Malaria Journal

REVIEW

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Coinfection of COVID-19 and malaria: clinical profiles, interactions, and strategies for effective control

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Abstract

Since SARS-CoV-2 has caused unprecedented changes in the epidemiology of other infectious diseases, investigations on coinfection between SARS-CoV-2 and one of the famous vector-borne diseases, malaria, are crucial for disease control, especially in malaria-endemic areas. The clinical profiles, possible mechanisms for interactions, and representative control measures of COVID-19 and malaria coinfections have recently garnered public attention. The overlap in epidemiology, infection incubation, and clinical symptoms between COVID-19 and malaria coinfections has been thoroughly discussed to provide a detailed diagnostic procedure for coinfections, thereby guiding appropriate clinical interventions. Immunological and genetic evidence has shown that previous malaria exposure may protect the body from the poor prognosis of COVID-19. ACE2 downregulation and TLR-induced pathways play a role in this protective effect, as do CD8 + and CD4 + T-cell activation and coinhibitory receptor upregulation, which help maintain a balance of immune reactions. Finally, multiple control measures for coinfections were discussed, and malaria control efforts were enriched in the context of COVID-19. These efforts included (1) developing vaccinations; (2) evaluating the efficacy of anti-malarial drugs in the SARS-CoV-2 treatment; (3) exploring recent advances in natural products that are potentially useful for coinfection treatment; (4) researching and implementing bioinsecticides for malaria control, such as gene-driven mosquitoes, fungi, and bacterial symbionts; and (5) improving national electronic disease surveillance platforms in malaria-endemic regions. At last, the above findings summarized valuable lessons about malaria and COVID-19 control and expedite further investigations on coinfections with complex clinical presentations.

Keywords COVID-19, Malaria, SARS-CoV-2, Coinfection, Effective control

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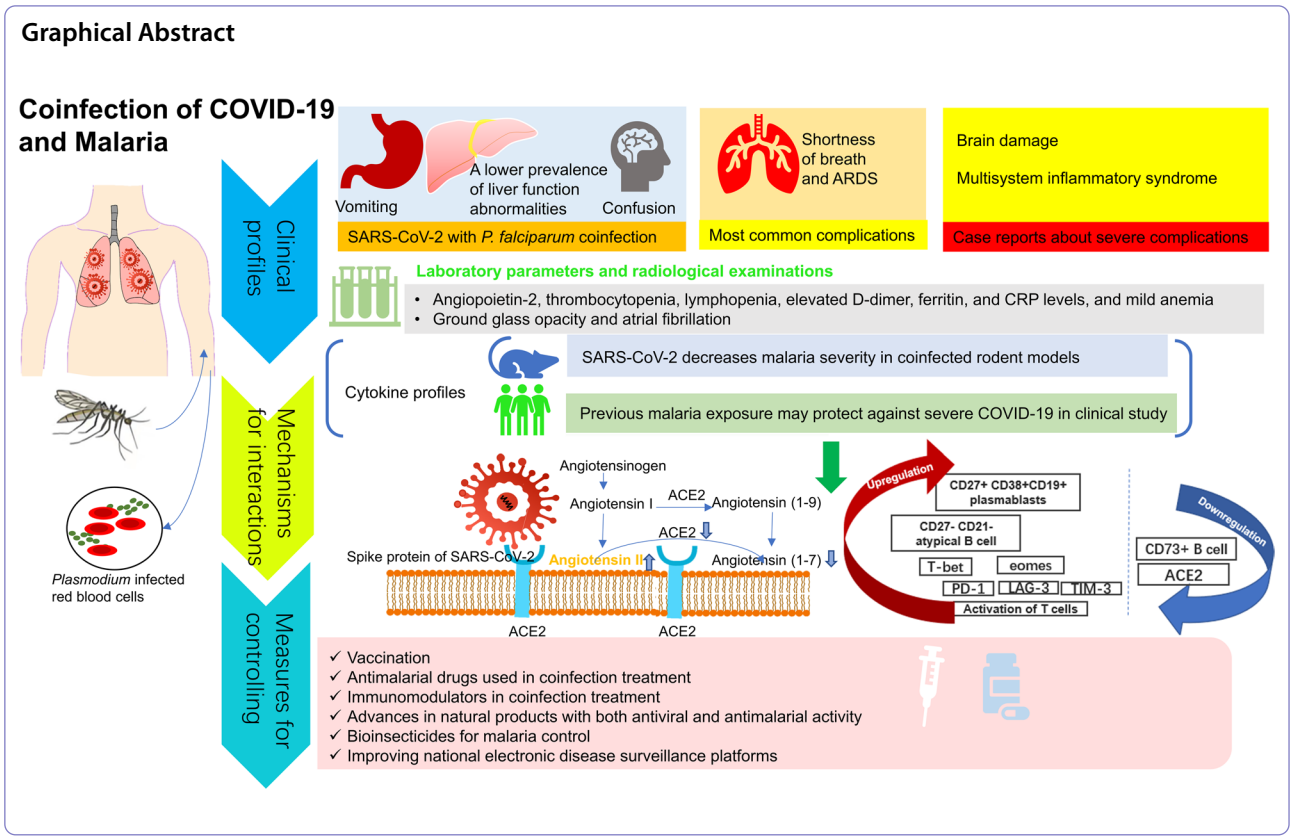

Background

The Corona Virus disease 2019 (COVID-19) was a public health emergency caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, with over 773 million confirmed cases and more than 6 million deaths worldwide as of May 7th, 2024 [1]. In the past three years, COVID-19 has caused unprecedented disruptions in socioeconomic development and public health systems worldwide. Under these circumstances, research on how COVID-19 might affect other infectious diseases has increasingly become a hot topic, among which malaria was frequently mentioned. Based on the World Health Organization (WHO) report, about 249 million malaria cases were detected in 2022 worldwide, which is well above the 247 million malaria cases, with 619 000 deaths in 2021 and 241 million malaria cases in 2020 when the COVID-19 pandemic was ongoing; these malaria cases elevated from 227 million in 2019[2, 3].

Although the prevalence of malaria tended to decrease from 2000 to 2019, the incidence increased in 2020, and an estimated 47,000 of the additional 69,000 global malaria deaths compared to 2019 were credited to the disturbed health service during the COVID-19 pandemic [2]. However, the incidence of malaria is quite different in non-malaria endemic regions. For example, an national surveillance data about notifiable infectious diseases in Germany revealed a 73% decline in imported malaria cases and 75% decrease in imported dengue fever during the early stage of the COVID-19 pandemic [4]. Furthermore, a nationwide study in Switzerland reported a decrease of more than 80% in the incidence of imported malaria cases during the COVID-19 lockdown [5]. After a decline caused by travel restrictions during the early stage of COVID-19 pandemic, an increase in imported malaria was recorded during the sporadic stage of the COVID-19 pandemic, causing delays in the diagnosis of malaria in nonendemic areas [6].

