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Independent Prognostic Factors of Burns Injury and Evaluation of RPR as an Important Risk Factor

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ABSTRACT

Background: Injuries from burn remain the second largest group of injuries after road traffic accidents. Approximately 1-1. 5 lakh people die from burns and around 2.8lakh people require multiple surgeries and prolonged rehabilitation.

Objectives: To evaluate independent prognostic factors of burns injury and evaluation of RPR as an important risk factor.

Methods: The present retrospective study patients of all age groups admitted to burns department from 1st March 2018 to 31st May 2018 with variable %TBSA burned were included. For 100 patients noted the clinical details like age, gender, burn index, inhalation injury if present, complete blood count, blood urea and serum creatinine levels. Medical notes were used to retrospectively record the patients. Their blood samples were routinely collected between 5 am and 7 am during 5th, 7th, 10th and 20th-day post-burn. The medical records were used to document the time from injury to adverse events.

Results: The age, % of burns, RDW, RPR, MPV, WBC, urea and creatinine values were considerably high in patients with mortality in the day 5, day 7, day 10 and day 20 datasets, whereas the haemoglobin, platelet values were low.

Conclusion: In this study, results indicated that parameters like haemoglobin, RDW, blood urea and serum creatinine and % of burns are statistically significant independent mortality predictors in burn patients. Whereas, RPR did not prove to be a statistically significant independent mortality predictor.

Key Words: Burn Injuries, independent Prognostic factors, RDW to platelet ratio, Burn injuries, Multiple surgeries

INTRODUCTION

India is the second-most populous country in the world with a population of more than 125 crores and has an estimated annual burn incidence of 6-7 million. Injuries from burn remain the second largest group of injuries after road traffic accidents. Nearly 10% of burn injuries are life-threatening and require hospitalization. Around 25% of those hospitalized gradually succumb to their injuries. Approximately 1-1.5 lakh people die from burns and around 2.8 lakh people require multiple surgeries and prolonged rehabilitation.[1] Burns is a three-dimensional injury and its severity depends on the quantum and depth of tissue burnt. The whole body surface area is taken as 100%. The proportion of surface burns is represented as a percentage. Rule of nine popularized by A.F Wallace of Edinburg is the most popular method of describing the surface burn. Lund and Browder's chart is used for the calculation of total body surface area burn in children. Any burn above 5% should be taken seriously.[1]

Ageing is an important and critical factor that contributes to the clinical outcome of burns patients. The very young and the elderly are more likely to succumb after major burn as compared to adults.[2,3] Indian women aged between 15 and 50 years are most prone to fire-related deaths compared to women in any country. Approximately 17,000 Indians die, of which 10,925 (62%) were women.[4] Women have significantly higher rates of inpatient mortality as compared to men. One of the reasons is that body surface area is significantly lower in women as compared to men.[5]

An increased burn index is an independent prognostic factor in burns cases. The higher the burn index higher is the rate of mortality. Burn index is the total of full-thickness, total body surface area (TBSA), and half of the part thickness TBSA. TBSA is calculated by the Rule of Nine by A.F.Wallace. It

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helps in describing the surface area of the burn. This body is divided into 11 equal parts; making this 99% and 1% is given to the perineum.[6-8] Inhalation injury is one of the most severe forms of burn injury and it is associated with a high rate of mortality.[9] The presence of inhalation injury is strongly associated with increased morbidity and mortality up to 20%. The incidence of pneumonia rises to 40%. It involves damage to the respiratory tract and lungs by heat, smoke, and toxicants.[10]

A severe burn patient with advanced age, large total body surface area, and inhalation injury have a high risk of substantial complication and death. [11] Burn cases feature varied and significant individual differences. Patients with the same total body surface area and depth of burn may have different outcomes.[12] The general physical response to burns is reported to be diverse. Therefore, reliable parameters to trace the general clinical course, particularly the pathological course of inflammation is required. Existing injury scores such as burn injury severity score and Ryan score have failed to demonstrate the severity of inflammation.[13] Inflammatory markers like C-reactive protein and procalcitonin do not correlate with the outcomes of severe burn injury.[13] Various laboratory variables, including complete blood count, urea and creatinine levels can help in demonstrating the severity of inflammation.

Haemoglobin levels decrease gradually to below control levels by 4th post-burn day in the non-survivors. Patients with severe burns demonstrate a steady drop in haemoglobin levels until death. 14 Whereas patients of burn injury who survive show relatively less drop in haemoglobin values and gradually the haemoglobin level increases.[2,14] Persistent anaemia plagues critically ill burn patients even after resolution of their initial acute event.[15] Red cell distribution width (RDW) provides useful information about burn severity and outcome. It can be used as a monitoring index in burns patients. Burn patients with higher RDW have increased mortality, third-degree burns, higher TBSA, increased infection rate, and higher length of hospital stay.[2] There are significant differences in RDW values of survivors and non-survivors.[16] It has been found that RDW is an independent predictor of burn severity. It is significantly higher in patients with increased TBSA and burns due to inhalation injury.[17]

The platelet count is significantly low in non-survivor burn patients, whereas it starts increasing by day 5 in patients who survived the burn injuries. An increase in platelet count represents a normal response to various inflammatory stimuli. Whereas thrombocytopenia is considered to be an important sign predicting worsening of the course of the disease thereby increased mortality.[2,18] In non-survivors gradual decline in platelet count is observed and the minimal platelet count is observed before the death of the burns patients. While in survivors gradual rise in platelet count is observed.[2,19-23] In the recent past, RDW platelet ratio (RPR) has gained substantial attention as a prognostic marker of various medical conditions such as severe burn injury, patent ductus arteriosus, hepatic fibrosis and cirrhosis in chronic hepatitis B, myocardial infarction, and non-alcoholic fatty liver disease. Higher RPR predicts higher fibrosis.[2,24] Non-survivor patients have a higher RPR as compared to survivors after burn injury. Recent studies have shown that RPR is an independent prognostic marker.[2] Mean platelet volume (MPV) correlates linearly with BAUX score thereby indicating that a rise in MPV correlates with poor prognosis in burn patients.[25] White blood cell count (WBC) is not very much clinically reliable in predicting bloodstream infection.[2,26]

