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Importance of ultrasound measurement of the liver and spleen size in the diagnosis of comorbidity with malaria and COVID-19

Značaj ultrazvučnog merenja veličine jetre i slezine u dijagnostici komorbiditeta malarije i COVID-19

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Abstract

Background/Aim. With the outbreak of the coronavirus disease 2019 (COVID-19) pandemic, patients who had malaria and COVID-19 simultaneously were also noticed. Hepatosplenomegaly is characteristic and almost always present in patients with malaria (without associated COVID-19). A significant increase in the size of the liver and spleen clearly indicates the possible development of severe malaria. The aim of this study was to determine the effect of COVID-19 on liver and spleen size in patients with malaria. **Methods.** This study was conducted while the authors were working in the Serbian Military Hospital of the United Nations Multidimensional Integrated Stabilization Mission (MINUSCA-UN) in Bangui, Central African Republic. Data from 1,710 patients who underwent ultrasound examination of the abdomen, where the diameters of the liver and spleen were monitored, were analyzed. The total number of examined patients was divided into four groups: group with 816 control patients without malaria (C group), 480 with active malaria (M^+), 353 patients who had malaria in the past 2–6 months (M^{past}), and 61 patients with active malaria and active COVID-19 (M^+Cov^+). **Results.** The liver size was significantly greater in the M^+, M^{past}, and M^+Cov^+ groups of respondents compared with the C group. Statistically significant spleen enlargement was observed only in the M^+ group but not in the M^+Cov^+ group compared to the C group. **Conclusion.** There is no enlargement of the spleen in patients with a coinfection with the severe acute respiratory syndrome coronavirus 2 and *Plasmodium malariae*. Therefore, in the presence of clear splenomegaly, we can indicate, with a high probability, the absence of COVID-19 while waiting for the results of the polymerase chain reaction test, even in the first hours of hospitalization.

Key words:
comorbidity; covid-19; diagnosis; liver; malaria; spleen; ultrasonography.

Apstrakt

Uvod/Cilj. Sa izbijanjem pandemije bolesti korona virusa 2019 [*coronavirus disease 2019* – (COVID-19)], zapaženi su i bolesnici koji su imali malariju i COVID-19 istovremeno. Hepatosplenomegalija je karakteristična i skoro uvek prisutna kod bolesnika sa malarijom (bez pridruženog COVID-19). Značajno povećanje veličine jetre i slezine jasno ukazuje na mogući razvoj teškog oblika malarije. Cilj rada bio je da se utvrdi uticaj COVID-19 na veličinu jetre i slezine kod obolelih od malarije. **Metode.** Istraživanje je sprovedeno dok su autori radili u srpskoj Vojnoj bolnici misije *United Nations Multidimensional Integrated Stabilization Mission* (MINUSCA-UN) u Bangiju, Centralnoafrička Republika. Analizirani su podaci 1 710 pacijenata, koji su podvrgnuti ultrazvučnom pregledu abdomena, kojim su mereni prečnici jetre i slezine. Ukupan broj pregledanih pacijenata podeljen je u četiri grupe: 816 kontrolnih pacijenata bez malarije (K grupa), 480 bolesnika sa aktivnom malarijom (M^+), 353 onih koji su imali malariju u poslednjih 2-6 meseci (M^{past}) i 61 bolesnik sa aktivnom malarijom i manifestacijama COVID-19 (M^+Cov^+). **Rezultati.** Jetra je bila značajno veća u M^+, M^{past} i M^+Cov^+ grupama, u poređenju sa K grupom. Statistički značajno povećanje slezine primećeno je samo u M^+ grupi ali ne i u M^+Cov^+ grupi, u poređenju sa K grupom. **Zaključak.** Kod bolesnika sa koinfekcijom korona 2 virusom izazivačem teškog akutnog respiratornog sindroma i *Plasmodium malariae* nema uvećanja slezine. To znači da se kod bolesnika sa jasnom

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splenomegalijom može već u prvim satima hospitalizacije, u fazi čekanja na rezultate testa lančane reakcije polimeraze, sa velikom verovatnoćom ukazati na odsustvo COVID-19.

Ključne reči:
komorbiditet; COVID-19; dijagnoza; jetra; malarija; slezina; ultrasonografija.

