



Impact of COVID-19 on Malaria: Clinical Changes before and during the COVID-19 Pandemic

—A Retrospective Study in a Reference Center

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Abstract

Malaria is a parasitic disease that has always been controlled by national programs worldwide but still remains a public health problem. COVID-19 continues to spread and have an impact on pre-existing diseases such as malaria. The management of COVID-19 and the malaria is difficult in low income countries because the two main diseases share the same symptoms and require regular screening. Our study is aimed to evaluate the impact of the COVID-19 pandemic on the epidemiological and clinical profile of malaria in a referral center in Madagascar. It was a retrospective comparative study, the study period was subdivided into two: before COVID-19 1st January to 31st December 2019 and during COVID-19 1st January 2020 to 31st September, 2021 in Infectious Disease department, a reference center for management of malaria and COVID-19. We retained 113 patients including 69 cases before COVID-19 and 44 cases during COVID-19. The statistical tests used for comparison were the parametric chi² and exact Fischer tests with a significant threshold $p \leq 0.05$. Even if the frequency of malaria decreased to 44 (38.94%), severe malaria (n = 44; 42.31%) is the predominant clinical form during COVID-19 period. Furthermore, the mean duration of disease progression to severe malaria was reduced to 2.4 days and the length of stay increased by 8 days. The death rate was broadly similar 17% (n = 12) before COVID-19 versus 16% (n = 7) during COVID-19. The gravity of malaria during COVID-19 may be explained by the disruption of malaria control related to COVID-19 pandemic which highlights that screening and awareness-raising for other

diseases such as malaria must be maintained and even reinforced, and included in COVID-19 response.

Subject Areas

Infectious Diseases

Keywords

Malaria, COVID-19, Impact, Severity, Madagascar

1. Background

COVID-19 is a highly contagious disease, declared by World Health Organization (WHO) as a pandemic on March 11, 2020 and continues to spread in several countries [1]. Malaria is a disease transmitted by the bite of a female Anopheles and caused by parasites of the genus Plasmodium. The African region holds the saddest record of having more than 90% of malaria cases followed by Southeast Asia and the Eastern Mediterranean region [2]. It is an endemic disease in Madagascar and rages all year round in high transmission areas, and from April to November in low transmission areas, with 800,661 cases and 370 deaths recorded in 2018 [3]. Madagascar was affected by COVID-19 with 67,787 cumulative confirmed cases, 1401 cumulative deaths on the month of July 2022 [4]. The two diseases share the same symptoms and can be associated in different cases reported in the literature [5]. But the devastating effect of COVID-19 which is a difficult pandemic to manage with pre-existing epidemic diseases sharing the same clinical aspects would be overwhelming for the Malagasy health system and for the management of these diseases. It is in this context that we conducted our study which aims to evaluate the impact of the COVID-19 pandemic on the epidemiological-clinical aspect of malaria in a reference center in Madagascar.

2. Materials and Methods

Our study was a retrospective study from the period before COVID-19: 1st January to 31st December 2019 and during the first two waves of COVID-19 in Madagascar: 1st January 2020 to 31st September 2021. Our study population was all patients hospitalized for malaria in the department of Infectious Diseases University Hospital of Befelatanana.

We included patients diagnosed and hospitalized as severe malaria. We excluded patients with incomplete medical records. We collected 115 patients; two files were excluded because of missing data so we retained 113 patients including 69 cases before the COVID-19 (1st January-31st December 2019) and 44 patients during the first two waves of COVID-19 in Madagascar (1st January 2020 to 31st September, 2021) (**Figure 1**).

We defined as severe malaria: signs and symptoms characterized a severe malaria according WHO criteria [6].

Data were collected using the questionnaires and analyzed by EPI-info 7.2.2 with a significance threshold set $p \leq 0.05$. For the comparison, the statistical tests used were the parametric χ^2 and exact Fischer tests with $p \leq 0.05$.

