ORIGINAL RESEARCH PAPER

Haematology

A PROSPECTIVE STUDY TO EVALUATE THE IMPACT OF BLOOD TRANSFUSION AMONG THALASSEMIA MAJOR PATIENTS IN A TERTIARY CARE CENTRE

KEY WORDS:

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Introduction-

In contemporary medicine, the transfusion of blood and other components has become crucial to patient care(1). Karl Landsteiner's discovery of the ABO blood type system significantly decreased the mortality brought on by blood transfusions(2). As a result, the blood transfusion services have a crucial role to play in making sure there is an adequate supply of high-quality, secure blood. Support for blood transfusions is essential for the treatment of individuals with hematologic diseases and cancers. Such patients frequently need blood transfusions throughout their sickness, or maybe their whole lives(1).

Thalassemia, whose name means "sea," is said to have its roots in the vicinity of the Mediterranean, according to historical theory(3).In more than 60 countries around the world, thalassemia is a significant public health issue.Thalassemia refers to a group of disorders of globin chain production in which there is an imbalance between the -globin and -globin chains, which results in a relative excess of the -globin chain. Alpha and beta thalassemia are its two types and are both inherited in an autosomal recessive fashion(3).In order for a child to be affected by the autosomal recessive variants of the illness, both of the parents must be carriers. An affected child has a 25% chance of being born if both parents have the hemoglobinopathy trait. Families carrying a thalassemia trait are advised to get genetic counselling and testing(3).In conformity with WHO in India, the prevalence of thalassemia carriers is on average 3.3 %.With an estimated incidence of 2 per 1,000 births and a carrier frequency of 3–4 %, beta-thalassemia poses a serious health burden in India, where there are an estimated 65,000–67,000 individuals. Every year, 9,000–10,000 new cases are reported(4). Madhya Pradesh has a high incidence of the -Thalassemia trait (20.70 %)(5).

There are many degrees of the disease's severity, ranging from thalassemia major, the severe form in which the patient requires regular blood transfusions to survive through thalassemia minor, and an asymptomatic carrier status, with patients with thalassemia intermedia in between(3).The protein that carries oxygen in red blood cells is called haemoglobin. Anaemia can be minor or severe in thalassemia patients because they produce less haemoglobin and circulating red blood cells than is typical. Microcytic anaemia, which distinguishes thalassemia from iron deficiency anaemia, is a symptom of the disease(3).Blood transfusion therapy and iron chelation are the cornerstones in management of thalassemia. Transfusion-dependent and non-transfusion-dependent -thalassaemia are the two main categories of -thalassaemia based on the need for red blood cell transfusions. Patients with transfusion-dependent -thalassaemia, including severe haemoglobin E (HbE) -thalassaemia, need regular blood transfusions 2–5 times per week for the rest of their lives. Patients with non-transfusion-dependent -thalassaemia, such as those with mild to moderate HbE -thalassaemia and -thalassaemia intermedia, on the other hand, only occasionally need blood transfusions(6).Although this comes with a number of complications, such as hemosiderosis, transfusion responses, alloimmunization, and infections. Due to the rarity with which these incidents are recorded and gathered, knowledge of additional transfusion-related consequences such allergy and haemolytic responses is equally limited. The population with thalassemia, which has thehighest transfusion exposure carry risks of iron excess that can cause endocrine dysfunction as well as the possibility of contracting a transfusion-transmitted infection(7).The patient needs to be monitored often for iron level measurements, and iron chelation therapy needs to be initiated when the levels rise(8).Among people with thalassemia major who get several blood transfusions, the three most prevalent chronic viral pathogens are hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV). Coinfection is another highly prevalent condition that has a negative impact on survival(9).Despite the significant burden of thalassemia in India, testing for transfusion-transmitted diseases is unsatisfactory and poorly regulated in the majority of blood banks, both private and public, across the country. As a result, individuals with thalassemia who get numerous blood transfusions continue to be at risk of infectious agent transmission. It is imperative to investigate the prevalence of transfusion-mediated illnesses among these patients. So present study was conducted in a tertiary care centre to study the clinical and laboratory profile along with sero-prevalence of blood borne infections among thalassemia major patients receiving multiple blood transfusion.