Malaria is a global vector-borne disease that has been a heavy burden on health systems for several decades. The transmission of malaria in humans relies mostly on the bites of infected female *Anopheles* mosquitoes, and less frequently through blood transfusions and contaminated needles [7, 8]. Human infection begins when a mosquito inoculates sporozoites into the skin during a blood meal. Following this, sporozoites infect hepatocytes, establish a clinically silent infection [9, 10]. Pre-erythrocytic incubation ends when hepatic schizonts release merozoites from the liver into the bloodstream. Asexual stages finish within erythrocytes followed by erythrocyte rupture, with subsequent reinvasion of merozoites into

uninfected erythrocytes causing clinical symptoms while sexual-stage development occurs in the bone marrow [9]. Mature gametocytes are released into the bloodstream and are then ingested by a mosquito during a blood meal, facilitating onward *Plasmodium* transmission [9, 10]. The major malaria parasites that can infect humans are *Plasmodium vivax*, *Plasmodium ovale*, *Plasmodium malariae*, *Plasmodium falciparum* and *Plasmodium knowlesi* [7]. When infected with malaria parasites, individuals tend to develop some typical clinical symptoms, such as paroxysm characterized by chills, fever and sweating, that occur at regular intervals [9]. Anaemia, renal impairment and cerebral malaria were common complications and were regarded as frequent causes of death.

During the early stage of the COVID-19 pandemic, SARS-CoV-2 infection was considered a priority for patients with pyrexia, leading to the underdiagnosis of malaria. In a severe malaria and COVID-19 coinfection case reported in 2020, a malaria diagnostic test was not conducted until symptoms did not improve after three days of COVID-19 treatment [11]. Likewise, a pregnant woman with both blackwater fever and severe *P. falciparum* malaria reported in December 2021, was first diagnosed with a urinary tract infection after excluding the possibility of COVID-19 infection [12]. However, her travel history of recent migration from Nigeria was overlooked at initial diagnosis, causing untimely malaria treatment and subsequent renal dysfunction [11]. During the following pandemic, which was characterized by sporadic infections with mild symptoms since 2023, malaria infection was still easily misdiagnosed as a second cause of SARS-CoV-2 infection, which has caused a deep coma in a patient [13].

Therefore, during the different stages of the COVID-19 pandemic, underdiagnosis of malaria infection and coinfections with COVID-19 were frequently reported. To achieve early diagnosis and treatment of this coinfection, healthcare professionals should be equipped with a thorough understanding of immune modulation between malaria and COVID-19 coinfection,, especially among low- and middle-income countries (LMICs). The weak disease surveillance systems in most LMICs were incapable of covering the massive costs of human resources, medical supplies and financial support needed to manage the coexistence of both outbreaks. Therefore, a synchronous, accurate and rapid diagnostic process for malaria and COVID-19 coinfections at the community level is the most economical and practical measure for preventing further large-scale transmission in LMICs. Moreover, investigations on the coinfection of SARS-CoV-2 with *Plasmodium* are promoted by the accumulation of positive clinical studies on clinical profiles, possible mechanisms for interactions, and representative control measures for SARS-CoV-2 with *Plasmodium* coinfections.

Clinical profiles of patients with COVID-19 and malaria coinfection

The clinical characteristics of COVID-19 and malaria coinfection

Generally, an overlap of epidemiology, infection incubation and clinical manifestations among the COVID-19 and malaria patients has raised a greater command for clinicians. For clinicians in LMICs with poor laboratory diagnostic capacity for rapid etiology diagnosis of malaria and COVID-19, the diagnosis can be targeted by detailed history-taking, specific attention to the patient's travel route, and the combination with good knowledge of geographic spread, such as North America, Western Europe, and South Asia [3, 10].

Some symptoms of malaria are similar to those of COVID-19, making the chances of misdiagnosis for one condition for the other remain high. The overlapping symptoms are mainly fever, myalgia, fatigue, headache and gastrointestinal symptoms [11]. Occasionally, acute respiratory distress syndrome (ARDS) induced by a cytokine storm was considered a severe complication of both COVID-19 and severe malaria [14–16]. Patients with a travelling history to malaria-endemic regions who present with the above overlapping symptoms must be explored for both diseases so that the right clinical interventions can be performed in a timely manner.

For concurrent infections, some retrospective clinical studies with large populations have been synthesized to examine overlapping symptoms, comorbidities, and complications (Table 1). Among the identified overlapping symptoms, fever, cough, shortness of breath, and chest pain were found to be more prevalent than gastrointestinal and neurological symptoms in coinfection patients [17–20]. The predominant comorbidities were diabetes and hypertension, while ARDS emerged as the most frequently encountered complication among individuals with coinfections [17–19].

Apart from the general clinical manifestations of SARS-CoV-2 with *Plasmodium* infections, case reports about severe complications resulting from this coinfection should be considered. In these cases, coinfection with malaria may contribute to severe COVID-19. For example, bilateral basal ganglia infarction along with bilateral thalamic lesions was reported in a 2 year-old female who coinfected with COVID-19 and malaria, which resulted in a deep coma [21]. Brain damage might be related to vascular insult, which increases vascular permeability by promoting the overproduction of proinflammatory cytokines [21]. Cytokines can capture pathogens via the formation of thrombus, and finally

Table 1 The clinical symptoms of COVID-19 and malaria coinfection

Author, year	Achan et al., 2022 [17]	Khabab et al., 2022 [18]	Onosakponome et al., 2022 [20]	Rasha et al., 2022 [19]
Patients(n)	50	156	300	270
Country	Uganda	Sudan	Nigeria	Sudan
Malaria species				
P. falciparum[1]	50	156	300	140
P. vivax[2]	0	1	0	9
Coinfected with *P. falciparum* and *P. vivax*	0	0	0	121
Symptoms n(%)				
Fever	15 (30%)	114 (73.1%)	61 (20%)	266 (98.5%)
Respiratory system				
Cough	19 (38%)	104 (66.7%)	53 (17.7%)	216 (80%)
Sore throat	2 (4%)	3 (1.9%)	14(4.7%)	–
Shortness of breath	13 (26%)	119 (76.3%)	21 (7%)	–
Chest pain	8 (16%)	6 (3.8%)	–	182 (67.4%)
Nervous system				
Headache	16 (32%)	10 (6.4%)	57(19%)	–
Decrease level of consciousness	4 (6%)	22 (14.1%)	–	–
Tiredness	1 (2%)	–	–	270(100%)
Digestive system				
Diarrhoea	4 (8%)	9 (5.8%)	–	–
Vomiting	4 (8%)	11 (7.1%)	–	–
Comorbidities				
Diabetes	7 (14%)	60 (38.5%)	–	111 (41%)
COPD[3]	1 (2%)	2 (4%)	–	–
Hypertension	11 (22%)	58 (37.2%)	–	55 (20%)
Complications				
Renal disease	–	13 (8.3%)	–	–
Heart disease	–	6 (3.8%)	–	
ARDS[4]	–	55 (35.3%)	–	–
Neurological diseases	–	4 (2.5%)	–	–

