Drug-drug interactions associated with adverse clinical outcomes and abnormal laboratory findings in patients with malaria

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Abstract

Background: Hospitalized patients with malaria often present with comorbidities or associated complications for which a variety of drugs are prescribed. Multiple drug therapy often leads to drug-drug interactions (DDIs). Therefore, we investigated the prevalence, levels, risk factors, clinical relevance, and monitoring parameters/management guidelines of potential DDIs (pDDIs) among inpatients with malaria. Methods: A retrospective cohort study was carried out at multiple hospital settings. A total of 398 patients' profiles were evaluated for pDDIs using the Micromedex Drug-Reax ® . Odds ratios were calculated to identify the strength of association between presence of DDIs and potential risk factors via logistic regression analysis. Further, the clinical relevance of frequent pDDIs was investigated. Results: Of 398 patients, pDDIs were observed in 37.2% patients, while major-pDDIs in 19.3% patients. Total 325 interaction were found, of which 45.5% were of major- and 34.5% moderate-severity. Patients with the most common pDDIs were found with signs/symptoms and abnormalities in laboratory findings representing nephrotoxicity, hepatotoxicity, QT interval prolongation, and reduced therapeutic efficacy . The adverse events were more common in patients prescribed with the higher doses of interacting drugs. Multivariate regression analysis showed statistically significant association of pDDIs with 5-6 prescribed medicines (p=0.01), >6 prescribed medicines (p<0.001), >5 days of hospital stay (p=0.03), and diabetes mellitus (p=0.04). Conclusions: PDDIs are commonly observed in patients with malaria. Healthcare professional's knowledge about the most common pDDIs could help in preventing pDDIs and their associated negative effects. Pertinent clinical parameters, such as laboratory findings and signs/symptoms need to be checked, particularly in patients with polypharmacy, longer hospital stay, and diabetes mellitus.

Background

Malaria is one of the infectious diseases that cause burden on the healthcare system. According to WHO, malaria accounts for 216 million cases in 91 countries in the year 2016. This was an increase of five million cases over 2015 [1]. Moreover, in 2016, an approximately 85% of vivax malaria cases were identified in five countries including Pakistan [2]. Worldwide, malaria remains one of the causes of death due to infectious diseases [3].

Hospitalization in malaria occurs due to disease severity, managing the associated symptoms or comorbid illnesses [4]. Anti-malarial drugs, anti-pyretic, and analgesics are usually prescribed to treat hospitalized malaria patients [5]. Besides these medicines, a variety of other medicines are also prescribed so as to manage the comorbid illnesses and associated symptoms [4-6]. Concomitant use of several drugs increased the chance of drug-drug interactions (DDIs)—affecting drug's pharmacokinetic parameters and pharmacodynamics profile [7, 8]. DDIs may lead to a variety of negative clinical outcomes such as hospitalization, reduced or abolished therapeutic efficacy, prolongation of hospital stay, toxicity, and adverse effects [7-9]. An approximately, 20-30% of adverse effects have been reported as due to DDIs, of which 1-2% are life-threatening and 70% need clinical intervention [10]. Hence,

particular consideration of DDIs and their timely management is crucial for the rational use of medicines in patients with malaria.

Potential DDIs (pDDIs) issue has been addressed generally in hospitalized patients [7] as well as in specific diseases such as liver cirrhosis [11], hypertension [12], diabetes mellitus (DM) [13], bone marrow transplant [14], cancer [15], stroke [16], pneumonia [17], urinary tract infections [18], and hepatitis C [19]. Despite, being the most prevalent causes of hospitalization [20], DDIs particularly among inpatients with malaria remains unaddressed. Moreover, in developing countries, literature has been least reported as well as irrational use of medicines is a common issue. Consequently, specific consideration is required to conduct studies evaluating pDDIs and their clinical relevance among hospitalized patients with malaria. Afterward, such studies will improve patients' safety and help healthcare professionals to manage pDDIs and reduce their associated negative clinical consequences.

This study aimed to evaluate the prescriptions of inpatients with malaria for pDDIs prevalence, and their levels. Investigate the risk factors contributing towards pDDIs prevalence, and clinical relevance of pDDIs. Secondary aim was to identify monitoring parameters and develop management guidelines for the most frequent pDDIs.

Methods

Study settings and design

A retrospective cohort study was conducted at tertiary care hospitals of Peshawar, Khyber Pakhtunkhwa, Pakistan such as Khyber Teaching Hospital and Hayatabad Medical Complex. Computerized drug interaction screening programs and clinical pharmacy services are lacking in both the hospitals. Patient's profiles are developed in hand written format and records are maintained manually.

Patient selection criteria

Following were the inclusion criteria:

- Patients diagnosed with malaria and hospitalized.
- Patients of all age.
- Both male or female patients.
- All medications, that were prescribed during hospitalization of the patient were included in analysis.

Patients' profiles lacking relevant data (hospital admissions, patients' demographics, diagnoses, comorbidities/complications, medications therapy, sign/symptoms, and laboratory test reports) required for the study were excluded.

Data source

A total of 398 patients were included for the study based on above criteria. The following date were collected from the patients' profiles such as hospital admissions, patients' demographics, diagnoses, comorbidities/complications, medications therapy, sign/symptoms, and laboratory test reports.

