

Clinical and Biochemical Profile and Outcome in Scrub Typhus Positive Patients

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Abstract: **Introduction:** Scrub typhus (*Tsutsugamushi* disease) is an acute (<2 weeks duration), febrile, and infectious illness caused by *Orientia tsutsugamushi* and transmitted by chiggers. The disease is endemic in South Asia, with reports of re-emergence from various regions in India. The present study aimed to study the clinical and biochemical profile, and outcome in cases of scrub typhus. **Methodology:** This hospital-based observational study included 240 patients of age 17 years and above with acute febrile illness with <2 weeks' duration with or without altered sensorium were included in the study. Clinico-demographical, and biochemical parameters, along with outcomes, were recorded. **Results:** Out of 240 patients, 89 (35.08%) were confirmed to have scrub typhus. Most of them were females (51.69%) and belonged to the lower class (34.83%). Fever of >1 week (86.52%), altered sensorium (43.82%), and icterus (59.55%) were the predominant clinical features. Hepatomegaly and splenomegaly were also reported. Diabetes (n=7) and hypertension (n=5) were the common comorbidities. The majority of the patients (n=41) had GCS of 11-15, of which 100% were survivors. Mortality (73.34%) was significantly found in those with GCS 3-6. Overall, the fatality was 14.60%. A significant difference was noted in haematological parameters. The majority of the non-survivors had total serum bilirubin >3mg/dl (n=6), creatinine >3mg/dl (n=8). A significantly negative correlation was also noted between Outcomes and serum creatinine ($r = -0.3569$). Furthermore, the sensitivity (69.23%) and specificity (59.21%) at a cut-off value of Serum Creatinine < 1.395 was observed with a maximum Likelihood ratio of 1.967. **Conclusion:** According to the results of the present study, TLC, serum creatinine, platelet counts, and total serum bilirubin can be utilized to predict fatality.

Keywords: Scrub Typhus, Febrile illness, Splenomegaly, Platelet count, Mortality

1. Introduction

Scrub typhus (*Tsutsugamushi* disease) is an acute (<2 weeks duration), febrile, and infectious illness caused by *Orientia tsutsugamushi* and transmitted by chiggers. The disease is endemic in South Asia, with reports of re-emergence from various regions in India. Clinically it presents as a nonspecific febrile illness with constitutional symptoms of fever, rash, myalgias, headache or gastrointestinal symptoms, regional lymphadenopathy, and maculopapular rash. Life-threatening complications may develop with multiorgan dysfunction. It is transmitted to humans by an arthropod vector of the Trombiculidae family. "tsutsuga" means small and dangerous and "mushi" means insect or mite. It affects people of all ages, including children. Humans are accidental hosts in this zoonotic disease. While scrub typhus is confined geographically to the Asia-Pacific region, a billion people are at risk. And nearly a million cases are reported every year. [1] Scrub typhus was first described in Japan in 1899. It was a myriad disease in the drug-resistant era and an important disease that affected nearly thousands of soldiers in the Far East during the second world war. [2] In India, scrub typhus broke out in an epidemic form in Assam and West Bengal during the second world war. Later, this disease is found throughout India in humans, trombiculid mites, and rodents. [3] The term "scrub" is used because of the type of vegetation (terrain between woods and clearings) that harbours the vector. The word "typhus" is derived from the Greek word "typhus" which means fever, stupor, or smoke. [4] If the diagnosis is delayed, the patient is not treated with appropriate antibiotics, the scrub typhus can present with serious complications such as renal failure, myocarditis, septic

shock and meningitis. We aimed to study the clinical profile, biochemical profile and outcome in scrub typhus-positive patients admitted to BRD Medical College, Gorakhpur, Uttar Pradesh.

2. Material and Methods

This cross-sectional, observational study was conducted in December 2021 - December 2022 in the Department of Medicine, B R D Medical College Gorakhpur, Uttar Pradesh, India. Total of 240 adult patients who presented with acute febrile illness with <2 weeks' duration with or without altered sensorium were included. Of these, 89 (35.08%) were diagnosed with scrub typhus and were analysed in this study. We excluded patients of age less than 17 years, those with a duration of fever more than 2 weeks, those who were positive for other aetiologies like JE, dengue, malaria, patients with a prior chronic disease like CKD, CLD, Malignancies and who did not give consent. Detailed patient history and examinations were recorded in a predefined proforma. Every patient was subjected to relevant Blood investigations. Lumbar puncture was done either in cases turning to altered sensorium or presented with altered sensorium, and CSF was analyzed for cytology, biochemical, IgM antibodies against JE virus, scrub typhus, anti-HSV1/2 fast ELISA. Non-contrast and contrast-enhanced computed tomography and MRI scan of the brain was done in selected patients if indicated. The outcome was analysed based on whether the patient was improved, discharged, or expired.

