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Comparative study of immune biomarkers and oxidative stress in patients with COVID-19, dengue, and malarial infection

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ABSTRACT: Dengue, a vector-borne virus-related contamination transferred by the Aedes mosquito. Malaria remains a main transferrable infection that affects billions of people, once diseased with Plasmodium organisms. The COVID-19 (coronavirus disease 2019) that took over the world in December 2019 has everlasting distressing effects on people's lives worldwide. Coronavirus infection is extremely contagious and pathogenic biological contamination produced by the severe respirational disorder coronavirus 2 (SARS-CoV-2), which affected the global epidemic. A significant decrease ($P < 0.05$) of GSH was observed in different groups of patients with dengue and malaria, while a significant increase in COVID-19. A Significant decrease in catalase in dengue, malaria, and COVID-19 was observed. Significant results in decreasing trend of vitamin C in dengue, malaria, and COVID-19 observed. In the peripheral film, ESR in dengue patients increased by 11.62 ± 3.85 in malarial patients by 53.52 ± 26.14 and in COVID-19 patients it is observed at 6.70 ± 2.91. CRP increasing trends were observed in all groups. To perform a comparative chemical analysis of patients with COVID-19, dengue, and malaria by evaluating key biochemical markers, oxidative stress parameters, and immune profiles, to identify distinctive patterns, overlapping features, and potential diagnostic or prognostic indicators associated with each infection.

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I. INTRODUCTION

Dengue fever is affected by contamination with four virulence different enterovirus of dengue infection. Dengue spread from Asia to Africa and the Americas generally affected by regular humanoid passages through the world's drink[1]. Dengue fever is currently endemic in 112 countries around the world. People in more than 100 countries become infected with dengue each year, and approximately 3.6 billion people are at risk[2]. Transmitted by bites of sick female Aedes aegypti mosquitoes. Dengue hemorrhagic fever (DHF) can be fatal. Cause dengue shock syndrome by severe of DHF (DSS). DSS is associated with a relatively high death ratio because blood pressure drops dramatically and tissues begin to collapse[3].

Malaria is a disease that has plagued people since time immemorial. HPV is currently one of the most widespread infectious diseases with 219 million people assessed worldwide in 2017 and 500,000 people diagnosed with it each year, according to WHO. Many of these deaths are in children under the age of five[4]. Several Plasmodium parasite classes of malaria can be caused in people. The most frequent parasites are Plasmodium falciparum and Plasmodium vivax, accounting for more than 95% of his biosphere cases, but there are other infections, including Plasmodium and Plasmodium vivax[5].

Biomarkers are advantageous in the detection, control, and design of prevention strategies in the case of asymptomatic malaria. Many P. falciparum-infected people have silent malaria in malaria-affected areas like Africa[6]. Coronaviruses are members of the Nidoviridae order and belong to the Corona viridae family. Three novel infective human coronaviruses emerged in the last three years, raising major concerns. The most recent, acute respiratory illness coronavirus was responsible for about 3 million contaminations and 230,000 deaths globally[7]. indications of dual pneumonia might occur, which can quickly evolve into a dangerous lung suffering condition[8]. Due to the high dispersion of levels and the lack of a proven treatment, medical assistance is

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strictly avoided, and strict hygiene practices are implemented to prevent infection[9]. The spread of COVID-19 is escalating a public health challenge. The true severity of Covid-19 and dengue co-infection is not yet fully understood and must be closely monitored to determine the cause[10].

CRP is a Hom pentameric protein composed of five indistinguishable, non-glycosylated 23 kDa polypeptide monomers of 206 amino acids each, uniformly noncovalently bound about a central pore. This binds to phosphocholines, phospholipids, histones, chromatin and fibronectin to recognize and eliminate numerous invading pathogens and damaged cells. CRP has developed as one of the initial pattern acknowledgment receptor biomarkers to identify COVID-19 and its harshness[11]. Quick and exact analysis in early-stage COVID-19 is mainly based on standard case classification, molecular analysis using RT-PCR, and immunological studies. Real biomarkers are of great help in communication[12]. Moreover, the discovery of new biomarkers related to disease development cannot be separated from better knowledge of virus-related pathogenesis and mechanisms of tissue and structural degradation. The use of frequent biomarkers for COVID-19 observation clearly explains the virulent character of the illness[13].

