

Research Article

The Role of COVID-19 Pandemic on Malaria Incidence; Meta-Analysis and Systematic Review Study

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Introduction

Acute respiratory syndrome-coronavirus (SARS-CoV-2) is a viral infection that is considered one of the most persistent, destructive and deadly infectious diseases [1]. On January 30, 2020, the World Health Organization declared the outbreak of the coronavirus as a public health emergency with international concern, and on March 11, 2020, it was recognized as a global pandemic [2]. Nowadays, the SARS-CoV-2 virus, the causative agent of coronavirus disease (COVID-19), has caused more than 690 million cases and 6.8 million deaths globally. The clinical manifestations of the corona virus infectious disease include fever, cough, fatigue, myalgia, headache, shortness of breath and in some cases lead to severe pneumonia and acute respiratory distress syndrome in patients [3]. Furthermore, the effects of the COVID-19 infection can significantly affect other diseases such as malaria. However, malaria and COVID-19 may resemble

Abstract

Background: Today, COVID-19 and malaria are the leading causes of death in the worldwide. Malaria and COVID-19 have common aspects and may be was a high potential for mutual influence. Hence, consequences and outcomes of COVID-19 become very dangerous and problematic. The aim of this study, investigate of the influence of COVID-19 mortality and malaria prevalence by systematic review and meta-analysis study.

Method: We searched authentic research databases by using the following keywords in English language. In additional, for statistical analysis, meta-analysis and random effect model and I² index were used. Statistical analysis was performed with STAT (version 11.2).

Result: In the present study, nine articles were selected from 1,014 articles that examined co-infection in COVID-19 and malaria. This study revealed that co-infection between malaria and COVID-19 has very interesting and surprising results. OR (odds ratio) =-1.2 (95% CI: -1.8 to -0.6). We encounter high values of I₂ in the study (I₂=98.549).

Conclusion: People with malaria who show symptoms such as fever should be evaluated by COVID-19 to prevent serious complications. The present study provided information on malaria and COVID-19 co-infection. Nevertheless, further prospective studies are needed to investigate the burden and consequences of COVID-19 in malaria endemic areas.

Keywords: COVID-19; SARS-CoV-2; Malaria; Meta analysis; Systematic Review

each other and present similar symptoms such as fever, fatigue and headache, cough, sweating, and breathing problems that are often misdiagnosed [4]. Despite this, malaria is one of the most dangerous and deadly parasitic diseases in the world and is widely distributed in tropical and subtropical regions, especially in Africa and Southeast Asia [5]. Despite being preventable and treatable, the parasitic disease of malaria still has a devastating effect on people's health and livelihood [6]. According to the some reports published by the WHO; this parasitic disease has accounted for a high percentage of deaths in African countries, while only about 3% of malaria cases have been reported in Southeast Asian regions such as India, Indonesia, Bangladesh, Nepal, Thailand, Sri Lanka, Myanmar and the Maldives [7]. Some statistical evidence shows that since the end of August 2020, the incidence rate of the COVID-19 disease in

Africa is not high compared to many regions around the world [8]. The relatively low spread of COVID-19 in Africa may depend on host genetic epidemiology and other relevant factors that protect the African population from SARS-CoV-2 infection. Thus, the infectious disease COVID-19 can affect the efforts of health care providers in malaria control and ultimately leads to significant changes in the statistics of malaria patients [9]. Epidemiological analysis of the global malaria situation in the corona virus pandemic helps to understand the dynamics of the changing malaria situation in different continents and helps us to implement control strategies and allocate financial and medical resources [10]. However, there is a significant knowledge gap regarding the co-infection of these two diseases. A better understanding of co-infection may lead to the development of control strategies for different regions. Hence, in this systematic review, we reviewed reports of co-infection with malaria and COVID-19 and assessed aspects such as symptoms, diagnosis and mortality.

Material and Methods

Study Protocol and Registration

This study was conducted in Hamadan University of Medical Sciences, Hamadan, Iran. This review is based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines was done.