Statistical Analysis:

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Statistical analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA) for the Windows program (15.0 version). The continuous variables were evaluated by mean (standard deviation) or range value when required. The dichotomous variables were presented in number/frequency and were analyzed using Chi - square test. For comparison of the means between the two groups, analysis by Mann - Whitney U test was used. Correlation analysis was done using Spearman correlation test. With 95% confidence interval, a p - value of < 0.05 or 0.001 was considered significant.

3. Results

The mean age of survivors was comparable to that of non - survivors [32.66±12.41] and non - survivors [34.41±11.89]. There was no significant difference in the demographic profile between survivors and non - survivors. [Table - 1; Figure - 1] The most common clinical manifestations were fever lasting over a week (86.52%), altered sensorium (43.82%), and icterus (59.55%). There were also reports of hepatomegaly 1 (1.12%) and splenomegaly 1 (1.12%). TB (n=2), diabetes (n=7), and hypertension (n=5) were the most prevalent comorbidities. 20.22 % of the patients had general body swelling. A significant difference was observed between all patients and those with altered sensorium in terms of their seizure history. [Table - 2] Mortality was significantly found in those who had GCS 3 - 6 (73.34%), BP <60mmHg (57.14%), TLC level >14, 000cell/ccmm (53.85%), serum creatinine level >3mg/dl (47.06%) and serum bilirubin >3mg/dl (54.55%). [Table - 3] The mean platelet count was higher in survivors [54018±21113] than in non - survivors [17245±14182]. The mean Serum glutamic oxaloacetic transaminase was higher in non - survivors [239.1±161.4] than in survivors [198.4±121.2]. The mean Serum glutamic pyruvic transaminase was higher in non - survivors [185.4 ±123.8] than in the survivor group [149.4±87.12]. Overall, the fatality rate was 14.60%. Analyzing the correlation between Outcome and LFT parameters (S. Creatinine/ S. Bilirubin/SGOT/SGPT), a statistically non - significant negative correlation was observed, except for the serum creatinine [p=0.0006*; r= - 0.3569]. [Table - 4; Figure - 2] The Receiver Operating characteristic (ROC) curve was analyzed for Serum Creatinine, showed an area under the curve of 0.7910 at a 95% confidence interval and was found to be significant [p=0.0008*]. [Table - 5; Figure - 3] Furthermore, at a cut - off value of < 1.395, the sensitivity and specificity of serum creatinine were 69.23% and 59.21%, respectively, with a maximum Likelihood ratio of 1.967.

4. Discussion

In our study, Scrub typhus was found in 35.08% of all individuals with an acute febrile illness (89 out of 240). This is slightly higher than the occurrences recorded in another Indian research [5, 6], which ranged from 8.6% to 24%. However, in a community - based study from Vellore, South India, its frequency was shown to be as high as 31.8 per cent. Thapa S et al. [7] and Takhar RP et al. [8] found an incidence of 29.2% and 22.8% among enrolled patients, respectively. The average age of all patients in this study was 33.97±12.53 years, with survivors being [32.66±12.41]

