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RESEARCH ARTICLE

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# Clinical characteristics, complications, and predictors of outcome of hospitalized adult Sudanese patients with COVID-19 and malaria coinfection in Sudan: A multicenter retrospective cross-sectional study

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## Abstract

Malaria and coronavirus disease 2019 (COVID-19) share several characteristics that could lead to cross-infection, particularly in malaria-endemic areas. Early COVID-19 symptoms might be misdiagnosed for malaria in clinical settings. Also, both diseases can cause fatal complications. So, laboratory testing for both diseases was recommended by the World Health Organization. To study the clinical characteristics and outcomes of Adult Sudanese patients with COVID-19 and malaria coinfection. This retrospective cross-sectional study was conducted from January 2021 to October 2021 in Wad Medani. Total coverage of all Sudanese patients above 18 years old with a confirmed diagnosis of coinfection with COVID-19 and malaria was included, and data were collected using a data collection sheet. Data were analyzed using R software version 4.0.2. Data were described and presented as mean, standard deviation, and number (percentage). To find associated factors with in-hospital outcome, $\chi^2$ test, fisher exact test, and independent $t$ test or Wilcoxon rank-sum test were used. In this study, 156 participants were diagnosed with COVID-19 and malaria coinfection. Most of them were between 60 and 70 years (30.8%), the majority were males (59%). Shortness of breath (76.3%) and acute respiratory distress syndrome (35.3%) were the most common symptom and complications among coinfected patients, respectively. Ground glass opacity ($n$ = 47/49, 95.9%) is the most common result for computed tomography scan. Atrial fibrillation was the most common abnormal electrocardiogram finding ($n$ = 6/62, 9.7%). Overall mortality among all participants was (63/156, 40.4%). High mortality rate was found among the coinfected patients. More attention is needed towards fighting COVID-19 and malaria coinfection. There may be a link between malaria and COVID-19.

**KEYWORDS**

multicenter, coinfection, COVID-19, isolation centers, malaria, Sudan

  

## 1 | INTRODUCTION

Malaria is a mosquito-borne infectious disease caused by a plasmodium-like eukaryotic protest.[1] Malaria is one of Africa's most frequent endemic diseases, affecting 250 million people and killing one to three million people, usually children, in Sub-Saharan Africa.[2] *Plasmodium falciparum* and *P. vivax*, two morphologically identical sympatric species of *P. ovale* (as suggested by recent data), *P. malariae*, and the monkey malaria parasite *P. knowlesi* are the five species known to cause malaria in humans. *P. falciparum* produces more deadly infections, and patients can quickly develop complications such as severe anemia, acute renal injury, cerebral malaria, spontaneous bleeding and coagulopathy, and others. Its incubation period is about 10–15 days.[3] In 2020 there were about 241 million cases worldwide, Africa accounts for 95% of all cases. Southeast Asia is ranked second, followed by the eastern Mediterranean region, which is ranked third.[4] It is one of Sudan's endemic diseases and a severe public health issue. So up to date, almost 1.8 million malaria cases have been documented across Sudan.[4] Fever, headache, generalized fatigability, nausea, and vomiting are typical clinical manifestations of malaria. The severity of an infection is determined by a number of factors, including the *Plasmodium* species, the patient's immunity, and the infected person's overall health and nutritional status.[5,6] Malaria laboratory diagnosis by microscopic thin and thick film, which is the gold standard for malaria identification, as well as fast antigen testing (e.g., immunochromatography [ICT]) and nucleic acid amplification procedures, may aid in the detection of acute conditions.[7]

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, a single-stranded RNA virus belonging to the Coronaviruses family, causes coronavirus disease 2019 (COVID-19). The outbreak began in December 2019[8] in Wuhan, China, and was declared a pandemic in March 2020 because of its rapid expansion.[9] More than 250 million instances of COVID-19 have been verified to date, with total mortality estimated over 5 million cases. As of the December 15, 2021, there are 45 112 instances in Sudan, with 3252 deaths.[10] When encountered, the major method of transmission is through respiratory droplets from person to person,[11] with an incubation period of about 5 days.[12] COVID-19's most common clinical symptoms are fever and cough. Fatigue, myalgia, headaches, and diarrhea are some of the other common symptoms. The most prevalent laboratory finding is high C-reactive protein, followed by lymphopenia and leukopenia.[13] The real-time polymerase chain reaction (RT-PCR) is a standard approach for diagnosing COVID-19, although its sensitivity is only about 71%, compared with 98% for CT chest.[14] Bilateral, peripheral, lower-lobe ground-glass opacities, and/or consolidation are typical findings of COVID patients on CT scans.[15] Fever (70%–90%), dry cough (60%–86%), shortness of breath (53%–80%), fatigue (38%), myalgias (15%–44 %), nausea/vomiting or diarrhea (15%–39%), headache, weakness (25%), and rhinorrhea (7%) are among the most common symptoms in admitted patients.[16] Pneumonia and acute respiratory distress syndrome are two of COVID-19's most common consequences (ARDS). Additionally, COVID has been linked to acute liver, heart, and renal injury.[17] Age, comorbidities, immunological response, radiographic findings, laboratory data, and signs of organ dysfunction are all characteristics that might help predict the severity of the disease.[18]

Malaria and COVID-19 share several characteristics that could lead to cross-infection, particularly in malaria-endemic areas. Early COVID-19 symptoms, such as fever, myalgia, and exhaustion, might be mistaken for malaria in clinical settings. Adult respiratory distress syndrome (ARDS) is a complication of both of them.[19,20] In the meanwhile, many investigations have found that malaria and COVID-19 coinfection can be diagnosed by positive lab findings for both infections.[21–23] As a result, the World Health Organization (WHO) said that the existence of one disease does not imply the absence of the other. This implies the need to do laboratory testing for both disorders.[24]

Approximately 270 million COVID-19 cases have been reported worldwide, with over 5 million deaths. From January 3, 2020, Sudan has around 45 000 confirmed cases and over 3000 deaths so far. In 2020, an estimated 241 million cases of malaria will have been reported worldwide, resulting in roughly 627 000 fatalities, with Africa bearing the brunt of the burden, particularly in the African Sub-Saharan area.

