European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 9, Issue 4, Summer 2022

ORIGINAL RESEARCH

A STUDY TO EVALUATE VON WILLEBRAND FACTOR IN TROPICAL DISEASES - SCRUB TYPHUS, DENGUE, CHIKUNGUNYA, MALARIA AND ITS ASSOCIATION WITH CLINICAL OUTCOME

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ABSTRACT

Introduction: Endothelial activation and dysfunction is a central process in the pathogenesis of tropical diseases and von-Willebrand Factor levels have been linked with damage to the endothelium. The purpose of the study is to evaluate von Willebrand Factor in tropical diseases-Scrub typhus, Dengue, Chikungunya, Malaria and its association with clinical outcome. vWF can be used as a novel prognostic marker of clinical outcome.

Methodology: Hospital-based prospective observational analytic study on36 subjects of each disease. Inclusion Criteria: Confirmed cases of Scrub typhus (IgM positive), Dengue (NS1/IgM positive), Chikungunya (IgM positive) and Malaria (slide positive/rapid antigen detection/severe malaria). Exclusion criteria: Patients with von-Willebrand disease, Thrombotic Thrombocytopenic Purpura, and other conditions characterized by vascular damage, including nephritis, myocardial infarction, sepsis, diabetic angiopathy, peripheral vascular disease. Complete history with the examination was done. Investigations including CBC, PBF, RBS, RFT, LFT, vWF activity were done.

Observation and Results: In our study, we observed that vWF levels were elevated in91% patients of malaria, 89% patients of dengue, 75% patients of chikungunya, 88% patients of scrub typhus. We also found that 6, 3, and 3 out of 36 patients died in Malaria, Dengue, and Scrub typhus respectively with mean vWF was 414.67 IU/dl, 420 IU/dl, and 420 IU/dl respectively against alive cases where mean vWF was 259.97 IU/dl, 272.97 IU/dl, and 233.94 IU/dl. There is a statistically significant difference in vWF among alive and dead cases.

Conclusion: Raised vWF shows the association of von- Willebrand Factor activity and its association with the complications in these tropical diseases. von- Willebrand Factor level can be used as a novel prognostic marker of clinical outcome.

Keywords: von Wilibrand Factor (vWF), Tropical Diseases, Dengue, Malaria, Chikungunya, Scrub Typhus, Clinical Outcome.

INTRODUCTION

Every year different parts of India are hit by seasonal fevers in the post-monsoon period. Febrile illnesses are very common in the monsoon and post-monsoon season in tropical countries. The term acute undifferentiated febrile illness (AUFI) is defined as a fever of <14 days duration without any localized source of infection.[1] The common causes of AUFI's are dengue fever, chikungunya, scrub typhus, malaria, etc. in tropical countries.[2]

These AUFI's is often under-diagnosed as their nonspecific clinical features, including high fever, lymphadenopathy, rash, myalgia, and headaches, make it difficult to differentiate from other febrile illnesses.

Infected erythrocytes adhere to and disrupt the inner lining, or endothelium, of small blood vessels. Systemic inflammatory response and endothelial cell damage are closely associated with the progression and development of this disease. Endothelial dysfunction is usually followed by an increase in procoagulant activation, a decrease in anticoagulant activation, an increase in synthesis and secretion of von Willebrand factor (vWF) as well.

vWF was considered only as a marker of inflammation in various pathologies, due to its acute release by the activated endothelium. vWF has commonly been used as an early marker to detect endothelial activation and injury, both of which mark two key events during the systemic inflammatory response. vWF is a multimeric glycoprotein synthesized in megakaryocytes, and endothelial cells also take part in the production and release of most circulating vWF.[2,3]vWF is best known for its crucial hemostatic role in serving as a molecular bridge linking platelets to subendothelial components following vascular injury.

Therefore, the purpose of the study is to see the association of von- Willebrand Factor activity and its association with the complications in these tropical diseases. High von-Willebrand Factor level can be used as a novel prognostic marker of clinical outcome.

MATERIALS AND METHODS

A Hospital-based prospective observational analytic study was done in Department of Medicine, SMS Medical College & Hospital, Jaipur, Rajasthan. In this study 36 subjects of each disease were included.

INCLUSION CRITERIA

1. Confirmed cases of Scrub typhus (IgM positive), Dengue (NS1/IgM positive), Chikungunya (IgM positive) and Malaria (slide positive/rapid antigen detection/severe malaria)
2. Willing to give written, informed consent.
3. Age more than 18 years.

EXCLUSION CRITERIA

1. Patients with von-Willebrand disease, Thrombotic Thrombocytopenic Purpura.
2. Patients with other conditions characterized by vascular damage, including nephritis, myocardial infarction, sepsis, diabetic angiopathy, peripheral vascular disease.
3. Pregnant patients.
4. Patients with sickle cell disease/trait, HIV co-infection

Complete history with the examination was done. Investigations including CBC, PBF, RBS, RFT, LFT, vWF activity were done. Results were assessed. Data were collected in pre-structured proforma.