and non - survivors being [34.41±11.89]. This is comparable to the mean ages reported by Varghese GM et al. [9] from Vellore, Jacob et al. [10] from Chennai, and Sivarajan et al. [11] from Chennai, India, which were 36.5, 30 and 39.6 years old, respectively. In this study, age is not a significant predictor of death (p=0.6377). However, mortality was higher (4 out of 13) in the 30-40 - year age group, and mortality was higher in females (8 out of 13). As a result, women have a greater mortality rate than men in the same age group; however, this difference was minor in our study. Scrub typhus was shown to be frequent among people aged 51 - 60 in a study by Thapa S et al. [7]. Furthermore, Takhar RP et al. [8] showed that the most common age group for scrub typhus was 20 - 50 years old (48 out of 66). On the contrary, Rajoor et al. [12] showed that men were more affected. This is most likely because men in various regions tend to go to cities for jobs while women do not. According to Ogawa et al. [13], age and gender influence the prevalence of scrub typhus. However, Narvencar et al. [14] did not mention a sex predilection. In the present study, the majority of the patients (34.83%) belonged to the lower socioeconomic class, and the majority were literate (76 out of 89). According to other studies, the majority of patients (37.8%) (80.3%) and (21.1%) were farmers. Among non - survivors (n=13), patients who reported with fever within one week had a more aggressive course of the disease and higher mortality (p<0.0001*) than those who had a fever for more than one week. Fever was the most common clinical symptom (100%) in all scrub typhus cases. [15, 16] Other clinical characteristics such as icterus (p=0.4725), altered sensorium (p=0.4305), and anasarca (p=0.3057) were inconsequential in terms of mortality, although Glasgow coma scale (p<0.0001), seizure (p<0.0001*), splenomegaly (p=0.0150*), hepatomegaly (p=0.0150*), and history of seizures in patients of altered sensorium (p=0.0012) were significant. Patients were examined for comorbidities, and it was observed that the majority of them (7.87%) had diabetes mellitus, followed by hypertension (5.62%) and tuberculosis (2.25%), and the mortality rate was significantly higher in those with comorbidities. Similarly, Varghese GM et al. [9] identified diabetes mellitus as a concomitant disease in scrub patients, followed by hypertension, COPD, and chronic renal failure. Diabetes mellitus was the most common comorbidity, affecting 7.87% (n=7) of the patients in the current study. Five (71.43%) of them were expired. In contrast, Attur et al. [17] and Kumar et al. [18] found a greater incidence of AKI in scrub typhus patients (23.2% and 53%, respectively). However, no individuals in their research needed dialysis. According to Narvencar et al. [14], hepatic dysfunction is the most common, followed by ARDS, circulatory collapse, and acute renal failure. Moreover, Takhar RP et al. [8] showed respiratory dysfunction in more than two - thirds of patients, followed by renal failure in more than half. When the clinical findings of scrub patients from survivor and non - survivor groups were compared, there was no substantial difference in SpO2 (p=0.7541), blood pressure (p=0.2543) and ventilation (p=0.1470). In the current study, 16.85% (n=15) of scrub patients required ventilation; out of these 15 patients, 4 could not survive. Similarly, Takhar RP et al. [8] reported that 46 (69.7%) of the patients required ventilation, 18 needed dialysis, and the overall fatality rate was 14 (21.2%). However, the number of patients who required ventilation

was higher than in the current study. Furthermore, Sivarajan S et al. [11] documented the 5 patients that required ventilation. Two of them survived mechanical ventilation, but the other three expired. In 65/82 (79.3%) patients, invasive or non - invasive ventilation was required. Dialysis was required for nine individuals (11.1%). Twenty (23.8%) of the patients died. [19] On the other hand, Kim DM et al. [20] observed that just one patient died of scrub typhus and that no one required ventilator or renal replacement treatment. When the biochemical parameters of scrub patients from survivors and non - survivors were compared, there was no substantial difference in Hb% ($p=0.6209$), SGOT ($p=0.2905$), SGPT ($p=0.2008$). Non - survivors had significantly higher TLC ($p<0.0001^*$), serum creatinine ($p<0.0001^*$), total serum bilirubin ($p<0.0001^*$), and a significantly lower platelet count ($p =0.0001^*$), was observed in non - survivors. Thapa S et al. [7] found thrombocytopenia, decreased haemoglobin levels, leukocytosis, and leucopenia. A higher level of transaminase enzymes (SGPT and SGOT), as well as serum bilirubin and creatinine. All patients had higher SGOT levels [239.1±161.4] than SGPT levels [185.4 ±123.8]. In our study, the expired patients had higher SGOT and SGPT levels than survivors. These findings were consistent with the current study and many other investigations. [21, 22] Other studies have found a correlation between outcomes and serum creatinine. [23, 24] Although prior research has found risk factors for serious diseases such as altered sensorium, hypoalbuminemia, anaemia, hepatic dysfunction, and hypotension, the current study failed to substantiate that these variables have a significant impact. [5, 6] Serum creatinine, total serum bilirubin, platelet counts, and TLC count were strongly correlated with scrub patient outcomes in this study. On the contrary, investigations have shown that a haemoglobin level of 12 g/dL, a WBC count of more than 10, 000/mm³, a platelet count of 150 000/mm³, and the absence of eschar are all independent predictors of illness severity in scrub typhus. [19, 24] Thus, the current study finds that the total fatality was 14.60%, and TLC, serum creatinine, platelet counts, and total serum bilirubin can be utilized to predict fatality. It also appears that a few host and agent factors act aggressively.