This study aims to measure the levels of biomarkers and antioxidants among the various groups of participants and compare the levels of all biochemical parameters in each group.

II. MATERIAL AND METHODS

A. Lipid profile, oxidative stress (Vitamin C, CAT and GSH) and hematological parameters (Hb, WBC, RBC,) were estimated at the Department of Chemistry University of Lahore, Sargodha campus with the collaboration of local diagnostic laboratories.

A. Sample Collection

Human sera were obtained from all group of patients. All samples were collected from Ashraf Medicare Sargodha, afterward approval of the Ethics Review Committee of the hospital, Sargodha, Pakistan and stored in the chemistry lab University of Lahore at $-20°C$ until further use.

B. Determination of Biochemical Markers Level

Biochemical indicators were measured, as well as oxidative stress in groups of patients having malaria, dengue and COVID-19. For this purpose, 50 blood samples were collected for each group. GSH was measured using the Moron technique[14]. Catalase was measured using the Aebi technique[15]. An Enzymatic Bioscience kit was used to perform the lipid profile and blood markers. The Wintrobe method is also used for ESR determination. Westergren's method for ESR estimation is commonly used. Record in millimeters from top surface of the column to top of RBC residues. CRP analyzed Behring Nephelometer II Analyzer System (BNII) with a different dilutor 840 nm wavelength analyzer. The instrument is fully automated. The analyzer includes a dilutor with temperature controlled (37°C) transfer arms; reagent standards rack stations, reagent, sample (with barcode reading); and buffer compartment. The Human DDimer ELISA quantitates Hu D-Dimer in human serum, plasma, or cell culture medium.

C. Estimation Glutathione (GSH)

Principle

GSH was assessed using the technique of[14]. GSH and Ellman's reagent (5, 5-dithiobis (nitrobenzoic acid) or DTNB) interacted with each other to generate the oxidized glutathione GSSG and the chromophore TNB through an absorbance maximum at 412 nm . Estimated concentration of glutathione represents the total amount. Amount of concentrated and oxidized glutathione present in section ([GSH] t = [GSH] + $2 \times$ [GSSG]). Amount of change of absorbance (A 412 nm/min) was made linear. The amount of unknown sample (Sample) that is linearly proportional to the concentration of GSH was calculated using a linear equation constructed from various glutathione standards.

Required chemicals

0.02 M EDTA.
TCA 50% (trichloroacetic acid) (trichloroacetic acid).
DTNB (dithiobis) 6mM (2-nitrobenzoic acid).
0.15M Tris- HCl
Purified water

Procedure

Sample of 0.1 ml serum was placed in test tube. 2.4 mL of 0.02 M EDTA was added to tube and immersed in an ice bath for 10 minutes. Then 2.0 ml of H 2 O (distilled water) was added to each tube. d. After adding H2O, 0.5 mL50% TCA was added to tube and placed again for 10-15 minutes in the ice bath. For 10 minutes the mixture was centrifuged at $3000-3500$rpm. Using a pipette, 1.0 mL of supernatant was collected, 2.0 mL of 0.15 M Tris- HCl and 0.05 mL of DTNB were added. After 2-3 minutes at 412 nm the absorbance was measured after overtaxing the liquid. Absorbance

TABLE I: Analyzed Parameters of Research.

Groups	Samples	Parameters Analyzed					
		Hematological profile	Oxidative Stress/antioxidant stress			Peripheral Film	
			CAT	GSH	Vit.C	ESR CRP	D.Dimer
COVID-19	50 samples						
Dengue patient	50 samples						
Malarial patient	50 samples						

was evaluated against a standard curve generated with known GSH content.