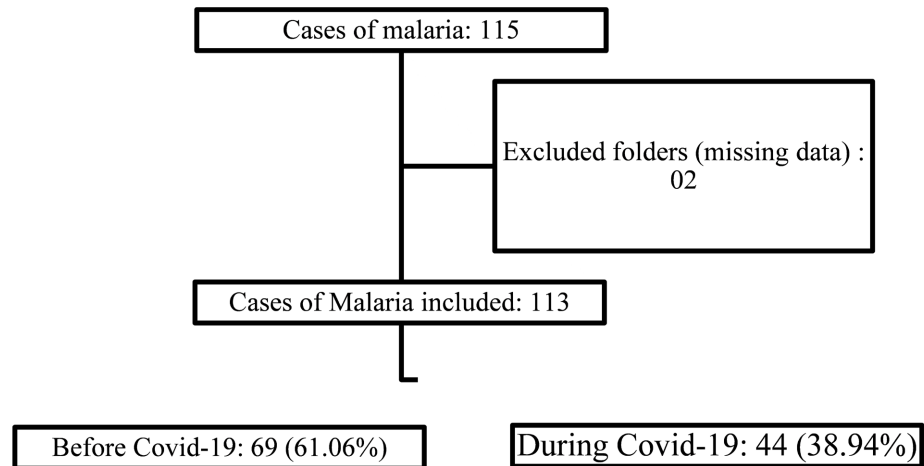


Figure 1. Flowchart.

3. Results

We noted a clear difference between the frequency of malaria before COVID-19: 69 (61.06%) versus 44 (38.94%) during COVID-19. No malaria cases were recorded during the peak of the epidemic from April 2021 to July 2021. Before COVID-19, severe malaria predominated 60 (57.69%) versus 44 (42.31%) during COVID-19. Our population was young with an average age of 30.7 before COVID-19 versus 35.2 and predominantly male with a sex ratio of 5.9 before COVID-19 and 5.2 during COVID-19 (**Table 1**). The mean duration of progression to severe disease decreased to 2.4 days during COVID-19 versus 6.8 days before COVID-19. Hospitalization time increased to 8 days during the COVID-19 period, compared with 4 days before COVID-19. The death rate was 16% during COVID-19 versus 17% in the period before COVID-19. **Table 1** reveals the demographic characteristics, clinical and paraclinical pattern of our population.

Regarding clinical signs, both diseases share the same symptoms, among the signs of severity: convulsions 17 (70.9%) and confusion 21 (36.2%) were the most frequent signs before COVID-19 versus respectively 7 (29.1%) and 21 (36.2%) during COVID-19. Among the signs of simple malaria, myalgia 29 (76.3%), arthralgia 35 (61.4%) and headache 41 (50.5%) were the most predominant signs during COVID-19 versus respectively 9 (23.7%), 22 (38.6%) and 42 (49.5%) before COVID-19. Renal failure ($n = 25$; 60.9%) is one of the most important signs of severity during COVID-19 [versus 11 (39.1%) before COVID-19 period], followed by anemia 30 (54.55%) before COVID-19 and 25 (45.45%) during

COVID-19. The death rate was 16% (n = 7) during COVID-19 versus 17% (n = 16) before COVID-19. In univariate analysis, no factor was found to be significantly associated with mortality (**Table 2**).

Table 1. Clinical and paraclinical characteristics of patients before and during COVID-19.