5. Conclusion

Based on the findings of this study, it was observed that higher level of serum creatinine, total serum bilirubin, TLC, thrombocytopenia, history of seizures, duration of fever <1week, GCS<6, presence of comorbidities (diabetes, hypertension, TB) were valuable parametersto the impending fatal outcomes. However, the current study's drawbacks were the limited sample size and single - centric study. Thus, we suggest a multicenter investigation with a larger sample size to improve the reliability and generalizability of the study findings.

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Consent:

As per international or university standards, the authors have collected and preserved written participant consent.

Ethical Approval:

As per international or university standards, the author (s) has collected and preserved written ethical permission.

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Tables and Figures

Table 1: Demographic parameters of enrolled patients

		Scrub Patients						P value
		Total [n=89]		Survivors [n=76]		Non Survivors [n=13]		
		N	%	N	%	N	%	
Age Distributions	10 - 20	19	21.35%	17	89.47%	2	10.53%	X=4.552 p=0.6024
	20 - 30	29	32.58%	27	93.10%	2	6.90%	
	30 - 40	20	22.47%	16	80.00%	4	20.00%	
	40 - 50	11	12.36%	8	72.73%	3	27.27%	
	50 - 60	6	6.74%	5	83.33%	1	16.67%	
	60 - 70	3	3.37%	2	66.67%	1	33.33%	
	70 - 80	1	1.12%	1	100.00%	0	0.00%	
Socioeconomic Status	Upper Class	5	5.62%	4	80.00%	1	20.00%	X=2.689 p=0.6111
	Upper Middle	11	12.36%	9	81.82%	2	18.18%	
	Lower Middle	18	20.22%	15	83.33%	3	16.67%	
	Upper Lower	24	26.97%	19	79.17%	5	20.83%	
	Lower	31	34.83%	29	93.55%	2	6.45%	
Education Status	Illiterate	13	14.61%	9	69.23%	4	30.77%	X=6.000 p=0.3062
	Primary	6	6.74%	5	83.33%	1	16.67%	
	High School	26	29.21%	24	92.31%	2	7.69%	
	Intermediate	9	10.11%	8	88.89%	1	11.11%	
	Undergraduate	33	37.08%	29	87.88%	4	12.12%	
	Postgraduate	2	2.25%	1	50.00%	1	50.00%	

Table 2: Clinical parameters of enrolled patients

Fever History				
	Total [n=89]	Survivors [n=76]	Non Survivors [n=13]	P value
Fever < 1wk	12 (13.48%)	2 (16.67%)	10 (83.33%)	X=55.52 p<0.0001*
Fever > 1wk	77 (86.52%)	74 (96.10%)	3 (3.90%)	
COMORBIDITIES				
Diabetes	7 (50.00%)	2 (28.57%)	5 (71.43%)	X=19.67 p<0.0001*
Hypertension	5 (35.71%)	2 (40.00%)	3 (60.00%)	X=8.752 p=0.0031*
TB	2 (14.29%)	0 (0.00%)	2 (100.00%)	X=11.96

