CORRELATING BIOCHEMICAL AND HEMATOLOGICAL PARAMETERS IN PATIENTS WITH DENGUE

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ABSTRACT

Objectives: The objectives of this study were to ascertain the correlation of the various biochemical and hematological parameters to dengue positive status.

Methods: Based on review of literature, we calculated the correlation of biochemical and hematological parameters of liver profile in dengue positive and dengue negative patients in a convenience sampling of 140 dengue negative and 49 dengue positive cases.

Results: Total bilirubin (TBI), total plasma protein, globulin, and alkaline phosphatase showed inverse correlation to dengue positive status, while albumin/globulin ratio elicited direct correlation. ($p<0.05$) Other parameters, namely, random blood sugar, direct bilirubin, indirect bilirubin, albumin, SGPT, and SGOT showed no clear cut correlation with dengue positive or negative status ($p>0.05$).

Conclusions: TBI, total plasma protein, globulin and alkaline phosphatase, and albumin/globulin ratio should be ascertained in a large equal group-size randomized study to establish their authenticity as prognosticators of the disease.

Keywords: Biochemical parameters, Hematological parameters, Liver profile, Dengue.

INTRODUCTION

Dengue virus taxonomically belongs to Flaviviridae family, having four serotypes. It spreads by the bite of Aedes species of mosquitoes. The wide spectrum of illness may end up to fatal dengue hemorrhagic fever or dengue shock syndrome [1]. Worldwide, 3.6 billion people live in risk-prone regions and 50 million infections per year occurring across 100 countries. India alone contributes to 34% (about 33 million infections) of the total global threat of dengue, leading to hyperendemicity, prevailing mostly in urban areas [2]. With increase in the size of population at risk, the cumulative diseases burden has vastly increased recently [1]. In India, dengue had been restricted to urban areas, but, now, it has encroached into rural regions too [2].

In India, the first documented epidemic of dengue was recorded in Chennai in 1780, but the first virologically proved epidemic occurred in Kolkata and Eastern Coast in 1963–1964 [1]. Since the mid-1990s, epidemics of dengue in India have become more frequent, especially in urban zones. Dengue has increased 30-times globally over the past five decades [2]. Diagnosis of infection is usually done by anti-DV IgM antibodies or NS-1 antigen in serum depending using ELISA kits (from National Institute of Virology, Pune). Molecular methods (reverse transcriptase PCR) are also being used in the diagnosis [1].

A study has reported that 6 million people in India had asymptomatic illness every year between 2006 and 2012. This study reported annual average of 5,778,406 non-laboratory diagnosed dengue cases during 2006–12, which is 282 times more than that reported by the Indian Ministry of Health [3]. As dengue fever is massively under-reported in India, hampering our response [4], a routine laboratory parameter significantly correlated to the disease can be an excellent alarm raising measure, based on which these specific and sensitive, but costly, tests can ensue.

As per the WHO/PAHO guidelines, a clinical maneuver (tourniquet test) with laboratory studies (platelet counts and hematocrit) should corroborate the diagnosis of dengue [5]. However, many researchers have reported of fallacies in the WHO case definition of the pathology itself [6,7].

For dengue, classical hematological laboratory triad is thrombocytopenia (platelet <65,000), atypical lymphocytosis (atypical lymphocyte >8%), and hemoconcentration (Hct <47%). A positive tourniquet test (TT) reflects hemorrhagic tendency and capillary fragility, but inclusion of positive TT could underestimate dengue occurrences in India [3].

That's why; diagnosis by the clinician is the most important for case reporting in India. The problem is further complicated by the fact that the clinical symptoms of dengue disease vary case by case. In endemic areas, physicians diagnose dengue by the classical triad of symptoms of fever, rash, and headache with a positive tourniquet test [3]. Based on review of the literature [8-14], some important liver profile parameters were chosen as the prospective biochemical laboratory values which may be correlated to dengue and thus relevant as non-immunological routine test indicators for the same. This study was planned to ascertain the correlation of the various biochemical and hematological parameters to dengue positive status.

METHODS

This observational study was conducted after approval from the Institutional Ethics Committee. In this retrospective observational cohort study (dengue negative vs. dengue positive cohorts), already existing laboratory data of all scrub typhus suspect cases from out patients and in-patients departments of tertiary care teaching hospital of Udaipur, Rajasthan between July and December 2021 was collected.