Introduction

Malaria is a disease caused by protozoa of the genus Plasmodium. It is transmitted by the bite of an infected female mosquito of the genus *Anopheles*. There are about 400 species of *Anopheles mosquitoes*, but about 40 species are significant for the transmission of *Plasmodium* [1]. After hatching and going through several stages of development, young female mosquitoes feed on plant nectar until they mature. In adulthood, in order to lay eggs, females need blood meals, which supply them with the protein needed for developing eggs. At this stage of development, the mosquito, after it bites a person suffering from malaria, becomes a carrier of *Plasmodium*, causing malaria [1].

The disease goes through several stages after the *Plasmodium* enters the host organism. The initial phase of the *Plasmodium* infection is necessary, followed by a phase of asymptomatic disease. Then a phase of uncomplicated disease develops, in which the infection can be cured after the provided therapy. Otherwise, the disease passes to the next stage of severe manifestation of malaria, which often leads to the patient dying [2].

Malaria is a disease that affects and kills the largest number of people. According to the World Health Organization (WHO), in 2019, about 229 million people worldwide fell ill, mostly in 87 endemic countries [3]. Among these countries, 29 are a part of sub-Saharan Africa, including the Central African Republic (CAR), where 94% (2,708,497) of all reported malaria cases are from [3]. Mortality from malaria is high, and in 2019, there was a total of 409,000 deaths. Out of this, 95% falls in 32 countries of sub-Saharan Africa (CAR – 2,017 malaria deaths) [4].

According to the WHO recommendations, the rapid diagnostic test (RDT) is used for rapid orientation in the diagnosis of malaria. In addition, as the main diagnostic method in all suspected patients with malaria, microscopy of thick blood smear (TBS) is used. In addition to these procedures, other diagnostic procedures must be performed such as laboratory analyses, ultrasound examination of the abdomen and small pelvis, X-rays of the heart and lungs, and others [5–9].

Most patients with malaria do not have specific physical findings, but some of them may come with splenomegaly. Symptoms may include a flu-like illness with fever, headache, malaise, fatigue, myalgia, diarrhea, and anemia. Severe malaria manifests as cerebral malaria, severe anemia, respiratory symptoms, and renal failure [9].

As the outbreak of the coronavirus disease 2019 (COVID-19) pandemic occurred at the end of 2019, so did the occurrence of patients with simultaneous infection of *Plasmodium* (the malaria causative agent) and infection with the severe acute respiratory syndrome coronavirus 2 – SARS-CoV-2 (the causative agent of COVID-19 disease). This is important both because of the diagnosis and the therapy, so in such patients, there was a need to modify the treatment protocol. As many authors have described, there is a great similarity between the symptoms of malaria and COVID-19, such as fever, headache, fatigue, shortness of breath, muscle aches, sweating, and feeling cold. All this indicates that it is difficult to distinguish between these two diseases without specific tests based only on the clinical picture and the low reliability of rapid tests [10–15].

The aim of this study was to determine the effect of COVID-19 on liver and spleen size in patients with malaria.

Methods

This study was created during the work of the authors in the Serbian military hospital level II and II+ within the three rotations of the United Nations Multidimensional Integrated Stabilization Mission in the Central African Republic (MINUSCA) in Bangui, the capital of the Central African Republic (CAR). The rotations were in 2017, 2018/2019, and 2021, for over 850 days. The hospital is in charge of treating members of the MINUSCA [military contingents, police forces, civilian personnel, employees of contractors, members of organizations under the auspices of the United Nations (UN), members of the European Union (EU) Military Assistance Mission (EUMAM) in the CAR, members of embassies in the CAR, members of the CAR government, and local population employed in the mission]. One of the most common and serious diseases we encountered in this region is malaria, and during the last rotation, COVID-19.

A prospective cohort study was conducted during three rotations of MINUSCA. Data from all 1,710 patients who underwent ultrasound examination of the abdomen and small pelvis, where the diameters of the liver and spleen were monitored, were processed. Patients were divided into four groups. The first group, which was also the control group (C), consisted of patients who had never suffered from malaria or had not had malaria in more than six months, and their ultrasound examination was performed due to other diseases or symptoms. The second group consisted of patients with active malaria and malaria in the past month (M^+) who did not have COVID-19. The third group consisted of patients who had malaria in the last two to six months (M^{past}) but not COVID-19. The fourth group consisted of patients with active malaria and active or past COVID-19 (M^+Cov^+). The exclusion criteria included patients with some form of chronic or active hepatitis (six of them), which affects the size of the liver.