Without Comorbidities	75 (84.27%)	72 (96.00%)	3 (4.00%)	p=0.0005* X=43.00 p<0.0001*
SPLENOMEGALY				
Absent	88 (98.88%)	76 (86.36%)	12 (13.64%)	X=5.913
Present	1 (1.12%)	0 (0.00%)	1 (100.00%)	p=0.0150*
HEPATOMEGALY				
Absent	88 (98.88%)	76 (86.36%)	12 (13.64%)	X=5.913
Present	1 (1.12%)	0 (0.00%)	1 (100.00%)	p=0.0150*
GENERAL BODY SWELLING				
Absent	71 (79.78%)	62 (87.32%)	9 (12.68%)	X=1.049
Present	18 (20.22%)	14 (77.78%)	4 (22.22%)	P=0.3057
ICTERUS				
Absent	36 (40.45%)	32 (88.89%)	4 (11.11%)	X=0.5162
Present	53 (59.55%)	44 (83.02%)	9 (16.98%)	p=0.4725
ALTERED SENSORIUM				
Absent	50 (56.18%)	44 (88.00%)	6 (12.00%)	X=0.6216
Present	39 (43.82%)	32 (82.05%)	7 (17.95%)	p=0.4305
H/O SEIZURE				
Yes	18 (20.22%)	8 (44.44%)	10 (55.56%)	X=30.33
No	71 (79.78%)	68 (95.77%)	3 (4.23%)	p<0.0001*
H/O Seizure in patients of Altered Sensorium				
Yes	13 (33.33%)	7 (21.88%)	6 (85.71%)	X=10.53
No	26 (66.67%)	25 (78.13%)	1 (14.29%)	p=0.0012*
GCS				
3 - 6	15 (16.85%)	4 (26.66%)	11 (73.34%)	X=50.42
7 - 10	33 (37.08%)	31 (93.94%)	2 (6.06%)	p<0.0001*
11 - 15	41 (46.07%)	41 (100%)	0 (0.00%)	
Blood Pressure				
<60 mmHg	14 (15.73%)	6 (42.85%)	8 (57.14%)	X=24.12
60 - 90 mmHg	57 (64.04%)	53 (92.98%)	4 (7.02%)	p<0.0001*
>90 mmHg	18 (20.22%)	17 (94.44%)	1 (5.55%)	
SPO2				
<90	9 (10.11%)	8 (88.89%)	1 (11.11%)	X=0.09809
>90	80 (89.89%)	68 (85.00%)	12 (15.00%)	p=0.7541
ON VENTILATION				
YES	15 (16.85%)	11 (73.33%)	4 (26.67%)	X=2.104
NO	74 (83.15%)	65 (87.84%)	9 (12.16%)	p=0.1470

Table 3: Biochemical parameters of enrolled patients

		Total [n=89]		Survivors [n=76]		Non - Survivors [n=13]		P - Value
		N	%	N	%	N	%	
Haemoglobin	<6	11	12.36%	10	90.91%	1	9.09%	X=0.9531 P=0.6209
	6 - 10	19	21.35%	15	78.95%	4	21.05%	
	>10	59	66.29%	51	86.44%	8	13.56%	
Total Leukocyte Count	<10,000	46	51.69%	43	93.48%	3	6.52%	X=18.97 p<0.0001*
	10,000 - 14,000	30	33.71%	27	90.00%	3	10.00%	
	>14,000	13	14.61%	6	46.15%	7	53.85%	
Serum Creatinine	<1	46	51.69%	44	95.65%	2	4.35%	X=18.43 p<0.0001*
	1 - 3	26	29.21%	23	88.46%	3	11.54%	
	>3	17	19.10%	9	52.94%	8	47.06%	
Serum Bilirubin	<1	62	69.66%	59	95.16%	3	4.84%	X=20.20 p<0.0001*
	1 - 3	16	17.98%	12	75.00%	4	25.00%	
	>3	11	12.36%	5	45.45%	6	54.55%	

Table 4: Correlational analysis of Outcome versus LFT parameters

Outcome VS.	Spearman r	95% confidence interval	P - value
S. Creatinine	- 0.3569	- 0.5306 to 0.1545	0.0006*
S. Bilirubin	- 0.1238	- 0.3293 to 0.0928	0.2475
SGOT	- 0.1368	- 0.3411 to 0.0797	0.2010
SGPT	- 0.01115	- 0.2248 to 0.2036	0.9174

Table 5: ROC cut - off of S. Creatinine between survivors and non - survivors

ROC ANALYSIS	
AUC	0.7910
Std. Error	0.08150
95% confidence interval	0.6312 to 0.9507
P - value	0.0008*
Cut - off	1.395
Sensitivity	69.23%
95% confidence interval	42.37% to 87.32%
Specificity	59.21
95% confidence interval	47.98% to 69.56%
Likelihood ratio	1.697