[1] *Plasmodium. Falciparum*

[2] *Plasmodium. Vivax*

[3] Chronic Obstructive Pulmonary Disease

[4] Acute Respiratory Distress Syndrome

lead to the outcome of stroke [22]. Moreover, multisystem inflammatory syndrome of childhood (MIS-C) and *Plasmodium vivax-P. falciparum* and SARS-CoV-2 coinfection have also been reported in children [23, 24]. MIS-C is a life-threatening complication characterized by persistent fever, digestive symptoms, rash, bilateral non-purulent conjunctivitis, mucocutaneous inflammation, and frequent cardiovascular involvement [25]. Coinfection with *Plasmodium* and SARS-CoV-2 may lead to an increased risk of developing MIS-C at a pediatric age due to cytokine storms. In a *P. vivax* and symptomatic COVID-19 coinfection case in Thailand, the patient received vaccinations against COVID-19 after coinfection discharge but was found to have asymptomatic recurrent COVID-19 infection and without *P. vivax* relapse one year later [26]. Interestingly, these patients also had faster clearance and shorter hospital stays than did the patients in the COVID-19 infection group without malaria, indicating that malaria exposure may protect against severe COVID-19 [26]. However, several case reports revealed that the SARS-CoV-2 infection might trigger *P. vivax* relapses, but the immune mechanism of COVID-19 associated *P. vivax* relapses was unclear [27–29]. For instance, a 10-year-old boy with a history of *P. vivax* infection six months previously experienced *P. vivax* infection relapse when coinfected with SARS-CoV-2 [27]. Therefore, coinfected patients with a previous malaria vivax

history should be evaluated for the possibility of a relapse of *P. vivax* infection when presented with viral illness symptoms.

Laboratory parameters and radiological examinations for COVID-19 and malaria coinfection

A complete laboratory assessment of blood counts, inflammatory biomarkers as well as kidney and liver function, should be performed in all suspected cases of COVID-19 and malaria coinfection. Radiological examinations, including chest X-ray, chest CT, ultrasound and MRI, were performed to determine the presence of pleural effusions, lung consolidation or interstitial patterns and other organ lesions involved [30]. For aetiology diagnosis, specimens such as nasopharyngeal or oropharyngeal swabs and bronchoalveolar lavage fluid were collected for SARS-CoV-2 polymerase chain reaction (PCR) and antibody IgG/IgM tests against SARS-CoV-2 to confirm COVID-19 infection [31]. Moreover, a peripheral smear for blood cell morphology analysis, rapid antigen test, and PCR were also carried out for malaria diagnosis [11, 18, 32].

Patients with sole infection of *Plasmodium* and SARS-CoV-2 exhibited anaemia, thrombocytopenia, and lymphopenia; however, the changes in white blood cell (WBC) counts were divergent (Table 2). Specifically, COVID-19 patients demonstrated elevated WBC counts, whereas malaria patients experienced a decrease in WBC counts [33, 34]. Additionally, higher levels of C-reactive protein (CRP), procalcitonin (PCT), D-dimer, and lactate dehydrogenase (LDH) were observed in COVID-19 patients and those with coinfections [18, 35, 36]. Ground glass opacity and atrial fibrillation were the most common CT and ECG findings among coinfection patients [18].

The possible mechanisms for interactions between SARS-CoV-2 with *Plasmodium* coinfection

The similarities in clinical manifestations and laboratory findings suggested potential interactions between COVID-19 and malaria. Therefore, immunological and

Table 2 Laboratory parameters for COVID-19 and malaria monoinfection and coinfection

Parameters	Malaria monoinfection		COVID-19 monoinfection	Malaria and COVID-19 coinfection	
WBCs[1] counts	↓	↓	↑	↑	–
Haemoglobin	↓	↓	↓	–	↓
Platelets	↓	↓	↓	↓	↓
Lymphocyte	↓	↓	↓	–	↓
Urea nitrogen	NA[7]	NA	↑	↑	–
CRP[2]	NA	NA	↑	↑	↑
PCT[3]	NA	NA	↑	NA	↑
D-dimer	NA	NA	↑	↑	↑
Creatinine	NA	NA	↑	–	–
AST[4] OR ALT[5]	NA	↑/↑	↑	NA	↑
Ferritin	NA	NA	↑	NA	↑
Bilirubin	NA	↑	↑	NA	↑
LDH[6]	NA	NA	↑	NA	↑
Study type	Cross-sectional study	Cross-sectional study	Systematic review	Cross-sectional study	Meta analysis of cases
Sample size	340 (170 malaria positive *vs* 170 malaria negative)	97 (67 malaria *vs* 30 healthy controls)	71,170	156	12
Malaria species	*P. falciparum* (105) *P. vivax* (61)	*P. falciparum* (67)	NA	*P. falciparum* (155) *P. vivax* (1)	*P. falciparum* (2) *P. vivax* (5) *P. ovale* (1) Unknown (4)
References	[33]	[34]	[36]	[18]	[35]