Aside from what has already been stated. Malaria and COVID-19 pose a serious threat to Sudan's already-fragmented health system. In addition, the mutual side effects of each of them add to the difficulty of determining the optimal care regimens for such deadly conditions. There was a scarcity in the literature regarding this topic, so we aimed at throwing a stone in a pond of water. In this study our aim was to assess the presenting symptoms of malaria and COVID-19 coinfection, to find complications of malaria and COVID-19 coinfection, to describe laboratory, X-ray, computed tomography (CT), and electrocardiogram (ECG) findings, and to assess the predictors of outcomes of malaria and COVID-19 coinfection.

## 2 | METHODS AND MATERIALS

### 2.1 | Study design and area

This was a retrospective cross-sectional study that was conducted from January 2021 to October 2021 in Wad Medani (the capital of Gezira state) which is the second largest state in Sudan, with a total population of 4 133 048. This city, composed of 32 secondary and tertiary hospitals, receives patients from Gezira, Sinnar, Blue Nile, Kassala, Gadarif, and White Nile states. Two isolation centers were involved in the study. The first (Soqatra isolation center) is composed of 65 beds for mild to moderate cases divided into a general ward (45 beds) and a high dependency unit (HDU) containing 20 beds, 24-h laboratory, pharmacy, and two ambulances. The second (Mycetoma center) for critical cases with a capacity of 10 inensive care unit (ICU) beds supplemented with 10 mechanical ventilators and two hemodialysis machines in addition to a laboratory, pharmacy, and two ambulances. The two centers are referral centers that receive

patients from all middle, eastern, and southern Sudan states (six states).

## 2.2 | Participants

We included all Sudanese patients above 18 years old with a confirmed diagnosis of co-infection with COVID-19 by RT-PCR and malaria by microscopy. All patients less than 18 years old or who tested negative for COVID-19 were excluded.

## 2.3 | Sampling

A total coverage for all consecutive patients was done in this study during the period of data collection.

## 2.4 | Data collection

Data were collected by a well-trained general practitioner using a data collection sheet containing the following items:

1. Demographic data and risk factors.
2. Vital signs (diastolic blood pressure, systolic blood pressure, respiratory rate, pulse, and oxygen saturation).
3. Presenting complaints of COVID-19 and malaria.
4. Complication of COVID-19 and malaria.
5. Laboratory investigations (WBC, hemoglobin, platelets, lymphocyte, C-reactive protein, creatinine, blood urea nitrogen, D-dimer, and random blood glucose).
6. Chest X-ray, CT, and ECG findings.
7. Length of stay.
8. In-hospital outcome (death or discharge).

## 2.5 | Data analysis

Data were analyzed using R software version 4.0.2. Data were described and presented as mean ± standard deviation (*SD*) and number (%age). To find associated factors with in-hospital outcome, $\chi^2$ test, Fisher exact test, and independent *t* test or Wilcoxon rank-sum test were used.

## 2.6 | Ethical considerations

Ethical approval was obtained from the Ministry of Higher Education, University of Gezira, Gezira State, Sudan. The ethical approval of each center's ethical committee was acquired. Both written and verbal consents were obtained from the participants or their guardians. Privacy and protection of the participant's files and information were of the highest priority.

# 3 | RESULT

## 3.1 | Characteristics of participants

In this study, 156 participants diagnosed with COVID-19 and malaria co-infection with mean ± *SD* of 65.2 ± 14.5 participated in this study. Most of them were between 60 and 70 years (30.8%) followed by 71–80 years (23.7%). Nearly half of the participants were males (59%). Hypertension (37.2%) and diabetes (38.5%) were the most common risk factors. The mean respiratory rate was 29.8 ± 9.8 breaths per minute. All species of malaria were *P. falciparum* except one participant with *P. vivax* (Table 1).

## 3.2 | Clinical presentation and complications

Shortness of breath (76.3%), and fever (73.1%) were the most common symptoms among coinfected participants.

Regarding complications, acute respiratory distress syndrome (35.3%), thrombocytopenia (16.0%), and acute kidney injury (8.3%) were reported as the most common complications of COVID-19 and malaria coinfection (Table 2).

## 3.3 | Clinical investigations

Overall mean of total white blood cells and C-reactive protein were 11.5 ± 8.5 and 233.3 ± 746.0, respectively. Other laboratory investigations were shown in Table 3.

Nearly more than two-third of urine samples (82.7%) were normal. The mean concentration of blood urea nitrogen was 61.6 ± 43.8 (Tables 3 and 4).

Bilateral consolidation was found in more than half of the participants who requested chest X-ray ($n = 9/16$, 56.2%). But for CT findings, most participants were having ground-glass opacity ($n = 47/49$, 95.9%). ECG findings were found normal in more than half of the participants ($n = 33/62$, 53.2%) and atrial fibrillation was the most common abnormal ECG finding ($n = 6/62$, 9.7%) (Table 4).

## 3.4 | Predictors of outcomes

Overall mortality among all participants was (63/156, 40.4%). Shorter length of stay ($p = 0.003$), usage of respiratory support ($p < 0.001$), presence of acute respiratory distress syndrome ($p < 0.001$), presence of black water fever ($p = 0.031$), and low platelets count ($p = 0.035$) were found significantly associated with death in hospital (Tables 1–4).

