Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Travel Medicine and Infectious Disease 50 (2022) 102460

Contents lists available at ScienceDirect

Travel Medicine and Infectious Disease

journal homepage: www.elsevier.com/locate/tmaid

Plasmodium vivax and SARS-CoV-2 co-infection in Venezuela: A case series from the malaria hotspot in Latin America

ARTICLE INFO

Dear Editor:

Malaria-endemic areas are not spared from the impact of COVID-19, leading to co-infection scenarios where overlapping symptoms pose serious diagnostic challenges. People who live in malaria-endemic areas and get infected by SARS-CoV-2 may be at increased risk of severe COVID-19 or unfavourable disease outcomes if their malaria status is overlooked. Most malaria and COVID-19 co-infections had been reported in Nigeria, India, and the Democratic Republic of Congo, where patients with *Plasmodium falciparum* and SARS-CoV-2 co-infection were typically symptomatic at presentation with mild or moderate parasitemia, thrombocytopenia, lymphopenia, and elevated bilirubin levels [1]. However, current knowledge on *Plasmodium* spp. and SARS-CoV-2 co-infection remains limited, especially in Latin America, where *Plasmodium vivax* infection is more prevalent than in other global regions.

Venezuela, where *P. vivax* is the predominant parasite, remains the malaria hotspot in the region, representing 35.5% of cases and 49.6% of disease-related deaths in America in 2020 [2]. We present here a case series of patients with *P. vivax* and SARS-CoV-2 co-infection seen at two main malaria referral centres of Venezuela between March 13, 2020 and December 31, 2021. COVID-19 diagnosis was performed by RT-PCR for SARS-CoV-2 infection. The severity of COVID-19 was characterised according to the National Institutes of Health (United States) guidelines [3]. Malaria diagnosis was performed by microscopy of thick and thin blood smear stained with Giemsa.

A total of 12 patients confirmed with *P. vivax* and SARS-CoV-2 co-infection were recorded (Table 1). The mean age of the patients was 42 (SD 18) years, eight were men. Fever (12/12), chills (11/12), dry cough (9/12), headache (7/12), and diaphoresis (6/12) were the most frequent symptoms reported by the patients. Four patients had available parasite density (range: 144–5,600/μL), three of them with high parasitaemia levels (parasite density >2,400/μL). Seven patients had elevated AST/ALT levels (AST/ALT >40 U/L); five had thrombocytopenia (platelets $<150 \times 10^3$/mL); four had leucocytosis (white blood cells $>11 \times 10^3$/mL), three of them with neutrophilia (neutrophils $>8 \times 10^3$/mL) and one with lymphocytosis (lymphocytes $>4.2 \times 10^3$/mL); two had elevated creatinine levels (creatinine >1.3 mg/dL); one had severe anaemia (haemoglobin <7 g/dL); and one had thrombocytosis (platelets $>450 \times 10^3$/mL). The mean time span between symptom onset and positive test for SARS-CoV-2 infection based on RT-PCR was 6.3 (SD 3.4; range: 3–15) days.

Nine patients had previously documented *P. vivax* malaria episodes (range: 1–11), three of whom had their last malaria episode within the past six months (possible relapse cases), while the other six had their last malaria episode more than six months (possible re-infection cases). Nine out of 12 patients had moderate to severe COVID-19 disease. All patients with severe COVID-19 disease received steroids, supplemental oxygen, and anticoagulants. None of the patients received remdesivir or tocilizumab for the management of COVID-19. Three patients had mild COVID-19 disease, two of whom were managed as inpatients because one was a pregnant woman and one was an infant. All patients were treated according to the last national antimalarial protocol approved (2017) by the Bolivarian Republic of Venezuela health authorities [4]. The mean time span between symptom onset and positive microscopy for *Plasmodium* spp. was 3.3 (SD 3.4; range: 1–13) days. All patients recovered uneventfully. The mean hospital stay was 11.5 (SD 7.2; range: 3–24) days.

To the best of our knowledge, this is currently the report with the most cases of *P. vivax* and SARS-CoV-2 co-infection in Latin America. Previous reports describe the malaria and COVID-19 co-infection status mainly as mild [1]; however, most of our patients experienced moderate COVID-19 disease instead. A recent meta-analysis reported that most *P. falciparum* and SARS-CoV-2 co-infected patients had characteristically low or moderate parasitaemia, thrombocytopenia, and lymphopenia [1]. However, three out of four of our *P. vivax* and SARS-CoV-2 co-infected patients had relatively high parasitaemia levels, and all except one showed normal to high lymphocyte levels. We therefore highlight the need for clinicians to provide early diagnosis and timely treatment to suspected malaria infections in patients with COVID-19, particularly in regions where *P. vivax* is the predominant parasite species.