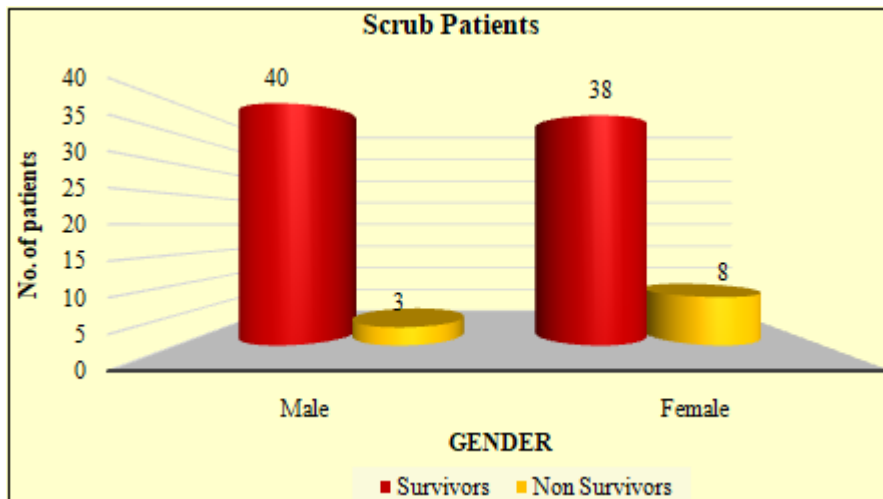


Figure 1: Gender - wise distribution of the enrolled patients

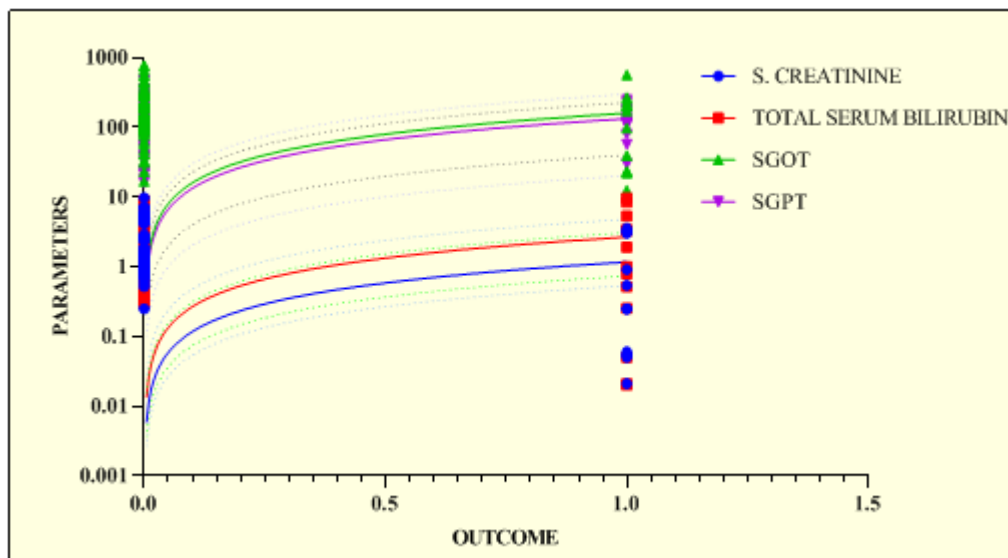


Figure 2: Spearman Correlational analysis of Outcome versus S. Creatinine/S. Bilirubin/SGOT/SGPT

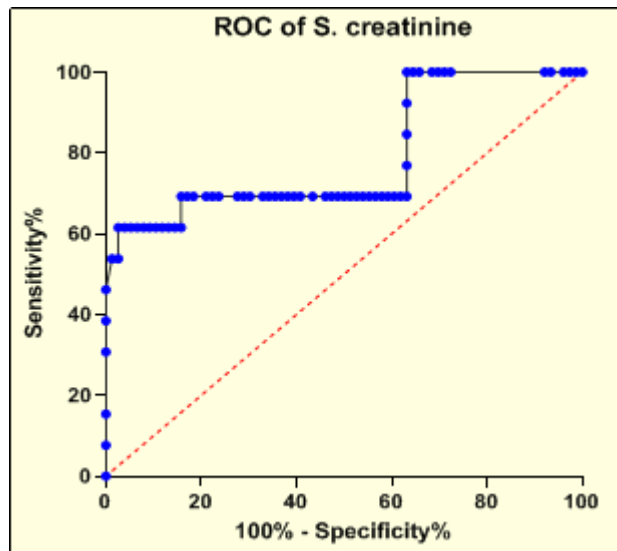


Figure 3: ROC Curve of Serum Creatinine between survivors and non - survivors.