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Hepatic dysfunction in falciparum malaria in West Bengal".

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Abstract: Aims and objectives*: Malaria, a devastating tropical disease, is very common in India and native countries. In West Bengal, the influence of falciparum and vivax malaria is so high, that each year, many people are affected by these parasites. Our aim is to evaluate the amount of hepatic dysfunction in case of plasmodium affected patients.* ***Materials and methods****: In clinically diagnosed 108 patients, admitted in our hospital in the years 2010-2013, confirmation were done thick and thin blood film and/or serology. After diagnosis, other hematological, serological and biochemical tests were carried out other diseases responsible for hepatitis. Then we compared bilirubin, SGOT, SGPT, alkaline phosphatase and hemoglobin as well as correlation between bilirubin and hemoglobin and liver enzymes amongst males (n=62) and females (n=46).* ***Results****: Mean values of bilirubin, SGPT and SGOT were significantly raised in males than females. Bilirubin showed significant positive correlation with SGPT and alkaline phosphatase and negative correlation with hemoglobin in both sexes, but positive correlation with males.* ***Conclusion****: Plasmodium falciparum was mainly responsible for hepatic dysfunction in the form of raised liver enzymes rather than only hyperbilirubinemia due to ruptured parasitized or nonparasitized red blood cells (RBC). In future, large scale studies are required justify the above correlations.*

I. Introduction:

Malaria, a devastating disease of Tropical and sub-tropical areas of Asia, North and South America, Middle-East, North Africa and South Pacific countries, is caused by Plasmodium species. Among four main types of Plasmodium species, plasmodium falciparum and vivax are responsible for major health problem in India and native countries, like, Pakistan, Bangladesh. These parasites are transmitted to human being by the bite of infected Anopheles mosquitoes. Malarial sporozoites, after their entry into the blood stream of human being, they cirulate and enter into the hepatocytes through the receptor for thrombospondin and Properdin[1, 2]. Here, sporozoites mature to form either schizonts or hypnozoites, last of which remain dormant in the liver for future relapse. Tissue schizonts break down into large number of merozoites (10000 to 30000) and are released into blood stream. Again, each merozoite invades the human red blood cell (RBC) and start asexual process of replication[3]. From each merozoite, 24 to 32 merozoites are formed and released into circulation again by the process of rupture of RBC within 48 to 72 hours, and produce febrile paroxysm. In this way, malarial parasites are responsible for liver cell damage, as evidenced by, jaundice with or without elevation of liver enzymes, like, Aspartate and Alanine aminotranferases[4]. Usually, raised bilirubin is unconjugated as a result of breakdown of parasitized and non-parasitized RBC and/or liver cell damage[5]. Hyperbilirubinemia (≥3 gm/dl), according to WHO, may be responsible for complication and mortality[6]. Alanine aminotransferase (SGPT) is mainly found in the liver, and acts as catalyst in the transfer of amino acid from donor molecule to recipient molecule. Whereas, Aspartate transaminase (SGOT) are found in the muscles, heart, kidney and brain in addition to liver. Hence, SGPT, not SGOT is the prime indicator of ongoing liver cell damage. Again, alkaline phosphatase is secreted by hepatocytes into the biliary canaliculi. So, raised serum alkaline phosphatase in patients affected by falciparum malaria, due to perturbation of host hepatocytes drainage pathways during the hepatic stage of falciparum malaria, as well as leakage from damaged hepatocytes membrane[7]. Our aim, in this study, is to correlate bilirubin and hemoglobin with hepatic enzymes to estimate whether hepatic damage or rupture of RBC is responsible for raised bilirubin in falciparum malaria in our community.

II. Materials and methods:

This study was carried out only after getting permission from the local Ethical Committee. Total 108 patients with high fever paroxysms were admitted in our hospital within the span of 2012-2013 years. After taking written consent from patient's party, proper history was taken in the form of structured questionnaire followed by proper physical examinations. The symptoms were febrile paroxysm, nausea and/or vomiting, headache, hepatomegaly with or without slpenomegaly. Then it was confirmed by thick and thin blood film stained by Leishman's stain and /or malarial antigen. Other hematological, serological and biochemical laboratory investigations were carried out. Hemoglobin level was estimated by Cynamet hemoglobin method, hematocrit by Microhematocrit method, serum bilirubin by Jedrassik Groff method, SGPT, SGOT and alkaline phosphatase by enzymatic method. Again, blood urea, creatinine, electrolytes, blood sugar, prothrombin time were performed, in addition, viral serology for hepatitis A, B, C and E, leptospiral antigen were carried out to exclude hepatic involvement other than falciparum malaria. They were interrogated regarding the intake of hepatotoxic drugs in last two to three months. All the above parameters were compared and co-rrelation coefficient between bilirubin and hemoglobin with liver enzymes, like, SGOT, SGPT and alkaline phosphatase with regression analysis were observed between affected males and females.

