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Original Research Article

Evaluation of potential drug-drug interactions and adverse drug reactions among chronic kidney disease patients: An experience from United Arab Emirates

Kowsar Mouhib Hammoud[1], Sathvik B Sridhar[1], Syed Arman Rabbani[1]*, Martin Thomas Kurian[2]

[1]Department of Clinical Pharmacy and Pharmacology, RAK College of Pharmaceutical Sciences, RAK Medical and Health Sciences University, [2]Ibrahim Bin Hamad Obaidallah Hospital, Ras Al Khaimah, United Arab Emirates

For correspondence:* ***Email:* *arman@rakmhsu.ac.ae*

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Abstract

Purpose: *To determine the prevalence and assessing nature of potential drug-drug interactions (pDDIs) and adverse drug reactions (ADRs) among chronic kidney disease (CKD) patients.*
Methods: *This was a prospective observational study involving adult CKD patients. Occurrence of pDDIs was evaluated using Micromedex database 2.0. Suspected ADRs during the study period were documented and assessed.*
Results: *Overall prevalence of pDDIs was found to be 85.3 %. A total of 811 pDDIs with 225 different pairs of interacting drugs were identified. Majority of the patients had ≥ 3 pDDIs regardless of type of severity. Thirty-five ADRs were identified in 25 CKD patients. Hyperkalemia was the most-commonly suspected ADR. Logistic regression analysis revealed that age (OR: 1.04, 95 % CI: 1.01 - 107), length of hospital stay (OR: 1.15, 95 % CI: 1.0 - 1.32), presence of comorbidity like diabetes (OR: 9.1, 95 % CI: 3.2 - 25.3) and number of drugs prescribed (OR: 6.88, 95 % CI: 1.5 - 30.0) were positively correlated with occurrence of pDDIs. Length of hospital stay (OR: 1.05, 95 % CI: 0.99 - 1.06) and number of drugs (OR: 0.16, 95 % CI 0.03 - 0.84) were identified as independent predictors of occurrence of ADRs.*
Conclusion: *Prevalence of pDDIs was high in the study population. A majority of the pDDIs were of major severity type, fair documentation grade, and of unspecified onset. A majority of suspected ADRs were probably of moderate in severity and not preventable type.*

Keywords: *Chronic kidney disease, Drug-related problems, Potential drug-drug interactions, Adverse Drug Reactions*

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INTRODUCTION

Chronic kidney disease (CKD) is a rising health burden globally. The global mean prevalence of CKD for all stages is 13.4 %, while for stage three to five it is 10.6 % [1]. Data on CKD in the Middle East countries is scare but the estimated incidence of end stage renal disease (ESRD) is 100 to 140 cases per million population [2]. Epidemiological data from Abu Dhabi, United Arab Emirates (UAE) revealed that around 370 patients per million population have ESRD and

are on maintenance hemodialysis [3] whereas the annual incidence of ESRD in Dubai, UAE is estimated to be 152 patients per million population [4].

Diabetes mellitus and hypertension are the leading causes of CKD [5] and are also the major contributors for the development of ESRD in the Middle East countries [2]. Moreover, CKD patients have multiple comorbid conditions like cardiovascular diseases, anemia, fluid and electrolyte abnormalities, hyperparathyroidism, renal osteodystrophy and malnutrition [6].

These comorbid conditions necessitate management with multiple medications leading to polypharmacy [7]. Polypharmacy contributes to the development of drug related problems like drug-drug interactions and adverse drug reactions [7]. Chronic kidney disease patients have altered pharmacokinetics parameters and pharmacodynamics responses to drugs which further adds to the problem [8].

Potential drug-drug interactions (pDDIs) are considered as one of the major concerns while prescribing medications to CKD patients [9]. Drug-drug interactions contribute 2 to 6 % of all hospital admissions [7] and are one of the contributing factors to increase in the duration of hospital stay and cost of care [10]. The early identification of pDDIs is important so as to undertake appropriate preventive measures and interventions [9]. A number of studies, conducted all around the world, have assessed and evaluated pDDIs in CKD patients. The data from these studies have highlighted both the incidence and nature of the pDDIs [7,11].