Search Strategy

In this study the reports of co-infection of COVID-19 and malaria in databases including PubMed, Web of Science, and Scopus from the beginning to February 2022 were collected and analyzed and keywords including "COVID-19", "malaria", "2019-nCoV", "Plasmodium falciparum", "2019 nCoV Infection", "2019-nCoV", "Coronavirus Disease-19", "Coronavirus Disease 19", "2019 Novel Coronavirus", "SARS Coronavirus 2", "SARS-CoV-2" were used.

Also, words "combinations and / or operators" were used as keywords. In this study, only the terms in the Medical Subject (MeSH) headings in the search strategy were used.

Inclusion and Exclusion Criteria

The inclusion criteria in the current study include observational and epidemiological articles such as cross-sectional studies, case-control studies and cohort studies in English that were conducted on the human population and published in relation to the co-infection of COVID-19 and malaria. **The study excluded** review papers with insufficient data, irrelevant to the subject, authors' comments, authors' corrections, news, letters to the editor, studies with short reports, laboratory studies. Also, in the present study, articles on COVID-19 and unrelated parameters, authors' predictions on COVID-19 models, molecular studies, case reports, systematic or limited studies, community assessment studies, clinical trials, animal studies, and analytical studies were excluded.

Articles Selection

In this study, the initial search of articles was done by two authors (S. SH and M.J). Any initial disagreement about the eligibility of the studies was resolved by discussion among all authors and then agreement between all authors. The authors reviewed the topics, titles, and abstracts of all identified articles. The full text of the articles was evaluated according to the inclusion and exclusion criteria of the present study. Any initial disagreement

about the eligibility of the articles was resolved by discussion among all authors. Finally, articles using the STROBE checklist (strengthening the reporting of observational studies in epidemiology) were evaluated. Eventually, articles that received a minimum score of 16 were selected as finalists.

Data Extraction and Data Item

The following data extracted from each study for further analysis included first author, year of publication, place of study including country/ continent, year of study, mean age and standard deviation, number of patients with co-infection, population size of studies including number of case, control, total, male and female in case and control groups, number of patients with SARS-CoV-2, and number of patients infected with *Plasmodium spp*, *P-value* and odds ratios and other data (Table 1). Also, all data excluded from the studies were placed in a standard experimental datasheet before further analysis.

Quality Assessment

The quality of this study was independently evaluated by two authors (A.M and A.NZ) according to the Newcastle-Ottawa Scale (NOS) to assess the quality of non-randomized studies (case-control and cohort study). The authors also used the Newcastle-Ottawa scale to evaluate cross-sectional studies. In addition, disputes between the two authors were resolved with the evaluation and guidance of the third arbitrator (F.AJ). To evaluate the quality of the studies, the quality of "high", "average" or "low" for each study was defined as: low quality (score less than 5), average quality (score 6-7) and high score (score 8-9).

Data Analysis

In this study, the prevalence of *Plasmodium spp* among infected individuals (among the studies included in this article) was estimated by using random effect models (DerSimonian and Laird). Also, data analysis was performed by comprehensive meta-analysis software version 2. In addition OR with 95% CI confidence interval was used as a selective correlation index. Forest plot was also used to present combined results and individual studies. Q-Cochran test and I_2 statistics were used to evaluate the heterogeneity of the studies (I_2 index less than 25%, 25% -75% and more than 75% were considered as a low, medium and high heterogeneity, respectively). Also, a random effect model was used to detect of substantial heterogeneity in this study.

Also, to evaluate no significant heterogeneity the fixed effect models were performed to effect measure. To evaluate publication bias, funnel plot and Egger's and Begger's tests for asymmetry was performed (if number of included article was more than 10). Furthermore, statistical analysis was performed by using STATA Statistical Software version 15.0. The Significance level was evaluated <0.05. The result of analysis was reported as a frequencies or graphs.

Result

Included of Study

762 articles were selected based on their relevance to COVID-19 and Malaria. Some articles were removed from the project due to duplication. Then, from the remaining studies, abstract and full text articles were reviewed. Some of these articles were deleted due to irrelevance to the main topic as well as lack of criteria and calibration (Figure 1). Eventually, nine ar-

Table 1: Characteristics of studies.