Aim-

To study clinical, laboratory and pathological profile along with sero-prevalence of blood borne infections among thalassemia major patients receiving multiple blood transfusion in a tertiary care centre

Objectives-

1. To study clinical and laboratory profile among thalassemia major patients receiving multiple blood transfusion in a tertiary care centre

2.To determine the sero-prevalence of blood borne infections among thalassemia major patients receiving multiple blood transfusion.

Material and Methods-
Study Design- A descriptive observational study

Study Period- one and half years

Sampling Method and size- Allthalassemia major patients receiving multiple blood transfusion during the study period. Sample size came to 125.

Inclusion Criteria-
1. Allthalassemia major patients receiving multiple blood transfusion.
2.Thalassemia patient who consent to participate in the study.

Exclusion Criteria-
1. Multiple congenital anomalies among with thalassemia major.
2. Coexisting cardiac and pulmonary disease.
3.Thalassemia Minor
4. Chronic haemolytic anaemia, other than -Thalassemia major

Data Collection-
1. A preformed and pre-checked proforma was used for data collection that included personal information, data regarding the number of transfusions and pre-transfusion haemoglobin and serum ferritin, at what dose of chelators they were with clinical examination finding and laboratory investigation reports.

2. The current study has collected the data by using predesigned and pretested proforma which was fulfilling the objective of the study.

3.A unique ID was given to each patient.

4. A detailed history of all the registered patients including personal data, history of consanguineous marriage, nutrition, frequency of transfusion, use of iron-chelating agent including dose, duration and compliance).

5. A thorough physical examination was performed including anthropometry, general examination and systemic examination and was recorded in the proforma.

6. The serum ferritin level was measured in all Thalassemia patients.

7. Iron chelating agents were advised to all patients with serum ferritin level above 1000 ng/ml.

8. Haemoglobin was measured before transfusion by Sahli's method.

9. Blood group cross-matching was done by blood typing. Standard references were used.

10. Serum and Plasma Samples- Serum and Plasma samples. Blood sample of all the patients was collected in 2 ml EDTA and plain tubes; plasma and serum were separated by centrifugation at room temperature, labelled appropriately in two aliquots, and stored at -30°C in a deep freezer, till the tests for TTI serology as well as NAT was performed.

11. Serological assays- All the serum samples of 196 patients were screened for anti-HIV-1/2, HBsAg, and ant-HCV using third-generation ELISA kits. For anti-HCV, SD HCV ELISA 3.0 test system (Boi SD standard diagnosis Pvt. Ltd, India); for anti-HIV-1/2, Microlisa (J. Mitra& Co. Pvt. Ltd, India) and for HBsAg, SD HBV ELISA 3.0 test system (Boi SD standard diagnosis Pvt. Ltd, India) was used.

12. NAT- All plasma samples of 125 patients were screened for research purposes for the viral genome of HBV, HCV, and HIV-1 with a commercially available RT-PCR kit (Altona Diagnostics GmbH, Germany). The PCR was performed on an ABI Prism 7500 Real-Time PCR System (Thermo Fisher, USA)

- Extraction of the viral genome: HBV-DNA, HCV-RNA, and HIV-1 RNA were extracted from plasma samples with the use of ChemagicPrepito-D automated nucleic acid extractor (PerkinElmer, USA), in combination with reagents/buffers of the Prepito Viral DNA/RNA Kit.
- Amplification of viral genome by Real-Time-PCR: HBV-DNA and HIV and HCV-RNA were amplified by Real Star HBV PCR Kit 1.0, Real Star HCV RT-PCR Kit 1.0, and Real-Star HIV RT-PCR Kit 1.0 (Altona Diagnostics GmbH, Germany) as described in the manufacturer's protocol. The PCR was performed on an ABI Prism 7500 Real-Time PCR System (Thermo Fisher, USA).

Bias-As the present study was conducted in a medical college hospital, the result observed are subject to bias arising from rate of reporting at the hospital (Berksonian Bias).

Data Management-Data was collected and entered simultaneously in statistical package for social sciences (SPSS) version 23 and coded appropriately. Descriptive statistics were calculated to summarize the sample characteristics in terms of frequency and percentage. Analytical and inferential analysis was applied between dependent variable and other independent variables. Significance was set at standard 0.05.