Characteristics of patients	Before COVID-19	During COVID-19	P value
Malaria rate	69 (61.06%)	44 (38.94%)	P = 0.01
Severe malaria	60 (57.69%)	44 (42.31%)	P = 0.01
Simple Malaria	9 (13.04%)	0	P = 0.01
Travel in endemic malaria areas	53	32	P = 0.01
Indigenous malaria	16	12	P = 0.01
Mean age	30.73 ± 11.7 sex ratio = 5.9	35.20 ± 10.6 sex ratio = 5.2	
Females	10	7	
Males	59	37	
Fever	69 (61.1%)	44 (38.9%)	P = 0.01
Chills	18 (47.4%)	20 (52.6%)	P = 0.03
Headache	42 (49.5%)	41 (50.5%)	P = 0.01
Vomiting	49 (56.9%)	44 (38.9%)	P = 0.11
Diarrhea	29 (46.1%)	34 (53.9%)	P = 0.02
Abdominal pain	22 (62.86%)	13 (37.14%)	P = 0.79
Myalgia	9 (23.7%)	29 (76.3%)	P = 0.01
Arthralgia	23 (38.6%)	35 (61.4%)	P = 0.01
Prostration	57 (56.4%)	44 (43.6%)	P = 0.03
Confusion	21 (36.2%)	37 (63.8%)	P = 0.01
Convulsion	7 (29.1%)	17 (70.9%)	P = 0.01
Respiratory Distress	0	13 (29.5%)	P = 0.01
Jaundice	10 (35.8%)	18 (64.2%)	P = 0.01
Bleeding	0 (44.5%)	9 (55.5%)	P = 0.01
Hémoglobin < 7 g/l	30 (54.55%)	25 (45.45%)	P = 0.20
Thrombocytopenia	17 (100%)	0	P = 0.01
Créatininémie > 265 µmol/l	25 (69.44%)	11 (30.56%)	P = 0.20
Mean duration of disease progression to severe form	6.8 ± 2.02	2.40 ± 0.62	
Duration of treatment IV Artésunate 2.4 mg/kg/day	1.8 ± 0.94	3.4 ± 1.22	
Duration of hospitalization	4.6 ± 0.80	7.7 ± 0.88	
Death rate	12 (17%)	7 (16%)	P = 0.80

Table 2. Factors associated to mortality of malaria.

Factors associated to the mortality of malaria		Alive 94 (83%)	Death 19 (17%)	OR	P
Confusion	yes	47 (41.50%)	11 (10%)	1.2 [0.4 - 3.2]	0.80
	no	47 (41.50%)	9 (7%)		
Convulsions	yes	19 (16.77%)	5 (4.47%)	1.4 [0.5 - 4.4]	0.61
	no	75 (66.23%)	14 (12.53%)		
Respiratory failure	yes	10 (8.82%)	03 (2.68%)	1.6 [0.4 - 6.4]	0.50
	no	84 (74.18%)	16 (14.32%)		
Anemia	yes	46 (40.21%)	10 (8.9%)	1.2 [0.4 - 3.1]	0.82
	no	48 (42.1%)	9 (7.5%)		

4. Discussion

Our study allows us to evaluate the changes in the epidemiological-clinical aspect of malaria during the first and second wave of the COVID-19 pandemic in the Infectious Diseases Department of the University Hospital of Antananarivo. This study showed that the frequency of malaria cases was decreased during the COVID-19 period. No case of co-infection of malaria and COVID-19 was recorded during the peak of the epidemic. The literature is still limited in terms of the epidemio-clinical aspect of malaria during COVID-19, but our study has shown this trend towards fewer cases. We noted a domination of signs of severity such as convulsions 63.8% (n = 37), prostration 43.7% (n = 44) and a significant mortality rate of 16% (n = 7). This decrease in cases can be explained by the fact that access to hospitalization was still low during this period. Patients are staying away from healthcare facilities for fear of the COVID-19 pandemic, for fear of contracting the infection there. Also, the management of endemic disease has been disrupted by COVID-19, including malaria control strategies.

Even statistically insignificant, renal failure with creatinine level > 265 $\mu\text{mol/l}$ (69.44%) and anemia (hemoglobin level < 7 g/l; 54.55%) were higher before COVID-19. Nevertheless, given the high mortality rate (16%), broadly similar to the mortality rate (17%) prior to COVID-19, the increased mean duration of treatment (3.4 days vs. 2 days before COVID-19), as well as the shorter time for disease progression to the severe form (2.4 days vs. 7 days before COVID-19), and the increased duration of hospitalization (8 days vs. 4 days before COVID-19), our study confirms the worsening clinical aspect of malaria. This implies that the symptoms progressed rapidly in the severe form and time for the symptoms to disappear were long. This is the specific change in the period after COVID-19.