Acute renal failure (ARF) is one of the major complications of burns and it is accompanied by a high mortality rate. Reduced urine output despite adequate fluid administration is usually the first sign of ARF. This is followed by a rise in serum creatinine and urea concentration. The prognosis of burn patients with acute renal failure is usually unfavourable. Patients having serum creatinine more than 1.5 mg/del above the initial values have mortality rates high as 72.7%, much higher than patients who have no renal dysfunction.[2,27]

MATERIAL AND METHODS

Our study was a retrospective study from 1st March 2018 to 31st May 2018. The sample size was 100 burn patients. There were 60 females and 40 males. Two patients, including one male and one female, succumbed to burn injury before day 5 hence were not included in our study. A total of 34 patients died within 40 days after the initial injury. We noted the clinical details like age, gender, burn index, inhalation injury if present, complete blood count, blood urea and serum creatinine levels. Medical notes were used to retrospectively record the patients. Their blood samples were routinely collected between 5 am and 7 am during 5th, 7th, 10th and 20th-day post-burn. The medical records were used to document the time from injury to adverse events. The follow up to evaluate endpoint was defined as the time interval from admission to death or discharge.

The inclusion criteria included burns patients of all age groups admitted to burns department from 1st March 2018 to 31st May with variable %TBSA burned. The excluded patients had known the previous history of cardiac disease, kidney disease, hemolytic anaemia, bone marrow arrest and inflammatory diseases.

Statistical Analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD. Quantitative variables were compared using an independent t-test between the two groups. Qualitative variables were correlated using Chi-Square test/ Fisher's Exact test. Receiver operating characteristic curve was used to find out cut off point of parameters for predicting mortality. Kaplan Meier survival analysis, the curve was used to find out survival rate at different time point. Univariate and multivariate cox-proportional hazard regression was used to find out the significant risk factors of mortality rate. A p-value of <0.05 was considered statistically significant. The data were entered in the MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

Our study was conducted in a tertiary hospital in north India. We included the data from 1st March 2018- 31st May 2018. The sample size was of 100 burn patients. Twelve variables were regarded as potential predictors of outcome(**Table 1).** The data were then classified into day 5, day 7, day 10 and day 20 datasets to reflect the association of the laboratory variables at different time points with the endpoint.

The following parameters showed significant differences between survivors and non-survivors on days 5, 7, 10 and 20: Gender, burn index (BI), inhalation injury, haemoglobin, red cell distribution width (RDW), platelets, RDW to platelet ratio (RPR), mean platelet volume (MPV), urea and creatinine. No significant difference was observed between survivors and non-survivors in terms of age and white blood cell count.

Table 1: Demographics and clinical characteristics of patients from follow-up results on days 5,7,10 and 20. The variables measured on days 5,7,10 and 20 postburn received Student's t-test or Pearson's chi squared test. Data were present as mean±SD, or number (%). BI indicates burn index; WBC, white blood cell count; RDW, red cell distribution width; RPR, RDW to platelet ratio; MPV, mean platelet volume.

	Day 5			Day 7			Day 10			Day 20		
	Survivor 66	Non Survivor 32	P	Survivor 66	Non Survivor 31	P	Survivor 66	Non Survivor 26	P	Survivor 66	Non Survivor 19	P
Age (Years)	26.89+19.77	33.6+20.2	0.121	26.89+19.77	33.8+20.13	0.113	26.89+19.77	35.73+21.85	0.064	26.89+19.77	39.3+22.4	0.021
Gender	F M	F M	0.003	F M	F M	0.004	F M	F M	0.009	F M	F M	0.035
	33 33	26 6		33 33	25 6		33 33	21 5		33 33	15 4	
BI	26.56+11.98	50.12+17.4	0.001	26.56+11.98	48.67±15.76	0.001	26.56+11.98	44.57±13.36	0.001	26.56+11.98	40.21±11.95	0.001
Inhalation Injury	2 (3%)	5 (15.6%)	0.023	2 (3%)	5(16.12%)	0.020	2 (3%)	5 (19.2%)	0.008	2 (3%)	3 (15.8%)	0.037
WBC (X 10^9)	13.49±9.50	16.04±11.3	0.244	11.61±10.95	17.24±13.84	0.032	11.29±10.70	15.4±13.90	0.233	11.47±13.36	12.60±12.85	0.744
Hemoglobin (g/dl)	10.60±2.30	8.93±2.71	0.002	12.99±1.99	6.91±1.62	0.001	13.14±1.91	6.87±1.31	0.001	13.28±1.89	6.48±1.28	0.001
RDW	13.79±1.91	15.35±2.1	0.001	13.75±2.66	15.32±2.24	0.005	13.64±2.03	15.7±2.02	0.001	13.54±2.46	15.89±2.16	0.001
Platelets (X10^9/L)	226±157.51	55.40±36.7	0.001	241.8±133	51.74±29.43	0.001	285.2±158.2	48.38±33.21	0.001	295±117.19	46±25.6	0.001
RPR	0.18±0.35	0.56±0.58	0.001	0.08±0.06	0.48±0.43	0.001	0.09±0.13	0.58±0.54	0.001	0.06±0.03	0.97±1.69	0.001
MPV	9.62±1.48	11.10±0.77	0.001	9.38±1.35	11.33±0.75	0.001	9.34±1.45	11.45±0.83	0.001	9.03±1.20	11.45±0.83	0.001
Urea (mg/dl)	37.44±11.74	51.01±22.6	0.001	35.49±11.74	59.58±20.47	0.001	33.18±9.81	61.61±15.92	0.001	33.36±9.74	72.68±20.20	0.001
Creatinine (mg/dl)	0.71±0.26	0.93±0.43	0.002	0.73±0.44	0.99±0.68	0.025	0.63±0.28	0.91±0.59	0.002	0.46±0.11	1.45±2.57	0.002

ROC curves of Age, Percentage of burn, Haemoglobin, RDW, Platelets, RPR, MPV, WBC, Urea and Creatinine and adverse outcome in a severe burn injury