Discussion-
One of the biggest issues with public health in India is beta-thalassemia. Between 3 and 17% of Indians have the thalassemia trait on average. In India, there are thought to be 65,000–67,000 beta-thalassemia patients, and there are an estimated 9,000–10,000 new cases every year(10).

Age and Gender-
The bulk of our patients are still young, despite the fact that the advancements made in thalassemia management have extended the life expectancy of thalassemic patients. In present study mean age of the study participants was 14 years and majority of the study participants were in the age group of 11-15 years (41.6%), followed by 30% participants of more than 15 years of age. Ragab et al(11) in their study reported that 66.8% of the study participants were younger than 12 years of age.

Beta thalassemia affect male and females equally but in present study, male preponderance was seen (62.4%). Similar results were reported by Sharma et al(12), where male preponderance was seen with 66.34% males. Similar results were reported by Ragab et al(11).

Religion and Consanguinity-
Majority of the study participants in our study were Hindu by religion. Although they are in the minority in India, Muslims and Sindhis make up a significant portion of thalassemic patients, accounting for 29.6% (37/1125) and 8.8% (11/125) respectively. Similar results were reported by Shah et al(13), where 20% of the study participants were Muslims and 16% were Sindhis. Consanguinity was discovered in a large percentage of the parents of the patients, or 22/125 or 17.6%, which is consistent with the inheritance pattern of autosomal recessive disorders (beta-thalassemia major being one such disease).Similar results were reported by Shah et al(13), where 12% pf the parents of the patients had consanguineous marriage.

Growth Retardation

In present study, majority of the study participant had varying degrees of growth retardation. 16.8% had weight for age <1SD, 57.6% had weight for age < 2SD and 20% had weight for age < 3 SD. Sharma S et al(12)in their study also reported that 17.64% of the study participants were underweight. Shah et al(13), in their study reported, out of the 142 patients, 103 (72%) were under 2 SD of ICMR 1990 weight for age standards (80% of W/A), and 76 (53%) were under 2 SD of ICMR 1990 height for age standards (90% of H/A). In contrast, 63 (44%) were stunted and wasted, lagging behind in both W/A and H/A. Due to insufficient chelation and excessive ferritin levels, a large percentage of patients exhibit growth retardation, which may be caused by iron accumulation in the pituitary gland.

Calcium and phosphorus-

Low bone marrow density and fractures are common in -thalassemia patients, regardless of the specific condition. The present study found 45 cases to have hypophosphatemia which account for 36%, which may be due to renal function derangements and abnormality of bone marrow turnover. Also, 10.4% of the study participants had hypocalcemia, 74% had normal calcium and 15% had hypercalcemia.In present study, hypocalcaemia and hypophosphatemia was seen with children under 8 years of age and also significant association was seen between age group and serum calcium and phosphorus levels.Similar results were reported by Sharma S et al(12), where 38.61% of the study participants had hypophosphatemia. In < 5 years, cases, 40% had low and 60% had a normal level of serum phosphorus. In 6-10years, 90% cases had low, 3.3% cases had high and 6.7% cases had normal serum phosphorus levels. In 11- 15years, 30.8% case had hypophosphatemia, 36.5% cases had high and 32.7%cases had a normal level of Serum Phosphorus. In > 15 years of age, 50% had normal and 50% had increased phosphorus levels.

Renal/Liver function test and serum ferritin-

Renal profile of the patients showed almost of study participants had high levels of urea and creatinine respectively. Though most of the urea and creatinine were only mildly elevated which may be due to chelator therapy in the higher age group. Our results are in line with findings of Sharma et al(12). Liver profile were also deranged among majority of study participants.

Blood transfusion-

There is a direct correlation between the age of thalassemia major patients and the quantity of blood transfusions. The graph shows that as children get older, they will receive an increasing total amount of blood transfusions. As children get older, they also require more blood transfusions each month. Such a relation is expected, as due to worsening of the disease with progression of age, the requirement for blood transfusions will increase. Most patients aged 0–5 years only require blood transfusions once a month, which is sufficient given their age. However, a large portion of patients between the ages of 11-15 years required transfusion twice a month still examining the haemoglobin levels prior to the transfusion, which appears to be insufficient and needs to be reviewed along with other pertinent factors.