Ref.	Author	Years	Country	Continent	Study type	Age	OR	CLOW	CLUPER	P Value	Quality
1	Yahaya	2020	Nigeria	Africa	CS	-	0.02	0.001	0.06	0.05	Moderate
2	Michael	2021	Uganda	Africa	CS	31	1.04	1.03	1.05	0.001	Moderate
3	Marissa	2020	Hamburg	Europe	CC	55	0.6	0.226	1.61	0.3	High
4	Junior	2020	Congo	Africa	CO	54	0.01	0.0	0.03	0.05	High
5	Niraj	2020	India	Asia	CS	32	0.53	0.33	0.855	0.009	Low
6	Jane	2021	London	Europe	CS	36	8.7	1.0	75.5	0.015	Moderate
7	Amoo	2020	Nigwria	Africa	CS	34	0.02	0.001	0.06	-	High
8	Jane	2020	Sanfrancisco	North America	CS	23	0.87	0.78	0.97	-	High
9	Vanroye	2021	Belgium	Europe	CC	42.5	5.07	3.506	7.34	0.001	Moderate

OR: Odds Ratio; CC: Case-Control Studies; CS: Cross-Sectional Study; CO: Cohort study; N= Number

articles were conducted to investigate the influence of COVID-19 mortality and malaria prevalence in the form of systematic review and meta-analysis study.

Characteristics of Research Articles

Inclusion criteria were articles on COVID-19 and malaria. The selected articles were in English. Also, exclusion criteria included studies with inappropriate sample size, lack of relevance to the main topic, letter to the editor, and case report reports. Studies with these characteristics were excluded from the project.

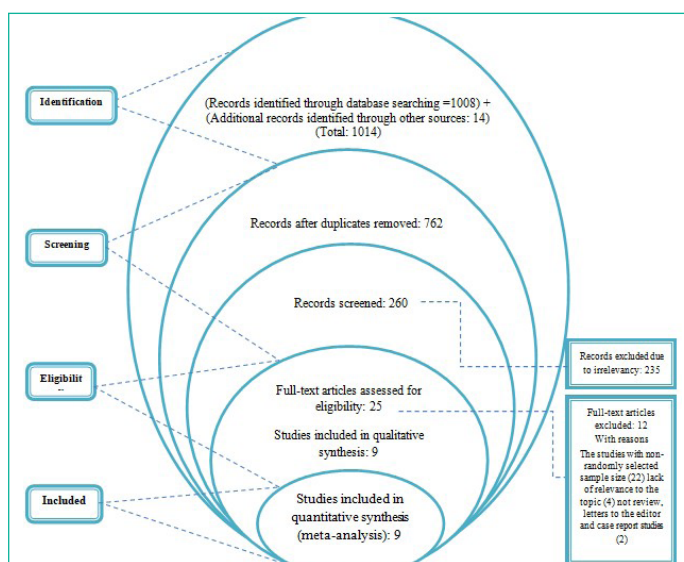
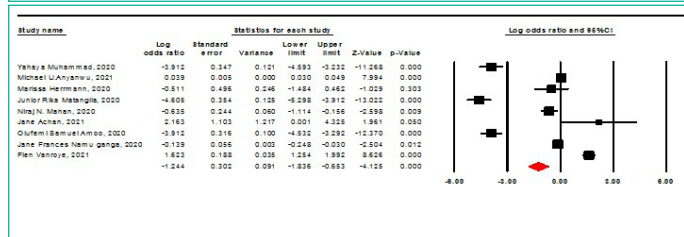


Figure 1: PRIMA Flowchart.



Meta Analysis under random-effects model

Figure 2: Forest Plot of 9 included studies fulfilled the inclusion criteria. In this presentation, information about the impact of the COVID-19 epidemic on malaria mortality was demonstrated.