Adverse drug reactions (ADRs) are one of the common causes of mortality and morbidity among hospitalized patients [12]. It is estimated that 2.9 to 5.6 % of all admissions are related to ADRs [13]. Moreover, studies have shown that the prevalence of ADR-induced hospital admissions varies from 0.2 – 21.7 % [14]. Chronic kidney disease patients in particular are more vulnerable to ADRs owing to their different comorbid conditions and multiple drug regimens [15,16].

Assessing and evaluating pDDIs and ADRs among CKD patients in UAE is important as the CKD burden in the local population is high [3] and very few studies have addressed these issues in the region. On the background of these observations, the present study was conducted to evaluate pDDIs and ADRs among CKD patients.

METHODS

Study design and sample

It was a prospective-observational study conducted in the CKD patients presenting to the nephrology department of Ibrahim Bin Hamad Obaidallah Hospital, Ras Al-Khaimah, UAE. Study sample was selected employing convenience sampling technique. The sample size was determined on the basis of number of patients visiting the inpatient nephrology department during the study period of six months. A total of 150 patients were enrolled in the study.

Ethical approval

Approval for the study was obtained from the Research and Ethics Committee of RAK Medical and Health Sciences University (RAKMHSU-REC-87-2018-PG-P) and Ministry of Health and Prevention (MOHAP) Research and Ethics Committee (MOHAP/REC/2019-PG-P), UAE. The study followed international guidelines for human studies.

Study criteria

Patients diagnosed with CKD, of either gender and aged ≥ 18 y, admitted for ≥ 24 h, registered under nephrology in-patient department of the study site, underwent maintenance hemodialysis (three days per week) and gave informed consent were included in the study. Patients admitted in nephrology department with diagnosis of acute renal failure or any other renal disorders and visited out-patient clinic of the nephrology department for follow-up were excluded from the study.

Data collection

Demographic and clinical data were documented by reviewing the electronic patient case records. The documented data included age, gender, family history, past medical history, medication history, co-morbidities, laboratory data, details of medications prescribed to manage CKD including the dose, frequency, route of administration and discharge medications.

For assessment of pDDIs, all the medicines received by each CKD patient were entered into Micromedex database 2.0 and were analyzed [17]. The identified pDDIs were classified based on the severity and documentation grade. The study investigators documented all the ADRs observed during the study period. The causality of ADRs was assessed using Naranjo and WHO

probability scales. In addition, the severity, predictability and preventability of suspected ADRs were also assessed and documented.

Statistical analysis

The study data was analyzed using Statistical Package for the Social Sciences (SPSS) version 26.0. The characteristics of the study patients were examined by descriptive analyses. Chi-square test was used for establishing relationship between different study variables. Univariate and multivariate logistic regression analyses were carried out to identify the predictors of pDDIs and ADRs. $P \leq 0.05$ was considered statistically significant.

RESULTS

Socio-demographic and clinical characteristics

Out of the total 150 CKD patients recruited for the study, majority (57.0 %) of the patients were males. The study population had a mean age of 63.3 ± 14.0 years, with majority of them aged between 61 to 70 years (29.0 %). Most of the study participants were UAE nationals (52 %) followed by Arabs (31.0 %) and non-Arabs (17.0 %). Majority of the CKD patients belonged to CKD Stage 5 on dialysis (70.7 %). The mean length of hospital stay of CKD patients was 8.6 ± 10.1 days with a minimum stay of one day and a maximum of 66 days.