Adequacy of chelation-

It is anticipated that serum ferritin levels will be kept within normal ranges under optimum chelation conditions, regardless of the total number of transfusions. Nevertheless, the lack of such a consistent maintenance of serum ferritin levels suggests inconsistent and ineffective chelation methods and/or variable responsiveness to chelation therapy. Dividing those with adequate chelation and those with inadequate chelation by a cut-off value for S. ferritin of 1000 ng/ml(14).61.6% of the study participants were chelated. In present study, only 27/125 (21.6%) of the study participants had serum ferritin <1000 ug/ml. Among those 27 study participants, only 6 (7.7%) were on chelation therapy and 5 out of them were adequately chelated. Shah et al(13) in their study reported that only 9/142 (6.3%) patients had S. ferritin <1000 ng/ml and 7 out of these 9 patients were not taking any chelation. Hence only 2 (1.4%) patients could be considered to be taking adequate chelation therapy

Blood borne infections-

The standard of care for people with beta-thalassemia is to provide regular, safe blood transfusions starting in early childhood, which enhances patients' quality of life and increases their chance of survival. Contrarily, patients receiving blood transfusions run the risk of contracting infections that are spread through blood transfusions (TTIs). The likelihood of contracting TTIs is correlated with the number of transfusions; as a result, the infection rate of TTIs rises with age in following years. As a result, each blood transfusion increases the potential of contracting TTI, and the risk of exposure rises with the number of transfusions(15).

In the present study, seropositivity for TTIs was 30.4% (38/125). HIV seropositivity was 1.6%, HBV was 3.2%, and HCV was 25.6%. Kanchan Mishra et al(16) in their study reported higher prevalence of infections (57%). HIV seropositivity was 3.1%, HBV was 1.5%, and HCV was 51%. Shah et al in their study reported that 45% had HCV positivity, 2% each were positive for HBV and HIV. With age the number of blood transfusions received increases and so does the risk of acquiring TTIs. Graph shows linear relationship between age and TTIs positivity specifically for HCV. Similar results were reported by Shah et al(13) where author reported linear relationship between age and HCV positivity which indicates that the more the age of the patient the more is the chance of him/her being HCV positive.

Summary and Conclusion-

The current study critically analysed the clinico-pathological profile, current transfusion regime, the sufficiency and regularity of the chelation programme, the adverse effects of multiple transfusions on iron accumulation and the resulting harm to various organs, and the prevalence of three major transfusion-associated infections, specifically infections by HIV, HCV, and HBV in thalassemia major patients. HBV, HCV, and HIV pose a serious problem in the care of thalassemia patients despite the routine practises blood banks use to assure blood safety. The chance of HCV infection is still very high. On the other hand, there is a small but constant risk of HBV and HIV infection in thalassemia patients. The incidence of viral hepatitis among patients with thalassemia major may be significantly reduced by administering HBV vaccine along with HCV treatment, in conjunction with sufficient iron chelation, maintaining the immunological status, and monitoring hepatitis indicators. In order to maintain a balance between appropriate transfusion and a minimum of negative effects from repeated transfusions, it is also advised to review and develop a proper transfusion schedule. Patients' chelation regimens should be reviewed on a regular basis. Patients with serum ferritin levels more than 1000 ng/ml who have not yet started a chelation programme urgently need to start one. Multiple transfusions' systemic consequences need to be thoroughly researched.

Funding- No funding sources

Limitations-The study reflects to the findings of a specific geographical area. Also different agents used for chelation were mot studied.

Conflicts of interest- No potential conflict of interest relevant to this article was reported

Ethical approval- Approved

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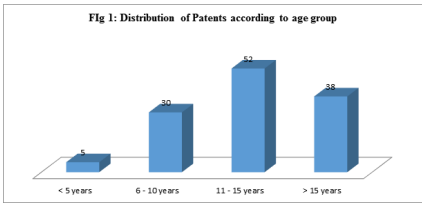
Observation Tables and Graphs:

Table 1: Distribution of Patents according to age group

Age Group	Frequency	Percentage
< 5 years	5	4.0%
6 - 10 years	30	24.0%
11 - 15 years	52	41.6%
> 15 years	38	30.4%
Total	125	100.0%