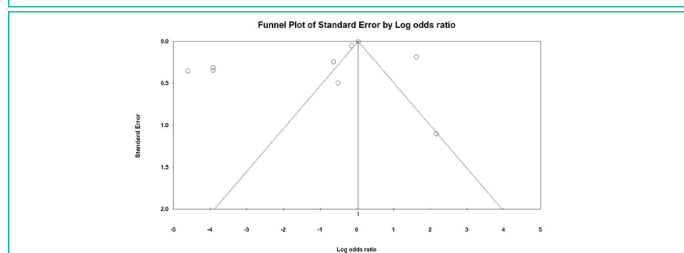


Figure 3: The funnel plot for 9 included studies; For interpretation of any publication bias among studies, visual inspection of the generated funnel plot under random-effects model employed to evaluate the asymmetry.

Quality of the Included Studies and Publication Bias

Two authors (M.J and S, Sh) evaluated the studies in terms of methodological aspects including sampling methods, description of sampling conditions, measurement parameters, statistical analysis. In the event of a dispute between the two authors, the third person (F.A) acted as the third reviewer. To evaluate the quality, "high", "medium" or "low" quality was considered for the articles. Hence, for each study that had a score of more than 7 "high quality", a score of 4-6 "average quality" and a score less than 4 "low quality" was awarded (Table 1).

Synthesis of Results

The forest Plot was designed for the included article in this study (Figure 2). This figure provides information about Odds ratio with 95 percent of the confidence interval, Lower limit, Upper limit, Z-value, and P-value for each of article. The initial analysis to evaluate the impact of the COVID-19 epidemic on malaria mortality has shown in this figure (Figure 2). In the present study, data were summarized based on two models. The two models include the random effect model and the fixed effect model. In fix effect model, all results were constant and unaltered. In random effect, the final answer model includes a return of numbers and we are faced with a random result. Also, there are no fixed results.

Indeed, there are some studies that analyze their data according to the random effects models. On the other hand, in this study, we calculated I_2 and showed its information in Table 2. We encounter high values of I_2 in the study. ($I_2=98.549$). Practically, in this report, we consider the random effect model because it is a more accurate and appropriated model. Since, this random effect model includes the return of numbers, the results are more realistic. As, in nature we encounter different sizes of plantain. Also, we consider a plantain tree in nature with different sizes of leaves. Following this example, in random effects model, there is a distributed of results. Also, random effects model looks more realistic. In this study, we considered this model (Table 3 & Figure 2).

Additional Result of Study

Additional information of studies performed: In this study, in addition to obtaining a statistical analysis about the impact of the COVID-19 epidemic on malaria patients, other factors are separated and examined (Table 3). Factors that was considered as additional results including year and place of publication, number of men and women separately in each study, exact locations of each study separately, methods of diagnosis of malaria and COVID-19 in each study separately, evaluation of the type of malaria in patients with this disease, negative number in terms of malaria and COVID-19, number of patients with COVID19. Please refer to Table 3.

Table 2: This table was shown fixed effect model and Random effect model according to information of this study.

Model	Effect size and 95% confidence interval						Test of null		Heterogeneity				Tau-squared			
	Number studies	Point estimate	Standard Error	Variance	Lower limit	Upper limit	Z-value	P-value	Q- value	df(Q)	P-value	I-squared	Tau Squared	Standard Error	Variance	Tau
Fixed	9	0.036	0.005	0.00	0.026	0.046	7.378	0.00	551.347	8	0.00	98.549	0.686	0.839	0.704	0.828
Random	9	-1.244	0.302	0.091	-1.836	-0.653	-4.125	0.00								

Table 3: Extracts additional information from the articles reviewed in this study.