D. Determination of Catalase (CAT)

Catalase was evaluated using the technique of[15]. Almost all living things that are exposed to oxygen include the common enzyme catalase, which is responsible catalyzes the decomposition of hydrogen peroxide to water and in a rate of one molecule per second. Four polypeptide chains, each longer than 500 amino acids, make up the tetramer catalase.

Chemicals required

Di sodium hydrogen phosphate
Hydrogen peroxide, and
Sodium dihydrogen phosphate

Procedure

Catalase activity was determined using the Aebi method. 0.1 ml of each sample taken into test tube. 1.9 ml of phosphate buffer 50 mM (pH 7.0) was added. Reactions were initiated by adding 1.0 mL freshly prepared 30mMH2O2.H2O2 disintegration rates were measured spectrophotometrically at 240 nm . Catalase action was measured in moles/mole protein.

E. Estimation of Vit C

A Di solution will obtain by adding 0.042 gram of sodium carbonate in 100 ml distil water with 0.05 g Phenaphthaline in 100 ml distil water. A stock solution is prepared by adding 4 g of oxalic acid in 100 ml distil water with 0.1 of vit c . Now we will add 1 ml blood serum sample, 1 ml stock solution and 1 ml di solution. The rate of decomposition of VIT C is calculated and VIT *C* Curve will obtain on the analyzer.

F. Estimation of Uric Acid in Serum

The end product of purine metabolism is uric acid. Uric acid is extracted to a large extent by the kidneys and to a lesser extent by microbial degradation in the intestinal tract[16].

Uricase primarily degrades uric acid into allantoin and hydrogen peroxide. Peroxidase catalyses the reaction of hydrogen peroxide with a phenolic compound and 4-aminoantipyrine to form a red coloured quinoneimine dye complex. The intensity of the colour formed is proportional to the present amount of uric acid.

$$H_2O_2 + \text{ Uric acid } \longrightarrow \text{ Allantoin } + H_2O_2$$

$$\text{Aminoantipyrine } + H_2O_2 + \text{ Phenolic compound } \longrightarrow \text{ Red quinoneimine dye } + H_2O_2$$

G. Erythrocyte Sedimentation Rate (ESR)

Principle of ESR

An anticoagulant is added to blood and this well mixed venous blood is retained in vertical tube; erythrocytes tend to settles towards bottom leaving clear plasma on top. That rate of sedimentation of red blood cells in given interval of time is called erythrocyte sedimentation rate (ESR). As the erythrocyte's sediments, in period of one hour, 3 stages can be detected.

Required chemicals

Anticoagulant: 0.1 M sodium citratein modified westergren method EDTA is used as anticoagulant Westergren tube Wintrobe tube

Procedure FOR ESR estimation

Wintrobe method is also used for ESR determination. Westergren method for ESR estimation is commonly used method. Wintrobe tube is smaller than westergren tube. Withdraw 4 ml of venous blood. Mix exact 10 ml sodium citrate with 4 ml venous blood in a tube. Invert tube 2-3 times to mix the blood thoroughly with anticoagulant. Fill westergren tube up to mark 0 and place in the rack at room temperature undisturbed and away from sunlight. Take analysis exactly after 1 hour. Record in millimeters from top surface of column to top of RBC residues.

Reference value of ESR

Female:
20 mm/hr-under 50 years
30 mm/hr-above 50 years
Male:
15 mm/hr-Under 50 years
20 mm/hr-Above 50 years