Statistics:

Mean values with standard deviations were carried out for bilirubin, SGPT, SGOT, alkaline phosphatase, hemoglobin. Then correlation co-efficient were deducted between bilirubin, hemoglobin and SGOT, SGPT and alkaline phosphatase with regression analysis through following formula:

$$\text{Correlation}(r) = [N\Sigma XY - (\Sigma X)(\Sigma Y) / \text{Squre root}([N\Sigma X^2 - (\Sigma X)^2][N\Sigma Y^2 - (\Sigma Y)^2])]$$

Where, n=numbers of variable, X and Y are the variables.

III. Results:

Total number of affected patients was 108, amongst which, females and males were 46 (42.59%) and 62 (57.40%) respectively. Mean age of females and males were 36.04 ±15.92 years (ranges from 20-82years) and 31.91± 8.30 years respectively. In these patients, 75 (69.44%) and 39 (36.11%) have palpable liver and spleen respectively. Mean values of males and females of bilirubin 1.61 ± 2.08 U/L and 1.13 ± 0.37 U/L, SGPT 80.96 ± 78.05 U/L and 63.13 ± 32.89 U/L, SGOT 75.1 ± 95.96 U/L and 46.65 ± 25.37 U/L, alkaline phosphatase 126.05 ± 48.13 U/L and 112.43 ± 38.42 U/L and hemoglobin 12.03 ±1.23 g/dl and 12.16 ± 1.37 g/dl respectively. This showed, mean values of bilirubin, SGOT, SGPT in case of males were statistically raised than that of females, but in case of hemoglobin and alkaline phosphatase, there were no statistical difference between males and females [Table 1]. Bilirubin showed statistically significant correlations with SGPT and alkaline phosphatase in both sexes and with SGOT in males, but negative correlation with hemoglobin in both sexes [Table 2]. Hemoglobin showed poorly positive correlation with SGOT in both sexes and with significant correlation with SGPT in females, but negative correlation in males [Table 3].

IV. Discussion:

Plasmodium falciparum affects any person of any age. Here, in our study, mean age of males and females were 31.91 ± 8.3 years and 36.04 ± 15.92 years, which was similar to the study done by Abro A H et al. Usually, in uncomplicated malaria, raised bilirubin is mainly due to hemolysis of parasitized and non parasitized RBC and and/or hepatocytes damage[8]. In acute falciparum malaria, reticulo-endothelial cells are hyperplasia is mainly responsible for hepatosplenomegaly[9]. In our study, 69.44% and 36.11% patients showed hepatic and splenic enlargement respectively. In the study of Abro A H et al.[8] and Kausar M. W et al.[10] incidence of slpenomegaly were 38% and 37.5% respectively, which were very near to the values in our study (36.11%), but the incidence of hepatomegaly was much higher than the incidence of above studies.

Since, SGPT is mainly formed in the liver; hence, its elevation is a prime indicator of liver dysfunction. In our study, it was raised both in males and females (80.96 ± 78.05 U/L and 63.17 ± 32.89U/L), which was more than that shown in the study of Kausar M.W et al.[10]

In our study, mean value of SGPT, SGOT and bilirubin in males were raised significantly than females (80.96 ± 78.05 U/L vs. 63.17 ± 32.89 U/L for SGPT, 75.1 ± 95.96 U/L vs. 46.652 ± 25.37 U/L for SGOT and 1.61 ± 2.08 mg% vs. 1.13 ± 0.37 mg% for bilirubin with p value =0.00 in each), which was not shown in any other study even after thorough internet search.