Medications profiles screening for pDDIs

Medicines prescribed to patients were evaluated for pDDIs using Micromedex Drug-Reax® [21]. This software classify drug interactions on the basis of severity- (contraindicated, major, moderate, and minor) and documentation-levels (excellent, good, and fair) [21]:

Overall-prevalence of pDDIs as well as prevalence of pDDIs based on severity-levels were reported.

Clinical relevance

The clinical relevance of ten most frequent pDDIs was reported, by correlating potential adverse consequences of pDDIs with patients' signs, symptoms and laboratory test results. The clinical manifestations were stratified based on dose differences of the interacting drugs. The following cut off points were used for defining higher daily doses, calcium containing products: ≥600mg/3L; ceftriaxone: ≥3gm; isoniazid: ≥300mg; rifampin: ≥450mg; pyrazinamide: ≥1500mg; acetaminophen: ≥1gm; prochlorperazine: ≥15mg; quinine: ≥1350mg; ranitidine: ≥150mg; metronidazole: ≥1500mg; domperidone: ≥30mg; dexamethasone: ≥24mg; and ciprofloxacin: ≥800mg. Potential adverse effects in this study were defined as follows, leukocytosis: total leukocyte count >11,000/μL; elevated blood urea nitrogen (BUN): BUN ≤20mg/dL; elevated serum creatinine: serum creatinine >1.06mg/dL; elevated alkaline phosphatase: >126U/L; elevated alanine aminotransferase: >59U/L (male), >36U/L (female); tachycardia: heart rate >100 beats/min; hypotension: systolic blood pressure (BP) <80mmHg and/or diastolic BP <50mmHg; hypokalaemia: serum potassium <3.5mmol/L. Management guidelines and monitoring parameters were developed for the most prevalent pDDIs. Widespread (most common) and clinically important pDDIs were enlisted along with their potential adverse consequences.

Statistical analysis

Data were presented in the form of frequencies and percentages alone or with median and interquartile range (IQR), where appropriate. A statistical method of logistic regression analysis was used to calculate odds ratios (OR) for various risk factors of pDDIs such as patients' gender, age, number of prescribed medicines, hospital stay, and comorbidities. Dependent variable in the model was exposure to pDDIs. While, patients' characteristics (gender, age, number of prescribed medicines, hospital stay, and comorbidities) were taken as independent variables in the model. Odds ratios and 95% confidence

intervals (CIs) were calculated for each independent variable. Univariate logistic regression analysis was run initially. Then, multivariate analyses were performed for variables with p-values of ≤0.15. A p-value of ≤0.05 was considered as statistically significant. SPSS-v23 was used for statistical analyses of the data.

Results

General characteristics of study patients

Patients' demographics are presented in Table 1. Of 398 patients, males were more prevalent (51.8%). Most of the patients were aged 21-40 years (44.2%). Majority were prescribed with >6 drugs (54.8%). Most frequent hospital stay was ≥4 days (64.6%). The median (IQR) age, prescribed drugs and hospital stay was 30 years (22-50), 7 drugs (5-9), and 4 days (3-6), respectively. Hypertension (n=52), DM (45), urinary tract infections (34), hepatitis (23), and ischemic heart diseases (IHD) (15) were the most prevalent comorbidities of the studied patients. Moreover, exposure to pDDIs stratified against the patient's characteristics are also shown in Table 1. In males, pDDIs were more prevalent as compared to females. Similarly, pDDIs were commonly reported in patients aged >40 years, prescribed with >6 medicines, and hospitalization of >5 days. Moreover, pDDIs were mostly reported in patients with DM, hypertension, urinary tract infections, and hepatitis as comorbidities.

Prevalence of potential drug-drug interactions

Out of total 398 patients, 148 (37.2%) met at least one pDDI. Based on severity-wise prevalence, 19.3% patients were identified with at least one major-pDDI while, 15.8% with at least one moderate-pDDI. However, a smaller number of patients were found with contraindicated- and minor-pDDIs (Figure 1).

Levels of potential drug-drug interactions

Figure 2 illustrates categorization of pDDIs based on severity- and documentation-levels. Total number of interactions were 325, among which 45.5% were of major- and 34.5% moderate-severity. Based on documentation-levels, 49.5% were of fair and 44.9% good scientific-evidence.

Risk factors of potential drug-drug interactions

Table 2 shows logistic regression analysis based on exposure to pDDIs. In the univariate logistic regression analysis, association for pDDIs was statistically significant with 5-6 prescribed medicines (p=0.005), >6 prescribed medicines (p<0.001), hospital stay of 4-5 days (p=0.003), and >5 days hospitalization (p<0.001). Moreover, concerning comorbidities, association of pDDIs with DM (p=0.001) and IHD (p=0.07) was statistically significant.

In the multivariate logistic regression analysis, the association remained significant with 5-6 prescribed medicines (p=0.01), >6 prescribed medicines (p<0.001), >5 days hospitalization (p=0.03), and DM (p=0.04).