We calculated the correlation of various biochemical and hematological parameters of liver profile, namely, random blood sugar, total bilirubin (TBI), direct bilirubin, indirect bilirubin, total plasma protein, albumin, globulin, albumin/globulin ratio, SGPT, SGOT, and alkaline phosphatase

in dengue positive and dengue negative patients in a convenience sampling of 140 dengue negative and 49 dengue positive cases.

Statistical analysis

As the two groups (Dengue positive and Dengue negative) are not equal sized samples, Pearson's correlation coefficient, or its non-parametric analogues calculating rank correlations such as Spearman's σ test or

Kendal's τ test won't work. Hence, mean versus median (to ascertain skew) and box whisker plot (with Tukey's truncating of outliers in the graph) was calculated. If standard deviation (wider or narrower against the value of 1/6 in normal distribution) was more than centrality value – the result was declared irrelevant.

RESULTS

TBI, total plasma protein, globulin, and alkaline phosphatase showed inverse correlation (decreased) to dengue positive status, while albumin/globulin ratio elicited direct correlation (increased). Other parameters, namely, random blood sugar, direct bilirubin, indirect bilirubin, albumin, SGPT, and SGOT showed no clear cut correlation with dengue positive or negative status (Table 1 and Fig. 1-11).

DISCUSSION

Random blood sugar level

As the box whisker diagram (Fig. 1) shows, both the dengue positive as well as dengue negative patients have their random blood sugar level non-normally distributed. In the dengue negative patients, gross difference in the arithmetic mean (98.36) and median (88.7) is seen, though the standard deviation (32.03; in a range of 193.5) is not critically narrower/wider than normal distribution (≈ 1:6).
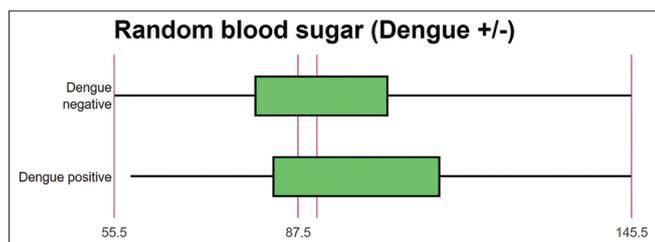

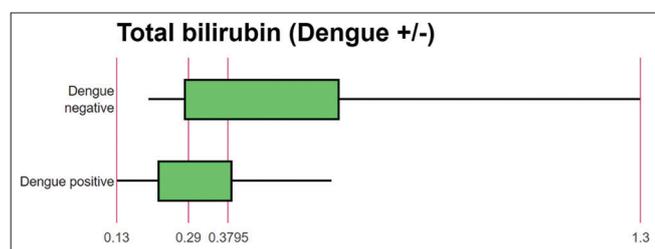**Fig. 1: Random blood sugar in dengue positive and dengue negative patients**

Fig. 2: Total bilirubin in dengue positive and dengue negative patients
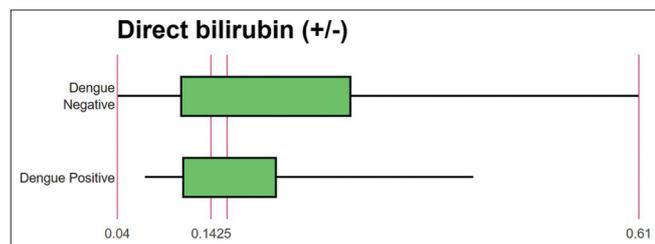

Fig. 3: Total bilirubin in dengue positive and dengue negative patients

In the dengue positive patients, gross difference in the arithmetic mean (103.2) and median (94) is seen again, though the standard deviation (36.134; in a range of 179.1) is a bit wider (which may be due to smaller sample size). Thus, the two data sets are not critically heteroscedastic and no significant correlation is blood sugar level to dengue positive or negative status could be established. In another study too, blood glucose level was found to be useful only in management (not a diagnostic indicator) [8].
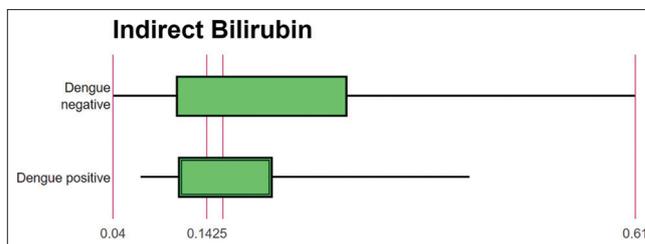