During using nonparametric tests, increased respiratory rate ($p = 0.037$) and high serum creatinine ($p = 0.035$) were found significantly associated with death in the hospital (Tables 1 and 3).

**TABLE 1** Baseline characteristics, risk factors, and vital signs in participants.

| Variables | *N* | Overall, *N* = 156[a] | Outcome | | *p* Value[b] |
|---|---|---|---|---|---|
| | | | Death, *N* = 63[a] | Discharge, *N* = 93[a] | |
| Age, years | 156 | | | | |
| Mean ± *SD* | | 65.2 ± 14.5 | 67.1 ± 14.4 | 63.9 ± 14.6 | 0.2 |
| Median (interquartile range) | | 65.0 (57.8–75.0) | 70.0 (60.0–78.5) | 65.0 (55.0–75.0) | 0.11 |
| Age (groups) | 156 | | | | 0.7 |
| 20–30 | | 4 (2.6%) | 2 (3.2%) | 2 (2.2%) | |
| 31–40 | | 4 (2.6%) | 0 (0.0%) | 4 (4.3%) | |
| 41–50 | | 20 (12.8%) | 8 (12.7%) | 12 (12.9%) | |
| 51–60 | | 27 (17.3%) | 9 (14.3%) | 18 (19.4%) | |
| 61–70 | | 48 (30.8%) | 20 (31.7%) | 28 (30.1%) | |
| 71–80 | | 37 (23.7%) | 16 (25.4%) | 21 (22.6%) | |
| 81–90 | | 16 (10.3%) | 8 (12.7%) | 8 (8.6%) | |
| Gender | 156 | | | | >0.9 |
| Female | | 64 (41.0%) | 26 (41.3%) | 38 (40.9%) | |
| Male | | 92 (59.0%) | 37 (58.7%) | 55 (59.1%) | |
| Marital status | 156 | | | | 0.7 |
| Married | | 131 (84.0%) | 53 (84.1%) | 78 (83.9%) | |
| Single | | 10 (6.4%) | 5 (7.9%) | 5 (5.4%) | |
| Widow | | 15 (9.6%) | 5 (7.9%) | 10 (10.8%) | |
| Length of stay (duration of illness), days | 144 | | | | |
| | | 7.0 ± 5.3 | 5.4 ± 4.3 | 8.1 ± 5.7 | **0.003** |
| | | 6.0 (3.0, 10.0) | 4.0 (2.0, 7.0) | 7.0 (3.0, 10.0) | **0.003** |
| Recent travel history (last 2 months) | 156 | 9 (5.8%) | 6 (9.5%) | 3 (3.2%) | 0.2 |
| Residence | 149 | | | | 0.4 |
| Kordofan state | | 1 (0.7%) | 1 (1.7%) | 0 (0.0%) | |
| Wad Medani | | 148 (99.3%) | 59 (98.3%) | 89 (100.0%) | |
| Occupation | 150 | | | | 0.056 |
| Housewife | | 26 (17.3%) | 12 (20.0%) | 14 (15.6%) | |
| Nonskilled laborer | | 13 (8.7%) | 4 (6.7%) | 9 (10.0%) | |
| Not working | | 65 (43.3%) | 33 (55.0%) | 32 (35.6%) | |
| Professional | | 20 (13.3%) | 4 (6.7%) | 16 (17.8%) | |
| Skilled laborer | | 26 (17.3%) | 7 (11.7%) | 19 (21.1%) | |
| Usage of respiratory support | 152 | 47 (30.9%) | 29 (46.8%) | 18 (20.0%) | **<0.001** |
| Previous medical history | 156 | | | | |
| Previous hospital admission | | 1 (0.6%) | 1 (1.6%) | 0 (0.0%) | 0.4 |
| DM | | 60 (38.5%) | 21 (33.3%) | 39 (41.9%) | 0.3 |
| Asthma | | 7 (4.5%) | 4 (6.3%) | 3 (3.2%) | 0.4 |
| COPD | | 2 (1.3%) | 0 (0.0%) | 2 (2.2%) | 0.5 |

**TABLE 1** (Continued)

| Variables | N | Overall, N = 156[a] | Outcome | | p Value[b] |
|---|---|---|---|---|---|
| | | | Death, N = 63[a] | Discharge, N = 93[a] | |
| HTN | | 58 (37.2%) | 26 (41.3%) | 32 (34.4%) | 0.4 |
| Immunodeficiency | | 1 (0.6%) | 0 (0.0%) | 1 (1.1%) | >0.9 |
| Cancer | | 5 (3.2%) | 2 (3.2%) | 3 (3.2%) | >0.9 |
| Recent surgery | | 2 (1.3%) | 0 (0.0%) | 2 (2.2%) | 0.5 |
| Others | | 46 (29.5%) | 24 (38.1%) | 22 (23.7%) | 0.052 |
| Malaria species | 145 | | | | >0.9 |
| *Plasmodium falciparum* | | 144 (99.3%) | 59 (100.0%) | 85 (98.8%) | |
| *P. vivax* | | 1 (0.7%) | 0 (0.0%) | 1 (1.2%) | |
| Vital signs | | | | | |
| Pulse rate, beat/min | 149 | | | | |
| Mean ± *SD* | | 96.6 ± 20.5 | 96.9 ± 21.1 | 96.4 ± 20.1 | 0.9 |
| Median (interquartile range) | | 93.0 (84.0–107.0) | 95.0 (86.0–106.0) | 90.0 (84.0–109.0) | >0.9 |
| Systolic blood pressure, mmHg | 150 | | | | |
| Mean ± *SD* | | 124.3 ± 24.5 | 122.4 ± 29.5 | 125.7 ± 20.4 | 0.4 |
| Median (interquartile range) | | 120.0 (110.0–140.0) | 120.0 (109.0–140.0) | 130.0 (110.0–140.0) | 0.2 |
| Diastolic blood pressure, mmHg | 149 | | | | |
| Mean ± *SD* | | 73.6 ± 12.0 | 71.9 ± 13.1 | 74.8 ± 11.1 | 0.14 |
| Median (interquartile range) | | 70.0 (70.0–80.0) | 70.0 (70.0–80.0) | 75.0 (70.0–80.0) | 0.2 |
| Respiratory rate, breath/min | 124 | | | | |
| Mean ± *SD* | | 29.8 ± 9.8 | 30.7 ± 7.9 | 29.2 ± 11.0 | 0.4 |
| Median (interquartile range) | | 28.0 (24.0–34.0) | 30.0 (25.5–34.5) | 26.0 (22.0–32.0) | **0.037** |

Abbreviations: COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, hypertension; *SD*, standard deviation.