Clinical relevance of potential drug-drug interactions

Table 3 presents daily prescribed dosage of the ten most frequent interacting drug pairs. In this study, the term high and low doses were used relatively. It was observed that the drugs were prescribed in varying doses and administration frequencies. Interacting drugs were prescribed more frequently in low doses, whereas, higher doses of the drugs were prescribed less frequently. Most frequent pDDIs along with their potential adverse consequences and levels are presented in Additional Table 1, while Additional Table 2 and Table 3 enlists most prevalent antimicrobial agents (AMAs) and drugs besides AMAs, respectively.

In Table 4, specific clinical features (signs, symptoms and/or laboratory findings) and management guidelines/monitoring parameters [21, 22] for ten most frequent pDDIs are reported. The clinical features were stratified based on dose differences of the interacting drug pairs. Signs, symptoms and abnormalities in laboratory findings indicating poor response and nephrotoxicity were detected in patients with the interaction, calcium containing products + ceftriaxone. Patients with the interactions pyrazinamide + rifampin, isoniazid + rifampin, and isoniazid + acetaminophen, were observed with the signs/symptoms of hepatotoxicity such as weight loss, anorexia, hepatomegaly, pale, weakness, body aches, and ascites, and abnormalities in labs such as elevated Alkaline Phosphatase and elevated Alanine Aminotransferase. Patients with the interacting pair, prochlorperazine + quinine, metronidazole + quinine, domperidone + ranitidine, and ciprofloxacin + metronidazole, were observed with clinical features and abnormalities in labs suggesting QT interval prolongation. Clinical features suggesting poor response of the drugs were observed in patients with the interacting pairs cefpodoxime + ranitidine and dexamethasone + rifampin. Table 4 further enlists monitoring parameters and management guidelines specifically for each interacting pair. Adverse consequences for the most frequent pDDIs were nephrotoxicity, hepatotoxicity, QT interval prolongation, and decreased therapeutic response. In general, monitoring parameters for the associated adverse effects includes related signs/symptoms and abnormal laboratory findings such as liver function tests, ECG, and renal function tests. Most of these associated adverse consequences can be managed by discontinuing the combination or adjusting the dose.

Discussion

DDIs remains one of the therapeutic challenges among inpatients [7]. Studies addressing pDDIs issues among hospitalized patients with malaria are lacking. The prevalence of pDDIs reported in the current research is higher (37.2%) in comparison to that among patients with acquired immune deficiency (33.5%) [23], liver cirrhosis (21.5%) [11], and hypertension (21.1%) [12]. Contrary, it is lower (37.2%) as compared to that among patients with hypertension (48%) [24], DM (52.2%) [13], and bone marrow

transplant (60%) [14]. Furthermore in current study, prevalence of major-pDDIs is higher (19.3%) as compared to that reported among patients with cancer (16%) [15]. Whereas, it is lower in comparison to that reported among patients with liver cirrhosis (21.4%) [11], hepatitis C (30-44%) [19], and stroke (61%) [16]. Similarly, the prevalence of contraindicated-pDDIs in patients with malaria is also lower (14.3%) in comparison to the prevalence reported among patients with hepatitis C (16.7%) [25]. This contradiction may be due to variable study population, drug prescribing patterns, study design, considering pDDIs types, and drug interaction screening software. Considering the findings of this study, malaria patients are more at risk to pDDIs. Published literature has proposed some evidence based approaches to minimize, prevent or manage DDIs in hospital settings such as screening medication profiles for pDDIs by using computerized screening programs [26], engaging clinical pharmacists in assesing patients' medication profiles for pDDIs [27-29], procedure for structured assessment of pDDIs [30], and checking pertinent laboratory findings for clinical relevance of interactions [7, 31].

Healthcare professionals can manage adverse outcomes related to interactions, by taking into considerations the levels of interactions. In our study, pDDIs of major and moderate types were commonly observed, while concerning documentation levels, pDDIs of fair and good types were more prevalent. These findings are inconsistent with the findings from other studies [11, 20, 32]. This situation is alarming as our results warrant about the exposure of malaria patients towards negative consequences of pDDIs. Therefore, identifying the type of interaction, by healthcare professional is crucial for managing pDDIs, minimizing the related risk, and designing prophylactic measures for prevention.

Hospitalized patients with malaria receive a variety of medications for the management of underlying disease, related complications, and/or comorbid illnesses [4-6]. Our findings support that provision of multiple therapy has been positively associated with pDDIs prevalence [15, 32-34]. Moreover, the statistically significant association of pDDIs with prolong hospitalization reported by our study is in accordance with the published reports [20, 35]. Furthermore, we observed a significant association of pDDIs with DM as comorbidity of malaria. The reason is that, in patients with DM, such drugs are prescribed, having higher risk of DDIs [36]. In this regard, hospitalized malaria patients having any of the above-mentioned risk factors are at higher risk to pDDIs. Healthcare professionals should have knowledge regarding the factors contributing towards pDDIs prevalence. This will help in reducing the risk of pDDIs—patients more at risk to pDDIs should be individualized to improve drug therapy and reduce the adverse outcomes of pDDIs.