The age, % of burns, RDW, RPR, MPV, WBC, urea and creatinine values were considerably high in patients with mortality in the day 5, day 7, day 10 and day 20 datasets, whereas the haemoglobin, platelet values were low. As shown in Table 2. the areas under the ROC curves of the age and WBC were poor with AUC of 0.598 (0.494 to 0.696) and 0.55 (0.447 to 0.651) respectively in the day 5 dataset (**Figure 1**), 0.601 (0.496 to 0.699) and 0.644 (0.540 to 0.738) respectively in the day 7 dataset (**Figure 3),** 0.621 (0.514 to 0.720) and 0.561 (0.453 to 0.664) respectively in the day 10 dataset and 0.635 (0.524 to 0.737) (**Figure 5)** and 0.505 (0.395 to 0.615) in the day 20 dataset (**Figure 7**). Areas under the ROC curves of % of burns, haemoglobin, RDW, platelets, RPR, MPV, urea and creatinine were 0.874 (0.791 to 0.932), 0.898 (0.820 to 0.950), 0.873 (0.791 to 0.932), 0.732 (0.633 to 0.816), 0.864 (0.780 to 0.925), 0.873 (0.791 to 0.932), 0.809 (0.717 to 0.881), 0.712 (0.611 to 0.799) and 0.673 (0.571 to 0.764) respectively for mortality prediction in the day 5 dataset (**Figure 2**), 0.87 (0.786 to 0.930), 0.996 (0.954 to 1.000), 0.765 (0.668 to 0.845), 0.978 (0.925 to 0.997), 0.978 (0.925 to 0.997), 0.915(0.841 to 0.962), 0.882 (0.800 to 0.938) and 0.588 (0.483 to 0.687) respectively for mortality prediction in the day 7 dataset (**Figure 4**), 0.845 (0.754 to 0.912), 0.997 (0.954 to 1.000), 0.793 (0.696 to 0.871), 0.951 (0.885 to 0.985), 0.958 (0.895 to 0.989), 0.904 (0.825 to 0.956), 0.939 (0.869 to 0.978) and 0.59 (0.482 to 0.691) respectively for mortality prediction in the day 10 dataset (**Figure 6**) and 0.787 (0.685 to 0.869), 0.999 (0.956 to 1.000), 0.835 (0.738 to 0.906), 0.994 (0.945 to 1.000), 0.998 (0.954 to 1.000), 0.976 (0.917 to 0.997), 0.976 (0.917 to 0.997) and 0.757 (0.652 to 0.844) respectively for mortality prediction in the day 20 dataset (**Figure 8**). The maximum value of Youden index was used as the criterion for selecting the optimum cut-off point to divide the variables to the high value group and the low value group. The Youden index was represented by the formula Youden index = sensitivity + specificity – 1. Percentage of burns, haemoglobin, RDW, platelets, RPR, MPV, urea and creatinine were statistically significant for mortality prediction in the day 5 dataset with sensitivity of 68.75%, 81.25%, 93.75%, 81.25%, 100%, 87.5%, 68.75% and 65.62% respectively and specificity of 90.91%, 86.36%, and 59.09%, 84.85%, 68.18%, 72.73%, 72.73% and 65.15% respectively. % of burns, haemoglobin, RDW, platelets, RPR, MPV, WBC and urea were statistically significant for mortality prediction in the day 7 dataset with sensitivity of 67.74%, 96.77%, 93.55%, 100%, 100%, 93.55%, 38.71% and 83.87% respectively, and specificity of 90.91%, 96.97%, and 62.12%, 90.91%, 93.94%, 81.54%, 89.39% and 86.36% respectively. % of burns, haemoglobin, RDW, platelets, RPR, MPV, and urea were statistically significant for mortality prediction in the day 10 datasets with sensitivity of 61.54%, 100%, 100%, 100%, 100%, 92.31%, and 88.46% respectively, and specificity of 90.91%, 98.48%, 62.12%, 83.33%, 86.36%, 86.36%, and 92.42% respectively. % of burns, haemoglobin, RDW, platelets, RPR, MPV, urea and creatinine were statistically significant for mortality prediction in the day 20 datasets with sensitivity of 78.95%, 100%, 100%, 100%, 100%, 94.74%, 89.47% and 63.16% respectively, and specificity of 65.15%, 98.48%, and 69.7%, 95.45%, 96.97%, 95.45%, 96.97% and 90.91% respectively **(Table 2).**

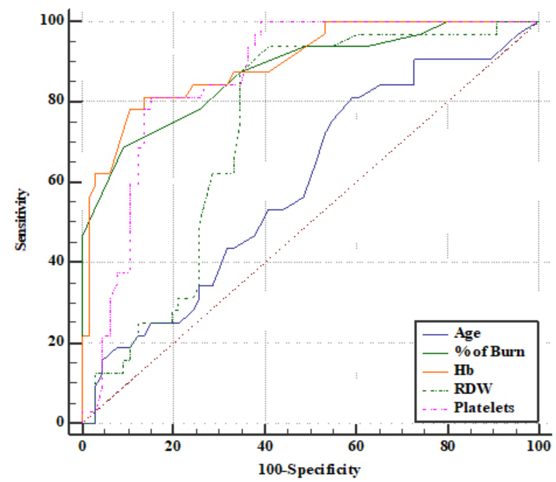

Figure 1: Receiver operating characteristic curve of Age, Percentage of burn, Hemoglobin (Hb), RDW and Platelets on days 5 for prediction of adverse endpoint at 40 days.

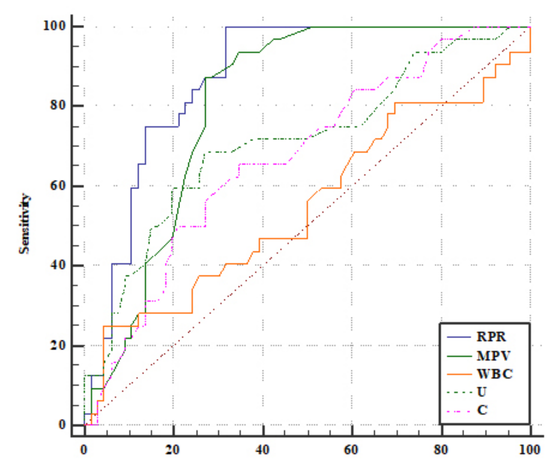

Figure 2: Receiver operating characteristic curve of RPR, MPV, WBC, Urea (U) and Creatinine (C) on days 5 for prediction of adverse endpoint at 40 days.