[a]Median (IQR); mean ± *SD*; *n* (%).

[b]Wilcoxon rank-sum test; two sample *t* test; Fisher's exact test; Pearson's $\chi^2$ test.

## 4 | DISCUSSION

In this study, we report the presenting symptoms and outcome of Adult Sudanese patients coinfected with COVID-19 and Malaria who were admitted to two isolation centers in Wad Madani, Sudan. Understanding clinical features and outcomes of COVID19 and malaria coinfections is essential for accurate diagnosis and predictability of treatment when a patient develops complications, to alleviate symptoms and reduce morbidity and mortality. To our knowledge, this is the first retrospective observational study providing clinical characteristics and outcomes of COVID19 and Malaria co-infection in Sudan, and one of the few in the whole literature. We found that the most common symptoms seen on presentation among coinfected participants include: shortness of breath (76.3%) and fever (73.1%). We found the overall mortality among all participants to be 40.4% (*n* = 63).

During this crisis period, a malaria case may be misclassified as COVID-19 due to symptoms that resemble COVID-19 such as fever, difficulty breathing, fatigue, and headaches of acute onset.[25] At present, given the alertness occurring at the community, health center, nation, regional, and global levels, it is expected that COVID-19 will remain the main target of suspicion; even though co-infection may be present. Sudan faces a number of other infectious diseases that must not be ignored. COVID-19 places additional strain on the already overburdened and resource-constrained health services, which are struggling to keep in check the high burden of existing infectious diseases and noninfectious diseases, such as malaria -which can be misdiagnosed as COVID-19 if it exhibits similar symptoms. Challenges arise from the fact that people with fever are more likely to be tested for COVID-19 and sent home as a result of a negative result, and conversely, febrile patients may be tested for malaria when they are in fact infected with

**TABLE 2** Clinical presentations and complication of COVID-19 and malaria coinfection.

| Variables | N | Overall, N = 156[a] | Outcome | | p Value[b] |
|---|---|---|---|---|---|
| | | | Death, N = 63[a] | Discharge, N = 93[a] | |
| COVID-19 and malaria general symptoms | 156 | | | | |
| Fever | | 114 (73.1%) | 46 (73.0%) | 68 (73.1%) | >0.9 |
| Cough | | 104 (66.7%) | 43 (68.3%) | 61 (65.6%) | 0.7 |
| Loss of smell | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Nasal obstruction | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Loss of taste | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Gustatory dysfunction | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Sore throat | | 3 (1.9%) | 2 (3.2%) | 1 (1.1%) | 0.6 |
| Shortness of breath | | 119 (76.3%) | 48 (76.2%) | 71 (76.3%) | >0.9 |
| Chest pain | | 6 (3.8%) | 1 (1.6%) | 5 (5.4%) | 0.4 |
| Myalgia | | 1 (0.6%) | 0 (0.0%) | 1 (1.1%) | >0.9 |
| Decrease level of consciousness | | 22 (14.1%) | 12 (19.0%) | 10 (10.8%) | 0.14 |
| Headache | | 10 (6.4%) | 5 (7.9%) | 5 (5.4%) | 0.5 |
| Chills | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Sleep disturbance | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Shivering | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Nausea | | 2 (1.3%) | 1 (1.6%) | 1 (1.1%) | >0.9 |
| Vomiting | | 11 (7.1%) | 6 (9.5%) | 5 (5.4%) | 0.4 |
| Diarrhea | | 9 (5.8%) | 6 (9.5%) | 3 (3.2%) | 0.2 |
| Others | | 18 (11.5%) | 5 (7.9%) | 13 (14.0%) | 0.2 |
| Complications of COVID-19 and malaria coinfection | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Acute respiratory distress syndrome | | 55 (35.3%) | 40 (63.5%) | 15 (16.1%) | **<0.001** |
| Heart failure | | 6 (3.8%) | 1 (1.6%) | 5 (5.4%) | 0.4 |
| Myocarditis | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Pulmonary embolism | | 2 (1.3%) | 2 (3.2%) | 0 (0.0%) | 0.2 |
| Dizziness | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Peripheral neuropathy | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Encephalitis | | 1 (0.6%) | 1 (1.6%) | 0 (0.0%) | 0.4 |
| Convulsions | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Stroke | | 3 (1.9%) | 0 (0.0%) | 3 (3.2%) | 0.3 |
| Gillian–Barrett syndrome | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Acute kidney injury | | 13 (8.3%) | 6 (9.5%) | 7 (7.5%) | 0.7 |
| Sepsis | | 8 (5.1%) | 5 (7.9%) | 3 (3.2%) | 0.3 |
| Hypoalbuminemia | | 1 (0.6%) | 0 (0.0%) | 1 (1.1%) | >0.9 |
| Hyponatremia | | 1 (0.6%) | 0 (0.0%) | 1 (1.1%) | >0.9 |
| Dysenteric malaria | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Biliuoric malaria | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |

**TABLE 2** (Continued)

| Variables | N | Overall, N = 156[a] | Outcome | | p Value[b] |
|---|---|---|---|---|---|
| | | | Death, N = 63[a] | Discharge, N = 93[a] | |
| Choleric malaria | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Malaria induced hepatitis | | 3 (1.9%) | 2 (3.2%) | 1 (1.1%) | 0.6 |
| Malaria pneumonitis | | 2 (1.3%) | 1 (1.6%) | 1 (1.1%) | >0.9 |
| Cerebral malaria | | 12 (7.7%) | 6 (9.5%) | 6 (6.5%) | 0.5 |
| Black water fever | | 9 (5.8%) | 7 (11.1%) | 2 (2.2%) | **0.031** |
| Algid malaria | | 4 (2.6%) | 3 (4.8%) | 1 (1.1%) | 0.3 |
| Thrombocytopenia | | 25 (16.0%) | 9 (14.3%) | 16 (17.2%) | 0.6 |
| Pulmonary edema | | 2 (1.3%) | 1 (1.6%) | 1 (1.1%) | >0.9 |
| Anemia | | 11 (7.1%) | 6 (9.5%) | 5 (5.4%) | 0.4 |
| Cerebllities | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Gillian–Barrett syndrome | | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | |
| Others (pancytopenia, psychosis, and sepsis) | | 3 (1.9%) | 0 (0.0%) | 3 (3.2%) | 0.3 |

Abbreviation: COVID-19, coronavirus disease 2019.

[a]*n*(%).

[b]Fisher's exact test; Pearson's $\chi^2$ test.

COVID-19; in other words, a patient may be infected with malaria and COVID-19 at the same time, and diagnosis and treatment of one may cause the other to be missed.[25] Malaria has been reported to threaten nearly half of the world's population as of 2018.[26] The deadly strain of *P. falciparum* malaria poses a challenge because it has the potential to result in severe cases; in Africa, *P. falciparum* is the most prevalent and deadliest malaria parasite causing the most severe malaria cases overall.[27,28] It's reported in the literature that Malaria infections caused by *P. falciparum* account for approximately 90% of global malaria mortality.[29,30] Regarding the prevalence of malaria species in Sudan, the majority (91%) are cases of severe falciparum infection, while *P. vivax* accounts for 8 (%) cases.[31] Overall Malaria incidence in Sudan was 12.4 % of all diseases that were reported, over 1.8 million cases are detected with a 13 per 10 000 mortality rate in 2019[4] which is considered low in comparison to the mortality rate (4.8%) in 2002.[32] Untreated malaria is a leading cause of illness and death in the developing world due to the further infectious among community.[33,34] On the other hand, up to 3.58 susceptible individuals can be infected by a single case of COVID-19.[35] Given that both COVID19 or malaria can cause severe disease, and both are highly infectious; then, coinfection is expected to occur—especially in areas endemic with malaria-like Sudan—and it's expected to be even more fatal than either of the two—COVID19 or malaria—isolated.

Overall mortality rate of COVID-19—mono-infection—is approximately 1%–14% in international studies, as well as 7.1% in Sudan.[36,37] However, the overall mortality rate of a country is not always representative for every state in that country. The majority of COVID-19 cases are in Khartoum state—the capital of Sudan—where the majority of health facilities are available, yet most of the deaths of the disease have been reported from areas outside the capital.[38] Regarding the comparison of coinfection mortality rate against mortality rate of COVID-19 isolated infection; the mortality rate in our study 40.4% ($n = 63$)—which is done in Gezira state— is comparable with a study done in Al Gadarif state, Eastern Sudan; that showed a high mortality rate of COVID-19—alone—of 37.5%.[39] And regarding comparison with other co-infection studies, the overall mortality among our coinfected participants was 40.4% ($n = 63$), in contrast to a cohort study done in Uganda that showed a mortality rate among COVID-19 and malaria coinfected patients of only 3%.[40] We believe that coinfection has a vital role prompting a high mortality rate due to the increased inflammatory response; also, we assume the mortality rate in our study to be inflated due to other factors; such as the lack of fundamental resources (lifesaving resources and adequate staff). *P. falciparum* overall mortality is difficult to obtain due to scarcity of data; but as stated in a study, *P. falciparum* mono infection overall mortality in Sudan, was approximately 0.13% in 2019.[4] It is considered low in comparison with the high mortality of coinfection in our study (40.4%). The substantial disparity in death rates is most likely related to two factors: one being the long history of endemic malaria in Sudan, which gave most of the community the knowledge, awareness, and immunity to avoid further severe infection, in addition to the cumulative experience gained by the health staff regarding responding to the infection; the other factor being the enhanced severity of disease during coinfection.

Other COVID19 coinfections have been documented, for instance, the co-infection of Dengue virus and COVID19 has been reported.[41] Dengue and Chikungunya—which are two zoonotic