All types of pDDIs are not clinically significant. Hence, developing the list of clinically significant DDIs of the drugs used by patients with malaria is of immense need. The list will be helpful for the healthcare professionals for selective screening and identification of DDIs. Further, physician's understanding and knowledge of DDIs helps in reducing the occurrence of associated adverse effects, providing quality care, adjusting therapeutic regimen, and avoiding related medicolegal concerns. Moreover, our frequently identified pDDIs may results in serious adverse outcomes such as hepatotoxicity, QT interval prolongation, hypoglycemia, hyperglycemia, bleeding, hypertension, reduction in therapeutic

effectiveness, and drug's toxicity. This is of particular concern because of associated risk of harm to patient.

A particular strength of this study is the assessment of clinical relevance of pDDIs. A limited number of studies focused on such an evaluation. Clinical relevance presents possible consequences of DDIs on clinical indicators/features and laboratory findings. In addition clinical relevance also highlights the importance of screening medication list for DDIs—enlightened by published literature [27, 31, 34]. Assessing patients' abnormal signs/symptoms and laboratory investigations help in monitoring the adverse consequences associated with DDIs. The potential negative consequences of ten most frequent pDDIs, observed in this study and published reports, emphasis the need of monitoring patients using these combinations [9, 37, 38]. In this study, doses of the interacting drugs have also been considered. Relatively higher doses of the interacting drugs may potentiate the harmful effects of the DDIs. This report showed that adverse effects were commonly observed among patients with higher doses of the interacting drugs. Adverse consequences related to DDIs can be reduced by checking patients' clinical manifestations and laboratory reports. Thus, this aspect of therapy needs appropriate attention. Furthermore, monitoring parameters and/ management guidelines for DDIs will be helpful for healthcare professionals to assess and manage DDIs in malaria patients.

Potential limitations of this study include inclusion of inpatients. As in hospitals, patients with malaria are chiefly admitted for the treatment of related signs/symptoms/complications or various comorbid illnesses. The pDDIs identified in this study are primarily associated with the use of medications for the management of such issues. Therefore, the findings of this study may not be generalizable to ambulatory patients in whom the drug utilization, drug interaction, and disease pattern possibly are different. Moreover, we use the term pDDIs, as, we do not actually observe DDIs. If such assessment, is made prospectively it will have positive clinical outcomes. Data are scarce regarding adverse clinical outcomes produced by drug interactions. However, in published literature some retrospective studies are available highlighting the importance of such an evaluation [8, 39].

Conclusions

PDDIs are commonly observed in patients with malaria. Healthcare professional's knowledge about the most common pDDIs could help in preventing pDDIs and their associated negative effects. Pertinent clinical parameters, such as laboratory findings and signs/symptoms need to be checked, particularly in patients with polypharmacy, longer hospital stay, and diabetes mellitus. Careful monitoring for adverse outcomes as well as prescribing drugs with a low risk for pDDIs are significant measures to decrease adverse effects associated with DDIs.

Abbreviations

AMAs: Antimicrobial agents; ALP: alkaline phosphatase; ATD: alternate day; ALT: alanine aminotransferase; BD: twice a day; BP: Blood pressure; BUN: Blood urea nitrogen; CI: Confidence interval;

DDIs: Drug-drug interactions; DM: Diabetes mellitus; FBS: fasting blood sugar; IHD: Ischemic heart diseases; IQR: Interquartile range; LFTs: liver function tests; OD: once a day; OR: Odds ratios; pDDIs: potential drug-drug interactions; QID: four times a day; TDS: three times a day.

Declarations

Ethics approval and consent to participate

Institutional Research and Ethics Board of Postgraduate Medical Institute, Peshawar, provided ethics approval (Reference number: 15442). This study contains data obtained from the hospital record, therefore informed consent from the patients was not applicable.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All the authors contributed substantially to the work presented in this paper. SN designed all the work under the supervision of MI, collected, analyzed and interpreted data, did DDIs screening, drafted the manuscript. MI designed the research, contributed substantially with data analysis, results interpretations and manuscript editing and approval. FK collected, analyzed and interpreted data, did DDIs screening, drafted the manuscript. All authors read and approved the final version of manuscript.

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Tables

Table 1. General characteristics of study subjects and exposure to potential drug-drug interactions

General characteristics	Patients: n (%)	Exposure to pDDIs (Patients: n (%))
Gender		
Male	206 (51.8)	77 (52)
Female	192 (48.2)	71 (48)
Age (years)		
≤20	96 (24.1)	40 (27)
21-40	176 (44.2)	53 (35.8)
>40	126 (31.7)	55 (37.2)
Median (Interquartile range)	30 (22-50)	
Drugs prescribed		
≤4	78 (19.6)	5 (3.4)
5-6	102 (25.6)	23 (15.5)
>6	218 (54.8)	120 (81.1)
Median (Interquartile range)	7 (5-9)	
Hospital stay (days)		
≤3	141 (35.4)	32 (21.6)
4-5	144 (36.2)	56 (37.8)
>5	113 (28.4)	60 (40.5)
Median (Interquartile range)	4 (3-6)	
Number of comorbidities		
No comorbidities	179 (45)	-
1-2	187 (46.9)	-
≥3	32 (8)	-
Comorbidities		
Hypertension	52 (13.1)	20 (13.5)
Diabetes mellitus	45 (11.3)	27 (18.2)
Urinary tract infection	34 (8.5)	13 (8.8)
Hepatitis	23 (5.8)	11 (7.4)
Ischemic heart disease	15 (3.8)	9 (6.1)
Anemia	13 (3.3)	3 (2)
Dengue fever	12 (3)	5 (3.4)
Meningitis	11 (2.8)	5 (3.4)
Respiratory tract infection	9 (2.3)	2 (1.4)
Thrombocytopenia	9 (2.3)	2 (1.4)
Typhoid	9 (2.3)	-
Bicytopenia	7 (1.8)	-
Acute gastroenteritis	6 (1.5)	-
Asthma	6 (1.5)	-
Tuberculosis	6 (1.5)	-
Acute kidney injury	5 (1.3)	-
Pancytopenia	5 (1.3)	-
Decompensated chronic liver disease	4 (1)	-
Pneumonia	4 (1)	-
Congestive cardiac failure	3 (0.8)	-
Miscellaneous	72 (18)	-