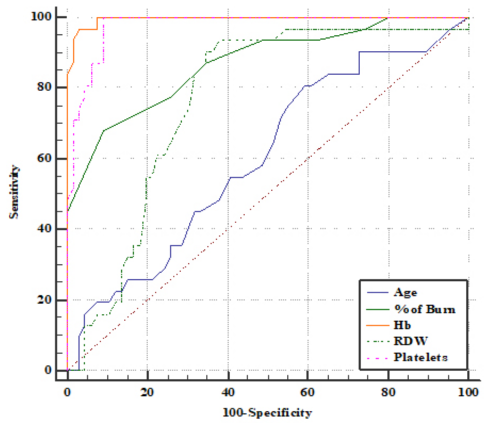

Figure 3: Receiver operating characteristic curve of Age, Percentage of burn, Hemoglobin (Hb), RDW and Platelets on days 7 for prediction of adverse endpoint at 40 days.

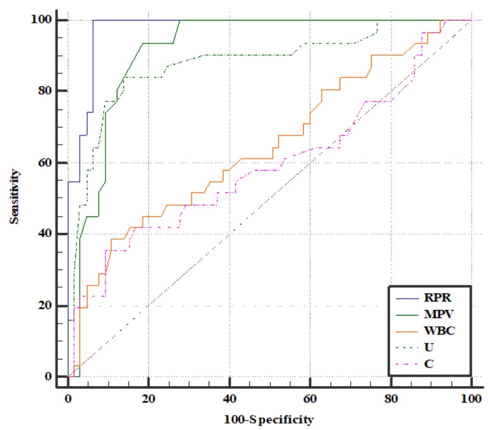

Figure 4: Receiver operating characteristic curve of RPR, MPV, WBC, Urea (U) and Creatinine (C) on days 7 for prediction of adverse endpoint at 40 days.

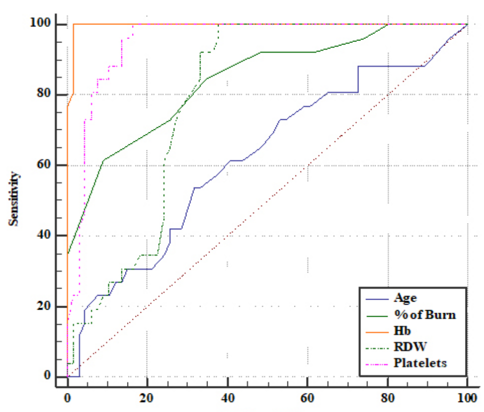

Figure 5: Receiver operating characteristic curve of Age, Percentage of burn, Hemoglobin (Hb), RDW and Platelets on days 10 for prediction of adverse endpoint at 40 days.

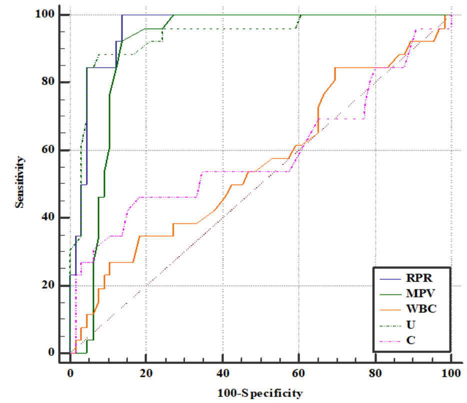

Figure 6: Receiver operating characteristic curve of RPR, MPV, WBC, Urea (U) and Creatinine (C) on day 10 for prediction of adverse endpoint at 40 days.

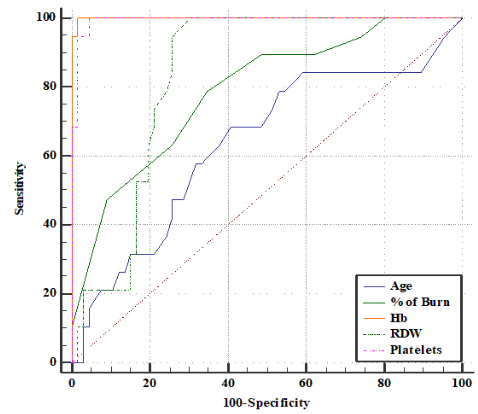

Figure 7: Receiver operating characteristic curve of Age, Percentage of burn, Hemoglobin (Hb), RDW and Platelets on day 20 for prediction of adverse endpoint at 40 days.

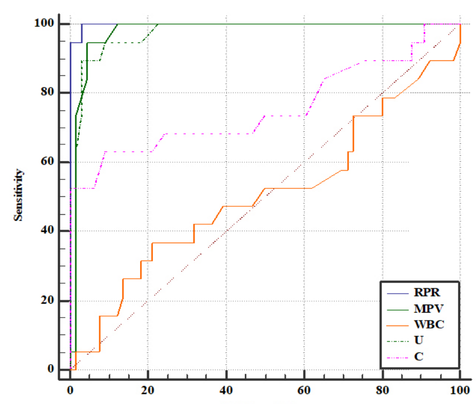

Figure 8: Receiver operating characteristic curve of RPR, MPV, WBC, Urea(U) and Creatinine (C) on day 20 for prediction of adverse endpoint at 40 days.