Table 1: Socio-demographic characteristics of the study population

Age (years)	63.3 ± 14.0	61.1 ± 12.2 - 65.6 ± 15.7
Gender		
Female	65 (43.3)	35.3 – 51.3
Male	85(56.7)	48.7 - 64.7
Nationality		
UAE Nationals	78 (52.0)	44.7 – 60.0
Arabs	45 (30.0)	22.7 - 37.3
Non-Arabs	27 (18.0)	12.0 - 24.0
Tobacco use		
Yes	12 (8.0)	4.0 – 12.7
No	138 (92.0)	87.3 – 96.0
Alcohol use		
Yes	0	0
No	150 (100.0)	100.0 – 100.0
Length of stay (days)	6.11 ± 9.0	4.85 ± 5.6 – 7.81 ± 12.3
CKD stage		
Stage 1	0	0
Stage 2	1 (0.7)	0.0 – 2.0
Stage 3	10 (6.7)	2.7 – 10.7
Stage 4	15 (10.0)	5.3 – 15.3
Stage 5 on dialysis	106 (70.7)	62.7 - 78.0
Stage 5 without dialysis	18 (12.0)	7.3 – 17.3
Number of comorbidities		
One to two comorbidities	4 (2.7)	0.7 – 5.3
More than two comorbidities	146 (97.3)	94.7 – 99.3
Comorbidities		
Hypertension	146 (97.3)	94.7 – 99.3
Diabetes Mellitus	105 (70.0)	62.7 – 77.3
Anemia	126 (84.0)	78.0 – 89.3
Hyperparathyroidism	105 (70.0)	62.7 – 78.0
Dyslipidemia	87 (58.0)	50.0 - 65.3
Ischemic heart disease	32 (21.3)	14.7 - 28.0
Electrolyte disturbances	96 (64.0)	56.7 - 72.0
Number of drugs	16.94 ± 6.1	15.97 ± 5.2 – 17.99 ± 7.1
Number of pDDIs	5.41 ± 4.9	4.61 ± 4.1 – 6.3 ± 5.6
Number of ADRs		
No ADR	125 (83.3)	77.3 – 89.3
One ADR	17(11.3)	6.7 – 16.7
More than one ADRs	8 (5.3)	2.0 – 9.3

UAE = United Arab Emirates; CKD = Chronic kidney disease; pDDIs = Potential drug-drug interactions; ADRs=Adverse drug reactions; SD = Standard deviation

Most of the patients had more than two comorbidities (97.3 %) with hypertension being the most common comorbidity followed by anemia and diabetes. A total of 2541 drugs were administered to 150 CKD patients during the study period. The mean number of drugs administered was 16.9 ± 6.1 per patient. Table 1 represents the socio-demographic and clinical characteristics of the study population.

Potential drug-drug interactions

The overall prevalence of pDDIs among the patients in this study was 85.3 %. Upon analysis, a total of 811 pDDIs with 225 different pairs of interacting drugs were identified among the CKD patients**.** Table 2 represents the commonly occurring major, moderate and minor pDDIs in the study population**.** The most common pDDIs were aspirin and insulin (4.93 %) followed by aspirin and bisoprolol (4.32 %), and atorvastatin and clopidogrel (3.58 %). The majority of the patients had ≥ 3 pDDIs regardless of type of severity (70 %). Figure 1 depicts the assessment of pDDIs in CKD patients. Univariate logistic regression analysis revealed that as the age increased the probability of occurrence of pDDIs also increased (OR 1.04, 95 % CI 1.01 - 107). The occurrence of a pDDI was positively correlated with the length of hospital stay (OR 1.15, 95 % CI 1.0 – 1.32). In this study, the probability of occurrence of a pDDI increased 9 folds (OR 9.1, 95 % CI 3.2 – 25.3) in the presence of comorbidity like diabetes. As the number of drugs prescribed increased, the probability of pDDI also increased (OR 6.88, 95 % CI 1.5 – 30.0). However, multivariate analysis identified comorbid diabetes as the only independent predictor of occurrence of pDDI (OR 6.89, 95 % CI 2.16 – 21.9) (Table 3).

Actual drug-drug interactions

During the study period, around 10 actual DDIs were detected in the study population. The most common actual DDI was bisoprolol and insulin (4) followed by levothyroxine and pantoprazole (2) and insulin and levofloxacin (1).

Adverse drug reactions

A total of 35 ADRs were identified in 25 CKD patients. Hyperkalemia (17%) was the most commonly suspected ADR followed by hypokalemia (14%), hyponatremia (11%) and elevated liver enzymes (11%). Figure 2 illustrates the spectrum of suspected ADRs in the study population. Regarding the drugs associated with suspected ADRs, furosemide and valsartan were the most common drugs involved in ADRs (20 %) followed by atorvastatin (11 %) and warfarin (8 %). The majority of suspected ADRs were possible (60 % as per Naranjo scale; 48.5 % as per WHO scale), moderate severity (57 %), predictable (66 %) and not preventable (66 %) type. For the management of ADRs the suspected drug was withdrawn in majority of the cases (77.1 %). Specific treatment was given to almost half of the patients (48 %) who experienced ADRs during the study period. Table 4 details the assessment and management of suspected ADRs in the study population. Univariate logistic regression analysis for occurrence of ADRs revealed that as the length of hospital stay increased, the probability of occurrence of ADR also increased (OR 1.04, 95 % CI 1.002 – 1.086; p = 0.037). The multivariate analysis revealed that the number of drugs (OR 0.167, 95% CI 0.033 – 0.841; p = 0.030) and length of hospital stay (OR 1.055, 95% CI 0.992 – 1.065; p = 0.017) were the independent predictors of occurrence of ADRs in the study population.