-pDDIs, potential drug-drug interactions

Table 2. Logistic regression analysis based on exposure to potential drug-drug interactions

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Gender				
Female	Reference		-	
Male	1 (0.7-1.5)	0.9	-	-
Age (Years)				
≤20	Reference		Reference	
21-40	0.6 (0.4-1)	0.05	0.6 (0.3-1.1)	0.1
>40	1.1 (0.6-1.9)	0.8	0.6 (0.3-1.1)	0.1
Drugs prescribed				
≤4	Reference		Reference	
5-6	4.3 (1.5-11.8)	0.005	3.9 (1.4-10.8)	0.01
>6	17.9 (6.9-45.9)	< 0.001	14.1 (5.4-37.3)	< 0.001
Hospital stay (days)				
≤3	Reference		Reference	
4-5	2.2 (1.3-3.6)	0.003	1.5 (0.8-2.6)	0.2
>5	3.9 (2.2-6.6)	< 0.001	1.9 (1.1-3.5)	0.03
Comorbidities				
Hypertension	1.1 (0.6-1.9)	0.8	-	-
Diabetes mellitus	2.9 (1.5-5.4)	0.001	2.2 (1-4.8)	0.04
Urinary tract infection	1.1 (0.5-2.2)	0.9	-	-
Hepatitis	1.6 (0.7-3.7)	0.3	-	-
Ischemic heart disease	2.6 (0.9-7.6)	0.07	2.4 (0.7-8.5)	0.2
Anemia	0.5 (0.1-1.8)	0.3	-	-
Dengue fever	1.2 (0.4-3.9)	0.7	-	-
Meningitis	1.4 (0.4-4.7)	0.6	-	-
Respiratory tract infection	0.5 (0.09-2.3)	0.4	-	-
Thrombocytopenia	0.5 (0.09-2.3)	0.4	-	-

-CI, confidence interval; OR, Odds ratio

Table 3. Dose regimen of the prescribed interacting drugs

Interacting pair	Dose categories[a]	Daily prescribed dose regimen	Number of patients
Calcium containing products – Ceftriaxone	Low + Low	200mg/L OD + 2gm OD ATD	10
	Low + Low	200mg/L BD + 2gm OD ATD	9
	Low + Low	200mg/L BD + 1gm BD ATD	8
	Low + High	200mg/L OD + 2gm BD ATD	6
	Low + High	200mg/L BD + 2gm BD ATD	5
	High + High	200mg/L TDS + 2gm BD ATD	3
	High + Low	200mg/L TDS + 2gm OD ATD	3
	Low + High	200mg/L OD + 3gm OD ATD	2
	High + Low	1gm OD +2gm OD ATD	2
	Low + High	200mg/L BD + 3gm OD ATD	1
	Low + High	200mg/L BD + 4gm OD ATD	1
	High + High	1gm OD +2gm BD ATD	1
	Low + Low	200mg/L OD + 1gm OD ATD	1
Isoniazid – Rifampin	High + High	300mg OD + 600mg OD	6
	Low + High	225mg OD + 450mg OD	2
	Low + Low	150mg OD + 300mg OD	2
Pyrazinamide – Rifampin	High + High	1600mg OD + 600mg OD	6
	Low + High	1200mg OD + 450mg OD	2
	High + Low	500mg TDS + 300mg OD	2
Isoniazid – Acetaminophen	High + High	300mg OD + 500mg TDS	2
	Low + High	300mg OD + 500mg TDS	2
	High + High	300mg OD + 1gm OD	2
	Low + Low	150mg OD + 300mg OD	1
	Low + High	150mg OD + 500mg TDS	1
	High + High	300mg OD + 500mg QID	1
Prochlorperazine – Quinine	High + High	5mg TDS + 600mg TDS	4
	Low + Low	5mg BD + 600mg BD	2

	High + High	5mg TDS + 450mg TDS	1
	High + Low	5mg TDS + 300mg TDS	1
Cefpodoxime – Ranitidine	Low + Low	100mg BD + 50mg BD	5
	Low + High	100mg BD + 50mg TDS	2
Metronidazole – Quinine	High + High	500mg TDS + 600mg TDS	5
	Low + Low	400mg TDS + 600mg BD	1
Domperidone – Ranitidine	High + Low	10mg TDS + 50mg BD	4
	Low + High	10mg BD + 50mg TDS	1
	High + High	10mg TDS + 50mg TDS	1
Dexamethasone – Rifampin	High + High	8mg TDS + 600mg OD	3
	Low + High	8mg BD + 600mg OD	1
	Low + Low	4mg TDS + 450mg OD	1
Ciprofloxacin – Metronidazole	High + Low	500mg BD + 500mg TDS	3
	High + Low	400mg BD + 500mg TDS	1
	Low + Low	250mg BD + 500mg TDS	1

-OD, once a day; BD, twice a day; QID, four times a day; TDS, three times a day; ATD, alternate day.

