Drug-drug interactions in patients with malaria: a multicenter retrospective study

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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 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: ≥600 mg/3L;

- ceftriaxone: ≥3 gm; isoniazid: ≥300 mg; rifampin: ≥450 mg; pyrazinamide: ≥1500 mg;
- acetaminophen: ≥1 gm; prochlorperazine: ≥15 mg; quinine: ≥1350 mg; ranitidine: ≥150 mg;
- metronidazole: ≥1500 mg; domperidone: ≥30 mg; dexamethasone: ≥24 mg; and ciprofloxacin:
≥800 mg. Potential adverse effects in this study were defined as follows, leukocytosis: total leukocyte count > 11,000/µL; elevated blood urea nitrogen (BUN): BUN ≤ 20 mg/dL; elevated serum creatinine: serum creatinine > 1.06 mg/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) < 80 mmHg and/or diastolic BP < 50 mmHg; hypokalaemia: serum potassium < 3.5 mmol/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.

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)        |                                     |
| 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)        | -                                   |

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.

| 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           | -                     | -                    | -                     |
| 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           | -                     | -                    | -                     |
| 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           | -                     | -                    | -                     |
| 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 (1.4–8.4)        | 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
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.

**Table 3. Dose regimen of the prescribed interacting drugs**
-OD, once a day; BD, twice a day; QID, four times a day; TDS, three times a day; ATD, alternate day.

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.

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

| Interacting pair | Dose categoriesa | 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 |
| | Low + Low | 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 |
| | Low + 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 | 3 |
| | High + High | 5mg TDS + 450mg TDS | 1 |
| | Low + 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 + High | 500mg BD + 500mg TDS | 3 |
| | High + Low | 400mg BD + 500mg TDS | 1 |
| | Low + Low | 250mg BD + 500mg TDS | 1 |
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.

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

| Interactionsa | Dose categoriesa | Signs and symptomsa | Laboratory investigationsa | 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 (1), anorexia (1) | Elevated ALT (1), elevated ALP (2) | |
| Pyrazinamide – | High + High (6) | Vomiting (1), body aches | Elevated ALT (1), | Monitor for signs and |
| Drug Combination | Frequency | Symptoms | Monitoring/Action |
|------------------|----------|---------|------------------|
| Rifampin (10)    |          |         | Elevations ALP 2 | Symptoms of hepatotoxicity such as jaundice, vomiting, fever, and anorexia. Also monitor baseline and periodic LFTs. |
|                   |          |        | Elevated ALP 1   |         |
|                   |          |        | Elevated ALP 2   |         |
|                   |          |        | Elevated ALP 1   |         |
|                   |          |        | Elevated ALP 2   |         |
| Isoniazid – Acetaminophen (9) |          | Anemia 1, pale 1, weakness 1, anorexia 1, body aches 1 | Monitor baseline and periodic LFTs. Avoid concomitant administration of hepatotoxic drugs. |
|                   |          | Body aches 1, pale 1, weight loss 1, ascites 1, hepatomegaly 1, anorexia 1 |         |
|                   |          |        | Elevated ALP 2   |         |
|                   |          |        | Elevated ALP 2   |         |
| Prochlorperazine – Quinine (8) |          | Vomiting 1, body aches 1, left hypochondrium pain 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. |
|                   |          |        | Elevated ALP 2   |         |
|                   |          |        | Elevated ALP 2   |         |
| Cefpodoxime – Ranitidine (7) |          | Fever 1 | Administer cefpodoxime at least 2 hours before ranitidine, or administer cefpodoxime with food. Monitor for improvement in patient condition. |
|                   |          |        | Leukocytosis 3    |         |
| Metronidazole – Quinine (6) |          | Tachycardia 3, hypotension 3, chest pain 1, confusion 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. |
|                   |          |        | Hypokalemia 2     |         |
| Domperidone – Ranitidine (6) |          | 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. |
|                   |          |        |                 |         |
| Dexamethasone – Rifampin (5) |          | Irritable 3, hypotension 2, fatigue 1, nausea 1, vomiting 1 | Monitor for signs and symptoms of adrenal insufficiency. Adjust dose of dexamethasone, if given combine. |
|                   |          |        | Elevated FBS 2    |         |
|                   |          |        |                 |         |
| Ciprofloxacin – Metronidazole (5) |          | Vomiting 1, fever 1, hypotension 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. |
|                   |          |        |                 |         |

-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.
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 assensing 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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No funding has been taken for this study.

Authors' contributions

Both 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. SN and MI read and approved the final version of manuscript.

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Figures
Figure 1

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

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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