Whereas all malaria and COVID-19 co-infections in the current case series were confirmed by microscopy and RT-PCR, respectively, a high level of false-positive results has been identified with the SARS-CoV-2 serological assay in highly malaria-endemic areas. Sero-surveillance is critical for monitoring and projecting the burden and risk of COVID-19 during the pandemic; however, routine use of serological assay may

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, reverse transcription polymerase chain reaction; SD, standard deviation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; NTDs, neglected tropical diseases.

https://doi.org/10.1016/j.tmaid.2022.102460
Received 26 April 2022; Received in revised form 7 September 2022; Accepted 8 September 2022
Available online 14 September 2022

Table 1
Demographic, clinical, and paraclinical profiles of 12 patients confirmed with *P. vivax* and SARS-CoV-2 co-infection.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12
Demographics												
Age, years	51	67	44	42	20	3 months	33	53	65	39	40	50
Sex	Female	Female	Male	Male	Female	Male	Male	Female	Male	Male	Male	Male
Occupation	Housewife	Housewife	Merchant	Merchant	Housewife	–	Merchant	Teacher	Engineer	Gold miner	Merchant	Mechanic
Clinics												
Comorbidities	Hypertension	Hypertension	Hypertension	No	Asthma	No	No	No	No	No	No	Diabetes
COVID-19 severity	Severe	Severe	Severe	Moderate	Mild	Mild	Moderate	Mild	Moderate	Moderate	Moderate	Severe
Current parasitic density,/μL	N/A	N/A	N/A	144	N/A	5600	N/A	5446	5183	N/A	N/A	N/A
Previous malaria episodes, no.	11	8	3	1	2	0	1	0	0	7	3	1
Past malaria parasite	*P. vivax*	*P. vivax*	*P. vivax*	*P. vivax*	Mixed	–	*P. vivax*	–	–	*P. vivax*	*P. vivax*	*P. vivax*
Outcome	Discharge	Discharge	Discharge	Discharge	Discharge	Discharge	Discharge	Discharge	Discharge	Discharge	Discharge	Discharge
Hospital stay, days	21	17	24	N/H	7	7	7	N/H	15	3	5	9
Paraclinics												
Haemoglobin, g/dL	13.3	11.3	12.9	N/A	11.2	6.1	13.7	11	12.3	10.2	8.9	11
White blood cells, $\times 10^3$/mL	4.1	11.2	7.3	N/A	9.6	13.5	6.5	18	4.3	6.2	8.1	12
Neutrophils, $\times 10^3$/mL	3.08	8.4	4.45	N/A	N/A	2.96	4.88	14.58	2.62	3.72	5.83	8.81
Lymphocytes, $\times 10^3$/mL	1.03	2.8	2.85	N/A	N/A	9.52	1.63	2.16	1.59	2.48	2.27	2.22
Platelets, $\times 10^3$/mL	217	396	179	N/A	146	216	52	95	290	88	123	743
Glycemia, mg/dL	137	136	N/A	N/A	73	107	89	111	110	75	N/A	83
Urea, mg/dL	31	39	N/A	N/A	37	13	27	22	25	33	N/A	42
Creatinine, mg/dL	0.88	1.06	N/A	N/A	0.6	N/A	0.89	1.4	1.5	0.9	N/A	0.61
AST, U/L	60	65	53	57	23	51	40	N/A	N/A	28	63	33
ALT, U/L	68	48	20	38	13	17	36	N/A	N/A	24	50	72

COVID-19, coronavirus disease 2019; AST, alanine aminotransferase; AST, aspartate aminotransferase; N/H, not hospitalised; N/A, not available.

overestimate the level of exposure and immunity of the population to SARS-CoV-2 in malaria-endemic countries [5]. Enhanced epidemiological surveillance platforms could provide cues that indicate whether malaria, NTDs, and COVID-19 are indeed syndemics.

Most cases reported here occurred in patients with previous malaria episodes, three of whom had recent *P. vivax*. These recent *P. vivax* episodes could be considered possible relapses, as reported previously [6]. One hypothesis for this phenomenon is that immune system dysregulation caused by a symptomatic SARS-CoV-2 infection could precipitate malaria relapse; this is related to activation of hypnozoites by the host pro-inflammatory response [6]. Excessive pro-inflammatory host response is associated with severe manifestations of malaria and COVID-19, suggesting that co-infection could lead to substantially unfavourable outcomes and a shift in the age pattern of severe COVID-19 to younger age groups [7].

Therefore, in malaria-endemic regions, suspected COVID-19 patients should also be monitored for malaria diagnosis without delays due to overlapping symptoms and confounding clinical laboratory results. Our findings indicate that *P. vivax* and SARS-CoV-2 co-infection could increase the severity of the disease.

Consent for publication

All patients —or patient's legal guardian, as appropriate— included in this study signed a consent form authorising the use of their medical records for the purpose of this publication. A copy of each patient's written consent is available for review by the Chief Editor of this journal.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of competing interest

The authors declare no competing interest.