-[a]The terms low and high doses were used relatively. For defining higher daily doses the following cut off points were used, calcium containing products: ≥600mg/3L; ceftriaxone: ≥3gm; isoniazid: ≥300mg; rifampin: ≥450mg; pyrazinamide: ≥1500mg; acetaminophen: ≥1gm; prochlorperazine: ≥15mg; quinine: ≥1350mg; ranitidine: ≥150mg; metronidazole: ≥1500mg; domperidone: ≥30mg; dexamethasone: ≥24mg; and ciprofloxacin: ≥800mg.

Table 4. Clinical relevance and management guidelines/monitoring parameters of most frequent potential drug-drug interactions in patients with malaria

Interactions[a]	Dose categories[a]	Signs and symptoms[a]	Laboratory investigations[a]	Management guidelines/monitoring parameters
Calcium containing products – Ceftriaxone (52)	High + High (4)	Fever (3), sepsis (1)	Elevated BUN (1), elevated serum creatinine (1), leukocytosis (2)	Avoid mixing or administering ceftriaxone concomitantly with calcium-containing IV solutions or infusions in the same IV administration line through a Y-site. Monitor for signs of nephrotoxicity, thrombosis, precipitates deposition in lungs, or decreased ceftriaxone effectiveness.
	High + Low (5)	Fever (3)	Elevated BUN (3), leukocytosis (1)	
	Low + High (15)	Fever (4), cough (4), congested chest (2), chest pain (1), breathing difficulty (1)	Elevated BUN (5), elevated serum creatinine (5), leukocytosis (5)	
	Low + Low (28)	Cough (6), fever (4), chest pain (3), orthopnea (2), tachypnea (1), wheezing (1)	Elevated BUN (5), elevated serum creatinine (7), leukocytosis (3)	
Isoniazid – Rifampin (10)	High + High (6)	Vomiting (1), body aches (1), left hypochondrium pain (1)	Elevated ALT (1), elevated ALP (2)	Monitor for signs and symptoms of hepatotoxicity such as jaundice, vomiting, fever, and anorexia. Also monitor baseline and periodic LFTs.
	Low + High (2)	Anemia (1), pale (1), weakness (1), anorexia (1), body aches (1)	Elevated ALP (1)	
	Low + Low (2)	Body aches (1), pale (1), weight loss (1), ascites (1), hepatomegaly	Elevated ALT (1), elevated ALP (2)	

		(1), anorexia (1)		
Pyrazinamide – Rifampin (10)	High + High (6)	Vomiting (1), body aches (1), left hypochondrium pain (1)	Elevated ALT (1), elevated ALP (2)	Monitor for signs and symptoms of hepatotoxicity such as jaundice, vomiting, fever, and anorexia. Also monitor baseline and periodic LFTs.
	Low + High (2)	Anemia (1), pale (1), weakness (1), anorexia (1), body aches (1)	Elevated ALP (1)	
	Low + Low (2)	Body aches (1), pale (1), weight loss (1), ascites (1), hepatomegaly (1), anorexia (1)	Elevated ALT (1), elevated ALP (2)	
Isoniazid – Acetaminophen (9)	High + High (5)	Vomiting (1), body aches (1), left hypochondrium pain (1)	Elevated ALT (1), elevated ALP (1)	Monitor for signs and symptoms of hepatotoxicity such as jaundice, vomiting, fever, and anorexia. Also monitor baseline and periodic LFTs. Avoid concomitant administration of hepatotoxic drugs.
	Low + High (3)	Anorexia (2), pale (1), anemia (1), vomiting (1), weakness (1), body aches (1), ascites (1), hepatomegaly (1)	Elevated ALT (1), elevated ALP (2)	
	Low + Low (1)	Body aches (1), pale (1), weight loss (1)	Elevated ALP (1)	
Prochlorperazine – Quinine (8)	High + High (5)	Tachycardia (4), hypotension (3), hypertension (1)	Hypokalemia (1)	Monitor ECG and signs and symptoms of QT interval prolongation, specifically in patients at higher risk. Concomitant administration of QT interval prolonging drugs needs to be avoided.
	High + Low (1)	Hypotension 1)		
	Low + Low (2)	Hypotension (2),	Hypokalemia (1)	