	Mean	Standard Deviation	Minimum	Maximum
Age	14	6	3	27

Table 2: Distribution of Patents according to Gender

Gender	Frequency	Percentage
Male	78	62.4%
Female	47	37.6%
Total	125	100.0%

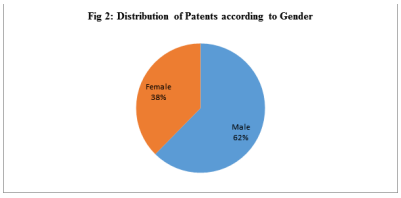


Table 3: Distribution of Patents according to Religion

Religion	Frequency	Percentage
Hindu	77	61.6%
Muslim	37	29.6%
Sindhi	11	8.8%
Total	125	100.0%

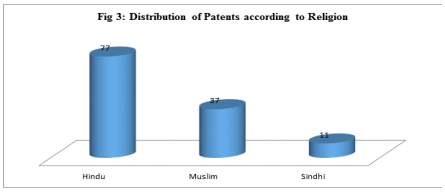


Table 4: Distribution of Patents according to Consanguineous marriage

Consanguineous marriage	Frequency	Percentage
Yes	22	17.6%
No	103	82.4%
Total	125	100.0%

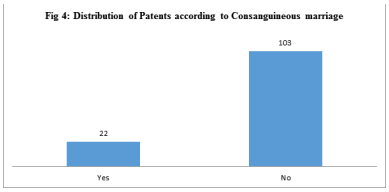


Table 5: Association between Age group and Frequency of blood transfusion

Age Group	Frequency of blood transfusion				Chi squar	p valu e
	Once a month	Twice a month	Thrice a month	Four times a month		
< 5 years	4 (80%)	1(20%)	0 (0%)	0 (0%)	35.906	0.000
6 - 10 years	13 (43.3%)	17 (56.7%)	0 (0%)	0 (0%)		
11 - 15 years	5 (9.6%)	41 (78.8%)	6 (11.5%)	0 (0%)		
> 15 years	6 (15.8%)	21 (55.3%)	8 (21.1%)			

Table 6: Distribution of Patents according to Frequency of blood transfusion

Frequency of blood transfusion	Frequency	Percentage
Once a month	28	22.4%
Twice a month	80	64.0%
Thrice a month	14	11.2%
Four times a month	3	2.4%
Total	125	100.0%

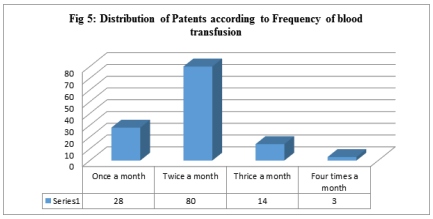


Table 7: Distribution of Patents according to growth retardation

Growth Retardation	Frequency	Percentage
Normal Growth	7	5.6%
Wieght for Age < 1 SD	21	16.8%
Weight for Age < 2 SD	72	57.6%
Weight for Age < 3 SD	25	20.0%
Total	125	100.0%

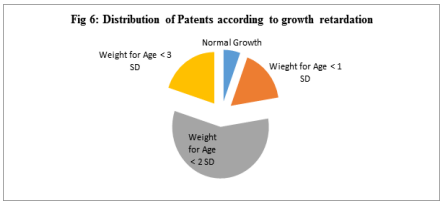


Table 8: Seroprevalence of blood borne infection among patients

	Frequency	Percentage
HCV	32	25.6%
HBV	4	3.2%
HIV	2	1.6%
Total	38	30.4%

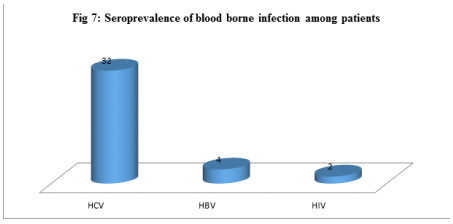


Fig 8: Line diagram showing trend of seroprevalence of blood borne infections

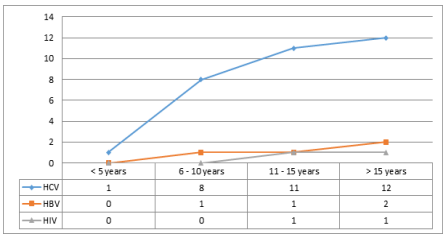


Table 9: Distribution of Patents according to level of serum ferrritin

Serum Ferritin	Frequency	Percentage
< 1000 ug/ml	27	21.6%
> 1000 g/ml	98	78.4%
Total	125	100.0%