H. The CRP Assay

Behring Nephelometer II Analyzer System (BNII) with a 3-valve, 3-channel dilutor with 2500uL, 250-ul syringes and 1000uL840 nm + 25 wavelength analyzer and terminal equipped with a Power Macintosh 7200/75 computer. The instrument is fully automated. Analyzer includes a dilutor with temperature controlled (37°C) transfer arms; reagent standards rack stations, reagent, sample (with barcode reading); buffer compartment; temperature controlled; dilution racks (37°C) cuvette rotor; bar code wand reader; cuvette washing device; and optical system. The CRP assay parameter settings for the BNII instrument are as follows:
Parameter Setting
Protein Name CRP
Sample Dilution * 1:100
Latex reagent 40 uT
Buffer for Reagent 60 uL. N Diluent
No. of Standard Points 6
Supplemental reagent 5 uL
Standard Dilutions 1:80-1:2560
Standard Curve Measuring Range (At initial dilution; approximate values, range is dependent upon standard value) 0.10 − 5.50mg/dL
*Automatic sample predilution with N Diluent

I. D-Dimer through ELISA Kit

The Human D-Dimer ELISA quantitates Hu D-Dimer in human serum, plasma, or cell culture medium[17].

Principle of the method
The human D-Dimer solid-phase sandwich ELISA (enzyme-linked immune-sorbent assay) is considered to measure the quantity of the target bound between a matched antibody pair. Target-specific antibody has been pre-coated in wells of supplied microplate. Samples, standards, or controls are then added into these wells and bind to the immobilized (capture) antibody. Sandwich is formed by addition of the second (detector) antibody, a substrate solution is added that reacts with the enzyme-antibody-target complex to produce measurable signal. Intensity of this signal is directly proportional to concentration of target extant in the original specimen.
Sample type/volume Plasma 1μ L, Serum 1μ L, Supernatant 100μ L
Hands-on time 1 hr 20 min
Time-to-result 4 hr 45 min
Homogenous (no wash) No
Instrument Colorimetric Microplate Reader
Product size 5×96 Tests
Contents pre-coated 96 well plate Standard Assay Diluent concentrate Biotinylated Detection Antibody SAV-HRP Wash Buffer Chromogen Stop Solution Adhesive Plate Covers
Shipping condition Wet or Dry Ice
Storage $2 - 8°$

J. Statistical Analysis

The analysis of variance was used for all statistical analysis (ANOVA). P values fewer than ($p < 0.05$) were considered statistically significant, while those greater than ($p > 0.05$) were considered insignificant[18].

III. RESULTS AND DISCUSSION

A. Oxidative Stress Biomarkers

A significant decrease is shown in Table I ($P < 0.05$) of GSH was observed in different groups of patients with dengue and malaria and a significant increase in COVID-19. Significantly decreased levels of catalase and vitamin C in dengue, malaria and COVID-19 were observed.

The measurement and comparison of GSh, CAT and Vitamin C levels in all patient groups as shown in Fig. 1.

TABLE II: Oxidative Stress Biomarkers Profile in dengue, malaria and Covid-19

Parameters	Dengue Patient	Malaria patient	COVID-19	p-value
GSH	1.32 ± 0.06	1.29 ± 0.06	12.68 ± 13.29	.000
CAT	37.41 ± 4.60	25.85 ± 4.19	2.46 ± 0.35	.000
Vit.C	73.50 ± 10.02	63.17 ± 5.26	63.53 ± 6.85	.000

Significant levels <0.05

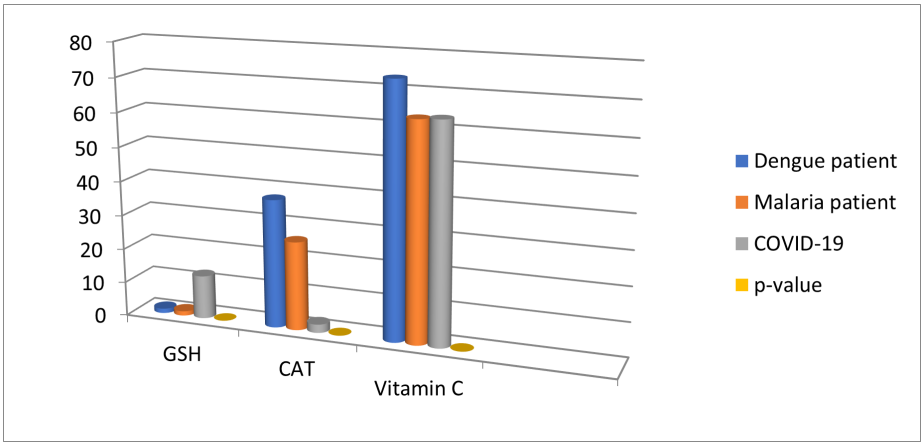

FIG. 1: Oxidative Stress Biomarkers Profile in dengue, malaria and Covid-19.