In our study, mean value of hemoglobin in both sexes were near normal, which was higher than the value (9.5 gm %) as shown by Kausar M. W et al.[10] Whereas, Nadeem et al.[2] showed the mean value of hemoglobin as

13.78 gm %, which was higher than our observed value. So, in our study, raised bilirubin was mainly due to hepatic dysfunction rather than hemolysis. The reason may be the early detection of malarial parasite in the blood and/or positivity of plasmodium falciparum antigen followed by specific treatment. Hyperbilirubinemia was present in 60.9% of patients, which was more or less similar to the study done by Kausar M.W et al.[10]

In our study, bilirubin showed poor negative correlation with hemoglobin, reflecting normal to mild anemia along with hyperbilirubinemia, indicating hyperbilirubinemia may be due to hepatic cell damage rather than hemolysis of parasitized or nonparasitized RBC, whereas, in the study of Kausar M.W et al.[10] there was negative correlation between bilirubin and hemoglobin, indicating hyperbilirubinemia is more due to hemolysis of RBC.

In our study, SGOT and SGPT showed positive correlation with hemoglobin in both sexes [for SGOT, females (r) = 0.331 and males (r) = 0.123; for SGPT, females (r) = 0.529 and males (r) = 0.076]. Again, SGPT showed significant positive correlation with bilirubin both in males ($r = 0.768$, $p = <0.001$) and females ($r = 0.505$, $p<0.05$), whereas, SGOT showed significant correlation with bilirubin in males ($r = 0.917$, $p<0.001$). So, In spite of raised hemoglobin, rise in SGPT and SGOT may be due to damage of hepatocytes during the hepatic phase of plasmodium cycle, which was found more in male patients. But in the study of Kausar M.W et al.[10], there was significant negative correlation of SGOT and SGPT and hemoglobin.

Raised mean value of alkaline phosphatase in both sexes as well as significant correlation ($r = 0.889$ for females with $p=<0.001$, and $r = 0.868$ for males with $p=<0.001$) between bilirubin and alkaline phosphatase was shown in our study, as also seen in other studies. This may be due to leakage of this enzyme into the hepatic drainage system followed by absorption in the blood. So it may be an essential indicator regarding the evaluation of hepatic drainage system.

V. Conclusion:

Plasmodium falciparum was mainly responsible for raised SGOT, SGPT, alkaline phosphatase and bilirubin in the affected patients due to hepatic phase of parasites containing schizonts and hypnozoites, rather than hyperbilirubinemia due to ruptured parasitized or nonparasitized RBC. But here, only 108 patients were included in our study. So, large scale studies are required to justify above correlations in hepatic dysfunction.

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Table: 1 Comparison of biochemical parameters between Plasmodium falciparum affected males and females

Biochemical parameters	Female	Male	P value
	Range (mean±SD)	Range (mean±SD)	
Bilirubin	0.6-2.1 (1.13±0.375)	0.4-11 (1.61±2.081)	0.000
SGPT (U/L)	17-112 (63.173±32.894)	24-560 (80.966±78.051)	0.000
SGOT (U/L)	25-140 (46.652±25.374)	30-404 (75.1±95.967)	0.000
Hemoglobin (g/dl)	8.7-14 (12.160±1.371)	8.5-14 (12.033±1.235)	0.224
Alkaline phosphatase (U/L)	75-202 (112.434±38.426)	76-370 (126.05±48.135)	0.058

Table: 2—Correlation coefficient (r) of bilirubin with biochemical parameters in Plasmodium falciparum affected males and females:

Biochemical parameters	Females	Males
Hemoglobin (g/dl)	-0.225	-0.249
SGPT (U/L)	0.505*	0.768**
SGOT (U/L)	0.025	0.917**
Alkaline phosphatase (U/L)	0.889**	0.868**