Patients with hepatic steatosis were monitored in all groups. In these patients, enlargement of the liver caused by

steatosis was certainly diagnosed. It turned out that in patients with hepatomegaly of steatotic origin, during malaria disease, there was an additional increase in the size of the liver in the same percentage as in patients without steatosis. Patients were examined on Mindray DC-N6 ultrasound devices until 2020, and after that, on Mindray DC-8 Exp ultrasound devices, with convex probes in the 1–5 megahertz frequency range. Within all groups, in addition to other parameters and pathological changes, the diameters of the liver and spleen were especially monitored.

There are numerous ways of measuring the liver in the literature [16-19]. Yet, for this paper, we used the measurement of the oblique line from the most caudal anterior part of the liver on the medioclavicular section to the most distant cranial-posterior point on the liver capsule. In order to standardize the measurements, they were performed on sections where the right kidney is at least partially visible in a completely lying position. The patient was required to take a deep breath, hold the air, and tense the abdomen in order to push the abdominal organs out of the costal arch artifacts.

Measurement of the spleen is much more standardized, and almost all authors agree to measure the longest longitudinal and transverse sections of the spleen in a supine or oblique position in a deep breath [20, 21].

Variations in the size of the liver and spleen concerning age, race, height, and weight were not taken into account in the data processing since, in each group of subjects, all these variations were present in a similar percentage. During the survey, respondents from 116 countries from all continents were examined. Most patients were of medium to short stature and without signs of obesity.

Statistical data analysis was performed in the statistical program IBM SPSS version 26.0. Attribute variables were presented in the form of frequencies, and statistical significance was tested by the Chi-square test. Continuous variables were presented in the form of mean value and standard deviation. The normality of the distribution was tested using the Kolmogorov-Smirnov test. The significance of the difference of continuous variables was tested by one-way analysis of variance followed by Tukey B *post hoc* test because more than two groups were compared. The correlation was tested using Pearson correlation. Analyses were estimated at the level of statistical significance of $p < 0.05$.

Results

The total number of examined patients (1,710) was divided into four groups: 816 patients in the C group, 480 in the M^+ group, 353 in the M^{past}, and 61 patients in the M^+Cov^+ group.

There were significantly more male patients in all groups but slightly more women in the M^+Cov^+ group than in the other two groups (Table 1). No significant difference was found between the groups regarding the age of the respondents. However, it could be noticed that patients in the M^+Cov^+ group were about two years older on average compared to other groups. The age range of the patients was generally 30 to 60 years.

The diameter of the liver and spleen differed significantly between these groups (Table 2). The liver size was significantly greater in the M^+ group, M^{past}, and M^+Cov^+

Table 1

Sociodemographic characteristics of examined patients

Characteristics	Groups				*p*-value
	C	M^+	M^+Cov^+	M^{past}	
Sex					
male	660 (80.9)	419 (87.3)	40 (65.6)	266 (75.4)	< 0.001#
female	156 (19.1)	61 (12.7)	21 (34.4)	87 (24.6)	
Age, years	40.45 ± 10.03	39.16 ± 9.40	42.08 ± 9.69	40.17 ± 10.18	0.051*
< 20	2 (0.2)	1 (0.2)	0	2 (0.6)	
20–29	114 (14.0)	67 (14.0)	7 (11.5)	48 (13.6)	
30–39	294 (36.0)	207 (43.1)	18 (29.5)	134 (38.0)	0.032#
40–49	236 (28.9)	131 (27.3)	18 (29.5)	98 (27.8)	
50–59	144 (17.6)	66 (13.8)	18 (29.5)	53 (15.0)	
> 60	26 (3.2)	8 (1.7)	0	18 (5.1)	

Values are given as numbers (percentages) or mean ± standard deviation.
***– One-way analysis of variance; # – Chi-square test.**
Description of the groups is given in the paragraph Methods.