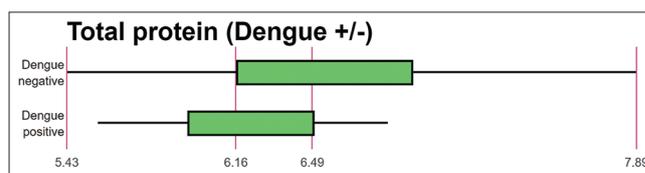**Fig. 4: Indirect bilirubin in dengue positive and dengue negative patients**

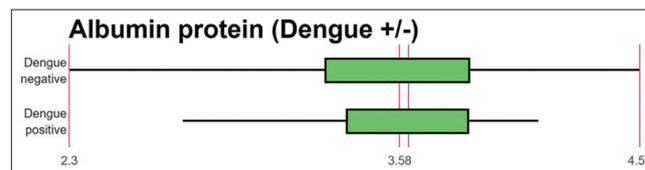**Fig. 5: Total protein in dengue positive and dengue negative patients**

Fig. 6: Albumin in dengue positive and dengue negative patients

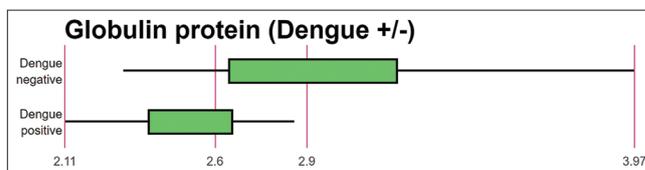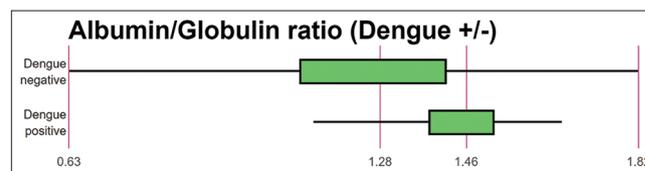**Fig. 7: Globulin in dengue positive and dengue negative patients**

Fig. 8: Albumin/globulin ratio in dengue positive and dengue negative patients

Fig. 9: SGPT in dengue positive and dengue negative patients

Table 1: Comparison of biochemical and hematological parameters in both the groups

| Parameters	p-value	Dengue negative (n=140) Mean±SD (median)	Dengue positive (n=49) Mean±SD (median)
Random blood glucose (mg/dL)	0.1326	98.36±32.03 (88.70)	103.20±36.13 (94.00)
Total bilirubin (mg/dL)	0.0373*	0.61±0.26 (0.36)	0.37±0.23 (0.30)
Direct bilirubin (mg/dL)	0.8422	0.28±0.44 (0.149)	0.15±0.10 (0.146)
Indirect bilirubin (mg/dL)	0.5901	0.31±0.35 (0.18)	0.24±0.21 (0.15)
Total plasma protein (g/dL)	0.0454*	6.39±0.81 (6.46)	6.14±0.46 (6.15)
Albumin (g/dL)	0.6937	3.44±0.65 (3.60)	3.58±0.35 (3.58)
Globulin (g/dL)	0.0417*	2.93±0.54 (2.90)	2.56±0.27 (2.61)
Albumin/globulin ratio	0.0349*	1.21±0.28 (1.25)	1.40±0.18 (1.44)
SGPT (units/L)	0.0462#	60.04±85.11 (35.50)	119.30±213.99 (67.80)
SGOT (units/L)	0.0470#	69.94±70.75 (39.85)	151.91±288.43 (87.30)
Alkaline phosphatase ((IU/L))	0.0418*	120.16±84.74 (92.50)	86.68±28.61 (79.00)