		tachycardia (1), chest pain (1), confusion (1)		
Cefpodoxime – Ranitidine (7)	Low + High (2)	Fever (1)	-	Administer cefpodoxime at least 2 hours before ranitidine, or administer cefpodoxime with food. Monitor for improvement in patient condition.
	Low + Low (5)	Fever (2), urosepsis (1)	Leukocytosis (3)	
Metronidazole – Quinine (6)	High + High (5)	Tachycardia (3), hypotension (3), hypertension (1), confusion (1), chest pain (1)	Hypokalemia (2)	Monitor ECG and signs and symptoms of QT interval prolongation, specifically in patients at higher risk. Concomitant administration of QT interval prolonging drugs needs to be avoided.
	Low + Low (1)	Chest pain (1), tachycardia (1), hypotension (1)	-	
Domperidone – Ranitidine (6)	High + High (1)	Hypotension (1)	-	Monitoring for signs and symptoms of domperidone toxicity is suggested. Start domperidone at low dose then titrate gradually with caution. Discontinue domperidone if patient experiences syncope, palpitations, dizziness, or seizure. Also monitor ECG and signs and symptoms of prolonged QT interval.
	High + Low (4)	Tachycardia (4), hypertension (3), headache (2), confusion (1), hypotension (1)	-	
	Low + High (1)	Tachycardia (1), hypotension (1)	-	
Dexamethasone – Rifampin (5)	High + High (3)	Irritable (3), hypertension (2), hypotension (1), fatigue (1), nausea (1), vomiting (1)	Elevated FBS (2)	Monitor for signs and symptoms of adrenal insufficiency. Adjust dose of dexamethasone, if given combine.
	Low +	Drowsiness	-	

	High (1)	(1), hypotension (1)		
	Low + Low (1)	Vomiting (1), fever (1), hypotension (1)	-	
Ciprofloxacin – Metronidazole (5)	High + Low (4)	Hypotension (3), tachycardia (2), hypertension (1), orthopnea (1), chest pain (1)	-	Monitor ECG and signs and symptoms of QT interval prolongation, specifically in patients at higher risk. Concomitant administration of QT interval prolonging drugs needs to be avoided.
	Low + Low (1)	Dizziness (1), tachycardia (1)	Hypokalemia (1)	

-BUN, blood urea nitrogen; ALT, alanine aminotransferase; ALP, alkaline phosphatase; LFTs, liver function tests; FBS, fasting blood sugar.

-[a]Frequencies are given in parenthesis and calculated among patients with respective interaction.