Table 2

Liver and spleen diameter measured by ultrasound examination of the abdomen

Diameter	Groups				*p*-value
	C	M^+	M^+Cov^+	M^{past}	
Liver	137.62 ± 12.91	168.97 ± 16.91	172.26 ± 13.28	157.30 ± 11.85	0.001*
Spleen AP	99.03 ± 14.96	131.93 ± 23.79	103.77 ± 17.04	104.50 ± 14.71	0.001*
Spleen CC	46.11 ± 9.51	59.67 ± 13.51	49.52 ± 13.09	50.94 ± 30.92	0.001*

AP – anterior-posterior; CC – craniocaudal.
Description of the groups is given in the paragraph Methods.
The ultrasound measurement unit is a millimeter (mm). Values are given as mean ± standard deviation.
***– One-way analysis of variance.**

compared to the C group. The liver diameter was increased by 22.78% on average in the M^+ group compared to the C group, while in the M^+Cov^+ group, there was an even bigger increase by 25.17% on average compared to the C group, and this increase was monitored for the next six months after the onset of malaria (Figure 1).

On the other hand, statistically significant spleen enlargement was observed only in the M^+ group compared to the C group but not in the M^+Cov^+ group compared to the C group and M^{past} group (Table 2). Anterior-posterior (AP) spleen diameter was increased by 33.22% on average in the M^+ group compared to the C group, while in the M^+Cov^+ group, there was an increase by only 4.79% compared to the C group (Figure 2). Similar data was observed for craniocaudal (CC) spleen diameter, when there was an increase in the M^+ group by 29.41% on average compared to the C group, while in the M^+Cov^+ group, there was an increase on average by 7.39% compared to the C group (Figure 3).

Correlation analysis showed that the size of the liver and spleen was statistically significantly related to the categories of subjects (Table 3). A strong positive correlation of all three measurements with the category of subjects was obtained. The strongest correlation was between liver size and groups of patients, which means that with the addition of a number of different infections, first only malaria, then

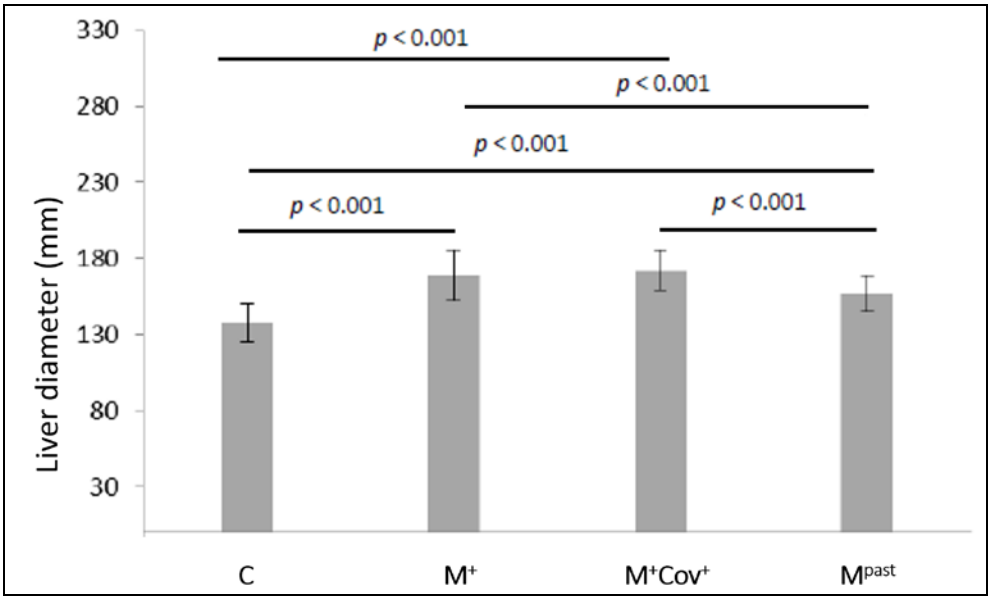

Fig. 1 – Comparison of the liver diameter among examined groups.
Description of the groups is given in the paragraph Methods.
One-way analysis of variance, *post hoc* Tukey B test.