Table 2: Diagnostic information for the prediction of mortality on days 5,7,10 and 20

Day	Variable	Optimal cut off point	Sensitivity (%)	Specificity (%)	AUC(95% CI)
Day 5	Age	>21	81.25	40.91	0.598(0.494 to 0.696)
	% of Burn	>40	68.75	90.91	0.874(0.791 to 0.932)
	Hb	≤8.6	81.25	86.36	0.898(0.820 to 0.950)
	RDW	>13.6	93.75	59.09	0.732(0.633 to 0.816)
	Platelets	≤87	81.25	84.85	0.864(0.780 to 0.925)
	RPR	>0.1141	100	68.18	0.873(0.791 to 0.932)
	MPV	>10.4	87.5	72.73	0.809(0.717 to 0.881)
	WBC	>24	25	95.45	0.55(0.447 to 0.651)
	Urea	>41	68.75	72.73	0.712(0.611 to 0.799)
	Creatinine	>0.76	65.62	65.15	0.673(0.571 to 0.764)
Day 7	Age	>21	80.65	40.91	0.601(0.496 to 0.699)
	% of Burn	>40	67.74	90.91	0.87(0.786 to 0.930)
	Hb	≤9.1	96.77	96.97	0.996(0.954 to 1.000)
	RDW	>13.4	93.55	62.12	0.765(0.668 to 0.845)
	Platelets	≤104	100	90.91	0.978(0.925 to 0.997)
	RPR	>0.1364	100	93.94	0.978(0.925 to 0.997)
	MPV	>10.4	93.55	81.54	0.915(0.841 to 0.962)
	WBC	>14.8	38.71	89.39	0.644(0.540 to 0.738)
	Urea	>43	83.87	86.36	0.882(0.800 to 0.938)
	Creatinine	>0.91	35.48	89.39	0.588(0.483 to 0.687)
Day 10	Age	>31	53.85	68.18	0.621(0.514 to 0.720)
	% of Burn	>40	61.54	90.91	0.845(0.754 to 0.912)
	Hb	≤9.2	100	98.48	0.997(0.954 to 1.000)
	RDW	>13.5	100	62.12	0.793(0.696 to 0.871)
	Platelets	≤130	100	83.33	0.951(0.885 to 0.985)
	RPR	>0.1035	100	86.36	0.958(0.895 to 0.989)
	MPV	>10.5	92.31	86.36	0.904(0.825 to 0.956)
	WBC	>12.4	34.62	81.82	0.561(0.453 to 0.664)
	Urea	>43	88.46	92.42	0.939(0.869 to 0.978)
	Creatinine	>0.71	46.15	81.82	0.59(0.482 to 0.691)
Day 20	Age	>27	68.42	59.09	0.635(0.524 to 0.737)
	% of Burn	>30	78.95	65.15	0.787(0.685 to 0.869)
	Hb	≤9.8	100	98.48	0.999(0.956 to 1.000)
	RDW	>13.8	100	69.7	0.835(0.738 to 0.906)
	Platelets	≤97	100	95.45	0.994(0.945 to 1.000)
	RPR	>0.1379	100	96.97	0.998(0.954 to 1.000)
	MPV	>10.7	94.74	95.45	0.976(0.917 to 0.997)
	WBC	>10.6	36.84	78.79	0.505(0.395 to 0.615)
	Urea	>52	89.47	96.97	0.976(0.917 to 0.997)
	Creatinine	>0.61	63.16	90.91	0.757(0.652 to 0.844)

CI: Confidence interval. The maximum value of Youden index (sensitivity +specificity -1) was used as the criteria for selecting the optimal cutoff point.

Survival analysis for predicting severe burn mortality rates

The age, % of burns, haemoglobin, RDW, PLT, RPR, MPV, WBC, urea, creatinine, gender, and inhalation injury of days 5 and days 7 were significant risk factors of mortality according to the univariate regression analysis results (P < 0.05). However, on multivariate Cox regression, only % of burn, haemoglobin and urea were significant risk factors of mortality in the day 5 dataset with adjusted HR = 2.991, 95% CI: 1.1-8.132, P = 0.032; adjusted HR = 3.361, 95% CI: 1.005-11.242, P = 0.049 and adjusted HR = 3.569, 95% CI: 1.356-9.392, P = 0.010 respectively (**Figure 9,10,11**) and % of burn, haemoglobin, RDW and creatinine were significant risk factors of mortality in the day 7 dataset with adjusted HR = 3.089, 95% CI: 1.126-8.478, P = 0.029; adjusted HR = 116.918, 95% CI: 5.135-2661.933, P = 0.003, adjusted HR = 0.093, 95% CI: 0.01-0.828, P = 0.033 and adjusted HR = 2.416, 95% CI: 1.004-5.814, P = 0.049 respectively (**Figure 12,13,14,15).** The % of burns, haemoglobin, RDW, PLT, RPR, MPV, urea, creatinine, gender, and inhalation injury of days 10 were significant risk factors of mortality according to the univariate regression analysis results (P < 0.05). However, on multivariate Cox regression, none of the factors was the independent risk factor of mortality. The % of burns, RDW, MPV, urea, creatinine, and gender of days 20 were significant risk factors of mortality according to the univariate regression analysis results (P < 0.05). However, on multivariate Cox regression, none of the factors was the independent risk factor of mortality. (Table 3, Table 4).

Table 3: Results of univariate and multivariate Cox proportional-hazards regression for the analysis of the effects of baseline variables on an adverse endpoint on day 5 and day 7.

	Day 5				Day 7			
	Univariate		Multivariate		Univariate		Multivariate	
Variable	HR(95%)	P value	HR(95%)	P value	HR(95%)	P value	HR(95%)	P-value
Age(>cut off point)	2.515(1.035-6.112)	0.0419	1.188(0.378-3.736)	0.768	2.428(0.996-5.92)	0.0512	-	-
% of Burn(>cut off point)	10.628(4.978-22.691)	<.0001	2.991(1.1-8.132)	0.032	10.323(4.81-22.154)	<.0001	3.089(1.126-8.478)	.029
Hb(>cut off point)	12.002(4.895-29.429)	<.0001	3.361(1.005-11.242)	0.049	163.9(21.904-1226.405)	<.0001	116.918(5.135-2661.933)	.003
RDW (>cut off point)	14.561(3.473-61.049)	0.0002	3.271(0.607-17.634)	0.168	15.708(3.74-65.977)	0.0002	0.093(0.01-0.828)	.033
Platelets (>cut off point)	11.602(4.736-28.422)	<.0001	1.289(0.48-3.461)	0.614	408.652(7.729-21606.155)	0.0030	78.751(0-2.05660277676892E+55)	.945
RPR(>cut off point)	79.365(4.506-1397.823)	0.0028	32923.767(0-7.22E+80)	0.908	612.036(7.473-50128.744)	0.0043	3681.694(0-7.37463111179202E+56)	.896
MPV(>cut off point)	11.507(4.024-32.907)	<.0001	2.456(0.78-7.728)	0.125	32.267(7.663-135.866)	<.0001	1.414(0.17-7.22E+80)	.749
WBC (>cut off point)	4.063(1.818-9.08)	0.0006	0.887(0.317-2.478)	0.819	3.526(1.706-7.29)	0.0007	0.511(0.202-1.291)	.156
Urea(>cut off point)	4.296(2.028-9.098)	0.0001	3.569(1.356-9.392)	0.010	14.878(5.667-39.063)	<.0001	2.121(0.631-7.135)	.224
Creatinine(>cut off point)	2.723(1.311-5.655)	0.0072	0.792(0.326-1.92)	0.605	3.615(1.724-7.58)	0.0007	2.416(1.004-5.814)	.049
Gender								
Female	1		1		1		1	
Male	0.289(0.119-0.704)	0.006	1.101(0.382-3.171)	0.859	0.299(0.123-0.73)	.008	1.25(0.307-5.091)	.755
Inhalation injury	2.638(1.013-6.871)	0.047	3.949(1.002-15.572)	0.050	2.763(1.058-7.218)	.038	2.138(0.571-7.998)	.259