B. Hematological and immune Profile

All the levels are shown in Table II. The Hb mean values in dengue, malarial and COVID-19 patients were $11.27 \pm 2.44, 11.45 \pm 1.9$ and COVID-19 was observed respectively. The mean value of uric acid in dengue increased in COVID-19, dengue, and malarial patients. The leucocyte decreased in dengue, malarial and COVID-19 patients. The Platelets in dengue patients, malarial patients and COVID-19 were observed as $2.17 \pm 197373.7, 2.50 \pm 221892$ and 339.5 ± 108.13 respectively. In this study total WBC decreased in dengue and COVID-19 patients. Neutrophils in dengue patients increased 71.67 ± 17.28, in malarial patients 74.73 ± 14.90 and in COVID-19 observed 67.88 ± 19.16. Lymphocytes in dengue patients increased by 35.87 ± 15.93, in malarial patients 28.00 ± 13.46. Monocyte decrease in dengue patients $4.73 \pm .2.01$, in malaria also decrease $6.73 + 2.79$ and in COVID -19 as 5.78 ± 2.80. Eosinophil decreases in dengue patients, malaria and COVID-19 as $3.50 \pm 2.38, 6.55 \pm 4.29$ and 6.72 ± 4.38 respectively. Basophils were observed to decrease in dengue patients, malaria and COVID-19 at $5.09 \pm 2.42, 5.09 \pm 2.52$ and 5.68 ± 2.23 respectively.

All the levels are shown in Table III. The Hb mean values in dengue, malarial and COVID-19 patients were $11.27 \pm 2.44, 11.45 \pm 1.9$ and COVID-19 was observed respectively. The mean value of uric acid in dengue increased in COVID-19, dengue, and malarial patients. The leucocyte decreased in dengue, malarial and COVID-19 patients. The Platelets in dengue patients, malarial patients and COVID-19 were observed as $2.17 \pm 197373.7, 2.50 \pm 221892$ and 339.5 ± 108.13 respectively. In this study total WBC decreased in dengue and COVID-19 patients. Neutrophils in dengue patients increased 71.67 ± 17.28, in malarial patients 74.73 ± 14.90 and in COVID-19 observed 67.88 ± 19.16. Lymphocytes in dengue patients increased by 35.87 ± 15.93, in malarial patients 28.00 ± 13.46. Monocyte decrease in dengue patients $4.73 \pm .2.01$, in malaria also decrease $6.73 + 2.79$ and in COVID -19 as 5.78 ± 2.80. Eosinophil decreases in dengue patients, malaria and COVID-19 as $3.50 \pm 2.38, 6.55 \pm 4.29$ and 6.72 ± 4.38 respectively. Basophils were observed to decrease in dengue patients, malaria and COVID-19 at $5.09 \pm 2.42, 5.09 \pm 2.52$ and 5.68 ± 2.23 respectively.

Fig. 2 (*a* and *b*) showed the comparison levels of Platelets were observed to significantly increase in dengue patients, malarial patients and COVID-19. Significant decrease levels ($P < 0.05$) of leucocytes were observed in different groups. The Platelets values significantly increased in all groups (Dengue, malarial, COVID).