References

[1] Wilairatana P, Masangkay FR, Kotepui KU, Milanez GJ, Kotepui M. Prevalence and characteristics of malaria among COVID-19 individuals: a systematic review, meta-analysis, and analysis of case reports. PLoS Neglected Trop Dis 2021;15:e0009766.
[2] World Health O. World malaria report 2021. Geneva: World Health Organization; 2021.
[3] Coronavirus disease 2019 (COVID-19) treatment guidelines. Bethesda (MD): National Institutes of Health (US); 2021.
[4] PAHO M. Pautas de tratamiento en Casos de Malaria: República Bolivariana de Venezuela, Ministerio del Poder Popular para la Salud 2017. Washington, DC: Pan American Health Organization; 2017.
[5] Lapidus S, Liu F, Casanovas-Massana A, Dai Y, Huck JD, Lucas C, et al. Plasmodium infection induces cross-reactive antibodies to carbohydrate epitopes on the SARS-CoV-2 Spike protein. medRxiv; 2021.
[6] Shahid Z, Karim N, Shahid F, Yousaf Z. COVID-19 associated imported Plasmodium vivax malaria relapse: first reported case and literature review. Res Rep Trop Med 2021;12:77–80.
[7] Gutman JR, Lucchi NW, Cantey PT, Steinhardt LC, Samuels AM, Kamb ML, et al. Malaria and parasitic neglected tropical diseases: potential syndemics with COVID-19? Am J Trop Med Hyg 2020;103:572–7.

David A. Forero-Peña [*,1]
Infectious Diseases Department, University Hospital of Caracas, Caracas, Venezuela
Biomedical Research and Therapeutic Vaccines Institute, Ciudad Bolivar, Venezuela

Fhabián S. Carrión-Nessi [**,1]
Biomedical Research and Therapeutic Vaccines Institute, Ciudad Bolivar, Venezuela
"Dr. Francisco Battistini Casalta" Health Sciences School, University of Oriente – Bolivar Nucleus, Ciudad Bolivar, Venezuela

Óscar D. Omaña-Ávila, Daniela L. Mendoza-Millán
Biomedical Research and Therapeutic Vaccines Institute, Ciudad Bolivar, Venezuela
"Luis Razetti" School of Medicine, Central University of Venezuela, Caracas, Venezuela
E-mail addresses: oscardoa.23@gmail.com (Ó.D. Omaña-Ávila), daniela.lm.millan@gmail.com (D.L. Mendoza-Millán).

Sinibaldo R. Romero
Biomedical Research and Therapeutic Vaccines Institute, Ciudad Bolivar, Venezuela
Medical Scientist Training Program (MD/PhD), University of Minnesota Medical School, Minneapolis, United States
E-mail address: romer302@umn.edu.

Iván A. Escalante-Pérez
Biomedical Research and Therapeutic Vaccines Institute, Ciudad Bolivar, Venezuela
"Luis Razetti" School of Medicine, Central University of Venezuela, Caracas, Venezuela
E-mail address: salvadorescalante1305@gmail.com.

Andrea L. Maricuto
Infectious Diseases Department, University Hospital of Caracas, Caracas, Venezuela
Biomedical Research and Therapeutic Vaccines Institute, Ciudad Bolivar, Venezuela
E-mail address: amaricutomadruga@gmail.com.

Natasha A. Camejo-Ávila
Biomedical Research and Therapeutic Vaccines Institute, Ciudad Bolivar, Venezuela
"Dr. Francisco Battistini Casalta" Health Sciences School, University of Oriente – Bolivar Nucleus, Ciudad Bolivar, Venezuela
E-mail address: natashacamejo@gmail.com.

Melynar Chavero, Luisamy Figuera
Biomedical Research and Therapeutic Vaccines Institute, Ciudad Bolivar, Venezuela
E-mail addresses: melichavero@gmail.com (M. Chavero), luisamyfiguera@gmail.com (L. Figuera).

Rosa Contreras, Jaime Torres
"Dr. Félix Pifano" Tropical Medicine Institute, Central University of Venezuela, Caracas, Venezuela
E-mail addresses: conrosa@gmail.com (R. Contreras), torresj@email.com (J. Torres).

Óscar Noya-González
"Dr. Félix Pifano" Tropical Medicine Institute, Central University of Venezuela, Caracas, Venezuela
Centro de Estudios Sobre Malaria, "Dr. Arnoldo Gabaldón" High Studies Institute, Caracas, Venezuela
E-mail address: noyaoo@yahoo.com.

[*] Corresponding author.

[**] Corresponding author.
E-mail address: vacter.cv@gmail.com (D.A. Forero-Peña).
E-mail address: fhabiancarrion@gmail.com (F.S. Carrión-Nessi).

[1] These authors have contributed equally to this work and share first authorship.