Table 4: Results of univariate and multivariate Cox proportional-hazards regression for the analysis of the effects of baseline variables on an adverse endpoint on day 10 and day 20.

	Day 10				Day 20			
	Univariate		Multivariate		Univariate		Multivariate	
Variable	HR(95%)	P value	HR(95%)	P value	HR(95%)	P value	HR(95%)	P-value
Age(>cut off point)	1.999(0.924-4.324)	.078	-	-	2.598(0.987-6.837)	.053	-	-
% of Burn(>cut off point)	8.685(3.912-19.282)	<.0001	1.455(0.522-4.056)	.474	5.702(1.89-17.206)	.0020	2.249(0.662-7.644)	.194
Hb(>cut off point)	2486.741(1.624-3807997.657)	.037	2283.048(0-716482687839.265)	.439	8590.636(0.005-14581015230.597)	.216	-	-
RDW (>cut off point)	71.777(3.026-1702.624)	.008	12.937(0-25155292267108500000)	.905	111.353(2.356-5262.383)	.017	39204.216(0-5.14946838713053E+84)	.911
Platelets (>cut off point)	234.032(5.191-10551.121)	.005	18.467(0-8.83444794017216E+59)	.966	2880.117(0.137-60385774.969)	.117	-	-
RPR(>cut off point)	313.08(5.205-18833.238)	.006	0.54(0-3.33858710843644E+61)	.993	4741.753(0.036-632323856.551)	.160	-	-
MPV(>cut off point)	35.292(8.29-150.247)	<.0001	1.335(0.227-7.22E+80)	.749	105.849(13.915-805.198)	<.0001	11.331(0.639-200.899)	.098
WBC (>cut off point)	2.06(0.917-4.625)	.080	-	-	1.927(0.759-4.897)	.168	-	-
Urea (>cut off point)	32.55(9.637-109.934)	<.0001	1.044(0.285-3.824)	.948	62.568(14.093-277.783)	<.0001	4.204(0.539-32.813)	.171
Creatinine (>cut off point)	3.031(1.399-6.567)	.005	1.175(0.48-2.877)	.724	9.015(3.527-23.044)	<.0001	0.976(0.337-2.826)	.965
Gender								
Female	1		1		1		1	
Male	0.363(0.146-0.905)	.030	1.64(0.552-4.87)	.373	0.313(0.104-0.943)	.039	0.883(0.273-2.858)	.835
Inhalation injury	3.601(1.353-9.58)	.010	1.309(0.422-4.064)	.642	3.169(0.922-10.89)	.067	-	-

Kaplan Meier Survival analysis curve

Kaplan Meier Survival analysis curve was plotted for parameters which proved to be a statistically significant independent prognostic factor on a multivariate analysis curve. These parameters included the % of burns, haemoglobin and urea on day 5 and % of burns, haemoglobin, RDW and creatinine on day 7.

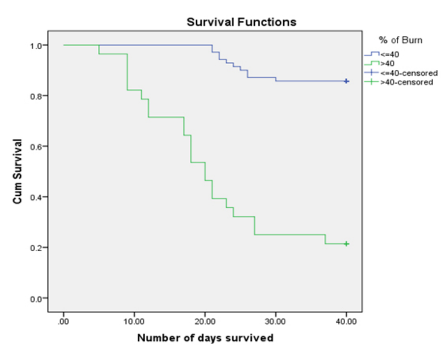

Figure 9: Kaplan Meier survival curve for % of burns on day 5.

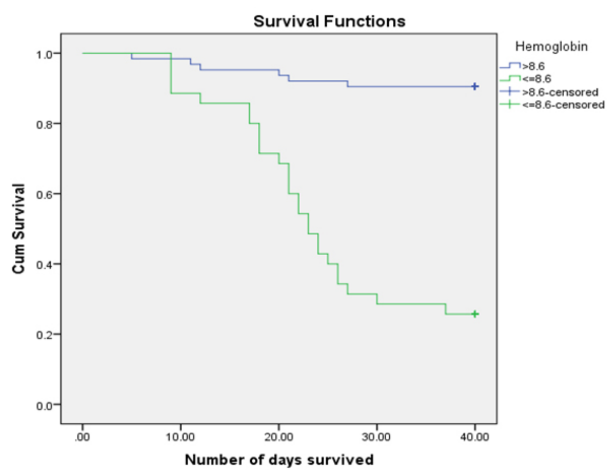

Figure 10: Kaplan Meier survival curve for haemoglobin on day 5.