OBSERVATIONS AND RESULTS

The mean age of cases having malaria, dengue, chikungunya, and scrub typhus is 40.86 years, 39.81 years, 42.47 years, and 44.39 years respectively.

There were 66.67% males and 33.33% females having malaria, 61.11% males and 38.89% females having dengue and Chikungunya each, and 55.56% males and 44.44% females having scrub typhus.

The most common symptoms in malaria are fever and myalgia (100%) followed by headache (88.89%). In Dengue most common symptoms are fever and myalgia (100%) followed by headache (91.67%). In chikungunya, the most common symptom is fever (100%) followed by myalgia (91.67%). Lastly, in scrub typhus, the most common symptoms are fever and myalgia (100%) followed by headache (86.11%).

In malaria, the most common sign is splenomegaly (75%) followed by hepatomegaly (41.67%). In dengue most common sign is ascites and pleural effusion (63.89%) followed by mucosal bleeding (27.78%). In chikungunya most common sign is ascites and pleural effusion (13.89%) followed by splenomegaly (8.33%). Lastly, in scrub typhus most common sign is pleural effusion (55.56%) followed by ascites (38.89%).

The mean random blood sugar of cases having malaria is 78.69 mg/dl, dengue is 103.36 mg/dl, chikungunya is 109.14 mg/dl and scrub typhus is 102.75 mg/dl. The mean SGOT of cases having malaria is 85.64 mg/dl, dengue is 145.75 mg/dl, chikungunya is 62.03 mg/dl and scrub typhus is 68.83 mg/dl. The mean SGPT of cases having malaria is 77.11 mg/dl, dengue is 128.47 mg/dl, chikungunya is 54.53 mg/dl and scrub typhus is 48.44 mg/dl. The mean LDH of cases having malaria is 389.72 mg/dl, dengue is 234.39 mg/dl, chikungunya is 201.67 mg/dl and scrub typhus is 300.19 mg/dl. The mean serum bilirubin of cases having malaria is 3.10 mg/dl, dengue is 1.13 mg/dl, chikungunya is 1.0 mg/dl and scrub typhus is 1.77 mg/dl. The mean blood urea of cases having malaria is 62.83 mg/dl, dengue is 43.69 mg/dl, chikungunya is 44.67 mg/dl and scrub typhus is 71.42 mg/dl. The mean serum creatinine of cases having malaria is 1.64 mg/dl, dengue is 1.06 mg/dl, chikungunya is 1.17 mg/dl and scrub typhus is 1.76 mg/dl.

The mean total leukocyte counts of cases having malaria, dengue, chikungunya, and scrub typhus is 11.46, 3.42, 6.08, and 7.08 thousand/cubic mm of blood respectively. The mean platelet counts of cases having malaria, dengue, chikungunya, and scrub typhus is 21.14, 18.31, 34.81, and 45.38 thousand/microliter of blood respectively. The mean hemoglobin of cases having malaria, dengue, chikungunya, and scrub typhus is 10.37, 12.49, 12.10, and 12.39 gm/dl respectively. The mean von Willebrand Factor activity of cases having malaria,

dengue, chikungunya, and scrub typhus is 285.75%, 285.22%, 210.33%, and 249.44% respectively. The mean immature platelet fraction of cases having malaria, dengue, chikungunya, and scrub typhus is 4.64%, 8.865, 6.75%, and 6.79% respectively. Mean Immature granulocyte % of cases having malaria, dengue, chikungunya, and scrub typhus is 1.66%, 1.63%, 0.85%, and 1.05% respectively.

In malaria 91.675 cases have elevated vWF followed by dengue 88.89%, scrub typhus 83.33%, and chikungunya 72.22%. The difference is statistically significant between normal and elevated vWF in all four tropical diseases (p-value<0.05).

Cases that require oxygen support have mean vWF activity 392.56%, 399.33%, 362.00%, and 342.25% in malaria, dengue, chikungunya, and scrub typhus respectively. Similarly, cases that require inotropic support have mean vWF activity 397.67%, 360.57%, 347.20%, and 396.22% respectively in malaria, dengue, chikungunya, and scrub typhus. Cases that require ventilator support have mean vWF 414.67%, 420%, 420%, and 420% in malaria, dengue, chikungunya, and scrub typhus respectively. Statistically, there is a significant difference in mean vWF among cases that require these supports and which does not require support (p-value <0.0001), And, in cases which died, mean vWF in malaria, dengue and scrub typhus is 414.67, 420.00, and 420.00 which is also significantly high as compared to discharged cases (p-value<0.0001).

vWF was significantly correlated with GCS score in all tropical diseases except chikungunya

vWF was significantly correlated with SOFA score in all tropical diseases

vWF was significantly correlated with days of hospital stay score in all tropical diseases except dengue.