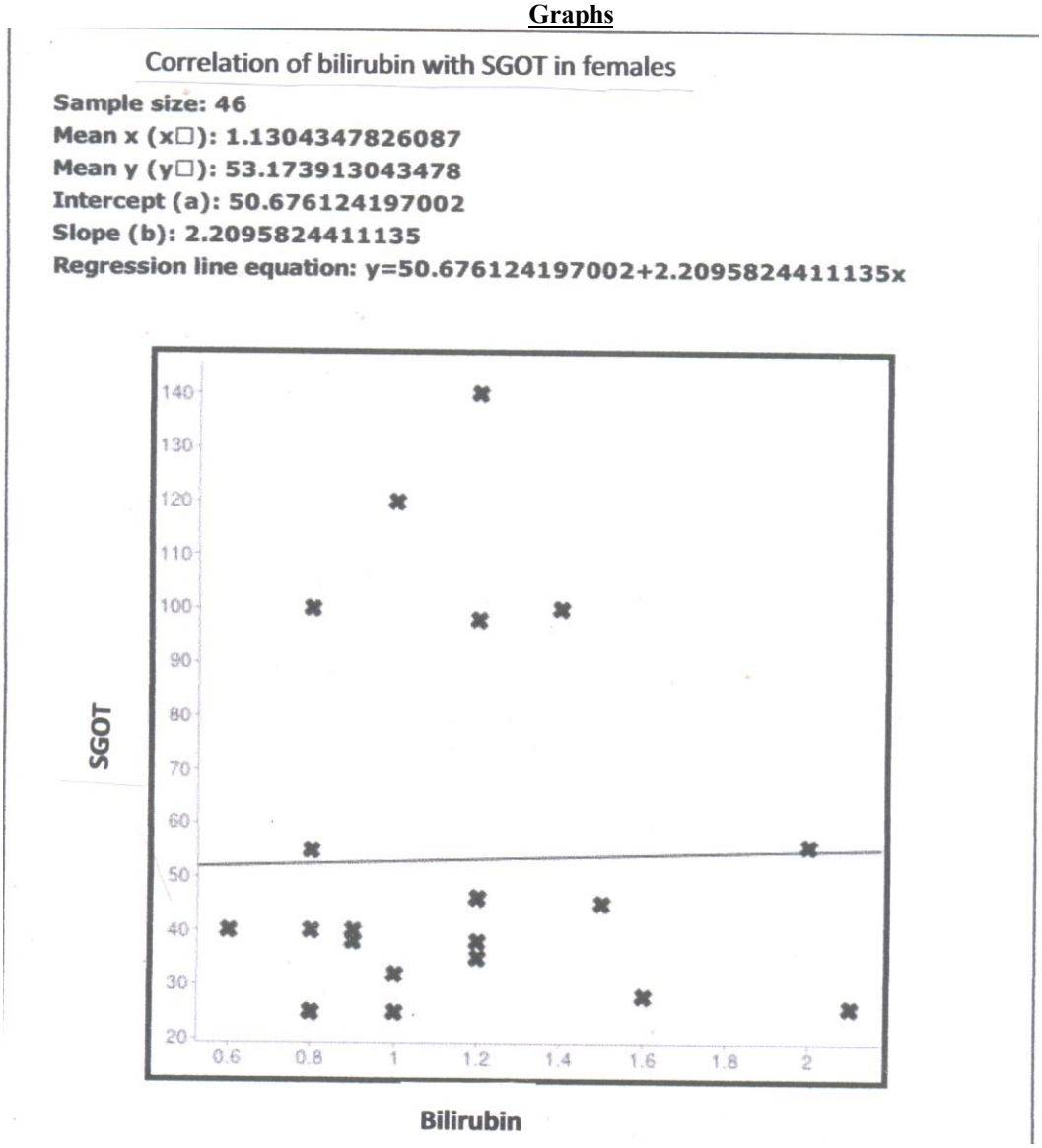
* = p<0.05, **= p<0.001

Table 3: Correlation coefficient (r) of hemoglobin with biochemical parameters in Plasmodium falciparum affected males and females:

Biochemical parameters	Females	Males
SGOT	0.3311	0.1230
SGPT	0.529*	-0.0761

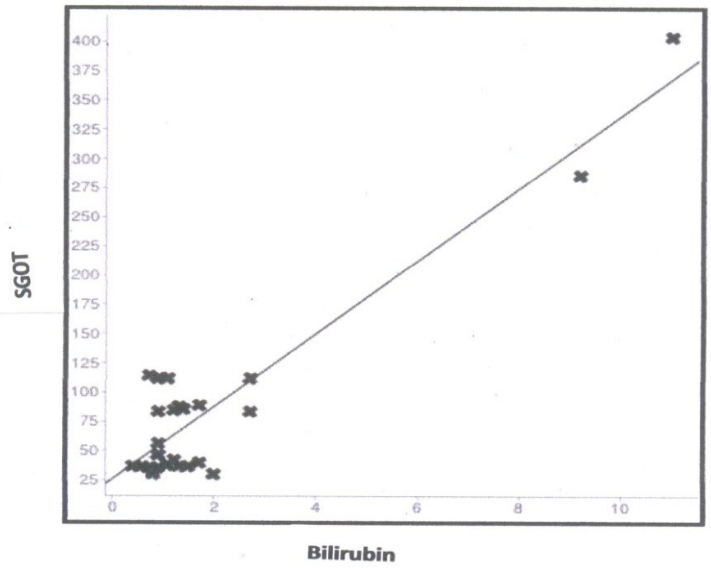
*= p<0.05

Graphs



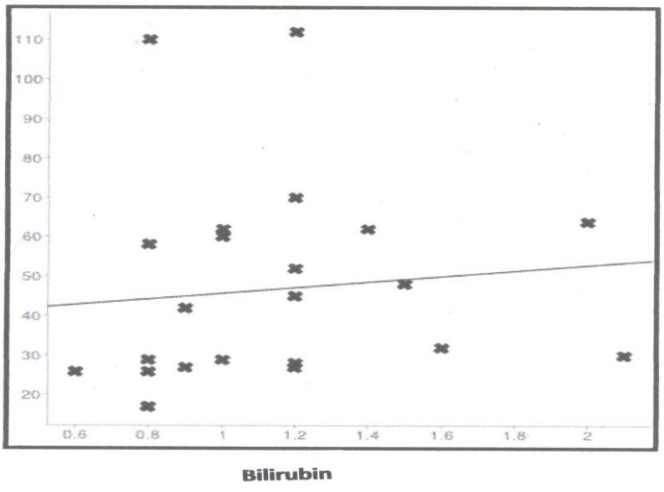
Correlation of bilirubin with SGOT in males

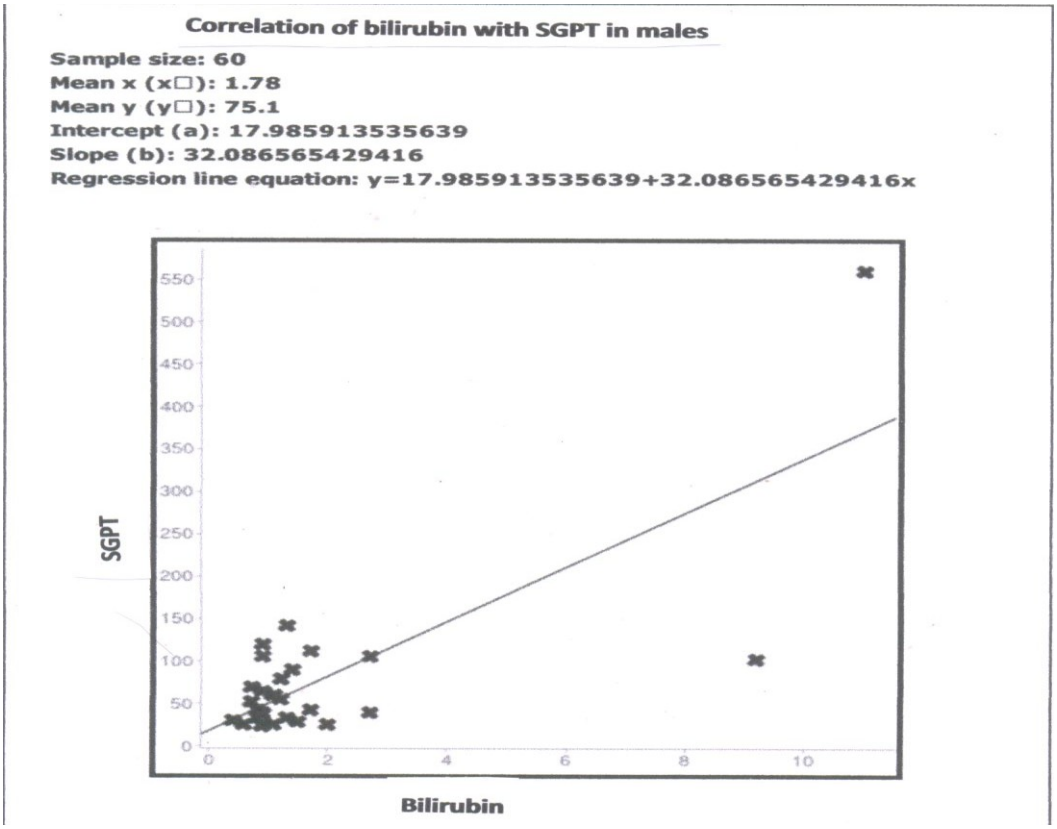
Sample size: 60
Mean x (x□): 1.78
Mean y (y□): 80.966666666667
Intercept (a): 25.519826330108
Slope (b): 31.149910301438
Regression line equation: y=25.519826330108+31.149910301438x