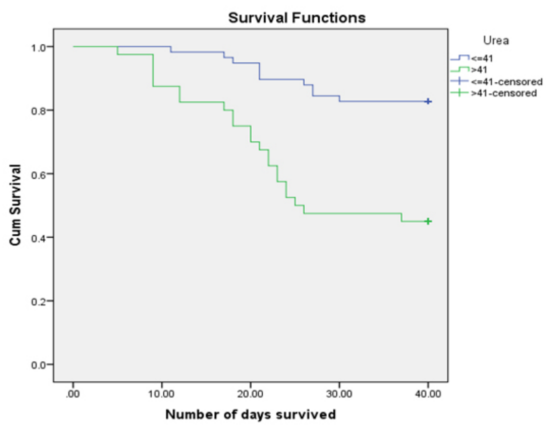

Figure 11: Kaplan Meier survival curve for urea levels on day 5.

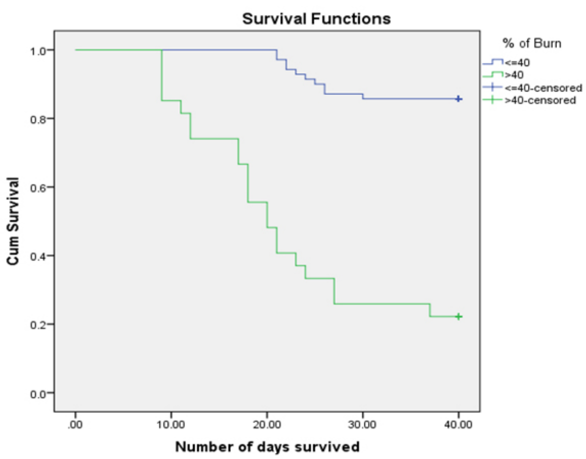

Figure 12: Kaplan Meier survival curve for % of burns on day 7

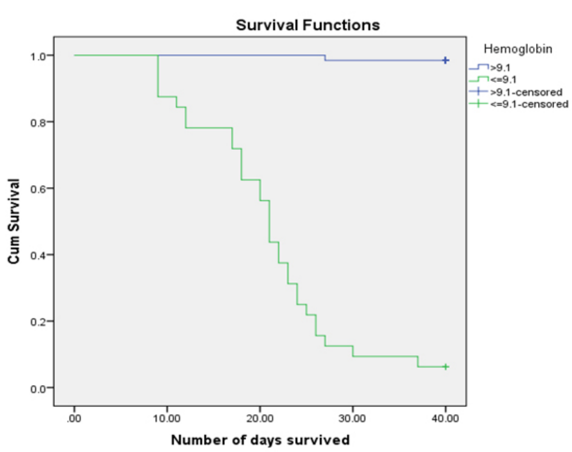

Figure 13: Kaplan Meier survival curve for haemoglobin on day 7.

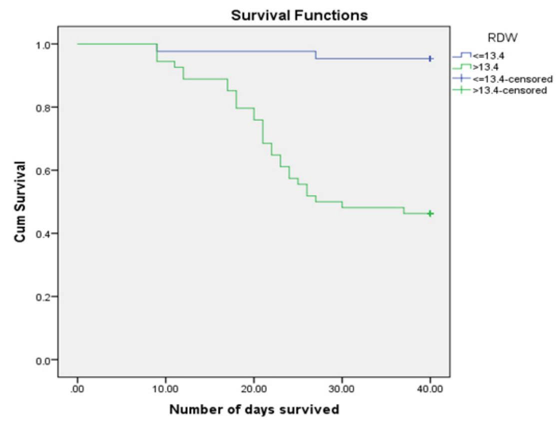

Figure 14: Kaplan Meier survival curve for RDW on day 7

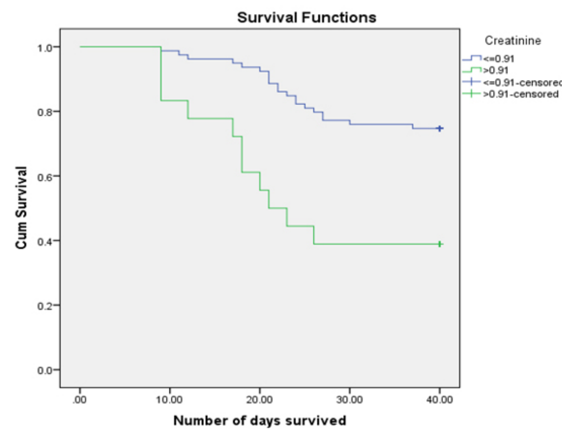

Figure 15: Kaplan Meier survival curve for creatine on day 7.

Kaplan Meier Survival Curve for RPR

Our study showed that RPR was not a statistically significant independent risk factor in multivariate-Cox proportional-hazards regression in burns patients, though it was statistically significant on univariatecox proportional-hazards regression curve.

Divided by the optimal RPR cutoff values, the Kaplan–Meier plots for the two categories at two-time points indicated that RPR values of more than the cutoff value have lower survival rates than the RPR values less than the cutoff value. On day 5, the 40-day mortality rate of the low RPR group was 0% and that of the high RPR group was 59.3% **(Figure 16**). On day 7, the mortality was 0% in the low RPR group and 88.6% in the high RPR group (**Figure 17),** on day 10 (**Figure 18),** the mortality was 0% in the low RPR group and 74.3% in the high RPR group and on day 20, the mortality was 0% in the low RPR group and 90.5% in the high RPR group (**Figure 19**). The difference between the low and high RPR groups in terms of the difference in time points was statistically significant ($P < 0.05$).

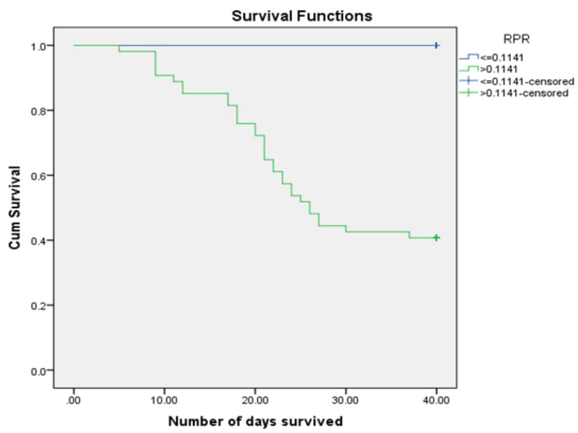

Figure 16: Kaplan – Mier survival curve for RPR higher or lower than 0.1141 at day 5.