author	Year and place of publication	Type of study	Male/female	Place of study	Median age	Malaria diagnostic method	Covid-19 diagnostic method	Plasmodium spp	Study time	Negative number in terms of malaria and covid-19	No. of patients with COVID19
Yahaya ¹¹	2020/nigeria	Cross sectional	-	Isolation center Dutse, Jigawa Nigeria	-	Stained with Giemsa; and examined through a microscope	RT-PCR	-	March, 2020 to July 2020.	20	54
Michael ¹²	2021/uganda	Cross sectional	-	This is an ecological study which compared population variables of 195 countries	31	-	-	-	-	-	-
Marissa ¹³	2020/hamburg	Cohort study	24/6	hospital	55	With Giemsa; and examined through a microscope	RT-PCR	Falciparum	-	13	20
Junior ¹⁴	2020/congo	Cohort study	82/78	hospital	54	With Giemsa; and examined through a microscope	RT-PCR	-	Mars 11 th to July 22 th 2020	-	160
Niraj ¹⁵	2020/india	Cross sectional	267/224	hospital	32	Microscopy or RDT	RT-PCR	Plasmodium vivax	April 18 th to October 31 st 2020	-	491
Jane ¹⁶	2021/london	Cohort study	502/95	hospital	36	Microscopy and PCR	RT-PCR	Falciparum	April 15, to 10/30/2020	-	600
Amoo ¹⁷	2020/nigeria	Cross sectional	358/259	COVID- 19 Drive-through testing center	34	RDT	RT-PCR	P Falciparum.	April and May 2020	489	121
Jane ¹⁸	2020/sanfrancisco	Cross sectional	-	Malaria reference center	23	RDT	-	-	April 2020-March 2021	-	-
Van-roye ¹⁹	2021/belgium	Cross sectional	79/91	Institute of Tropical Medicine	42.5	RT-PCR and microscopy	Ab Rapid Test RT-PCR	Falciparum	-	-	196

Table 4: extracts additional clinical information from the articles reviewed in this study.

Author	No. of malaria as a co-infection	Treatment for COVID-19	Symptoms	Co-morbidities	Hospitalization duration
Yahaya ¹¹	34	NS	NS	NS	NS
Michael ¹²	-	NS	NS	NS	NS
Marissa ¹³	-	One COVID-19 patient had received treatment with Rituximab	NS	Hypertension, Diabetes, Coronary heart disease, Lung disease, Cancer	The COVID-19 patients spent 9.9 days and the malaria patients spent 4.9 days in the hospital.
Junior ¹⁴	1	Hydroxychloroquine or chloroquine phosphate	Fever, cough, fatigue,	Hypertension, diabetes, obesity, heart disease, asthma/ chronic pulmonary disease	15 (4–20)

Niraj ¹⁵	27	Hydroxychloroquine	Fever, dry cough, and sore throat	Hypertension (11%), diabetes (8%), bronchial asthma (4%), hypothyroidism (2.8%), tuberculosis (1.1%), ischemic heart disease (1.3%), other comorbidity (1.7%), more than 1 comorbidity (6.5%)	21 (14–35)
Jane ¹⁶	70	Vitamin D, zinc, paracetamol, azithromycin oxygen therapy, dexamethasone, heparin and oral warfarin,	Cough, runny nose, fever, headache, shortness of breath	Diabetes and heart disease	NS
Amoo ¹⁷	2	As chloroquine (CQ), doxycycline, quinine, mefloquine, atovaquone/proguanil (Malarone),	Fever, chills, headaches, nausea, fatigue	NS	NS
Jane ¹⁸	-	NS	NS	NS	NS
Van-roye ¹⁹	170	NS	NS	NS	NS

Discussion

Summary of Evidence

One of the latest crises that have happened in human societies is the outbreak of the Corona virus (2019-nCoV) [11]. Although, COVID-19 infection that first started in China and then it later became a widespread pandemic in the worldwide. Patients infected with COVID-19 may exhibit symptoms ranging from asymptomatic to severe and fatal respiratory complications. Pandemics of infectious diseases such as COVID-19 can cause irreparable damage to health systems, especially when there are similarities in clinical manifestations with other infectious diseases such as the parasitic infection malaria [12]. In addition, malaria is still one of the significant infectious diseases in endemic areas, which significantly affect people's health, medical and health systems, and the health economy, and its diagnosis requires a detailed examination of the previous history [13]. Significantly, during the coronavirus pandemic, the diagnosis and treatment of malaria was affected by the COVID-19 infection, so that in malaria-endemic areas, there were reports of disruptions in the process of detection, diagnosis and control of malaria [14]. Also, Quarantine in endemic areas during the corona virus epidemic limited the access to medical and health services and for a long time the chemical prevention of malaria and the distribution of nets impregnated with insecticides were suspended, as a result the spread of malaria and its mortality increased [15].