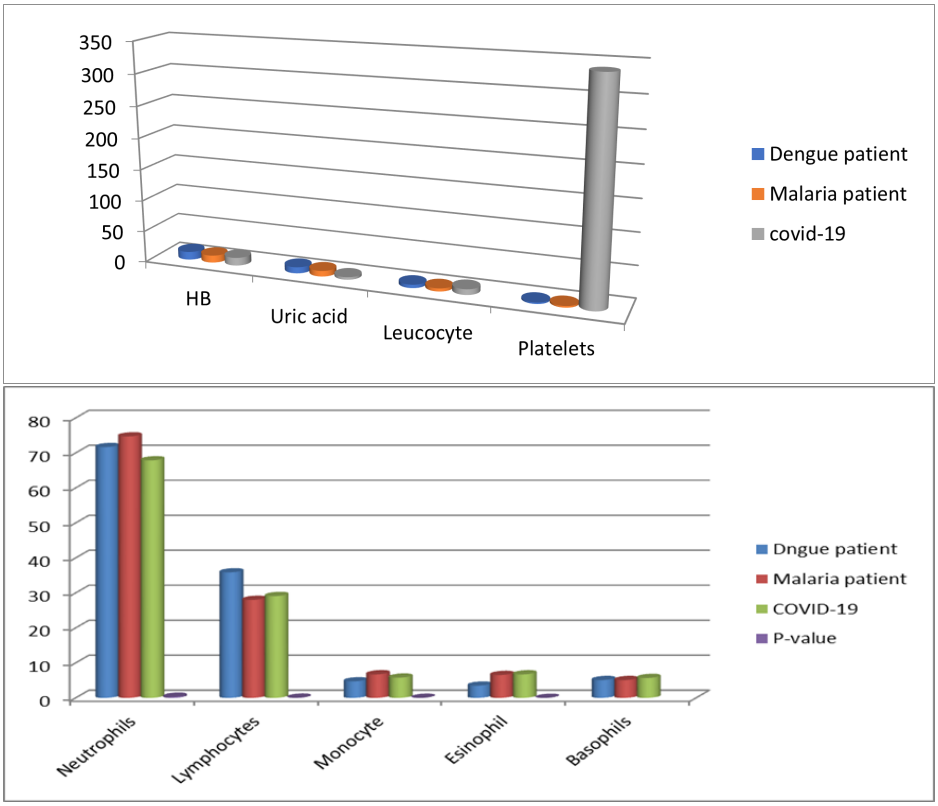

FIG. 2: Hematological profiles of dengue, malaria and Covid-19.

TABLE III: Hematological profile and WBC absolute counts of dengue, malaria and COVID-19.

Parameter	Dengue Patient	Malaria patient	COVID-19	P value
Hb g/dl	11.27 ± 2.44	11.45 ± 1.99	12.58 ± 1.68	.018
Uric Acid mg/dl	9.76 ± 1.45	8.89 ± 9.6	4.03 ± 0.78	.000
Leucocyte	5.28 ± 1870.53	4.80 ± 1941.38	8.82 ± 9.14	.000
Platelets	2.17 ± 197373.7	2.50 ± 221892	339.5 ± 108.13	.000
Neutrophils	71.67 ± 17.28	74.73 ± 14.90	67.88 ± 19.16	.027
Lymphocyte	35.87 ± 15.93	28.00 ± 13.46	29.10 ± 11.91	.066
Monocyte	4.73 ± 2.01	6.73 ± 2.79	5.78 ± 2.80	.024
Eosinophil	3.50 ± 2.38	6.55 ± 4.29	6.72 ± 4.38	.002
Basophils	5.09 ± 2.42	5.09 ± 2.52	5.68 ± 2.23	.016

C. Peripheral film

In Table IV. the peripheral film, ESR in dengue patients increased by 11.62 ± 3.85 in malarial patients by 53.52 ± 26.14 and in COVID-19 patients it is observed 6.70 ± 2.91. CRP in the dengue patient increases by 25.42 ± 2.24, in malarial patients increases by 15.35 ± 2.138 and in COVID-19 this is 5.02 ± 1.8.D. Dimer in dengue patients decreases by 7.45 ± 174.64, in malarial patients by 1.82 ± 0.14 and in COVID-19 it decreases by 2.45 ± 73.63. Fig. 3 shows the peripheral film comparison.