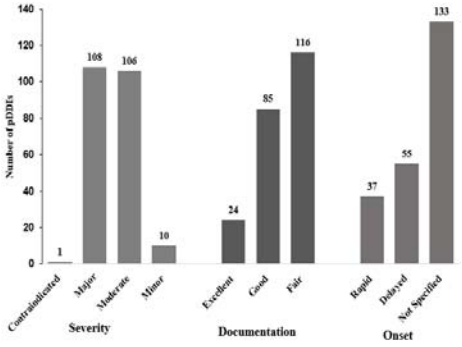

Figure 1: Assessment of pDDIs in CKD patients. ***Note:*** *pDDIs = Potential drug-drug interactions*

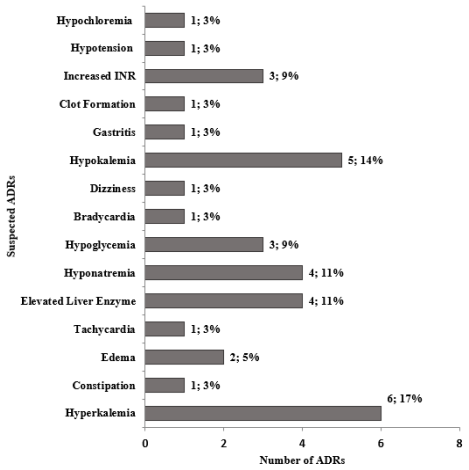

Figure 2: Spectrum of suspected ADRs. *ADRs = Adverse drug reactions; INR = International Normalized Ratio*

Table 2: Commonly occurring major, moderate and minor pDDIs in the study population

Drug	N (%)	Severity	Documentation	Onset	Pharmacological Consequences
Aspirin + Insulin	40 (4.93)	Moderate	Fair	Not Specified	Concurrent use of insulin and salicylates may result in increased risk of hypoglycemia.
Aspirin + Bisoprolol	35 (4.32)	Moderate	Good	Delayed	Concurrent use of beta-adrenergic blockers and non-steroidal anti-inflammatory may result in increased blood pressure.
Atorvastatin + Clopidogrel	29 (3.58)	Moderate	Excellent	Not specified	Concurrent use of clopidogrel and CYP3A4 metabolized statins may result in decreased formation of clopidogrel active metabolite resulting in high on-treatment platelet reactivity.
Aspirin + Calcium salt	28 (3.45)	Moderate	Fair	Delayed	Concurrent use of aspirin and aluminum, calcium or magnesium containing products may result in decreased salicylate effectiveness.
Amlodipine + Clopidogrel	27 (3.33)	Major	Excellent	Not specified	Concurrent use of amlodipine and clopidogrel may result in decreased antiplatelet effect and increased risk of thrombotic events.
Furosemide + Insulin	22 (2.71)	Moderate	Fair	Not specified	Concurrent use of antidiabetic agents and selected diuretics may result in increased hyperglycemia risk; increased insulin requirement.
Albuterol + Furosemide	21 (2.59)	Moderate	Fair	Not specified	Concurrent use of albuterol and potassium-depleting diuretics may result in ECG changes or hypokalemia.
Aspirin + Clopidogrel	20 (2.47)	Major	Fair	Not specified	Concurrent use of aspirin and clopidogrel may result in an increased risk of bleeding.
Bisoprolol + Insulin	19 (2.34)	Moderate	Good	Delayed	Concurrent use of antidiabetic agents and beta-adrenergic blockers may result in hypoglycemia or hyperglycemia; decreased symptoms of hypoglycemia.
Clopidogrel + Enoxaparin	18 (2.22)	Major	Fair	Not specified	Concurrent use of antiplatelets and low molecular weight heparin may result in increased risk of bleeding.
Calcium salt + Ferrous Sulfate	14 (1.73)	Minor	Fair	Delayed	Concurrent use of iron and aluminum, calcium or magnesium containing products may result in decreased iron effectiveness.
Budesonide + Levofloxacin	9 (1.11)	Major	Excellent	Delayed	Concurrent use of selected corticosteroids and selected fluoroquinolones may result in an increased risk of tendon rupture.