Our study reveals the fact that the co-infection of malaria and covid-19 in some people may be misdiagnosed and the late diagnosis of these two diseases and their differentiation from each other can affect the mortality and complications caused by them. Our analysis shows the prevalence of different *Plasmodium* species during the coronavirus pandemic, characteristics, organism characteristics and diagnostic methods of COVID-19 in patients with co-infection of malaria and COVID-19 [20,21]. However, the prevalence of co-infection of covid-19 and malaria seems to be heterogeneous and the lowest prevalence of *Plasmodium* spp was observed among patients with covid-19, our results are very similar to those reported by Matangila et al [14]. Matangila et al believe that patients who were admitted to hospitals due to malaria infection and received anti-malarial drugs have a recovery process in the infection caused by COVID-19 [14]. Mahajan and et al demonstrated a low prevalence of co-infection of malaria and COVID-19 in India (5%), suggesting that co-infection may enhance recovery from COVID -19. Also, Mahajan et al reported a low prevalence of co-infection in India (5%), suggesting that co-infection with COVID-19 and

malaria may enhance recovery from the coronavirus by clearing the virus through glycosylphosphatidylinositol antibodies (GPI) against different *Plasmodium* species that cross-react with SARS-CoV-2 antibodies. Also, in their study, they reported that a population exposed to malaria has a naturally selected genotype of ACE2 rs2106806 TT/T, which leads to the down-regulation of ACE2 in suppressing and reducing the chance of coronavirus entering the epithelial cells in the lung [15]. In contrast to these two studies, there is another study that reported a high prevalence (63% to 100%) in Nigeria. The results of Muhammad et al show that in patients with co-infection, the worsening of the disease is due to inflammatory responses caused by high oxidative stress against SARS-COV-2 infection [22]. In addition, Many reasons can have a direct impact on our current study, such as asymptomatic infection in patients in malaria endemic areas, especially in young people who are infected with COVID-19 without any symptoms, the lack of access to diagnostic tests with high sensitivity such as RT-PCR, the lack of health care workers who have received training based on the separation of these two diseases, the lack of similarity in the age characteristics of patients infected with malaria (children) and Covid-19 (adults) [23].

In this study, the systematic review is highlights and necessary the importance of screening and diagnosing for other diseases and does not focus only on COVID-19, and it is also important to consider the differential diagnosis in patients with overlapping symptoms [24]. The presence of some infectious diseases with symptoms similar to the coronavirus may lead to severe COVID-19 infection. Malaria can be life-threatening in untreated patients. Therefore, screening and segregation of diseases in such conditions, especially in endemic areas, is absolutely necessary [25]. In this systematic review, one of our goals was to investigate factors that could have detrimental effects on malaria control achievements, and we evaluated factors such as malaria and covid-19 co-infection and aspects such as symptoms, diagnosis and mortality.

Limitation

Nevertheless, the present study has limitations that include: in meta-analysis studies, sample size has many challenges. Also, a small number of countries have published reports of co-infection with malaria and COVID-19 from their regions. A number of studies have ambiguous data and enigmatic results. Extracting data from these studies is very difficult. In addition, in malaria endemic areas such as Africa, there are very limited and vague reports of co-infection with malaria and COVID-19. Eventually, the present study helps to develop management strategies in

people with malaria and COVID-19 co-infection. Nevertheless, Extensive studies in this field seem essential and necessary.

Author Statements

Competing Interests

The authors declare no conflict of interest, financial or otherwise.

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Authors' Contributions

M.J - FS.A - H.A: wrote the manuscript, S.S – A.NZ: edited the manuscript and designed Figure, M.S: design and Supervision.

All authors read and approved the final manuscript.

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