[1] WBC: white blood cell

[2] CRP: C-reactive protein

[3] PCT: procalcitonin

[4] AST: aspartate aminotransferase

[5] ALT: alanine aminotransferase

[6] LDH: lactatedehydrogenase; ↑ Elevated; ↓ Decreased; – Normal

[7] NA: Not applicable

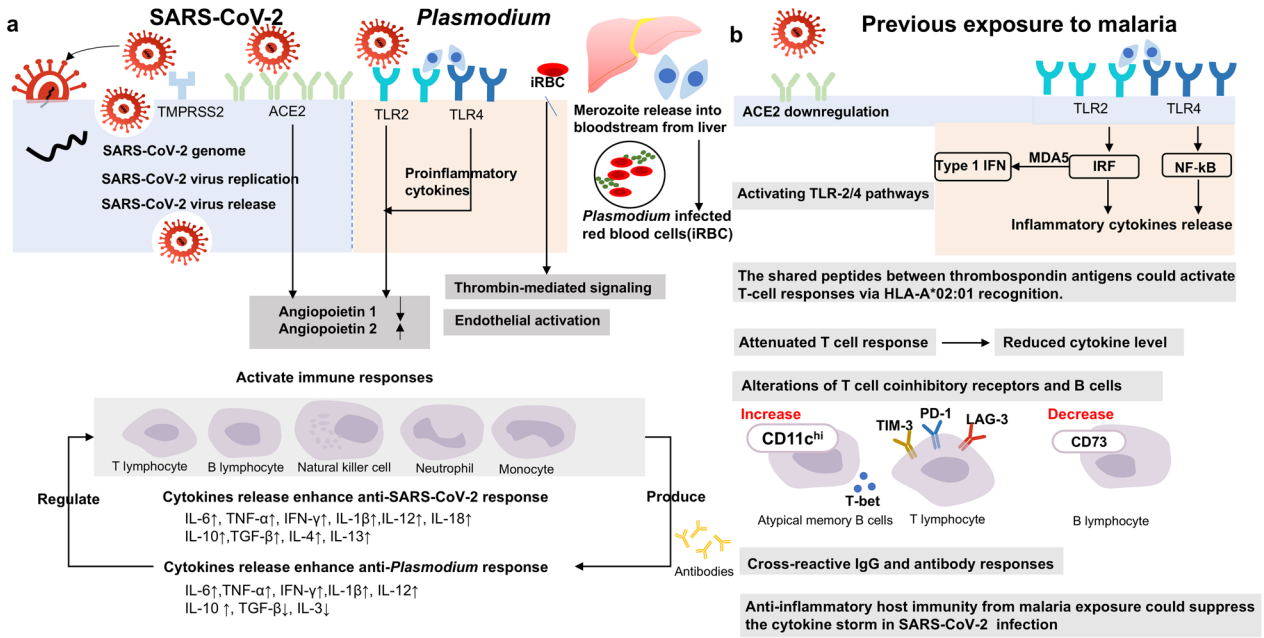

Fig. 1 Host responses to the COVID-19 and malaria infections and immune regulations. (**a**) immune mechanisms in single infection of SARS-CoV-2 *vs Plasmodium*. (**b**) immunological and genetic elements associated with protection against severe COVID-19 from previous malaria exposure. Abbreviations: TMPRSS2: transmembrane protease, serine 2; ACE2: angiotensin converting enzyme2; TLR: Toll-like receptor; TIM-3: T-cell immunoglobulin mucin-3; PD-1: coinhibitory molecules such as death pro-tein-1; LAG-3:lymphocyte-activating gene-3

genetic evidence was comprehensively collected and summarized to explain the correlations (Fig. 1).

ACE2 downregulation and angiotensin pathway modulation

The angiotensin-converting enzyme 2 (ACE2) receptor was the major receptor involved in the cellular invasion of SARS-CoV-2 into the hosts. The S protein of SARS-CoV-2 binds to ACE2 as a cellular receptor, and ACE2 cleaves angiotensin II (Ang II) to Ang II (1–7) (Fig. 1a). ACE2 enzymatically cleaves angiotensin II (Ang II) to produce angiotensin (1–7). Ang(1–7) exerts a variety of physiological effects via Mas receptor signaling, including the downregulation of chemokines as well as cytokines, growth inhibitory effects on endothelial cells and vasodilation [37]. The study by Sun et al. has also demonstrated that expression level of human ACE2 directly correlates with the viral load in SARS-CoV-2 infected cells, indicating ACE2 might be critical for the COVID-19 disease status [38]. Downregulation of ACE2 expression plays a role in the poor outcome of COVID-19 infection caused by malaria via reducing SARS-CoV-2 entry into lung epithelial cells. Certain genetic variants of ACE2 were preponderant among malaria-exposed populations which have even impacted susceptibility to COVID-19. For instance, the ACE2 T-allele of rs2106809 was found to downregulate ACE2 expression to prevent severe malaria [39]. SARS-CoV-2 invades the human body by binding to the S protein via the ACE2 receptor. With ACE2 downregulation, the infiltration of SARS-CoV-2 is hindered, then Ang II levels increase, causing varying effects on malaria and COVID-19. Although Ang II can suppress sporozoite growth in mosquitoes to prevent the spread of malaria, it may also increase the severity of COVID-19 [39]. Furthermore, the frequency of ACE1/D, which is linked to an increase in Ang II, was inversely associated with the log-transformed incidence of COVID-19 infection [40]. This may suggest that positive selection of ACE1/D and ACE2/T in malaria-endemic areas can downregulate ACE2 and thus offer protection against severe COVID-19 infection.

Toll-like receptors (TLRs) and innate immune activation

Toll-like receptors (TLRs) also involve in viral recognition and activation of the innate immune system. For example, TLR-4 protects against high parasitemia in malaria patients but also has a greater affinity for the S protein of SARS-CoV-2 than other TLRs [41, 42]. In that case, TLR-4 upregulation resulting from a previous malaria infection likely boosted immune responses against COVID-19. Moreover, TLR-2 was found to protect against severe malaria and severe COVID-19 via the suppression of excessive inflammation [41, 42].

Activation of the TLR-2/4 pathway stimulates nuclear factor-kB (NF-kB) and interferon regulatory factor (IRF), which produce proinflammatory cytokines like type 1 IFNs, reducing virus and infected cell production and replication [41, 43]. Type I IFN signaling activated by malaria infection could compensate for inadequate production of type 1 IFNs during the COVID-19 infection. Melanoma differentiation associated protein 5 (MDA5), a retinoic acid inducible gene I-like receptor that participates in type 1 IFN production, recognizes RNA from malaria parasites and triggers interferon production in SARS-CoV-2 [44]. As a consequence, we speculate that malaria-related immunity provides protection against COVID-19 by upregulating and activating TLR-2/4, type I IFNs and MDA5.

T-cell and B-cell responses in coinfections

Previous malaria exposure might influence the T-cell and B-cell immune response to SARS-CoV-2 and might be linked to milder COVID-19 cases in malaria-endemic regions. Kesego et al. discovered that asymptomatic COVID-19 shows attenuated T cell response, higher *P. falciparum* antibodies and reduced production of cytokines than those with symptomatic COVID-19 [45]. The clinical outcomes of both SARS-CoV-2 with *Plasmodium* infection were determined by the balance between coactivation and coinhibition of T cells. Both infections resulted in activation and differentiation of CD8 + and CD4 + T-cell populations. Increases in the co-inhibitory receptors such as T-cell immunoglobulin mucin-3 (TIM-3), coinhibitory molecules such as death protein-1 (PD-1), and lymphocyte-activating gene-3 (LAG-3), in addition to promoted expression of T-bet and other transcription factors, are capable of preventing acute clinical illness induced by an excessive immune response [46]. More specifically, malaria patients had higher levels of PD1 + LAG-3− and PD1 + TIM-3− as well as PD1 + TIM-3 + and PD1 + LAG-3 + T cells. Moreover, compared with healthy individuals, patients with COVID-19 had higher frequencies of PD1− LAG-3 + and PD1− TIM-3 + CD8 + and CD4 + T cells [46]. In summary, the activation of CD8 + and CD4 + T cells and coinhibitory receptor upregulation in malaria patients are conducive to activating immune responses against COVID-19 and preventing poor outcomes in patients with this disease. Furthermore, B cells are also known to play a crucial role in antiparasitic and antiviral immunity. Both malaria and COVID-19 patients exhibited an increased frequency of CD27− and CD21− atypical memory B cells in addition to CD19 +, CD 27 +, and CD38 + plasmablasts compared to healthy donors. Like in T-cell response regulation, PD-1 is expressed on atypical memory B cells in malaria and COVID-19 patients, and a reduction in CD73 + B cells inhibits an excessive immune response [47]. After activation by antigens and helper T cells, plasmablasts further differentiate into plasma cells to produce IgG, the main potentiator of humoral immunity against both *Plasmodium* and SARS-CoV-2 infections. A significant cross-reactive antibody response to the SARS-CoV-2 S protein was recorded in blood samples of malaria patients collected before the pandemic. However, malaria infections did not accelerate the production of IgG against COVID-19 [48].