Table 3: Univariate and multivariate analysis of factors associated with pDDIs in CKD patients

Variable (Reference)	Univariate model			Multivariate model		
	Odds ratio	*95% CI*	*P-value*	*Odds ratio*	*95% CI*	*P-value*
Age, years	1.04	1.01-1.07	**0.009**	1.02	0.98–1.05	0.241
Gender						
(Female)						
Male	0.56	0.21-1.47	0.242	0.74	0.23–2.39	0.621
Nationality (Non-Arabs)						
UAE nationals	1.94	0.63-5.98	0.247	-	-	-
Arabs	1.86	0.53-6.48	0.332	-	-	-
CKD stage						
(Stage 2 and 3)						
Stage 4	1.40	0.07-25.1	0.819	-	-	-
Stage 5 with dialysis	0.52	0.06-4.36	0.550	-	-	-
Stage 5 without dialysis	0.50	0.45-5.51	0.571	-	-	-
Length of stay, days	1.15	1.0-1.32	**0.050**	1.14	0.97–1.34	0.090
Number of comorbidities						
(1 to 2 comorbidities)						
>2 Comorbidities	1.98	0.19-19.9	0.561	-	-	-
Type of comorbidities						
Hypertension	1.97	0.18-19.8	0.560	-	-	-
Diabetes	9.10	3.26-25.3	**<0.001**	6.89	2.16–21.9	**0.001**
Anemia	0.80	0.21-2.96	0.744	-	-	-
Dyslipidemia	6.06	2.09-17.5	**0.001**	2.564	0.76–8.62	0.128
Ischemic heart disease	1.85	0.51-6.71	0.346	-	-	-
Electrolyte abnormalities	1.27	0.50-3.21	0.604	-	-	-
Hyperparathyroidism	1.76	0.69-4.49	0.231	1.704	0.50–5.80	0.394
Number of drugs (≤ 7)						
> 7	6.88	1.58–30.0	**0.01**	2.486	0.38–16.02	0.338

UAE = United Arab Emirates; CKD = Chronic kidney disease; CI = Confidence interval; Statistically significant values are in bold

DISCUSSION

The present study assessed and evaluated drug related problems like pDDIs and ADRs among CKD patients in a secondary care setting. The majority of the study population belonged to CKD stage 5, while a small proportion of the study patients were CKD stage 4. Results obtained are in contrast with the findings of a study conducted by Marquito *et al* [10] to identify pDDIs in CKD patients, where the majority of the study population were CKD stage 3, while only a small fraction of the patients were CKD stage 5. In the present study, CKD patients had a high burden of comorbidities. Similar comorbidity status has previously been reported by other studies done in CKD patients [18,19] Furthermore, hypertension was the most common comorbidity followed by anemia. This finding is in agreement with the findings of a study done by Abhishek *et al* [20]. High medication burden is reported in the present study (mean prescribed medications per patient was 16.9 ± 6.1). Similar medication burden was reported by Alshamrani *et al* in CKD population [18]. Majority of the patients received more than seven drugs, which is in line with the results of another study [11]. This finding could be attributed to the fact that the study comprised of an aging population, the study setting being a government hospital and high prevalence polypharmacy. The higher number of prescribed drugs could also be due to increased number of comorbidities, as well as advanced CKD stage [7,18].

This study reports a high frequency of pDDIs among the study population, which is in agreement with the findings of similar studies which reported a frequency of 80.8 and 89.1 %, respectively [11,21]. While a study by Chacko *et al* [22] reported a frequency of 58.0 %, which is lower than the findings obtained. This variation in results may be due to the difference in the average number of drugs received by the patients in this study. Other factors like aged study population, number of comorbidities and length of hospital stay may have contributed to this difference. The majority of identified pDDIs were major, followed by moderate, minor and contraindicated type. While in a study conducted by Alshamrani *et al* majority were moderate, followed by major and contraindicated pDDIs [18]. With regards to documentation grades, majority of the pDDIs were fair, followed by good and excellent type. These findings differ from the results of other studies which identified the majority of pDDIs as of good documentation grade [22,23].

