	10 (3.4)	15 (5.5)†
Electrolyte imbalance	16 (4.3)	26 (13.1)†	14 (4.8)	27 (9.9)
Cutaneous complications	4 (1.1)	2 (1.0)	1 (0.3)	4 (1.5)†
Nonsignificant variables				
Cardiovascular complications	33 (8.8)	13 (6.5)	21 (7.2)	24 (8.8)
Haematological complications	17 (4.6)	5 (2.5)	13 (4.5)	9 (3.3)
Metabolic complications	8 (2.1)	2 (1.0)	4 (1.4)	6 (2.2)
GI system complications	7 (1.9)	6 (3.0)	3 (1.0)	10 (3.6)
CNS complications	5 (1.3)	1 (0.5)	2 (0.7)	4 (1.5)
Liver complications	2 (0.5)	0 (0)	1 (0.3)	1 (0.4)
Respiratory complications	1 (0.3)	1 (0.5)	1 (0.3)	1 (0.4)
Hypersensitivity	0 (0)	1 (0.5)	1 (0.3)	0 (0)
Skeletal complications	0 (0)	1 (0.5)	1 (0.3)	0 (0)

Data is presented as no. (%). *Significant in any one parameter assessed. †Statistically significant (p < 0.05). CNS: central nervous system; GI: gastrointestinal

Table VI. Duration of hospital stay and the coronary care unit (CCU), according to gender and age.

Parameter	Hospital stay (days)		p-value*	CCU stay (days)		p-value*
	Mean ± SD	Median (IQR)		Mean ± SD	Median (IQR)	
Gender			0.008†			0.523
Male	8.9 ± 7.3	7 (4,11)		3.2 ± 4.1	3 (2,3)	
Female	7.3 ± 6.5	6 (4,9)		2.9 ± 2.1	3 (2,3)	
Age (yrs)			0.109			0.013†
18–59	8.3 ± 7.6	6 (4,10)		3.1 ± 4.6	2.5 (2,3)	
≥ 60	8.5 ± 6.6	7 (5,11)		3.2 ± 2.1	3 (2,3)	
Gender by age						
Male (yrs)			0.800			0.013†
18–59	8.9 ± 8.5	6 (4,10)		3.2 ± 5.3	2 (2,3)	
≥ 60	8.8 ± 5.4	7.5 (5,12)		3.2 ± 1.9	3 (2,4)	
Female (yrs)			0.436			0.338
18–59	6.7 ± 4.0	6 (4,9)		2.8 ± 1.9	3 (2,3)	
≥ 60	7.9 ± 8.1	6 (4,9)		3.1 ± 2.3	3 (2,3)	

*Mann-Whitney *U* test was used for analysis. †Statistically significant (p < 0.05). IQR: interquartile range; SD: standard deviation

comorbidities and associated infections, such as lower respiratory tract infections, urinary tract infections and COPD, in the elderly population.

In the present study, higher rates of utilisation of anti-platelets, lipid-lowering drugs and diuretics were observed in male and female patients aged ≥ 60 years. Banerjee et al[25] and Sharma and Ganguly[26] reported similar results in male patients and patients aged > 65 years. The higher rates of utilisation of diuretics in our study could be attributed to the higher occurrences of heart failure and renal dysfunction in the patients aged ≥ 60 years (both male and female). This correlates well with standard management guidelines.[27-29] A higher percentage of patients aged 18–59 years were taking lipid-lowering drugs compared to patients aged ≥ 60 years (78.1% vs 74.8%). Ko et al showed that in addition to statin prescription rates being low in their study cohort, the likelihood of statin treatment was 6.4% lower with every one-year increase in age.[10]

Similar to the trend observed in the utilisation of lipid-lowering drugs, we observed that the utilisation of beta blockers in patients aged 18–59 years (62.7%) was higher than that in patients aged ≥ 60 years. The CREATE registry reported a similar percentage of beta blocker use in STEMI (57.5%) and non-STEMI/unstable angina (61.9%) patients with the mean ages of 56.3 years and 59.3 years, respectively.[30] The less frequent use of beta blockers in patients aged ≥ 60 years (52.6%) could be due to the higher incidence of heart failure, DM, COPD and heart block in this age group. While the benefits of beta blocker use on mortality has been well established in several large trials conducted among patients with mild-to-moderate heart failure,[31,32] guidelines recommend initiation of beta blocker therapy once a patient's clinical condition has remained stable for at least 24–48 hours.[33]

The use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACE-i/ARBs) in female patients was not significantly different from their use in male patients (70.4% vs 71.3%; p = 0.809). Driscoll et al[11] reported that women are less likely to be prescribed antihypertensives as compared to men (58% vs 62%; p < 0.001). While an Estonian study in 2010 reported that only 40% of their patients were treated with ACE-i/ARBs,[34] the use of ACE-i/ARBs in our study cohort was 70%. However, compared to the study by

Ghosh et al[35] that reported the use of ACE-i/ARBs in 87% of their patients, it appears that there is an underutilisation of ACE-i/ARBs in CVDs. The underutilisation of drugs is a multifactorial problem that could be due to misperceptions and concerns regarding drug safety and adverse effects. Other reasons may be related to polypharmacy, the patient's compliance with treatment, and the physician's compliance with evidence-based practice.