Correlation of bilirubin with SGPT in females

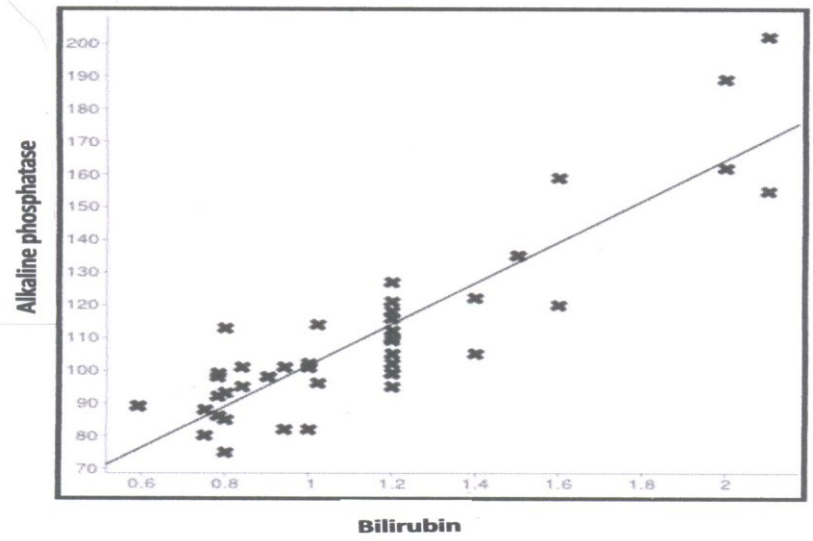
Sample size: 46
Mean x (x□): 1.1304347826087
Mean y (y□): 46.652173913043
Intercept (a): 38.59903640257
Slope (b): 7.1239293361884
Regression line equation: y=38.59903640257+7.1239293361884x




Correlation of bilirubin with SGPT in males
Sample size: 60
Mean x (x□): 1.78
Mean y (y□): 75.1
Intercept (a): 17.985913535639
Slope (b): 32.086565429416
Regression line equation: y=17.985913535639+32.086565429416x
SGPT
Bilirubin
0
50
100
150
200
250
300
350
400
450
500
550
0
2
4
6
8
10

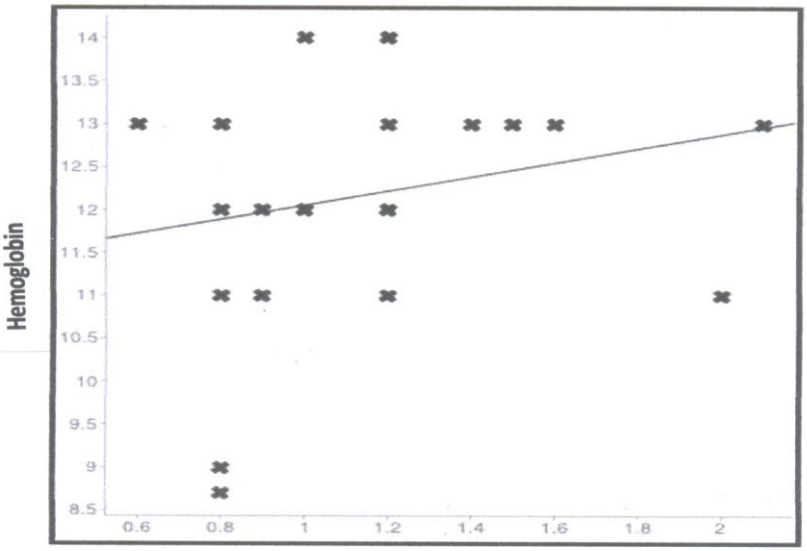
Correlation of bilirubin with alkaline phosphatase in females

Sample size: 46
Mean x (x□): 1.1304347826087
Mean y (y□): 109.89130434783
Intercept (a): 38.847407122284
Slope (b): 62.846524468749
Regression line equation: y=38.847407122284+62.846524468749x



Correlation of bilirubin with hemoglobin in females

Sample size: 46
Mean x (x□): 1.1304347826087
Mean y (y□): 12.160869565217
Intercept (a): 11.229229122056
Slope (b): 0.82414346895074
Regression line equation: y=11.229229122056+0.82414346895074x



Correlation of bilirubin with hemoglobin in males

Sample size: 60
Mean x (x□): 1.78
Mean y (y□): 12.033333333333
Intercept (a): 12.273728007007
Slope (b): -0.13505318745736
Regression line equation: y=12.273728007007-0.13505318745736x