Furthermore, prior SARS-CoV-2 exposure could also alleviate malaria severity. To evaluate the effect of COVID-19 infection on the progression of malaria, Fraga et al. established novel coinfection mouse models with an ancestral variant and a mouse-adapted variant of SARS-CoV-2 and *Plasmodium berghei* [49]. In their study, primary SARS-CoV-2 exposure partially alleviated the liver stage of *Plasmodium* infection by decreasing the number of *P. berghei*-infected hepatocytes. Further testing revealed that the unique circulating leukocyte landscape and upregulation of PD-1 might constitute distinct immune responses in coinfected mice.

In brief, attenuated T cell response, increased frequencies of atypical memory B cells, plasmablasts and PD-1 cells as along with decreased CD73 + B cells in patients with previous malaria infection might protect from the current COVID-19 infection.

Cross-reactive immunity and antibody responses

IgG is the main potentiator of humoral immunity and is associated with immunological defense against malaria and COVID-19 infection. For SARS-CoV-2 infection, IgG antibodies are usually specific for the full-length spike (S) protein, the receptor-binding motif (RBM), and the receptor-binding domain (RBD), among which the positivity for IgG against spike RBD could be predictive of patients' survival [50]. In the blood samples of malaria-infected persons collected before COVID-19, Abugri et al. reported a cross-reactive antibody response to the S protein (21.9%) compared to the response to the RBD (6.7%) and RBM (8.8%), which highlighted the role of the S protein in this coinfection immunity [51]. Additionally, some evidence might indicate that natural immunity is developing rapidly. For instance, through an investigation in two Tanzanian rural communities, Lyimo et al. reported that the recognition of *Plasmodium* antigens and odds of being SARS-CoV-2 spike IgG seropositive increased significantly with age [52].

Notably, cross-reactive IgG antibodies are not independent genetic determinants of the severity of malaria. However, based on the findings of Briggs and colleagues, no connection was detected between the incidence of malaria, including asymptomatic parasitaemia, and

SARS-CoV-2 seroconversion [48]. Moreover, the density of malarial parasitaemia showed no connection with the level of cross-reactive antibodies, which appeared to be more common in sera without active *P. falciparum* infection or blood smear-negative samples [48]. Manning et al. reported that no neutralizing activity was detected for these cross-reactive antibodies, which was the same with the results of Grassia et al. and does not support the concept that *P. falciparum* infections improve functional humoral responses [53, 54].

Individuals in blood group O might be protected from the severity of clinical disease and with the development of cerebral malaria, and also possess higher seropositivity of SARS-CoV-2 IgG than those in non-blood group O [55, 56]. Children with blood group O had lower the odds of developing severe malarial anaemia and lower parasitaemia than those with blood group A [55]. Although both of blood group O and non-blood group O could form parasite-triggered red blood cell rosettes, the protective effect of blood group O against severe malaria might attribute to a smaller size and reduced stability of *Plasmodium*-infected red blood cell rosettes compared to non-O blood groups [57–59]. Furthermore, evaluation of the seroprevalence of SARS-CoV-2 IgG revealed that the O blood group was closely correlated with seropositivity among unvaccinated adults, indicating potential protection against the SARS-CoV-2 infection [56].

Genetic and environmental influences

In addition, common immunodominant epitopes between SARS-CoV-2 and *P. falciparum* have been found to contribute to cross-reactivity, which might explain the protection of malaria immunity against COVID-19. Specifically, two pairs of shared peptides have been identified between thrombospondin antigens: one related to the *P. falciparum* anonymous protein and the N protein of SARS-CoV-2 and the other related to the SARS-CoV-2 S protein and SSP-2 in *P. falciparum* [60]. Both pairs were found to activate T-cell responses via HLA-A*02:01 recognition. Poor outcomes from these infections are associated with an imbalance between coactivation and co-inhibition of immune cells.

Cytokine profiles and inflammatory pathways

Cytokines play a crucial role in coordinating antimicrobial effector immune cells and managing both innate and adaptive immune responses. The cytokine storm which characterized with an overproduction and imbalance of proinflammatory and anti-inflammatory cytokines has been associated with the onset of ARDS among coinfection patients. Additionally, the cytokine profiles of COVID-19 and malaria coinfections were also distinguished from those of single infections (Table 3). Both SARS-CoV-2 with *Plasmodium* sole infected patients have undergone an overproduction of cytokines and activation of the coagulation cascade, with significant increases in five shared proinflammatory cytokines (IL-6,TNF, IFN-γ,IL-1β and IL-12) and one anti-inflammatory cytokines (IL-10). Notably, TNF levels were found to be higher in patients with coinfection of COVID-19 and malaria than those with sole infection.

Adaptive CD4 + and CD8 + T cells together with innate antigen-presenting cells such as macrophages and dendritic cells were all involved in the strike of cytokine storm [61]. Specifically, T cell exhaustion and impaired early antiviral response are unique in severe COVID-19 with circulating NKT cell frequencies been a predictive biomarker for severe COVID-19 [62]. In particular, IL-6 and TNF, two major players in modulating cytokine storm, were considered to participate in T cell and NK cell exhaustion and strongly associated with severity and mortality in severe SARS-CoV-2 infected cohorts [63,

Table 3 Cytokine profiles for COVID-19 and malaria infections

Cytokines	Infection types			
	Malaria *vs* healthy controls	**COVID-19 *vs* heathy controls**	**High previous malaria exposure *vs* low previous malaria exposure in COVID-19 patients**	**Production of cytokines stimulated with *P. falciparum* merozoites lysates in asymptomatic COVID-19 patients *vs* those in symptomatic COVID-19 patients**
Proinflammatory cytokines	IL-6↑,TNF↑, IFN-γ↑,IL-1β↑, IL-12↑	IL-6↑, TNF↑, IFN-γ↑, IL-1β↑, IL-12↑, IL-18↑	TNF↓, IL-8↓, IL-6↓, IL-2↓, IL-7↓	IFN-γ↓, TNF↓
Anti-inflammatory cytokines	IL-10 ↑ TGF-β↓, IL-3↓	IL-10↑ TGF-β↑ IL-4↑, IL-13↑	IL-17↓, TGF-β1↓, IL-10↓	IL-10↑
References	[115]	[116, 117]	[17]	[45]

↑ Elevated

↓ Decreased

64]. The concurrent infection could further proceed the onset of cytokine storm than the sole infection via double stimulations of two pathogens. The cytokine storm changes the subset proportion of T cells, aggravating the imbalance of cytokines, thus disturbing differentiation of Th0 cells presented as Th1/Th2 and Th17/Treg cells axis imbalance [65]. This process might further exhaust T cell and NK cell compromising their anti-SARS-CoV-2 and anti-malaria activity in concurrent infection patients. What's more, negative regulators of cytokines storm, such as Tregs, decoy cytokine receptors (IL1RA) and anti-cytokine monoclonal antibodies(infliximab, emapalumab and tocilizumab) were practical therapies for coinfection treatment [61].