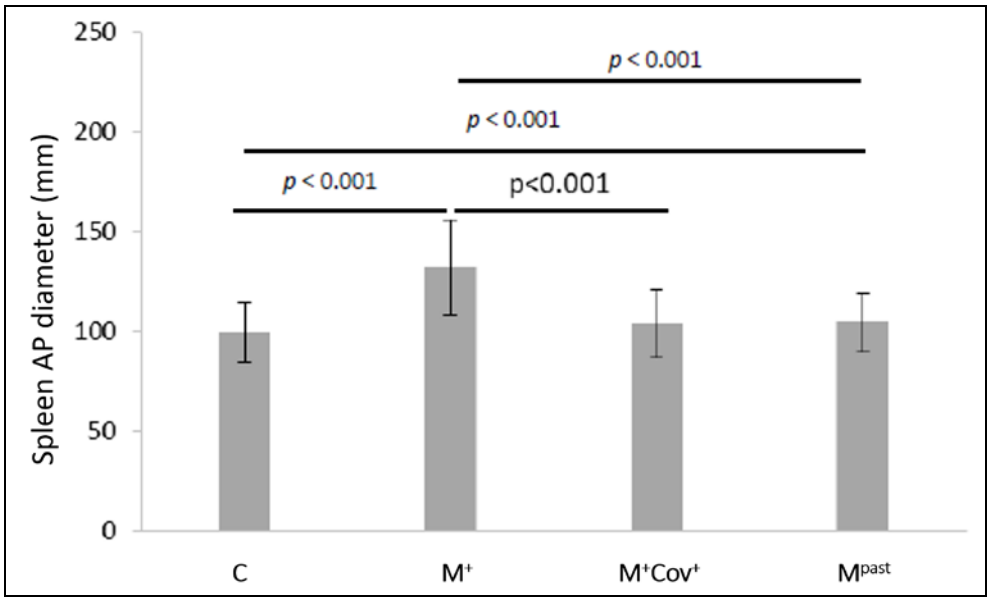

Fig. 2 – Comparison of the spleen anterior-posterior (AP) diameter among examined groups.
Description of the groups is given in the paragraph Methods.
One-way analysis of variance, *post hoc* Tukey B test.

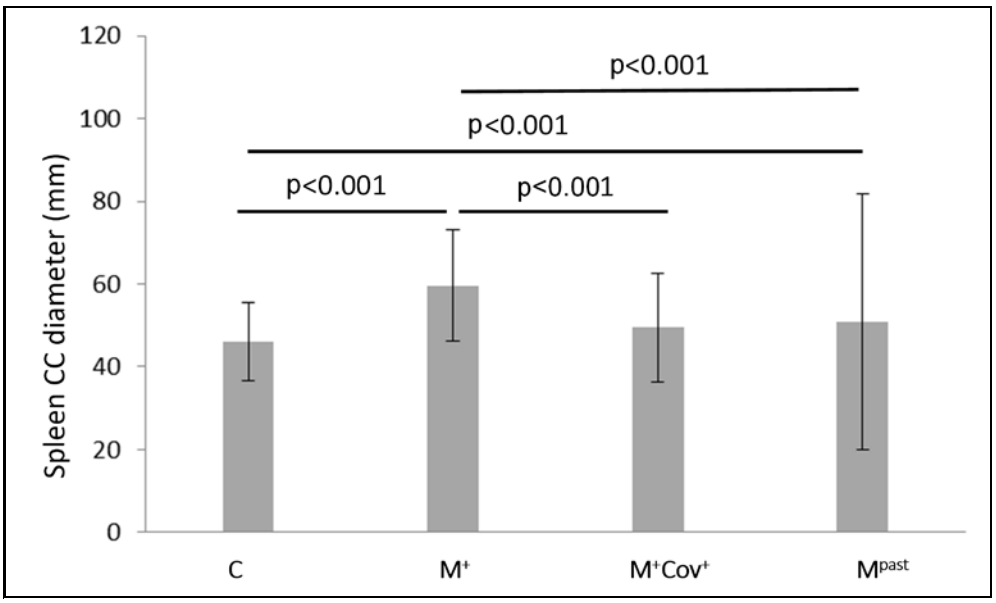

Fig. 3 – Comparison of the spleen craniocaudal (CC) diameter among examined groups. Description of the groups is given in the paragraph Methods. One-way analysis of variance, *post hoc* Tukey B test.

Table 3

Correlation of ultrasound findings with analyzed groups of respondents

Parameter	Liver diameter	Spleen AP diameter	Spleen CC diameter
Spleen AP diameter			
r	0.439		
p	< 0.001		
Spleen CC diameter			
r	0.248	0.418	
p	< 0.001	< 0.001	
Groups			
C			
M^+			
M^+Cov^+			
r	0.425	0.103	0.107
p	< 0.001	< 0.001	< 0.001

AP – anterior-posterior; CC – craniocaudal.
Description of the groups is given in the paragraph Methods. *r* – Pearson correlation.
Note: M^{past} group was not included in this correlation analysis since the results acquired did not match the results of other subgroups due to patient recovery.

malaria and COVID-19, the size of the liver also increased. A similar finding was shown for the spleen in malaria, but in the combined malaria and COVID-19, this expected increase in the spleen was conspicuously absent.