*Significant #Irrelevant
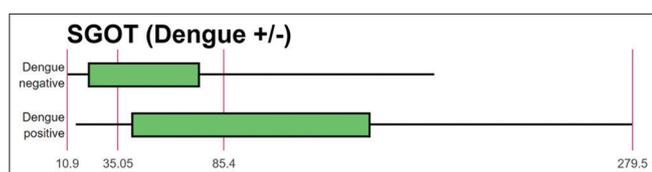
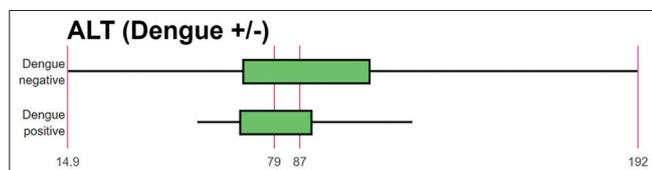**Fig. 10: SGOT in dengue positive and dengue negative patients**

Fig. 11: Alkaline phosphatase in dengue positive and dengue negative patients

TBI

As the box whisker diagram shows (Fig. 2), both the dengue positive as well as dengue negative patients have their TBI level non-normally distributed. In the dengue negative patients, gross difference in the arithmetic mean (0.61) and median (0.36) is seen, though the standard deviation (0.363; in a range of 5.58) is vastly narrower.

In the dengue positive patients, gross difference in the arithmetic mean (0.37) and median (0.30) is seen again, though the standard deviation (0.235; in a range of 1.07) is a vastly wider (which can be assigned to the smaller sample size). Thus, the two data sets are critically heteroscedastic and inverse correlation to TBI to dengue positive status could be elicited. Quite in unison, another study found that higher bilirubin level is rather favors a diagnosis of malaria [9].

Direct bilirubin

As the box whisker diagram shows (Fig. 3), both the dengue positive as well as dengue negative patients have their direct bilirubin level non-normally distributed. In the dengue negative patients, gross difference in the arithmetic mean (0.28) and median (0.15) is seen, though the standard deviation (0.442; in a range of 2.971) is a bit narrower.

In the dengue positive patients, there is no gross difference in the arithmetic mean (0.16) and median (0.15) is seen though the standard deviation (0.097; in a range of 0.353) is a lot wider (which can be assigned to the smaller sample size). Thus, the two data sets are critically heteroscedastic and but correlation of TBI to dengue positive status could not be elicited. Such a discerning study with direct/indirect bilirubin has not been done yet.

Indirect bilirubin

As the box whisker diagram shows (Fig. 4), both the dengue positive as well as dengue negative patients have their indirect bilirubin level non-normally distributed. In the dengue negative patients, gross difference in the arithmetic mean (0.31) and median (0.18) is seen, though the standard deviation (0.35; in a range of 2.15) is usual.

In the dengue positive patients, gross difference in the arithmetic mean (0.24) and median (0.15) is seen again, though the standard deviation (0.21; in a range of 0.75) is a vastly wider (which can be assigned to the smaller sample size). Thus, the two data sets are critically heteroscedastic, but the difference is not significant. Such a discerning study with direct/indirect bilirubin has not been done yet.

Total Protein

As the box whisker diagram shows (Fig. 5), both the dengue positive as well as dengue negative patients have their total protein level non-normally distributed. In the dengue negative patients, there is no significant difference in the arithmetic mean (6.39) and median (6.46) is seen, though the standard deviation (0.8; in a range of 4.24) is a bit wider.

In the dengue positive patients, there is no significant difference in the arithmetic mean (6.141) and median (6.145) is seen, though the standard deviation (0.46; in a range of1.95) is vastly wider (which can be assigned to the smaller sample size). Thus, the two data sets are critically heteroscedastic and the difference (mean/median) is significant too – inverse correlation of total protein to dengue positive status could be elicited. Such a cumulative study with total protein has not been done yet.

Albumin

As the box whisker diagram shows (Fig. 6), both the dengue positive as well as dengue negative patients have their albumin level non-normally distributed. In the dengue negative patients, there is no significant difference in the arithmetic mean (3.4) and median (3.6) is seen, though the standard deviation (0.65; in a range of 2.6) is vastly wider.

In the dengue positive patients, there is no significant difference in the arithmetic mean (3.57) and median (3.58) is seen though the standard deviation (0.35; in a range of 1.38) is vastly wider (which can be assigned to the smaller sample size). Thus, the two data sets are critically heteroscedastic, but the difference (mean/median) is insignificant. This finding is in agreement of another study [10].