Although concurrent infection patients might develop worse laboratory parameters and more severe complications than those with sole infection, previous malaria or COVID-19 exposure could provide protection effect against new infections. In regards of the protection against SARS-CoV-2 infection by previous malaria exposure, lower levels of anti-inflammatory cytokines, including IL-17, TGF-β1 and IL-10, were found in COVID-19 patients with high malaria exposure than in those with low exposure [17]. In the context of sole *Plasmodium* infection, the anti-inflammatory cytokines including TGF-β, IL-10 and IL-27 were more highly expressed in asymptomatic malaria patients than in symptomatic patients [66]. These shared anti-inflammatory cytokines maintain anti-inflammatory host immunity in patients with high exposure to malaria so that cytokine storms can be suppressed when they are solely infected with SARS-CoV-2. Due to multiple exposures to malaria infection, residents in malaria endemic regions tend to have high anti-inflammatory responses, resulting in asymptomatic malaria infection, where the main goal is on controlling clinical symptoms rather than clearing parasites [67].

Implications for pathogenesis and clinical outcomes

Previous malaria exposure may protect against severe COVID-19. A greater burden of diabetes and heart disease, along with a higher incidence of fever and a series of respiratory symptoms including chest pain, cough and shortness of breath, was recorded among patients with low previous *P. falciparum* exposure than among those with high exposure [17]. Moreover, COVID-19 patients with high malaria exposure possessed a lower prevalence of fever and respiratory symptoms than those with low malaria exposure, indicating that respiratory syndrome might be relieved via the common immune elements of the two infections [17].

Summarily, this protective effect can be attributed to several factors, including the ACE2 downregulation, attenuated T cell response, increased atypical memory B cells, as well as upregulation of T-cell activation and coinhibitory receptors. Additionally, cross-reactive immunity, antibody responses, TLR-induced pathways, and shared inflammatory cytokines also contribute to this protective effect. Furthermore, prior exposure to SARS-CoV-2 may alleviate the severity of malaria by reducing the number of *Plasmodium*-infected hepatocytes and enhancing the expression of PD-1.

Measures for controlling COVID-19 and malaria coinfection

Vaccination

Vaccination has always been a cost-effective prevention tool for both malaria and COVID-19. According to the WHO report, vast progress has been made in combating COVID-19 in nearly every country, and over 13 billion doses have been administered globally, reaching nearly 60% of the world's population [1, 68]. SARS-CoV-2 vaccines vary from inactivated, live attenuated, viral vector, protein subunit, RNA, and DNA to virus-like particle (VLP) vaccines [69]. The mRNA-based COVID-19 vaccines are the most prospective vaccine candidates for pandemic control because of their relative short production period, cost effectiveness, versatility in vaccine design, and ability to induce an immune response [70]. For malaria control, preerythrocytic vaccines endorsed by the WHO in 2021 and 2023 were able to continuous reduce malaria morbidity. The RTS,S vaccine, officially permitted for wider use by the WHO in 2021, has protected nearly 2 million children in a multiyear malaria vaccine pilot programme in Ghana, Kenya and Malawi since 2019[2, 71]. Now, a second vaccine called R21/Matrix M is expected to fill the short supply of the RTS,S vaccine with more cheap costs and greater quantities [72]. Moreover, the *P. falciparum* circumsporozoite protein (PfCSP) mRNA vaccine was promoted by advances in COVID-19 vaccines [73]. However, low vaccination rates in LMICs are a major threat to the control of COVID-19 and malaria infections and require long-lasting efforts.

Anti-malarial drugs used in coinfection treatment

Growing evidence has confirmed that anti-malarial drugs might suppress the replication or attachment to ACE2 receptors of SARS-CoV-2. Individuals who are constantly exposed to these anti-malarial drugs and in malaria-endemic regions are more likely to develop resistance to SARS-CoV-2, which might contribute to the low mortality rate of SARS-CoV-2 infection in malaria-endemic regions and protection from previous malaria

exposure. Artemisinin inhibits spike protein-mediated and TGF-β-dependent steps in the infection process and disrupts post-entry intracellular events in the SARS-CoV-2 infection cycle [74]. Meanwhile, quinoline analogs such as chloroquine (CQ), hydroxychloroquine (HCQ), ferroquine, amodiaquine and mefloquine along with artemisinin-related compounds including arteannuin B, lumefantrine and dihydroartemisinin all presented rather active anti-SARS-CoV-2 potential [75, 76]. However, due to the adverse cardiac effects of CQ and HCQ, such as corrected QT interval prolongation, the application of CQ and HCQ shouldn't been considered for the treatment of COVID-19 patients with arrhythmia [77]. Besides, the identification of new analogs with both anti-SARS-CoV-2 and anti-malaria efficacy through the structure–activity relationship of the above antimalarial agents has recently been promoted. For instance, 9-aminoacridines, pyronaridine and quinacrine scaffolds, along with their analogs, were proven to be active against SARS-CoV-2 [78].

Immunomodulators in coinfection treatment

Corticosteroids

Given that COVID-19 and malaria coinfections are more likely to cause severe inflammatory responses like ARDS, we proposed the early application of medium or higher-dose corticosteroids in coinfection cases for anti-inflammatory effect. Current evidence has suggested that the administration of corticosteroids including dexamethasone and methylprednisolone could reduce ARDS-related mortality, and higher-dose dexamethasone (12 mg or higher) may reduce all-cause mortality (up to 30 days) in patients treated for COVID-19 [79, 80]. Although some clinical trials of corticosteroids alone for cerebral malaria treatment failed in the past, early pulse of methylprednisolone (20–30 mg/kg/day IV)was highly effective for patients coinfected with MIS-C, and often combined with intravenous immunoglobulins (IVIGs) or plasmapheresis in clinical practice [23, 24, 81, 82].

Intravenous immunoglobulins (IVIGs) and monoclonal antibodies (mAbs)

IVIG, a polyclonal serum IgG, could prevent the development of ARDS by influencing complement cells, innate immune cells, effector T cells, and Tregs, but lack antigenic specificity [83, 84]. Conversely, monoclonal antibodies possess rather high antigenic specificity and are a very promising strategy for treating COVID-19 and malaria. The following COVID-19 monoclonal antibodies (mAbs) have been shown to have therapeutic effects in clinical use: bamlanivimab, etesevimab, casirivimab, imdevimab, cilgavimab, tixagevimab and regazolvimab [85]. The combined monoclonal antibody therapy recommended by the WHO, namely, cytovibimab and imdesvimab, which bind to the S protein of SARS-CoV-2 to block viral entry into host cells, has been shown to reduce mortality in seronegative patients and reduce the incidence of symptomatic COVID-19 in asymptomatic COVID-19 individuals [86–88]. Additionally, a single bispecific antibody that combines the specificities of two antibodies in one molecule have shown broader coverage of SARS-CoV-2 variants than the combined monoclonal antibody therapy [89].