Red blood cells were significantly lower in malaria patients. That may be due to the parasite's main target being erythrocytes, with increased clearance of infested and uninfected erythrocytes through erythrocyte damage and bone marrow dysfunction. Malaria infection is associated with hematological and altered biochemical parameters in affected individuals Degrees that lead to changes in body physiology[19]. Both COVID-19 and

TABLE IV: Peripheral film in dengue, malaria and COVID-19.

Parameters	Dengue patient	Malarial patient	COVID-19	P-value
ESR	11.62 ± 3.85	53.52 ± 26.14	6.70 ± 2.91	.000
CRP	25.42 ± 2.24	15.35 ± 2.138	5.02 ± 1.83	.000
D.Dimer	7.45 ± 174.64	1.82 ± 0.14	2.45 ± 73.63	.000

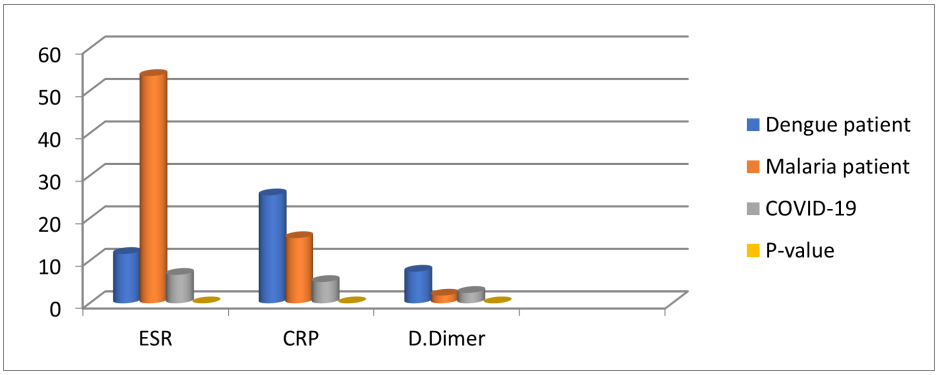

FIG. 3: Peripheral film in dengue, malaria and COVID-19.

dengue fever pose a severe threat to world. They share resemblances in medical symptoms which can lead to analytical confusion. The common medical features of dengue fever and COVID-19 are confusing. This study found that the average age of patients who died from COVID-19 was more complex than the survival cohort. These outcomes are available consistently through previous studies on patients with COVID-19[20]. In the present study, we investigated the role of oxidative stress biomarkers in different groups of hospitalized patients. According to previous studies, an imbalance in the production of reactive species and the body's inability to detoxify these reactive species is referred to as oxidative stress. Our results demonstrated that the oxidative stress profile in COVID-19 patients is closely related to patients' health level and demographic characteristics of dengue patients but in the entire study population amongst patients having Hb $>$ 15gm% dengue was seen in 40%. Hb $>$ 15gm% was also seen in P . falciparum in 33.3% and *P.* vivax in 26.6% of patients[21].

IV. EDITORIAL POLICY

Since the data utilized in this study were sourced from diagnostic Labs, institutional review board approval was not necessary for its completion.

V. CONCLUSION

In our study, we observed that a hematological profile can help predict the need for ICU care and mortality. The conclusion of this study suggests several clinical and experimental processes may be able to distinguish between dengue fever, malarial and COVID-19 patients. Despite enormous efforts to combat malaria, dengue fever and COVID-19, these diseases still have a huge impact on people's health, well-being and economies. Critical success in controlling mosquito-borne diseases depends not only on the services of public health officials. There is a need to understand and improve existing knowledge and practices regarding mosquito-borne diseases and their control in the community. Most importantly, there is a need to develop human coronavirus-targeted vaccines and antiviral drugs that can be used against current and future epidemics.

DECLARATION OF COMPETING INTEREST

The authors have no conflicts to disclose.

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