Globulin

As the box whisker diagram shows (Fig. 7), only dengue positive patients have their albumin level non-normally distributed. In the dengue negative patients, there is no significant difference in the arithmetic mean (2.93) and median (2.90) is seen, though the standard deviation (0.54; in a range of 3.1) is nearly normal ($\approx 1/6$).

In the dengue positive patients, there is no significant difference in the arithmetic mean (2.56) and median (2.61), though the standard deviation (0.274; in a range of1.29) is vastly wider (which can be assigned to the smaller sample size). Thus, the two data sets are critically heteroscedastic and the difference (mean/median) is

significant too – inverse correlation of globulin to dengue positive status could be elicited. Such an analogical study with globulin level has not been done yet.

Albumin/Globulin ratio

As the box whisker diagram shows (Fig. 8), both the dengue positive as well as dengue negative patients have their albumin level non-normally distributed. In the dengue negative patients, there is no significant difference in the arithmetic mean (1.21) and median (1.25) is seen, though the standard deviation (0.286; in a range of 1.31) is vastly wider.

In the dengue positive patients, there is no significant difference in the arithmetic mean (1.41) and median (1.44) is seen, though the standard deviation (0.18; in a range of 0.72) is vastly wider (which can be assigned to the smaller sample size). Thus, the two data sets are critically heteroscedastic and the difference (mean/median) is significant too – direct correlation of albumin/globulin ratio to dengue positive status could be elicited. This finding is similar to another study [11].

SGPT

As the box whisker diagram shows (Fig. 9), both the dengue positive as well as dengue negative patients have their SGPT level non-normally distributed. In the dengue negative patients, there is a significant difference in the arithmetic mean (60.0) and median (35.5), though the standard deviation (85.1; in a range of 743.4) is very narrow. As the standard deviation is more than centrality measure (mean/median), the statistical relevance of central values is lost.

In the dengue positive patients, there is a significant difference in the arithmetic mean (119.3) and median (67.8), though the standard deviation (213.9; in a range of 1238.1) is usual. As the standard deviation is more than centrality measure (mean/median), the statistical relevance of central values is lost. In a larger study, too SGPT was found normal in dengue fever (rather it was raised in non-dengue fever) [12], while, in another study, this normalcy was equivocal [13].

SGOT

As the box whisker diagram shows (Fig. 10), both the dengue positive as well as dengue negative patients have their SGPT level non-normally distributed. In the dengue negative patients, there is a gross difference in the arithmetic mean (69.9) and median (39.9), though the standard deviation (70.7; in a range of 295) is vastly wider. As the standard deviation is more than centrality measure (mean/median), the statistical relevance of central values is lost.

In the dengue positive patients, there is a gross difference in the arithmetic mean (151.9) and median (87.3) is seen though the standard deviation (288.4; in a range of 1691.5) is usual. As the standard deviation is more than centrality measure (mean/median), the statistical relevance of central values is lost. In other larger studies, SGOT was conclusively found raised in dengue [12,13].

Alkaline phosphatase (ALP)

As the box whisker diagram shows (Fig. 11), both the dengue positive as well as dengue negative patients have their ALP level non-normally distributed. In the dengue negative patients, there is wide difference in the arithmetic mean (120.1) and median (92.5), though the standard deviation (84.7; in a range of 493.1) is wide. As the standard deviation is more than centrality measure (mean/median), the statistical relevance of central values is lost.

In the dengue positive patients, there is no significant difference in the arithmetic mean (86.7) and median (79), though the standard deviation (28.6; in a range of128) is vastly wide – inverse correlation of alkaline phosphatase to dengue positive status could be elicited. In another study, secreted alkaline phosphatase level was found increased in dengue [14].

Limitations

Sample size of dengue positive patients was smaller in present study and there was no randomization in sampling.

CONCLUSIONS

Out of all parameters, TBI, total plasma protein, globulin, and alkaline phosphatase showed inverse correlation (decreased) to dengue positive status, while albumin/globulin ratio elicited direct correlation (increased). Other parameters, namely, random blood sugar, direct bilirubin, indirect bilirubin, albumin, SGPT, and SGOT showed no clear cut correlation with dengue positive or negative status.

AUTHORS' CONTRIBUTIONS

All the authors contributed to the preparation of the final manuscript.

CONFLICTS OF INTEREST

None.

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