Table 1: Distribution according to age

Disease	Age (years)
	Mean± SD
Malaria (N=36)	40.86±16.83
Dengue (N=36)	39.81±15.60
Chikungunya (N=36)	42.47±14.20
Scrub typhus (N=36)	44.39±15.83

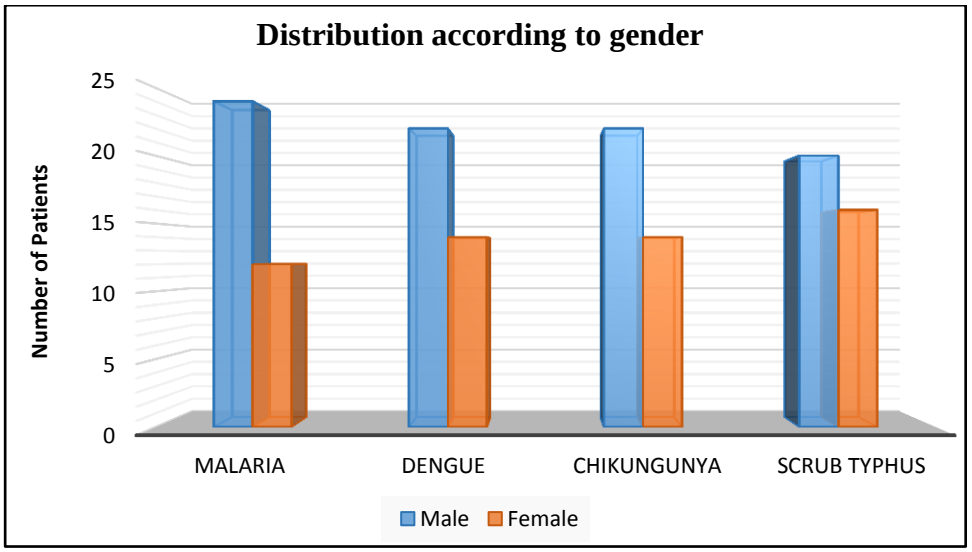


Table 2: Distribution according to the symptoms

Symptoms	Malaria		Dengue		Chikungunya		Scrub typhus	
	N	%	N	%	N	%	N	%
Fever	36	100	36	100	36	100	36	100
Myalgia	36	100	36	100	33	91.67	36	100
Headache	32	88.89	33	91.67	06	16.67	31	86.11
Joint pain	00	0.00	14	38.89	23	63.89	00	0.00
Nausea and vomiting	22	61.11	25	69.44	7	19.44	19	52.78
Abdominal pain	0	0.00	26	72.22	06	16.67	18	50.00
Skin rashes	2	5.56	20	55.56	31	86.11	7	19.44
Altered Sensorium	9	25	3	8.33	1	2.78	6	16.66

Table 3: Distribution according to clinical findings

Signs	Malaria		Dengue		Chikungunya		Scrub typhus	
	N	%	N	%	N	%	N	%
Hepatomegaly	15	41.67	8	22.22	2	5.56	13	36.11
Splenomegaly	27	75.00	3	8.33	3	8.33	4	11.11
Ascites	4	11.11	23	63.89	5	13.89	14	38.89
Pleural Effusion	1	2.78	23	63.89	5	13.89	20	55.56
Pneumonia	2	5.56	8	22.22	2	5.56	5	13.89
Mucosal Bleeding	5	13.89	10	27.78	1	2.78	2	5.56
Eschar	0	0.00	0	0.00	0	0.00	2	5.56
Lymphadenopathy	0	0.00	0	0.00	0	0.00	16	44.44

Table 4: Distribution according to biochemical parameters

Biochemical Parameter	Malaria	Dengue	Chikungunya	Scrub typhus	p-value
	Mean± SD	Mean± SD	Mean± SD	Mean± SD	
SGOT (units/l)	85.64±40.87	145.75±92.48	62.03±20.67	68.83±77.67	<0.0001
SGPT (units/l)	77.11±45.23	128.47±66.07	54.53±18.97	48.44±39.33	<0.0001
Serum Bilirubin (mg/dl)	3.10±1.35	1.13±0.42	1.00±0.23	1.77±1.16	<0.0001
Serum LDH (mg/dl)	389.72±263.16	234.39±170.03	201.67±117.61	300.19±121.33	<0.0001
Blood urea (mg/dl)	62.83±40.05	43.69±17.90	44.67±18.92	71.42±48.53	<0.0001
Serum creatinine (mg/dl)	1.64±0.79	1.06±0.34	1.17±0.37	1.76±0.88	0.2238
Random blood sugar (mg/dl)	78.69±40.87	103.36±25.23	109.14±26.19	102.75±22.62	<0.0001