Figures

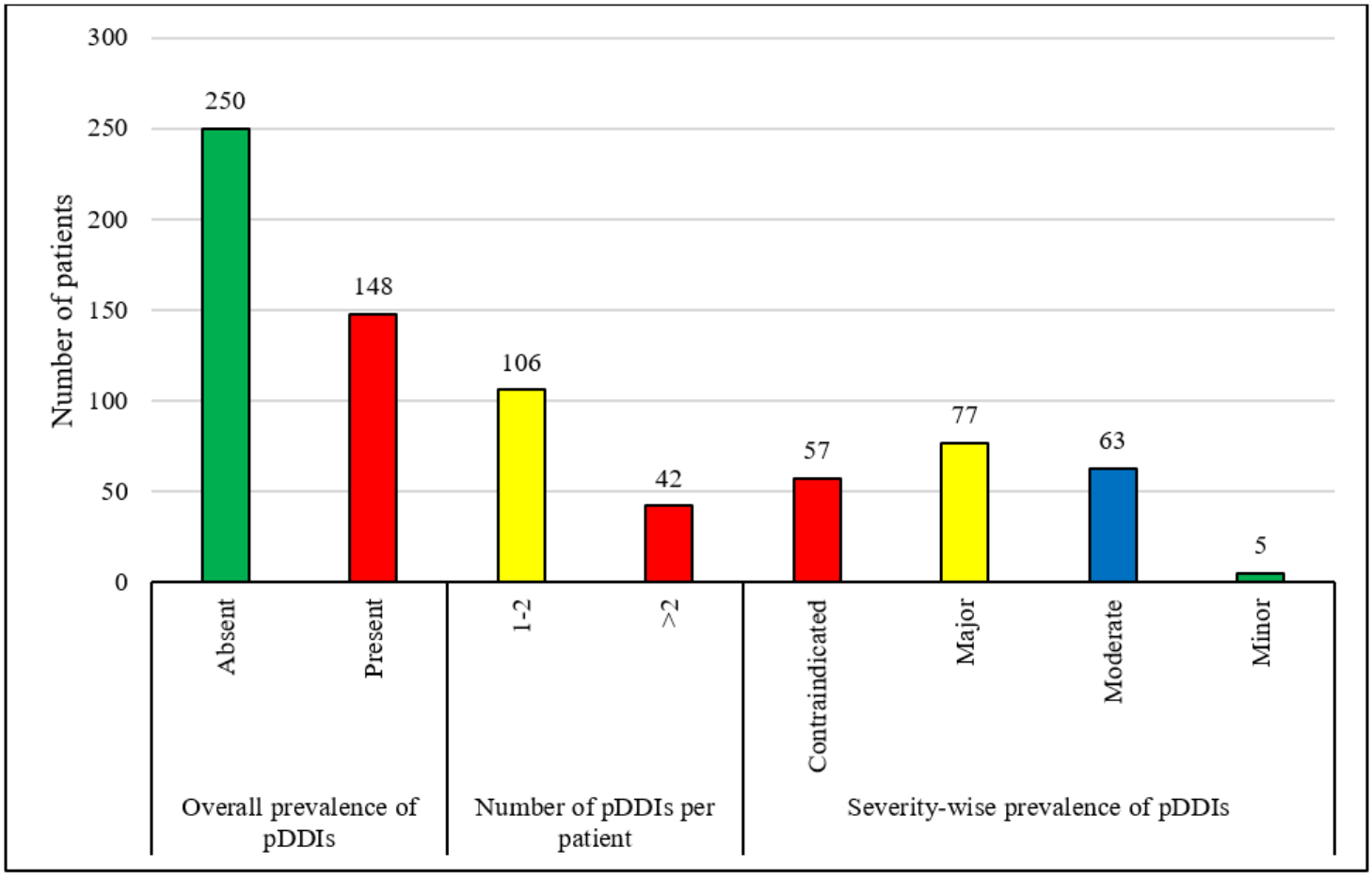

Figure 1

Prevalence of potential drug-drug interactions -pDDIs, potential drug-drug interactions. -Data are presented in the form of frequencies. -Overall-prevalence means the presence of at least one pDDI regardless of severity type. Study sample were 398 malaria patients. While, patients with pDDIs were 148 (overall prevalence of pDDIs = 37.2%). -PDDIs prevalence was also reported based on severity-levels.

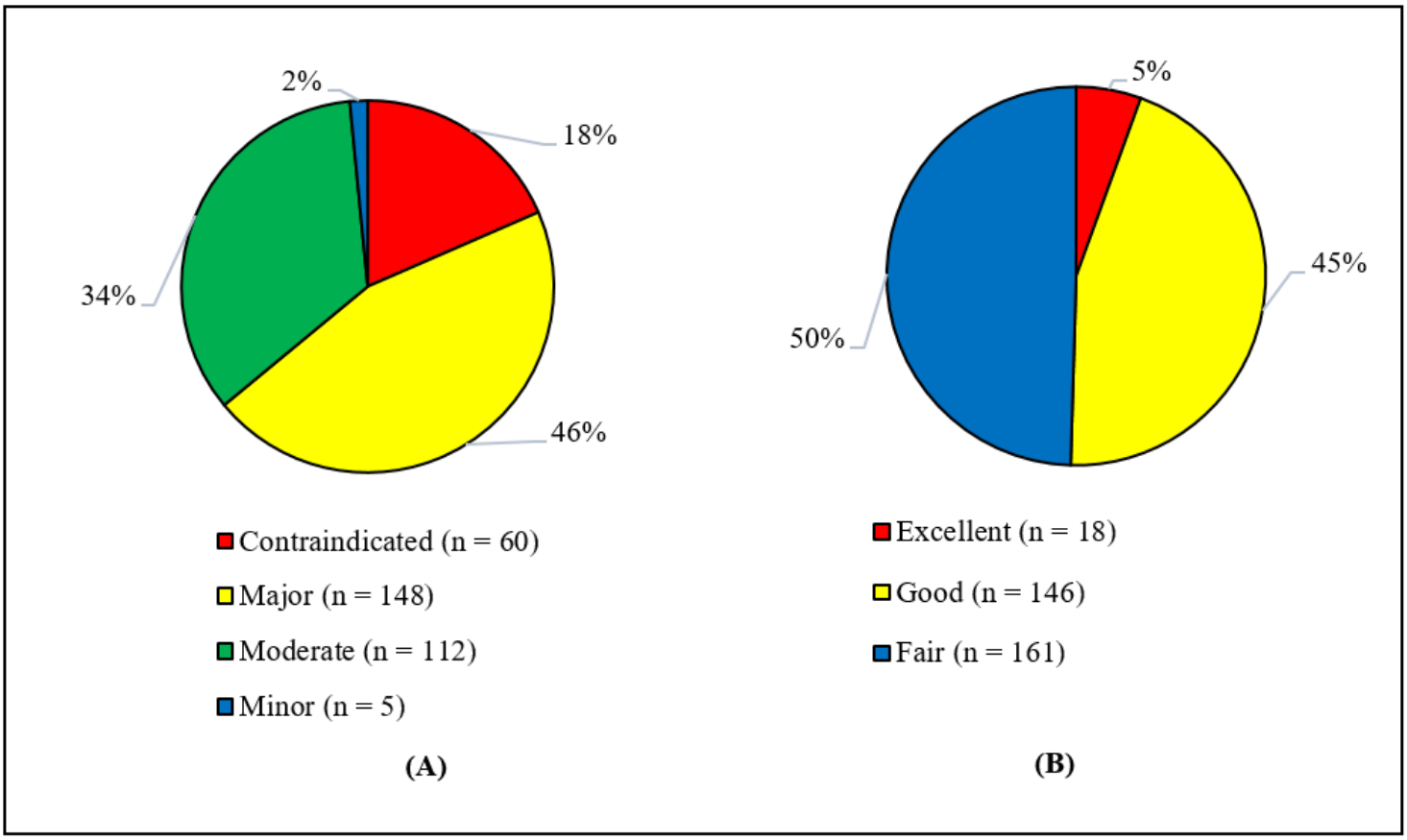

Figure 2

Levels of potential drug-drug interactions in patients with malaria. (A) Severity-levels of pDDIs. (B) Documentation-levels of pDDIs. -pDDIs, potential drug-drug interactions. -The total recorded pDDIs 325 were classified based on severity- and documentation-levels.

Supplementary Files

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