**TABLE 3** Laboratory investigations in participants.

| Variables | *N* | Overall, *N* = 156[a] | Outcome | | *p* Value[b] |
|---|---|---|---|---|---|
| | | | Death, *N* = 63[a] | Discharge, *N* = 93[a] | |
| Lab findings | | | | | |
| WBCs counts, × $10^3$/L | 155 | | | | |
| Mean ± *SD* | | 11.5 ± 8.5 | 11.7 ± 9.6 | 11.3 ± 7.8 | 0.7 |
| Median (interquartile range) | | 9.7 (6.8–13.4) | 9.9 (6.9–13.0) | 9.6 (6.7–13.6) | 0.8 |
| Hemoglobin, g/dL | 153 | | | | |
| Mean ± *SD* | | 11.9 ± 2.0 | 11.6 ± 2.2 | 12.1 ± 1.8 | 0.13 |
| Median (interquartile range) | | 12.0 (10.6–13.3) | 11.7 (10.3–13.2) | 12.1 (10.8–13.4) | 0.3 |
| Platelets, × $10^9$/L | 148 | | | | |
| Mean ± *SD* | | 248.9 ± 175.9 | 212.0 ± 119.9 | 274.0 ± 202.4 | **0.035** |
| Median (interquartile range) | | 210.0 (134.8–310.8) | 194.0 (126.8–247.5) | 217.0 (144.2–350.8) | 0.091 |
| Lymphocyte, × $10^3$/L | 116 | | | | |
| Mean ± *SD* | | 3.5 ± 7.3 | 4.3 ± 9.8 | 3.1 ± 5.4 | 0.4 |
| Median (interquartile range) | | 1.2 (0.8–2.0) | 1.2 (0.6–2.0) | 1.3 (0.9–2.0) | 0.5 |
| CRP, mg/dL | 114 | | | | |
| Mean ± *SD* | | 233.3 ± 746.0 | 143.7 ± 92.2 | 289.6 ± 947.6 | 0.3 |
| Median (interquartile range) | | 105.5 (72.5–200.0) | 108.5 (83.2–244.2) | 93.5 (65.2–198.8) | 0.3 |
| Creatinine, mg/dL | 144 | | | | |
| Mean ± *SD* | | 1.7 ± 2.0 | 1.8 ± 1.4 | 1.6 ± 2.3 | 0.5 |
| Median (interquartile range) | | 1.1 (0.9–1.7) | 1.2 (0.9–2.1) | 1.1 (0.9–1.5) | **0.035** |
| Blood urea nitrogen, mg/dL | 65 | | | | |
| Mean ± *SD* | | 61.6 ± 43.8 | 69.5 ± 41.6 | 56.0 ± 45.1 | 0.2 |
| Median (interquartile range) | | 49.0 (33.0–71.0) | 59.0 (43.5–76.5) | 44.0 (32.0–68.5) | 0.069 |
| D-dimer, mcg/ml | 113 | | | | |
| Mean ± *SD* | | 4102.3 ± 3656.7 | 4276.0 ± 3916.9 | 3974.1 ± 3477.6 | 0.7 |
| Median (interquartile range) | | 2510.0 (1200.0–6939.0) | 2459.4 (1327.8–7164.2) | 2662.0 (1189.0–6238.0) | 0.7 |
| Random blood sugar, mg/dL | 82 | | | | |
| Mean ± *SD* | | 197.9 ± 118.5 | 195.9 ± 105.3 | 199.5 ± 129.1 | 0.9 |
| Median (interquartile range) | | 158.5 (125.2–238.8) | 156.5 (127.2–228.2) | 165.5 (120.8–238.8) | >0.9 |
| $SpO_2$, %age | 147 | | | | |
| Mean ± *SD* | | 79.7 ± 16.0 | 76.8 ± 17.9 | 81.6 ± 14.4 | 0.078 |
| Median (interquartile range) | | 85.0 (72.0–90.0) | 80.0 (66.0–88.0) | 85.0 (74.0–92.0) | 0.1 |

Abbreviation: *SD*, standard deviation.

[a]Median (IQR); mean ± *SD*.

[b]Wilcoxon rank-sum test; two sample *t* test.

arboviral diseases - are endemic in Sudan, as well as malaria.[42,43] Tropical and subtropical countries experience high levels of infection with Dengue virus and Chikungunya virus during the monsoon season, and co-occurrence has been documented.[44] Malaria and dengue virus coinfection, as well as malaria and Chikungunya virus coinfection have been reported in Sudan.[43,45] A co-infection with any or all of malaria, dengue virus, and Chikungunya virus; with COVID19 is predicted during the rainy season due to favorable breeding conditions for the mosquitoes, at the same time as the COVID19 pandemic could have a significant impact on public health.[46]

Fever, cough, and lethargy are frequent symptoms of COVID-19.[47] Malaria symptoms are many; low-grade fever, shivering chills, and muscle pain, as well as gastrointestinal issues in children, are common first complaints. Such symptoms may appear abruptly,