Table 5: Distribution according to hematological parameters

Hematological parameter	Malaria	Dengue	Chikungunya	Scrub typhus	p-value
	Mean	Mean	Mean	Mean	
Hemoglobin (gm/dl)	10.37±2.48	12.49±1.86	12.10±2.23	12.39±2.40	0.0010
Total leukocyte count (thousand /cubic mm of blood)	11.46±5.93	3.42±0.96	6.08±2.06	7.08±3.58	<0.0001
Plateletcount(thousand/microliter of blood)	21.14±31.27	18.31±5.95	34.81±22.34	45.38±34.93	0.0002
Immature platelet fraction (%)*	4.64±2.74	8.86±5.51	6.75±3.12	6.79±5.66	0.0028
Immature granulocyte (%)*	1.66±1.76	1.63±1.66	0.85±0.80	1.05±0.82	0.0203
von Willebrand Factor activity(%)*	285.75±95.52	285.22±93.16	210.33±94.76	249.44±106.64	0.0090

*Reference range of immature platelet fraction (IPF) is 0.9-5.4%, immature granulocyte (Ig) % is 0-0.5% and von Willebrand Factor (vWF) activity is 50-160% (source- HLA and advanced hematological lab, SMS Medical College, Jaipur, Rajasthan)

Table 6: Distribution according to elevated von Willebrand Factor

	vWF				p-value
	Normal (50-160%)		Elevated (>160%)		
	N	%	N	%	
Malaria	3	8.33	33	91.67	<0.0001
Dengue	4	11.11	32	88.89	<0.0001
Chikungunya	10	27.78	26	72.22	0.0002
Scrub typhus	6	16.67	30	83.33	<0.0001
Chi-square statistic is 4.7246					