Table 4: Assessment and management of suspected ADRs in CKD patients

Assessment/Management of suspected ADRs	Type/strategy	Frequency, n (%)
Assessment		
Causality		
Naranjo scale	Definite	1 (3)
	Probable	13 (37)
	Possible	21 (60)
WHO scale	Certain	1 (3)
	Probable	17 (48.5)
	Possible	17 (48.5)
Severity	Mild	15 (43)
	Moderate	20 (57)
	Severe	0 (0)
Preventability	Definitely preventable	5 (14)
	Probably preventable	7 (20)
	Not preventable	23(66)
Predictability	Predictable	23 (66)
	Not predictable	12 (34)
	Drug withdrawn	27 (77.1)
Management		
	Dose alteration	1 (2.8)
	No change	7 (20)
	Specific treatment	17 (48.5)
	Symptomatic treatment	1 (3)
	No treatment	17 (48.5)
	Recovered	25 (71)
Outcome		
	Continuing	7 (20)
	Unknown	3 (9)
Dechallenge and rechallenge		
	No Dechallenge	9 (25.7)
Dechallenge		
	Definite Improvement	24 (6.5)
	No Improvement	1 (2.9)
	Unknown	1 (2.9)
	No Rechallenge	26 (74.3)
Rechallenge		
	Recurrence of Symptoms	1 (2.9)
	No Occurrence of Symptoms	4 (11.4)
	Unknown	4 (11.4)

ADRs = Adverse drug reactions; WHO = World Health Organization

The onset of the majority of the pDDIs was unspecified followed by delayed and rapid. These results are in contrast with previous studies which reported that the majority of pDDIs were of delayed onset [11,22–25]. The prevalence of ADRs was 16.7 % which is higher than reported by studies conducted in CKD patients in UAE (12.1 %) [15] and India (12.19 %) [26]. The higher prevalence of ADRs may be attributed to the older age, polypharmacy and longer length of hospital stay of the patients. The most common ADR reported was hyperkalemia caused by valsartan. This finding is in line with a study conducted in CKD veterans in US where hyperkalemia due to angiotensin converting enzyme inhibitors/angiotensin receptor blockers was the common ADR [27]. The causality assessment of ADRs revealed that the majority of them were possible, followed by probable and definite. These findings differ from the findings of Danial *et al* [28], where majority of the ADRs were probable followed by possible. This incoherence can be attributed to the variance in the number of study patients who experienced ADRs between the studies. Furthermore, the severity assessment showed that the majority of the suspected ADRs were of moderate type, which is similar to Danial et *al* [28] findings, where major category of ADRs was moderate on modified Hartwig and Siegel scale.

Regarding the management of ADRs the suspected drug was withdrawn in majority of the cases and specific treatment was given to almost half of the patients who experienced ADRs during the study. The number of drugs and length of hospital stay were identified as the independent predictors of ADRs. High medication burden [29] and increased hospital stay [28] have been associated with ADRs among CKD patients.

Limitations of the study

This study had some limitations. Firstly, it was a single center study with limited sample size. Secondly, the study was carried out in a government hospital which may have limited the selection of prescribed drugs. Thirdly, identifying ADRs was challenging as it was difficult to precisely conclude that whether the ADR was due to the symptom or due to abnormal laboratory values resulting from the drug or the disease itself. Finally, the analysis of pDDIs was theoretical and was based on the assumption without being manifested clinically.

CONCLUSION

The majority of the pDDIs are of severity type, fair documentation grade and of not specified onset. The commonly identified pDDIs are between aspirin and insulin, followed by aspirin and bisoprolol, and atorvastatin and clopidogrel. The high prevalence of pDDIs among CKD necessitates the need to optimize the therapy management and to monitor the outcomes for possible DDIs. The majority of suspected ADRs were possible, of moderate severity and not preventable type. Clinical pharmacist can participate in monitoring of possible DDIs and ADRs along with other health care professionals. In addition, the clinical pharmacist can recommend the appropriate management plan for any actual DDIs and ADRs and for preventing the occurrence of these drug-related problems. Further large-scale studies are required to substantiate these findings.

DECLARATIONS

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Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. KMH contributed in conducting the study, acquisition of data, drafting the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. SBS contributed in the conception of the work, analysis of data, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. SAR contributed in the conception of the work, analysis of data, drafting and revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. MTK contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work.

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