Among the mAbs against malaria, current mAbs targeting the PfCSP, such as CIS43LS and L9LS, were proven to be protective against *P. falciparum* infection without evident safety concerns in clinical trials [90, 91]. In addition, further studies of mAbs against malaria will likely focus on the unique life cycle of the malaria parasite and various antigenic targets, especially mosquito proteins responsible for parasite transmission [92]. Despite the tremendous progress that antibody therapy has made in both COVID-19 and malaria treatment, there is no direct efficacy report on the concomitant use of multiple antibodies in patients infected with COVID-19 and malaria. In addition, the development of Abs targeting the common immunodominant epitopes and immune pathways related with COVID-19 and malaria coinfections is likely promising. In addition to the flexible choice of medications, airway management such as noninvasive ventilation or mechanical ventilation and extracorporeal membrane oxygenation (ECMO) should also be considered as supportive care in ARDS patients [93].

Advances in natural products with both antiviral and anti-malarial activity

In recent years, biologically active compounds from natural products have been recognized as promising candidates for antimalaria and anti-COVID-19 treatment. A summary of the main natural products with both antimalarial and anti-covid-19 efficacy is provided in Table 4. The majority of these active compounds were found to inhibit the replication of the SARS-CoV-2 via regulation of the ACE2 receptor. However, the mechanism of *Plasmodium* suppression remains to be elucidated. Specifically, β-glucan, derived from the metabolites of bacteria and fungi, was found to impede the proliferation of malarial merozoites in vivo [94, 95], while the antimalarial efficacy of *Glycyrrhiza glabra* has been linked to HMGB1 proteins [96, 97]. Apart from the regulation of the ACE2 receptor in the context of SARS-CoV-2, 2,5-dimethoxy-substituted phenyl piperamide 5 (derived from *Piper nigrum*) and *Scutellaria* have also been shown to suppress the activity of the 3C-like main protease and RNA-dependent RNA polymerase of SARS-CoV-2, respectively [98, 99]. Concurrently, active compounds

Table 4 Main natural products with both anti-malarial and anti-covid-19 efficacy

Natural products	Anti-malarial efficacy	Anti-COVID-19 efficacy	References
Pomegranate peel extract	Reduce parasitaemia and the spleen indices	Inhibit the interaction of SARS-Cov-2 spikes and ACE2 receptor in vitro	[118–120]
2,5-dimethoxy-substituted phenyl piperamide 5 (from *Piper nigrum*)	Anti-malarial activity against the 3D7 strain of *P. falciparum* at the IC50 of 24.55 ± 1.91 μM	Suppress SARS-CoV-2 3C-like main protease activity at the IC50[1] of 106.9 ± 1.2 μM	[98]
Thymoquinone (from *Nigella sativa*)	Depress oxidative stress and NO production in macrophages	Inhibits the replication and attachment to ACE2 receptor of SARS-CoV-2	[99]
β-glucan (from metabolites of bacterium and fungal)	Prevent the proliferation of malarial merozoites in vivo	Reduce coagulopathy Reduce IL-1β, IL-6 in in vitro lung injury Activate macrophages	[94, 95, 102]
Scutellaria	Baicalein derivatives demonstrated a significant 44% suppression of *P. falciparum* growth by day 4 of treatment	Suppress the RNA-dependent RNA polymerase activity of SARS-CoV-2 Regulate ACE2 receptor binding	[100, 121]
Sambiloto (andrographolide and flavonoids)	Reduce parasitaemia	Inhibited the replication of the SARS-CoV-2, with an IC50 of 0.034 μM	[122–124]
Glycyrrhiza glabra	Formation of stable complexes with both human and *Plasmodium* HMGB1 proteins	Reduce ACE2 and HMGB1 levels Reduce proinflammatory cytokines Regulate Th2 and Th17 differentiation	[96, 97, 101, 125, 126]

[1] IC50: half-maximal inhibitory concentration

such as β-glucan, thymoquinone from *Nigella sativa* and *Glycyrrhiza glabra* also exhibited anti-inflammatory effect through the downregulation of proinflammatory cytokines [99–101]. In addition, β-glucans has been found to enhance the proliferation of hematopoietic cells, which might be used to improve thrombocyte counts, lymphopenia and anime during malaria and COVID-19 coinfection [102]. Despite the many trials conducted in vitro and on animals, the number of human studies of the above compounds is rather limited, so their application in clinical practice has a long way from being known.

Notably, some natural plants and their active compounds for treating both COVID-19 and malaria are mainly targeted at common immunodominant elements and pathways associated with two diseases, ACE2 and HMGB1, which in turn supports the hypothesis that the administration of anti-malarial drugs could protect COVID-19 patients from poor prognosis. For confirmed and suspected cases of malaria and COVID-19 coinfection, the above traditional herb formulas and preparations approved for clinical use could complement standardized therapy to reduce hospital stays.

Based on the repositioning of existing drugs and further investigations of natural products for treating malaria and COVID-19 coinfection, owing to advances in nanomedicines, nitric oxide (NO) with multifunctional nanocarriers has been said to exsert improved therapeutic efficacy against SARS-CoV-2 and malaria parasites with reduced side effects [103]. Compared to the cell cultivation-dependent method, molecular docking-based virtual screening of compounds from the database and prediction of parameters such as drug likeness and pharmacokinetics are more cost effective for identifying potential drugs for treating malaria and COVID-19 coinfection [104, 105].

Taken together, phenotypic screening, targeted-based screens, modified natural substances and biologicals are the dominant approaches for identifying promising lead compounds needed as viruses mutate and overcome existing small-molecule antivirals.

New prospects into malaria control in the context of the COVID-19 pandemic

The COVID-19 pandemic has disrupted malaria control activities worldwide. More importantly, high levels of malaria morbidity and mortality in LMICs have been reported [106]. Effective measures, including planned insecticide-treated mosquito net (ITN) campaigns, seasonal malaria chemoprevention (SMC) and planned indoor residual spraying (IRS), were halted by the COVID-19 pandemic, which presented major challenges for malaria control in many malaria-endemic countries [2]. Since malnutrition and undernutrition are major health problems in malaria-endemic regions, the immune status of children in malaria-endemic regions is rather unpleasant, which may result in poor outcomes in patients with malaria and COVID-19 infection. In addition, overuse of anti-malarial agents during COVID-19 and malaria coinfection might exacerbate the emergence of anti-malarial resistance in regions endemic for malaria.