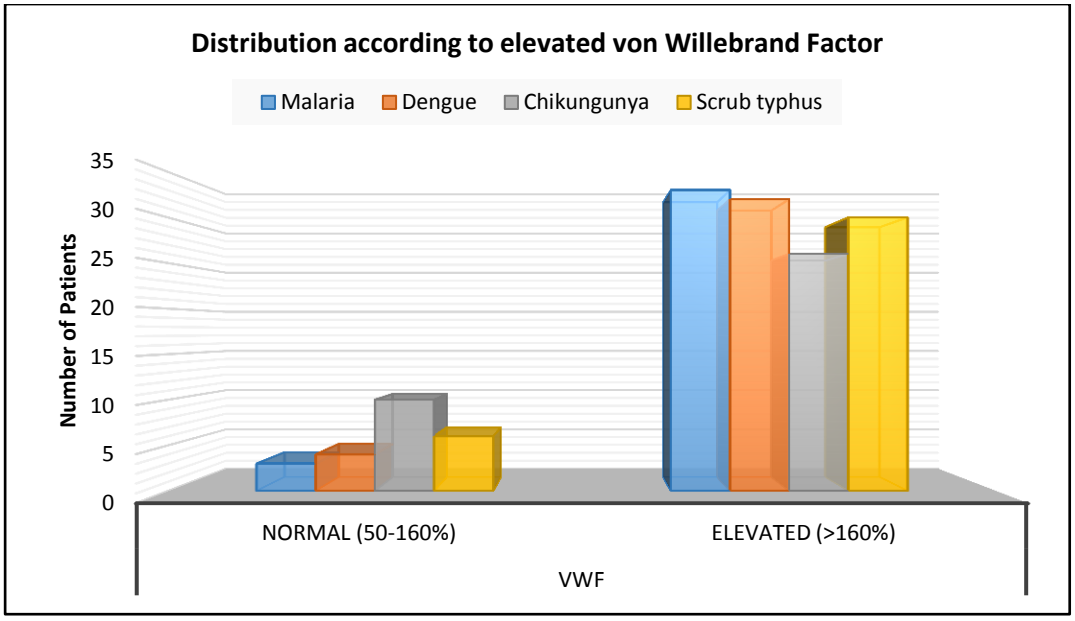


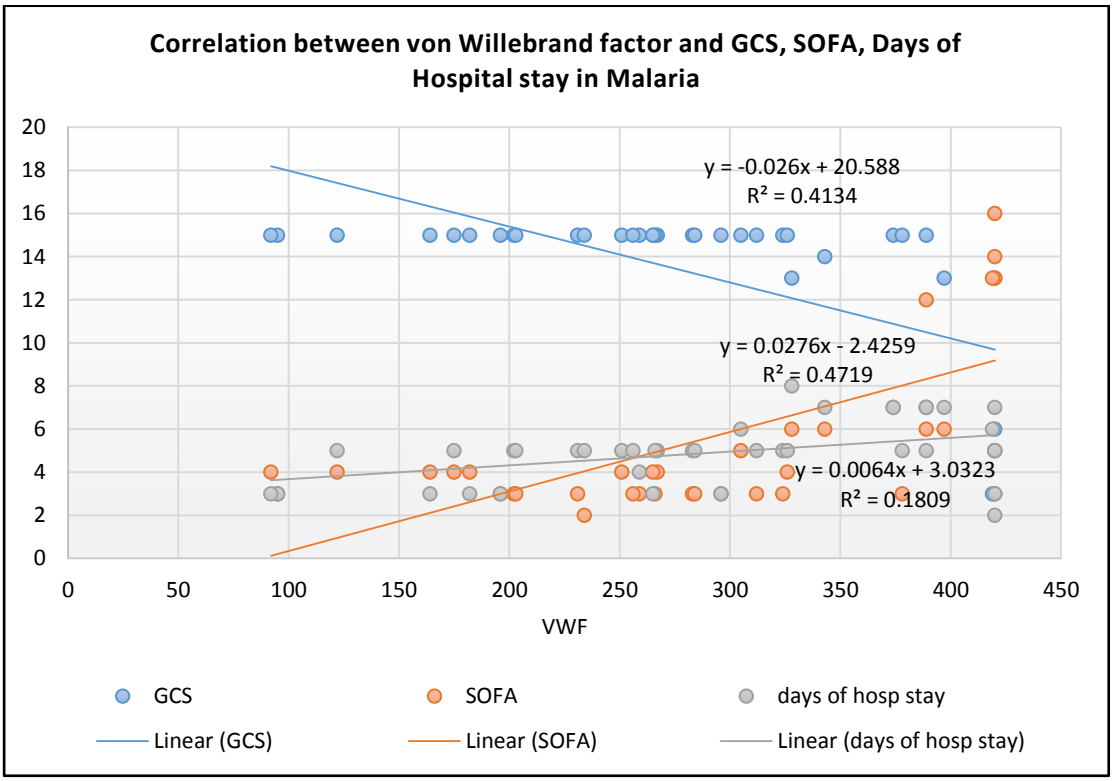
Table 7: Correlation of vWF with clinical course in hospital

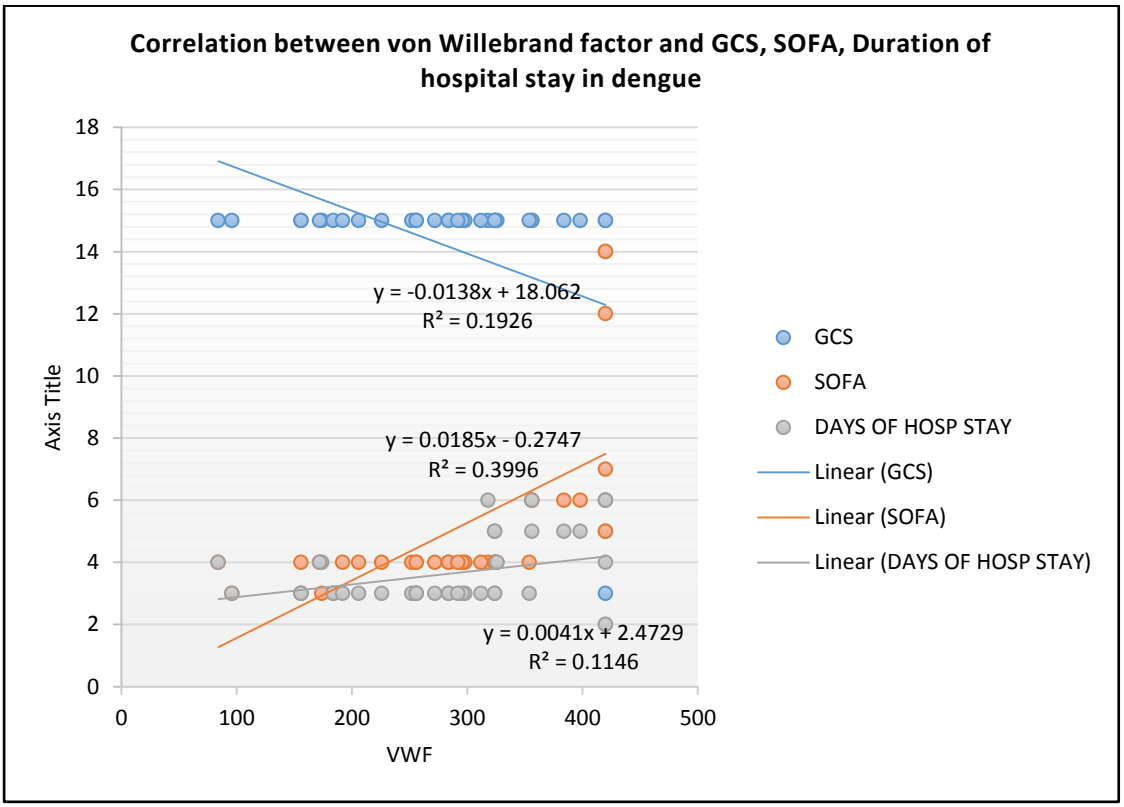
Clinical course in hospital		vWF% in Malaria	vWF% in Dengue	vWF% in Chikungunya	vWF% in Scrub typhus
		Mean±SD	Mean±SD	Mean±SD	Mean±SD
Oxygen requirement	Yes	392.56±36.56	399.33±27.68	362.00±58.17	342.25±74.31
	No	250.15±81.28	247.19±73.75	185.87±74.65	175.20±59.43
Inotropic requirement	Yes	397.67±37.40	360.57±56.27	347.20±54.45	396.22±28.78
	No	248.44±77.91	267.03±91.70	182.71±74.07	200.52±71.48
Ventilator requirement	Yes	414.67±12.58	420±0	420±0	420±0
	No	259.97±82.81	272.9±787.38	204.34±88.96	233.94±97.27
Outcome	Death	414.67±12.58	420.00±0	0±0	420.00±0
	Discharge	259.7±82.81	272.97±87.38	210.33±94.76	233.94±97.27
p-value		<0.0001	<0.0001	<0.0001	<0.0001