Table 10: Distribution of patients according to dministration of chelation therpy, adequacy of chelation therapy and history of chelation therapy

On Chelation Therapy	Frequency	Percentage
Yes	77	61.6%
No	48	38.4%
Adequate Chelation Therapy	Frequency	Percentage
Adequate	10	8.0%
Inadequate	67	53.6%
No Chelation Therapy	48	38.4%
Any History of Chelation therapy	Frequency	Percentage
Yes	97	77.6%
No	28	22.4%

Table11: Association of Serum Ferritin and Administration of chelation therapy

		On Chelation Therapy		Chi square value	p value
		Yes	No		
Serum Ferritin	< 1000 ug/ml	6 (7.7%)	21 (44.7%)	23.694	.000*
	> 1000 g/ml	72 (93.2%)	26 (55.3%)		

Table 12: Association of Serum Ferritin and Adequacy of chelation therapy

	Adequate Chelation Threapy				Chi square value	p value
	Ade quate	Inade quate	n Therapy	No Chelatio		
Serum Ferritin	< 1000 ug/ml	5 (41.7%)	1 (1.5%)	21 (44.7%)	33.361	.000*
	> 1000 g/ml	7 (58.3%)	65 (98.5%)	26 (55.3%)		

Table 13: Distribution of patients on basis of liver function test and renal function test

		Frequency	Percentage
Serum Calcium	Hypocalemia	13	10.40%
	Normal	93	74.40%
	Hypercalcemia	19	15.20%
Serum Phosphorous (mg/dl)	Decreased	45	36.00%
	Normal	41	32.80%
	Increased	39	31.20%
Serum Alkaline Phosphatase (I/U)	Normal	63	50.40%
	Increased	62	49.60%
SGOT (mg/dl)	Normal	57	45.60%
	Increased	68	54.40%
SGPT (mg/dl)	Normal	55	44.00%
	Increased	70	56.00%
Serum Bilirubin (mg/dl)	Normal	55	44.00%
	Increased	70	56.00%
Serum Urea (mg/dl)	Normal	63	50.4%
	Increased	62	49.6%
Serum Creatinine (mg/dl)	Normal	61	48.8%
	Increased	64	51.2%

Table 14: Association of liver function test, renal function test with age group.

		Age Group					
		< 8 years		> 8 years			
		Count	Column N %	Count	Column N %		
Serum Calcium	Hypocalcemia	6	25.0%	7	6.9%	16.791	.000*
	Normal	10	41.7%	83	82.2%		
	Hypercalcemia	8	33.3%	11	10.9%		
Serum Phosphorous (mg/dl)	Decreased	20	83.3%	25	24.8%	30.110	.000*
	Normal	4	16.7%	37	36.6%		
	Increased	0	0.0%	39	38.6%		
Serum Alkaline Phosphatase (I/U)	Normal	19	79.2%	44	43.6%	9.833	.002*
	Increased	5	20.8%	57	56.4%		
SGOT (mg/dl)	Normal	9	37.5%	48	47.5%	.786	.375
	Increased	15	62.5%	53	52.5%		
SGPT (mg/dl)	Normal	9	37.5%	49	48.5%	.946	.331
	Increased	15	62.5%	52	51.5%		
Serum Bilirubi	Normal	10	41.7%	45	44.6%	.066	.798
	Increased	14	58.3%	56	55.4%		
Serum Urea	Normal	10	41.7%	53	52.5%	.936	.341
	Increased	14	58.3%	48	47.5%		
Serum Creatinine	Normal	10	41.7%	51	50.5%	.605	.437
	Increased	14	58.3%	50	49.5%		

Table 15: Correlation of liver function test, renal function test with serum ferritin.

	Serum Ferritin	
	Pearson Correlation	Sig. (2-tailed)
Serum Calcium	.025	.779
Serum Phosphorous (mg/dl)	0.181	.043
Serum Alkaline Phosphatase (I/U)	.104	.248

SGOT (mg/dl)	.032	.719
SGPT (mg/dl)	.022	.808
Serum Bilirubin (mg/dl)	.026	.772
Seum Creatiine (mg/dl)	.056	.630
Serun Urea (mg/dl)	.059	.652

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