This severe clinical profile may be related to the decrease in pre-malaria immunity during the pandemic. Confinement has limited movement and exchanges within the island, restricted access to health facilities and testing, suspended malaria chemoprevention and drug distribution, as well as the distribution of long-acting insecticide-treated mosquito nets [7]. This was confirmed by WHO,

15 high malaria burden countries reported reductions in malaria testing by more than 20% in April-June 2020 compared to the same period in 2019. This change was seen in all malaria-endemic countries including Madagascar. According to WHO, national malaria programs distributed about 48 million fewer treatments in 2020 compared to the previous year. And of the 11 countries in the world with the highest disease burden, only India has made progress against malaria. The other 10 countries, all in Africa, reported an increase in cases and deaths [8].

Our study joins the literature including a larger study conducted in Zimbabwe that used malaria surveillance data collected from all public and private facilities from January 2017 to June 2020 revealed more than 30,000 malaria cases compared to an average over the same period of data in 2017, 2018, 2019. It also revealed the number of recorded malaria deaths that exceeded annual totals from 2018-2019 [9]. COVID-19 disrupts pre-existing diseases including an increase in HIV deaths by up to 10%, tuberculosis by up to 20% and up to 36% for malaria [10]. Thus, the reduction in pre-munition immunity through confinement and the absence of control strategies during the pandemic may explain this evolution. It is important to pay attention to malaria during COVID-19 because of this change in clinical profile [11]: a long hospital stay, rapid progression to the severe form which can lead to patient death.

In our study, co-infection was not observed during the peak of pandemic. The result of a meta-analysis showed that the combined prevalence of *Plasmodium* spp. infection (364 cases) among individuals in the COVID-19 study (1126 cases) was 11%, with a high degree of heterogeneity. Most co-infections were reported from Nigeria (336 cases), India (27 cases) and the Democratic Republic of the Congo (1 case) [12]. The study by Mahajan *et al.* and by Matangila *et al.* showed a low level of prevalence of co-infection respectively in India (5%) and Democratic Republic of the Congo (1%) [13] [14]. The prevalence of co-infection appears to be heterogeneous. This heterogeneity may explain the lack of co-infection in our study.

Muhammad *et al.* reported 63% malaria infection among COVID-19 cases and malaria could favor the cure of COVID-19 by the clearance of the virus being obtained by virus glycosylation [15]. Cross immunity is explained by the presence of Immunoglobulin G against *Plasmodium* specific antigens cross-reacting with SARS-COV-2 antibodies, or the malaria-exposed population has a higher prevalence of ACE2 rs210601 antibody, which results in down-regulation of ACE2, which in turn reduces the risk of SARS and lowers the chances of SARS-COV-2 penetration into the lung epithelial cells [16]. However, this co-infection is under-reported and under-investigated in Africa due to the lack of testing and also because some patients with COVID-19 may be asymptomatic leading to under-reporting of the co-infection.

Our study allowed us to show the change in the clinical profile of malaria during the first two waves of COVID-19 in Madagascar. The principal limitation of the study was its small sample size and those related to monocentric study. The study details about clinical change due to COVID-19 not the control strategy efforts, this change may be a cause of lack of control strategy due to

COVID-19. Data on the study of this clinical change remain limited, and this is the specificity of our study.

5. Conclusion

Malaria has been controlled by an effective control strategy during the last decade worldwide. COVID-19 has disrupted pre-existing diseases like malaria. The impact of COVID-19 on malaria in Madagascar is the increase in severe forms linked to various factors, including the disruption to malaria control caused by the COVID-19 pandemic. Indeed, even though there were fewer cases of malaria during the pandemic than before, the mortality rate was just as high, with longer hospital stays and a shorter average duration of progression to a severe form than in the period preceding the COVID-19 pandemic. Thus, this study underlines the importance of screening and awareness-raising for other diseases such as malaria, which must be maintained and even reinforced as part of the response to COVID-19 in order to avoid excess mortality.

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Ethics Approval and Consent to Participate

The study and publication has been approved by the University hospital of Befelatanana Ethic committee.

Authors' Contributions

All authors made substantial contribution to conception, design, and acquisition of data, analysis and interpretation. They took part in drafting the paper and revising it critically for important intellectual content. They agreed to submit to the current journal and gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Authors' Information

All authors took part on the management of COVID-19 at the Infectious Disease Unit. They were physicians and involved on the outbreak management.

Conflicts of Interest

The authors declare that they have no competing interests.

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