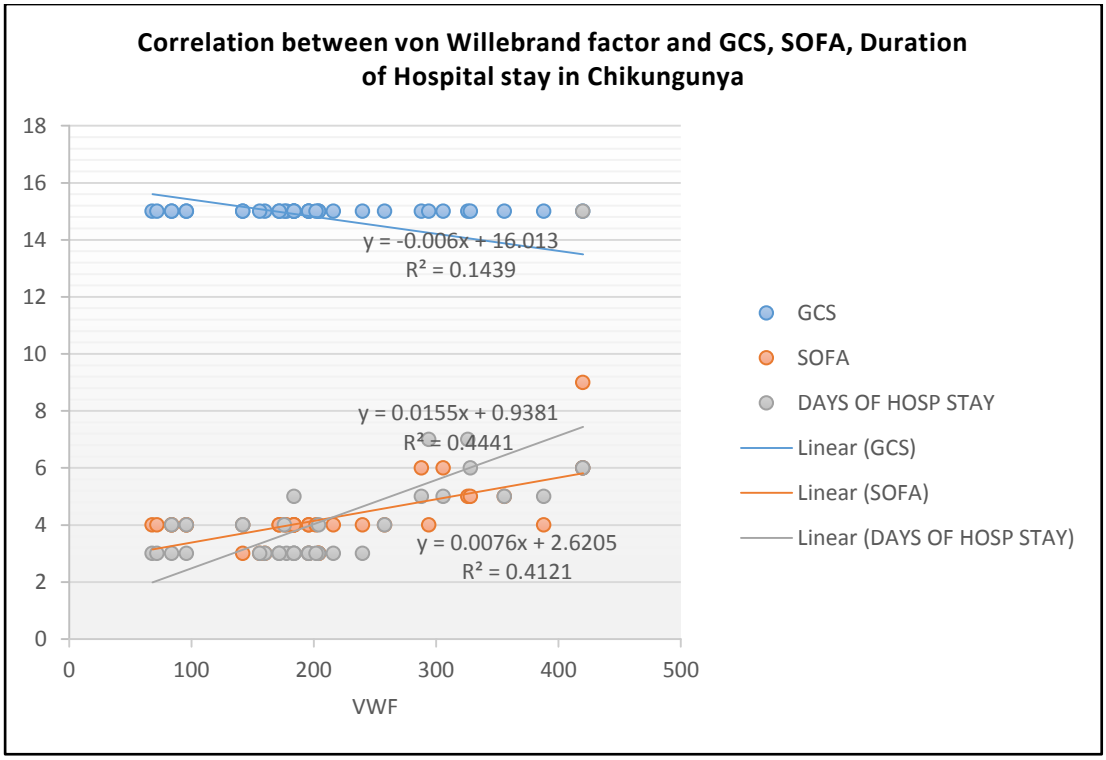
Table 8: Correlation of vWF with GCS, SOFA, and duration of hospital stay