**TABLE 4** Urine analysis, Chest X-ray, CT, and ECG findings.

| Variables | N | Overall, N = 156[a] | Outcome | | p Value[b] |
|---|---|---|---|---|---|
| | | | Death, N = 63[a] | Discharge, N = 93[a] | |
| Urine analysis | 156 | | | | 0.093 |
| Bilirubin | | 1 (0.6%) | 1 (1.6%) | 0 (0.0%) | |
| Granular cast | | 1 (0.6%) | 1 (1.6%) | 0 (0.0%) | |
| Normal | | 10 (6.4%) | 1 (1.6%) | 9 (9.7%) | |
| Not done | | 129 (82.7%) | 52 (82.5%) | 77 (82.8%) | |
| Protein | | 3 (1.9%) | 2 (3.2%) | 1 (1.1%) | |
| Pus cells | | 7 (4.5%) | 4 (6.3%) | 3 (3.2%) | |
| RBCS | | 1 (0.6%) | 1 (1.6%) | 0 (0.0%) | |
| Sugar | | 4 (2.6%) | 1 (1.6%) | 3 (3.2%) | |
| COVID-19 diagnosis tool | 156 | | | | |
| RT-PCR | | 99 (63.5%) | 37 (58.7%) | 62 (66.7%) | 0.3 |
| CT | | 54 (34.6%) | 21 (33.3%) | 33 (35.5%) | 0.8 |
| Clinical | | 13 (8.3%) | 7 (11.1%) | 6 (6.5%) | 0.3 |
| Chest X-ray findings | 16 | | | | **0.019** |
| Bilateral consolidation | | 9 (56.2%) | 0 (0.0%) | 9 (75.0%) | |
| Bilateral infiltration + suspected diaphragmatic hernia + lung collapse | | 1 (6.2%) | 0 (0.0%) | 1 (8.3%) | |
| Bilateral peripheral lung consolidation | | 1 (6.2%) | 1 (25.0%) | 0 (0.0%) | |
| Cardiomegaly + right side consolidation | | 1 (6.2%) | 1 (25.0%) | 0 (0.0%) | |
| Congestion + consolidation | | 1 (6.2%) | 1 (25.0%) | 0 (0.0%) | |
| Midzone bilateral consolidation | | 1 (6.2%) | 1 (25.0%) | 0 (0.0%) | |
| Right side middle lobe consolidation | | 1 (6.2%) | 0 (0.0%) | 1 (8.3%) | |
| Right side pleural effusion | | 1 (6.2%) | 0 (0.0%) | 1 (8.3%) | |
| Respiratory investigation COVID related CT chest | 49 | | | | |
| Ground grass opacity | | 47 (95.9%) | 21 (100.0%) | 26 (92.9%) | 0.5 |
| Pleural effusion | | 1 (2.0%) | 0 (0.0%) | 1 (3.6%) | >0.9 |
| Patchy or lobar consolidation | | 3 (6.1%) | 1 (4.8%) | 2 (7.1%) | >0.9 |
| Alveolar congestion and fibrotic change | | 1 (2.0%) | 0 (0.0%) | 1 (3.6%) | >0.9 |
| ECG findings | 62 | | | | **0.035** |
| Atrial fibrillation | | 6 (9.7%) | 6 (23.1%) | 0 (0.0%) | |
| Atrial tachycardia | | 1 (1.6%) | 1 (3.8%) | 0 (0.0%) | |
| Complete heart block | | 1 (1.6%) | 0 (0.0%) | 1 (2.8%) | |
| Hyperacute T-wave | | 1 (1.6%) | 0 (0.0%) | 1 (2.8%) | |
| Left anterior descending artery occlusion | | 5 (8.1%) | 2 (7.7%) | 3 (8.3%) | |
| Left anterior descending artery occlusion bradycardia | | 1 (1.6%) | 1 (3.8%) | 0 (0.0%) | |
| Left anterior descending artery occlusion + R-wave in v1 | | 1 (1.6%) | 1 (3.8%) | 0 (0.0%) | |
| Left bundle branch block | | 3 (4.8%) | 1 (3.8%) | 2 (5.6%) | |

(Continues)

**TABLE 4** (Continued)

| Variables | N | Overall, N = 156[a] | Outcome | | p Value[b] |
|---|---|---|---|---|---|
| | | | Death, N = 63[a] | Discharge, N = 93[a] | |
| Normal | | 33 (53.2%) | 11 (42.3%) | 22 (61.1%) | |
| Q-wave | | 1 (1.6%) | 1 (3.8%) | 0 (0.0%) | |
| Q-wave + T-wave | | 2 (3.2%) | 0 (0.0%) | 2 (5.6%) | |
| Right axis deviation | | 2 (3.2%) | 1 (3.8%) | 1 (2.8%) | |
| ST-segment elevation | | 1 (1.6%) | 0 (0.0%) | 1 (2.8%) | |
| ST-segment elevation | | 2 (3.2%) | 1 (3.8%) | 1 (2.8%) | |
| T wave inversion | | 1 (1.6%) | 0 (0.0%) | 1 (2.8%) | |
| T wave inversion + left ventricular hypertrophy | | 1 (1.6%) | 0 (0.0%) | 1 (2.8%) | |

Abbreviations: COVID-19, coronavirus disease 2019; CT, computed tomography; ECG, electrocardiogram; RT-PCR, real-time polymerase chain reaction.
[a]*n*(%).
[b]Fisher's exact test; Pearson's $\chi^2$ test.

followed by heavy sweats, a high fever, and fatigue.[48] There is a scarcity in data regarding COVID-19 and malaria coinfection, but a study reported that most of the patients with coinfection had a fever as a presenting complaint, while some patients had headaches, difficulty breathing, and sore throats on presentation.[49] Regarding symptoms among our coinfected patients, we found shortness of breath (76.3%) and fever (73.1%) to be the most prevalent symptoms. Our findings align with a study done in Uganda, where fever (21%, *n* = 70) and shortness of breath (19%, *n* = 70) were the second and fourth most common symptoms among COVID-19 and malaria coinfected patients, respectively.[40] Although both symptoms are considered among the most to occur, there is a substantial difference between the prevalence of occurrence among the two studies. This might be due to the treatment-seeking behavior of our patients, as many individuals wait until symptoms arise before seeking treatment.

As a general rule COVID-19 complications are mainly attributed to cytokine release syndrome or a cytokine storm. Complications regarding COVID-19 include: Coagulopathy, cardiovascular complications, and acute respiratory failure.[50] Severe cases may experience dyspnea and hypoxia within a week of the commencement of the illness, which can lead to ARDS or end-organ failure.[51] Acute respiratory distress syndrome produce alveolar damage in the lungs, and the prognosis is worse when COVID-19 is the cause.[52] Concerning complications among our coinfected patients, we found the most common to be acute respiratory distress syndrome, in 35.3% (*n* = 156) of patients. This is in contrast to a study where the most common complication among COVID-19 mono-infected patients was acute kidney injury followed by probable acute respiratory distress syndrome in 24.3% (*n* = 73 197) and 18.4% (*n* = 73 197) of patients, respectively.[53] The greater %age in our patients could be ascribed to the enhanced severity caused by the synergistic co-infection pathogenicity effects. Regarding malaria, the most common pathogenic mechanism is the hemolysis of the *Plasmodium*-infected red blood cell, which releases plasmodium endotoxin, resulting in high levels of tumor necrosis factor (TNF) generation and findings like fever.[48] Malaria complications are diverse; the most common include: Cerebral malaria, acute renal failure, pulmonary edema, severe anemia, and bleeding.[54] We found thrombocytopenia to be present in 16% (*n* = 156) of our patients. This is in contrast to a study, where Thrombocytopenia complicated 41.7% (*n* = 12) of COVID-19 and malaria coinfections.[55] This may be attributed to the difference in sample size and further studies are needed to clarify the ambiguity.