Discussion

A total of 480 patients with malaria (87.3% male and 12.7% female) were examined by the end of this study. The average age of the patients was 39.16 years. Already in the first phase of the examination, a significant increase in the size of the liver and spleen was noticed, which later turned out to be correct in a large number of patients. Control examinations of malaria patients showed that the enlargement of the spleen was maintained for up to a month from the day of the disease.

We observed a significant increase in the liver size, especially the spleen size, even in patients with a negative RDT test and incomplete TBS microscopy. Based on the experience gained, after noticing this regularity, we were able to tell our colleagues who treated these patients that it was a case of malaria and that it could even be predicted, based on the size of the liver and spleen, that a severe form of malaria would develop. Based on that, they could apply appropriate therapy promptly.

Control examinations of a group of patients with malaria after the first month from the day of the disease showed that the enlargement of the liver was maintained for up to six months from the day of the disease, unlike the spleen, which returns to normal after the first month of malaria.

Out of the total of 202 patients with COVID-19 examined in our ward, 66 were suspected of having co-

infection with the SARS-CoV-2 virus and *Plasmodium malariae*. In addition to the prescribed protection measures, we performed radiographic examinations of the lungs and heart and ultrasound examinations of the abdomen and pelvis. Out of these 66 patients, the coexistence of *Plasmodium malariae* infection and SARS-CoV-2 infection was confirmed in 61 patients based on polymerase chain reaction (PCR) SARS-CoV-2 test and TBS microscopy.

As there were a large number of patients with COVID-19 in the first 15 days of March and April 2021 and sporadic cases of malaria, we, like our colleagues across Africa and the world, were afraid, both because of the already tense hospital capacities and because of the expectation of a "super COVID-19/malaria disease", whether we would be able to care for all patients [22–29].

The first cases heightened fears that the combined COVID-19/malaria comorbidity would be severe for patients, as two of the first three patients had died. However, it turned out that the real reasons for the fatal outcome were the late reporting of the patient to the doctor and the delayed air transport to the hospital due to bad weather in the first case and combat operations in the second case. Fortunately, almost all patients with associated diseases had milder forms of the clinical picture of both COVID-19 and malaria. This coincided with the research of other authors [14, 30].

Over time, by inserting liver and spleen size measurement data into the already existing database, to our surprise, it was noticed that there was a deviation from the already, as a rule of large numbers, confirmed regularities in patients with malaria. Deviations were observed only in patients with active or previous SARS-COV-2 infection, so we were forced to single out a new group of patients with co-infection with SARS-CoV-2 and *Plasmodium malariae*, which included 61 patients.

The absence of splenic enlargement in malaria patients with concomitant disease or a history of COVID-19 has been shown to be a significant feature. The absence of splenic enlargement proved to be a pattern in patients with COVID-19 and malaria. This finding allowed us to indicate in three cases, with a high probability, that the patient does not have SARS-CoV-2 infection but a severe malaria picture based on marked enlargement of the spleen and enable rapid and adequate treatment of the patients.

Interestingly, the curve of the number of malaria and COVID-19 patients examined in our hospital almost coincides with the curve published by WHO in the World Malaria Report 2020 [31]. It has been observed that there is a reverse reciprocity of patients with COVID-19 and malaria. All this is accompanied by the seasonal schedule of the dry and rainy period, which directly determines the number of patients with malaria because their number in the rainy season (May to October) is incomparably higher than in the dry season (November to April) [32].

Conclusion

This study proved in a large number of patients that ultrasound examination of the abdomen and pelvis is not only useful but also necessary in patients with suspected malaria. Based on these examinations, the following conclusions can be drawn: the existence of hepato-splenomegaly, which is very clearly and simply determined by ultrasound examination of the abdomen, is characteristic and almost always present in patients with malaria (without associated COVID-19); a significant increase in the size of the liver and spleen clearly indicates the possible development of severe malaria; in a patient with a coinfection with the SARS-CoV-2 and *Plasmodium malariae*, there is an absence of spleen enlargement. Therefore, in the presence of clear splenomegaly, we can indicate, with a high probability, the absence of COVID-19 while waiting for the results of the polymerase chain reaction SARS-CoV-2 test in the first hours of hospitalization.

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