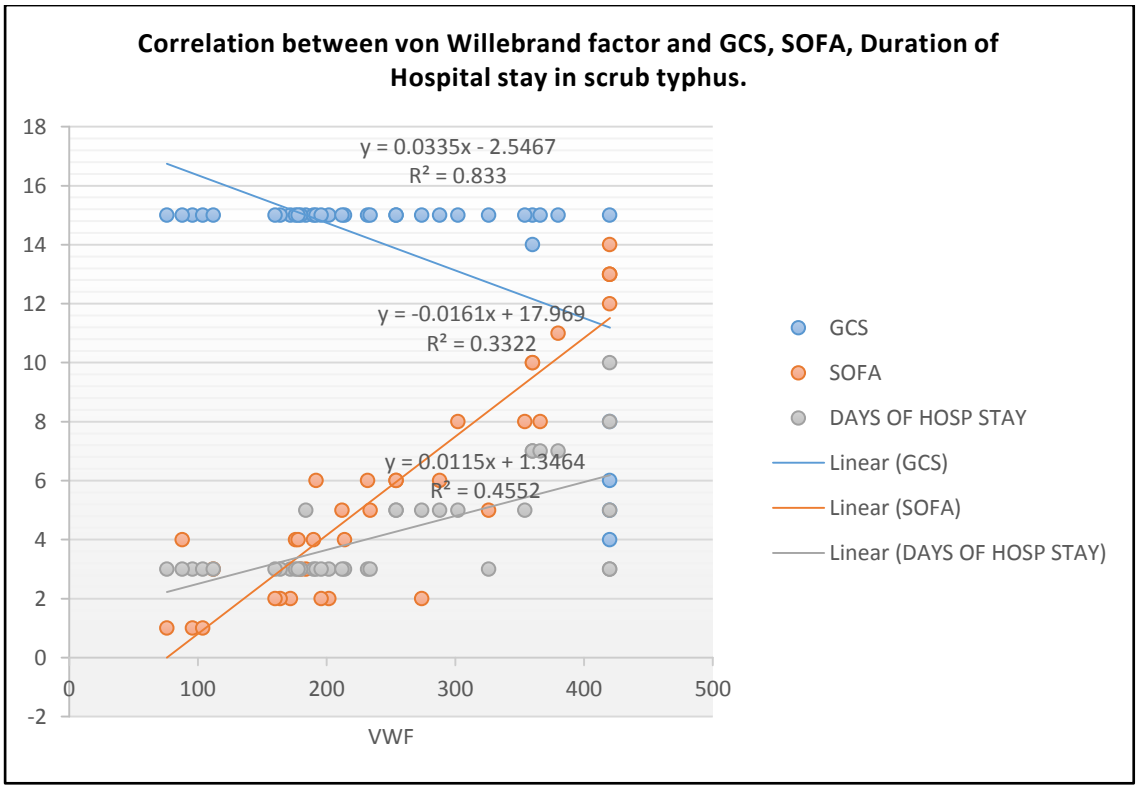
vWF		GCS	SOFA	Duration of hospital stay (in days)
Malaria	Rho*	-0.7226	0.6175	0.439
	p-value	<0.0001	<0.0001	0.0073
Dengue	Rho*	0.45027	0.8142	0.29621
	p-value	0.0058	<0.0001	0.0794
Chikungunya	Rho*	-0.2769	0.509	0.58288
	p-value	0.1019	0.0015	0.0001
Scrub typhus	Rho*	-0.56022	0.8829	0.67061
	p-value	0.0003	<0.0001	<0.0001

* Spearman's coefficient of rank correlation (Rho)


Correlation between von Willebrand factor and GCS, SOFA, Days of Hospital stay in Malaria
y = -0.026x + 20.588
R² = 0.4134
y = 0.0276x - 2.4259
R² = 0.4719
y = 0.0064x + 3.0323
R² = 0.1809
VWF
GCS
SOFA
days of hosp stay
Linear (GCS)
Linear (SOFA)
Linear (days of hosp stay)


Correlation between von Willebrand factor and GCS, SOFA, Duration of hospital stay in dengue
y = -0.0138x + 18.062
R² = 0.1926
y = 0.0185x - 0.2747
R² = 0.3996
y = 0.0041x + 2.4729
R² = 0.1146
Axis Title
VWF
GCS
SOFA
DAYS OF HOSP STAY
Linear (GCS)
Linear (SOFA)
Linear (DAYS OF HOSP STAY)





DISCUSSION

Correlation between infection and vWF activity- In the present study, we demonstrated that vWF secretion was significantly increased in malaria infection, dengue, scrub typhus, and chikungunya pointing at acute endothelial cell activation in malaria. Increased amounts of activated vWF, exposing the gpIba-binding site of vWF for platelets, were observed as

well. Platelet numbers and levels of both vWF and activated vWF showed a strong inverse correlation. Activated vWF may therefore be an important inducer of thrombocytopenia during early malaria and may as such contribute to the pathogenesis of malaria.[4]

Clinical features- In our study, the most common symptoms in malaria are fever and myalgia (100%) followed by headache (88.89%). In Dengue most common symptoms are fever and myalgia (100%) followed by headache (91.67%). In chikungunya, the most common symptom is fever (100%) followed by myalgia (91.67%). Lastly, in scrub typhus, the most common symptoms are fever and myalgia (100%) followed by headache (86.11%). And, the most common sign in malaria is splenomegaly (75%) followed by hepatomegaly (41.67%). In dengue most common sign is ascites and pleural effusion (63.89%) followed by mucosal bleeding (27.78%). In chikungunya, most common sign is ascites and pleural effusion (13.89%) followed by splenomegaly (8.33%). Lastly, in scrub typhus most common sign is pleural effusion (55.56%) followed by ascites (38.89%).