In our patients, the overall concentration of total white blood cells was decreased, and C-reactive protein levels were increased. During malaria, white blood cell (WBC) counts are low or normal, a characteristic that is commonly regarded to represent leukocyte localization away from the peripheral circulation to the spleen and other marginal pools, instead of real deficiency or stasis.[56] In African studies, serum CRP levels have been linked to parasite burden and consequences in malaria, particularly falciparum malaria.[57] In up to 86% of severe COVID = 19 patients, CRP levels were found to be significantly elevated. CRP levels were much higher in patients with severe disease courses than in mild or nonsevere patients, hence it was employed for classification and treatment counseling in severe COVID-19 cases.[58] Elevated D-dimer is a known predictor of COVID-19 infection severity; it's linked to an elevated risk of complications—such as deep vein thrombosis and pulmonary embolism—and is one of the most important determinants of severity.[59] The most common abnormality seen in patients with COVID-19, according to the literature, is sinus tachycardia. Other abnormalities include supraventricular tachycardias like atrial fibrillation or flutter, ventricular arrhythmias like ventricular tachycardia or fibrillation, various bradycardias, interval, and axis changes, and ST-segment and T wave changes.[60]

Malaria's clinical outcome can be impacted by a wide range of factors, including parasite species, host genetics, innate and acquired immunity, access to adequate treatment, comorbidities, and antimalarial

resistance. Infections can lead to various outcomes, such as asymptomatic illness, influenza-like symptoms, organ dysfunction, and death.[61] Regarding COVID-19 outcome, extended hospital admission, and greater death can be due to multiorgan failure as well as various metabolic disturbances and respiratory insufficiency, in addition to the multisystem involvement.[62,63] Older age, neutrophilia, and organ and clotting failure (e.g., higher LDH and D-dimer) were all linked to the development of acute respiratory distress syndrome in COVID-19 patients hence death.[51] We found acute respiratory distress syndrome to be significantly associated with in-hospital mortality; 63.5% ($n = 55$) of our patients with acute respiratory distress syndrome died. This is similar to a study where mortality was 52.4% ($n = 84$) among patients with acute respiratory distress syndrome.[51] The increased mortality rate is probably due to the increased inflammatory response due to the coinfection. Also, we found a length of stay of 5.4 ± 4.3 days to be significantly associated with in-hospital death ($p = 0.003$); and this is similar to a systematic review where—in terms of overall stay—those who died had a shorter stay than those who were discharged alive.[63]

There is a possibility of a higher rate of COVID-19 coinfections during the ongoing pandemic; especially in areas endemic to infectious diseases like Sudan, hence more efforts should be done to raise the awareness of the community regarding both diseases—COVID-19 and malaria—in addition to emphasis on the possibility of co-infection between COVID-19 and malaria in specific, or COVID19 and other infectious diseases in general. A greater clinical suspicion of COVID-19 co-infection should be held; obtaining a correct diagnosis of a treatable infection, and identifying the presence of co-infections requires careful investigation, hence, it would be beneficial to provide malaria testing kits to the COVID-19 testing laboratories, thereby reducing missed opportunities for malaria testing. As a crucial component of helping to solve this difficult conundrum, convenient health infrastructure needs to be prioritized; lifesaving resources and an adequate number of qualified health workers are essential. Further research is needed for the identification of etiology as well as a better understanding of the pathophysiology behind COVID19 and malaria coinfection.

Our study had several limitations, first, although our careful approach, the retrospective design in itself increased chances of bias; secondly, we selectively included patients with COVID-19 and malaria coinfection only, without including patients infected with COVID-19 or malaria mono-infection, so our results cannot be directly compared between patients; lastly, due to inconvenience, we were not able to include isolation centers in other states, so findings cannot be generalized. Despite these limitations, our study has strong points, such as the large sample size of coinfected patients, and diagnostic and immunological tests, in addition to the comprehensive laboratory, imaging, and ECG diagnostic techniques, among others.

## 5 | CONCLUSION

Almost two in five of our participants died with acute respiratory distress syndrome being the most common complication significantly associated with mortality; such a high rate is regarded as a public health concern, and more attention needs to be focused on fighting COVID19 and malaria coinfection. There may be a link between malaria and COVID-19, since both diseases present with similar symptoms and complications, resulting in one of them being underdiagnosed, therefore, undertreated.

## AUTHOR CONTRIBUTIONS

Khabab Abbasher Hussien Mohamed Ahmed, Elfatih A. Hasabo, Mazin S. Haroun, and Moh.Mah.Fadelallah Eljack did proposal writing, built a questionnaire, and collected and analyzed data. Yousif F. O. Altayeb, Alshareef B. Nour, Esraa Hassan Salih, and Abdallah M. Abdallah wrote first draft. Waddah Aljaely Mohammed Osman and Mohammed Yousif Elnaeem Yousif did examinations, and investigations and supervised the study. All authors wrote the final draft, revised the final draft, and contributed significantly to this study.

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this paper is available with the corresponding author upon reasonable request.

## CONSENT FOR PUBLICATION

All authors gave their verbal and written consent for publication.

## ETHICS STATEMENT

Ethical approval was obtained from the Ministry of Higher Education, University of Gezira, Gezira State, Sudan. The ethical approval of each center's ethical committee was acquired. Both written and verbal consents were obtained from the participants or their guardians. Privacy and protection of the participant's files and information were of the highest priority.

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