However, the COVID-19 pandemic has also provided a significant chance to achieve malaria control through a more comprehensive approach. The development of bioinsecticides, such as gene-driven mosquitoes, fungi,

Table 5 Measures for controlling COVID-19 and malaria coinfection

Measures		
Vaccination	*SARS-CoV-2 vaccines*	*Malaria vaccines*
	Live attenuated, viral vector, protein subunit RNA, and DNA, virus-like particle (VLP)	Pre-erythrocytic vaccines, RTS,S vaccine, R21/Matrix M, PfCSP mRNA vaccine
Antimalarial drugs	*Traditional drug*	*New analogs*
	Chloroquine:400/500 mg twice daily [126, 127] Hydroxychloroquine: 200 mg twice per day/500 mg per day [126, 127] Ferroquine, amodiaquine, mefloquine, artemisinin, artean-nuin B, lumefantrine, dihydroartemisinin	9-aminoacridines, pyronaridine and quinacrine scaffolds, along with their analogs
Immunomodulators	*Corticosteroids*	*Intravenous immunoglobulins(IVIGs)*
	Dexamethasone, methylprednisolone	1–2 g/kg
	Monoclonal antibodies(mAbs)	
	mAbs against COVID-19: Bamlanivimab, etesevimab, casiriv-imab, imdevimab, cilgavimab, tixagevimab and regazolvimab	mAbs against malaria: PfCSP such as CIS43LS and L9LS
Active compounds from natural products	Pomegranate peel extract 2,5-dimethoxy-substituted phenyl piperamide 5 Thymoquinone from *Nigella sativa* β-glucan(from metabolites of bacterium and fungal)	*Scutellaria* *Sambiloto* (andrographolide and flavonoids) *Glycyrrhiza glabra*
New prospects into malaria control in the context of the COVID-19 pandemic	*Negative effect of COVID-19 pandemic on malaria control*	*Positive effect of COVID-19 pandemic on malaria control*
	Malaria control measures were halted by the COVID-19 pandemic	Development of bioinsecticides for malaria control
	Overuse of antimalarial agents in coinfection cases might exacerbate the emergence of antimalarial resistance	Promotion of national electronic disease surveillance platforms

and bacterial symbionts, could reduce malaria transmission while decreasing human contact and human resources during the COVID-19 pandemic. In detail, RNA interference, which can inhibit the mosquito genes responsible for mosquito survival and reproduction, was applied to control the mosquito population [107]. The use of fungal entomopathogens could reduce mosquito longevity and alter behavior correlated with flight and host location [108]. The avirulent bacterium *Wolbachia* causes femalization of males and male killing among mosquitoes [109]. Furthermore, it is necessary to focus on imported malaria infection cases characterized by sporadic infections during the present pandemic. On the one hand, passengers headed for malaria-endemic regions should be equipped with professional pretravel advice about malaria, especially about the accurate use of anti-malarial chemoprophylaxis.

On the other hand, local authorities should monitor and screen for high-risk personnel who are passing through malaria-endemic areas. As soon as symptoms such as diarrhea and fever are detected among travelers from tropical and subtropical areas, both malaria and COVID-19 epidemic responses are activated; reported cases are detected, reported and confirmed; and epidemiological investigations and evaluations of transmission blockade are implemented [110].

However, with various viral mutations, such as Omicron, BQ.1 and XBB, which have upgraded transmissibility and immune escape capacity, different waves of the COVID-19 pandemic have already occurred [111]. In addition, the occurrence and spread of antimalarial drug resistance in Africa has also greatly threatened malaria elimination. In view of these findings, the poor disease surveillance systems in malaria-endemic regions are unprepared for long-term SARS-CoV-2 with *Plasmodium* coinfection situations. Persistent efforts have been made to strengthen national electronic disease surveillance platforms that are able to detect emerging pathogens and quickly react to public health emergencies. For instance, the District Health Information Software version 2 platform (DHIS2), which was established globally before the COVID-19 pandemic, has been reported to make impressive contributions to more than 25 countries during the COVID-19 pandemic [112]. Several malaria-endemic countries, such as Sri Lanka, Uganda, and Sierra Leone, have reinforced and configured their DHIS2 systems to conduct COVID-19 detection, tracking, and vaccination at lower costs. Likewise, the existing acute febrile illness (AFI) surveillance systems successfully integrate the identification of new pathogens such as SARS-CoV-2 within AFI care-seeking populations [113]. An integrated case surveillance system for both malaria and COVID-19 has also been established in Sri Lanka [114]. In general, sufficient prior investments in disease surveillance systems have made public health agencies better prepared for new infectious disease threats, and

different regions should adjust the focus of systems based on their epidemiological investigations to make the best use of resources in LMICs.

In summary, the main control measures for malaria parasite and SARS-CoV-2 coinfection are anti-malarial drugs, related supportive therapies, vaccines and the management of epidemic responses (Table 5). Anti-malarial drugs were applied to treat SARS-CoV-2 infection. Corticosteroid therapies, IVIG and other supporting therapies also could prevent the poor prognosis of patients with COVID-19 and malaria coinfection. The development of mRNA vaccines for COVID-19 has accelerated the development of malaria vaccines, but the vaccination goal of malaria control has still been beyond reach compared to the large scale of COVID-19 vaccination. Overall, the COVID-19 pandemic indeed disrupted malaria control activities, but it also offered an opportunity to rethink malaria in the context of COVID-19, where bioinsecticides came into the stage center and imported malaria cases were given increased attention.

Conclusion

The above clinical characteristics illustrate the common symptoms and severe complications between COVID-19 and malaria coinfections. The detailed diagnostic procedure for coinfections was also summarized to determine the appropriate clinical intervention. For possible interactions, immunological and genetic evidence was obtained to explain the correlation between COVID-19 and malaria incidence. Finally, multiple control measures for coinfections were discussed, and malaria control efforts were fulfilled in the context of COVID-19. In summary, these findings provide insight into malaria and COVID-19 control and the study of similar infectious diseases.

Abbreviations

COVID-19	Corona virus disease 2019
SARS-CoV-2	Acute respiratory syndrome coronavirus 2
WHO	World Health Organization
LMICs	Low- and middle-income countries
ARDS	Acute respiratory distress syndrome
MIS-C	Multisystem inflammatory syndrome
CRP	C-reactive protein
PCR	Polymerase chain reaction
ACE2	Angiotensin-converting enzyme 2
Ang II	Angiotensin II
TLR	Toll-like receptor
NF-kB	Nuclear factor-kB
IRF	Interferon regulatory factor
MDA5	Melanoma differentiation associated protein 5
TIM-3	T-cell immunoglobulin mucin-3
PD-1	Death protein-1
LAG-3	Lymphocyte-activating gene-3
VLP	Virus-like particle
ACT	Artemisinin combination therapy
CQ	Chloroquine
HCQ	Hydroxychloroquine
IVIGs	Intravenous immunoglobulins
mAbs	Monoclonal antibodies
PfCSP	Falciparum circumsporozoite protein
ECMO	Extracorporeal membrane oxygenation
PPE	Pomegranate peel extract
NO	Nitric oxide
ITN	Insecticide-treated mosquito net
SMC	Seasonal malaria chemoprevention
IRS	Indoor residual spraying
DHIS2	District Health Information Software version 2 platform
AFI	Acute febrile illness

Acknowledgements
Not applicable.

Author contributions
Conceptualization and methodology, SQD and MZH; investigation, MZH, HTZ, YY, YF, and MZ; writing—original draft preparation, MZH and HTZ; writing—review and editing, SQD, and XS; supervision, SQD, and XS; funding acquisition, SQD and MZ. All authors have read and agreed to the published version of the manuscript.

Funding
This research was funded by the National Natural Science Foundation of China (82102432), Anhui Provincial Natural Science Foundation Project (2108085QH347), and the Foundation of Education Department of Anhui province (2023AH050649).

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 8 May 2024 Accepted: 27 February 2025
Published online: 25 March 2025

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