Behera et al[5] found that in dengue most common symptoms in fever (100%) followed by headache (36.8%). And most common sign includes Hepatosplenomegaly in (34.2%), Lymphadenopathy (18.54%) and Jaundice (9.56%). Bashir et al[6] found most of the cases in the present study were dengue fever (80.2%),

Total Leukocyte Count- Here we found that the mean total leukocyte counts of cases having malaria, dengue, chikungunya, and scrub typhus is 11.46, 3.42, 6.08, and 7.08 thousand/cubic mm of blood respectively.

Mean Platelet Count- The mean platelet count of cases having malaria, dengue, chikungunya, and scrub typhus is 21.14, 18.31, 34.81, and 45.38 thousand/microliter of blood respectively.

Mean Hemoglobin- The mean hemoglobin of cases having malaria, dengue, chikungunya, and scrub typhus is 10.37, 12.49, 12.10, and 12.39 gm/dl respectively.

Mean vWF Activity- The mean von Willebrand Factor activity of cases having malaria, dengue, chikungunya, and scrub typhus is 285.75%, 285.22%, 210.33%, and 249.44% respectively.

Mean Immature Platelet Fraction- The mean immature platelet fraction of cases having malaria, dengue, chikungunya, and scrub typhus is 4.64%, 8.865, 6.75%, and 6.79% respectively. Mean Immature granulocyte % of cases having malaria, dengue, chikungunya, and scrub typhus is 1.66%, 1.63%, 0.85%, and 1.05% respectively.

Bhargava et al7 suggest Anaemia in patients with malaria, rising hematocrit in severe dengue. Leucocytosis may be associated with severe forms of, scrub typhus, malaria, and dengue fever. Falling TLC + thrombocytopenia + rising hematocrit seen with severe dengue and Raised bilirubin distinguishes malaria from dengue.

Bashir BA6 reported a considerable number of patients had thrombocytopenia with dengue fever. They also reported that Prothrombin time was significantly prolonged in 30 (29.7%) of the patients and normal level in 71 (70.3%). Activated partial thromboplastin is also significantly prolonged.

Chen et al8 studied scrub typhus and reported thrombocytopenia, leucocytosis, leukocytopenia, decreased hemoglobin, elevated ALT, Scr, and CK. Also, reported scrub typhus patients revealed significantly higher serum levels of vWF. vWF is usually used as an early indicator of endothelial injury and dysfunction and is closely relevant to systemic

inflammation and infection.26 vWF recruits platelet and leukocyte into the injured vascular endothelium, leading to vascular occlusion and amplified inflammatory response.9 A previous study indicated that significantly increased plasma levels of vWF and vWF propeptide amid children with severe malaria.[8] Another study concerning children with Dengue virus infection introduced the level of vWF: Ag as a significant indicator of disease severity.[10]

Biochemical Parameters- In our study we found that the mean random blood sugar of cases having malaria is 78.69 mg/dl, dengue is 103.36 mg/dl, chikungunya is 109.14 mg/dl and scrub typhus is 102.75 mg/dl. The mean SGOT of cases having malaria is 85.64 mg/dl, dengue is 145.75 mg/dl, chikungunya is 62.03 mg/dl and scrub typhus is 68.83 mg/dl. The mean SGPT of cases having malaria is 77.11 mg/dl, dengue is 128.47 mg/dl, chikungunya is 54.53 mg/dl and scrub typhus is 48.44 mg/dl. The mean LDH of cases having malaria is 389.72 mg/dl, dengue is 234.39 mg/dl, chikungunya is 201.67 mg/dl and scrub typhus is 300.19 mg/dl. The mean serum bilirubin of cases having malaria is 3.10 mg/dl, dengue is 1.13 mg/dl, chikungunya is 1.0 mg/dl and scrub typhus is 1.77 mg/dl. The mean blood urea of cases having malaria is 62.83 mg/dl, dengue is 43.69 mg/dl, chikungunya is 44.67 mg/dl and scrub typhus is 71.42 mg/dl. The mean serum creatinine of cases having malaria is 1.64 mg/dl, dengue is 1.06 mg/dl, chikungunya is 1.17 mg/dl and scrub typhus is 1.76 mg/dl.

Mortality- In our study 16.67% of cases died in malaria, in dengue 8.33% of cases died, in Scrub typhus 8.33% of cases died and in chikungunya no death occurs. Here, the von Willebrand Factor is compared between alive and death cases and found that there was a statistically significant difference in von Willebrand Factor among cases who were alive and who died.

vWF was significantly correlated with GCS score in all tropical diseases except chikungunya, with SOFA score in all tropical diseases, and with days of hospital stay score in all tropical diseases except dengue.

CONCLUSION

Vascular endothelial cell injury and amplified immune response are linked to the progression of these tropical diseases and elevated levels of vWF are associated with disease severity and mortality of dengue, chikungunya, scrub typhus, and malaria which is promising for vWF to be new markers used in the assessment and prediction of this infection.

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