The use of antiarrhythmics was significantly higher in female patients aged ≥ 60 years (13.0%) and in patients aged ≥ 60 years (12.0%). This might be due to the high rate of arrhythmias observed in female patients aged ≥ 60 years (13.0%) and in patients aged ≥ 60 years (12.4%). Compared to normal myocytes, failing myocytes have longer action potentials and a greater susceptibility to early after-depolarisations. Longer action potentials and a greater susceptibility to early after-depolarisations are more commonly seen in the myocytes of female patients due to the slightly larger depolarising of L-type calcium channels and slightly smaller repolarising of potassium channels.[36]

A significantly higher use of CCBs was observed in male patients aged ≥ 60 years. This observation is in line with the 2011 NICE guidelines, which recommend the use of CCBs in patients aged ≥ 55 years.[37] Blood pressure is more effectively lowered with the use of calcium antagonists in older than younger patients with hypertension. CCBs, which are preferred in elderly patients, prevent calcium from entering the muscle cells of the heart and blood vessels, relaxing the blood vessels and decreasing the blood pressure.

When examining polypharmacy in our study cohort, we found that patients aged ≥ 60 years had a significantly higher rate of polypharmacy than patients aged 18–59 years. However, when further stratified according to age in gender, the difference was only significant for male patients. For female patients, the prevalence of polypharmacy was not significantly different between the two age groups. This may be because there is a greater use of medications in younger women, as well as a lower use of medications in older women. The greater use of medications in younger women could be because, compared to men, younger women tend to be more concerned about their health. They also tend to recognise and experience health problems early, and therefore consult physicians more often and earlier than men. Younger women are also more accustomed to the use of drugs.[38,39] The lower use of medications in older women, however, could be due to the differences in the pharmacokinetic parameters of older women, which increases their risk of ADRs.[13]

In our study, patients aged ≥ 60 years had a higher rate of ADRs (29.9%), and the ADRs were predominantly associated with the renal system and skin. Patients aged ≥ 60 years are more prone to renal dysfunction, decreased renal clearance and decreased drug metabolism capacity. Renal dysfunction enhances the risk of developing Type A pharmacologically predictable reactions for renally excreted drugs.[40] As the proportion of patients with renal dysfunction in the CCU is relatively high, the proportion of ADRs, such as hyperkalaemia, azotaemia and acute renal failure, induced by ACE-i was also high. In many instances, these ADRs were potentially preventable with the use of better dose titrations and diuretic level adjustments. As these are general risk factors that have been shown to increase the risk of ADRs, special care has to be exercised when prescribing medications to patients aged ≥ 60 years. We did not observe any significant difference in the ADR rates of the male and female patients.

Electrolyte imbalance was more commonly reported in female patients (13.1%) in our study. However, previous studies have reported female patients to have a high risk of hypersensitivity reactions and ADRs that are related to the gastrointestinal system.[41] In our study, the number of ADRs involving the cardiovascular system were almost equal in the two age groups, and more commonly observed in male patients. Mohebbi et al reported that patients in their ADR group were significantly older and that the cardiovascular system was the main organ system involved in the ADRs.[16] One study reported that ADRs related to the central and peripheral nervous systems were more common in CCUs.[42] Cardiovascular drugs could result in fatal adverse reactions in CCU patients. The primary diagnosis at admission and the duration of CCU stay were reported to be risk factors for ADR development.[42]

In the present study, the duration of hospital stay was significantly longer for the male patients than for the female patients. CCU stay was significantly longer for patients aged ≥ 60 years and male patients aged ≥ 60 years. This can be attributed to the greater number of comorbidities, the higher incidence of polypharmacy and the higher rates of ADRs in male patients and patients aged ≥ 60 years. It has been hypothesised that the risk of having an ADR increases exponentially as the number of medicines taken by the patient increases.[43]

This study has its strengths and limitations. One of the strengths of the present study is that it is one of the few studies conducted to examine age and gender differences in CVDs, including the use of drugs and the characteristics of ADRs in a CCU. The findings of the present study clearly highlight the need for patient age to be taken into consideration when initiating pharmacotherapy for CVDs, especially in critical care settings. Unlike other studies,[7-11,13] the present study did not find any major differences in the use of drugs and the patterns of ADRs between male and female patients. This suggests that ADRs in female patients are potentially preventable if pharmacotherapy is optimised according to gender.

The present study was a retrospective cohort study based on the review of hospital medical records. Retrospective collection of data in ADR studies may lead to lower ADR rates. However, although prospective studies in theory generate more accurate data due to the greater intensity of data

collection, retrospective studies are acceptable for examining drug utilisation and ADRs. Large prospective studies with larger sample sizes are recommended to accurately estimate the age- and gender-related differences in the rate of CVDs, drug utilisation pattern, and characteristics of ADRs in a critical care setting.

In conclusion, no major gender-related differences were observed in drug utilisation or ADR pattern in the present study. Higher rates of drug utilisation and ADRs, and longer duration of CCU stay were observed in patients aged ≥ 60 years. With continued improvements in healthcare, people are living longer, thus leading to an increased elderly population size. Frequent reviews of drug utilisation, and newer strategies for active and vigilant monitoring of ADRs, are essential to prevent ADRs and optimise pharmacotherapy, especially in elderly patients in intensive care settings.

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