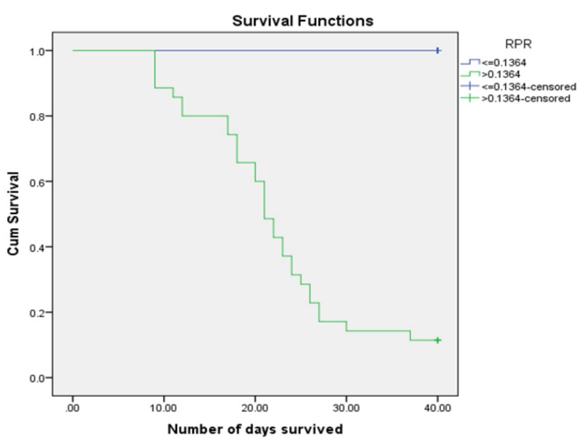

Figure 17: Kaplan – Mier survival curve for RPR higher or lower than 0.1364 at day 7.

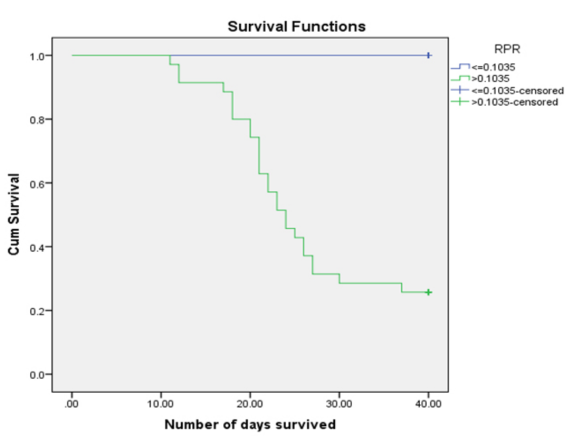

Figure 18: Kaplan – Mier survival curve for RPR higher or lower than 0.1364 at day 10.

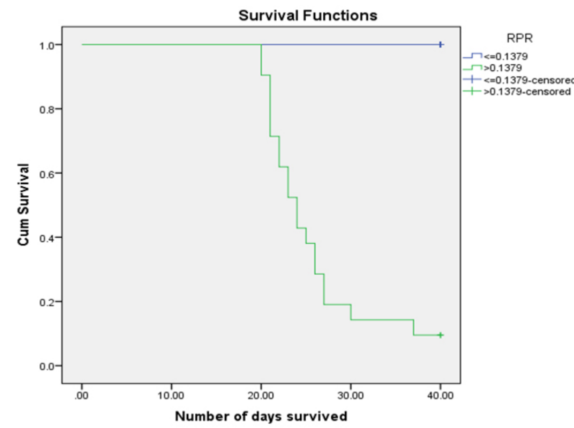

Figure 19: Kaplan – Mier survival curve for RPR higher or lower than 0.1364 at day 20.

DISCUSSION

An increased burn index is an independent prognostic factor in burn patients. We observed in our study that with the higher the burn index, the rate of mortality is high. Mean burn index in survivors was 26.5%, whereas in non-survivors it was 50.1% in day 5 data set (Table 1). In Kaplan Meier survival curve patients with $>$ 40% TBSA had a greater risk of mortality. The area under the receiver operating characteristic curve for a percentage of burns was 0.87 (95% CI, 0.791-0.932) on day 5 post-burn (Figure 1, Table 2). Percentage of burns were a significant risk factor of mortality according to the univariate and multivariate cox regression curve (Table 3, Figure 9 and Figure 12).

The mean haemoglobin value dropped in non-survivors from 8.93g/Dl on day 5 to 6.4g/Dl on day 20. Whereas in survivors the mean haemoglobin values gradually increased from 10.6g/Dl on day 5 to 13.28g/Dl on day 20 respectively. (Table 1) By day 20 the receiver operating characteristic curve analysis demonstrated 100% sensitivity at a cut off value of $\leq$ 9.8g/Dl for haemoglobin (Table 2, Figure 7). Low haemoglobin values were a significant risk factor of mortality according to univariate and multivariate cox regression curve. On the Kaplan Meier survival curve, it was seen that patient with haemoglobin values of $<$ 8.6 g/dl had an increased risk of mortality (Table 3, Table 4, Figure 10 and Figure 13). Significant differences in haemoglobin values between survivors and non-survivors is also reported.[2] In survivors, the mean haemoglobin value on day 3 and day 7 was 130.62g/l and 105.97 g/l. whereas in non-survivors the haemoglobin values were 124.34 g/l and 93.56g/l on day 3 and 7 respectively.

We observed that in non-survivors the RDW values were significantly higher as compared to survivors. By day 20 mean RDW in non-survivors were 15.89% and in survivors being 13.54%. (p=0.000) Table 1. ROC curve analysis demonstrated 100% sensitivity at a cut off value of 13.8% on day 20. (Figure 7, Table 2). High RDW values were a significant risk factor of mortality according to univariate and multivariate cox regression curve. Kaplan Meier survival curve showed that patients with RDW >13.4 % had a greater risk of succumbing to burn injury (Table 3, Table 4, Figure 14). Many studies suggest the importance of RDW as a prognostic indicator in various chronic diseases.[2,16,17] RDW value is a good predictor of mortality in the oesophagal burn.[17] An RDW of over 12.20% showed an increased risk of mortality to oesophagal burn.

We noticed a gradual increase in mean platelet values among the post-burn survivors on days 5, 7, 10 and 20 being 226 X 10^9/L, 241.8 X 10^9/L, 285.2 x 10^9/L and 295 x 10^9/L respectively. Whereas the mean platelet values decreased on days 5,7,10 and 20 in non-survivors being 55X 10^9/L, 51.74X 10^9/L, 48.38X 10^9/L and 46X 10^9/L respectively. ROC curve analysis expressed 100% sensitivity at a cut off value of ≤ 97X 10^9/L on day 20 with the area under ROC curve being 0.994(95 CI, 0.945-1.000). Low platelet values were a significant risk factor of mortality according to univariate cox regression curve (Table 1-4, Figure 7). The platelet count in survivors and non-survivors are correlated.[19] They showed that out of 206 burn patients with low platelet count (< 1.5 lakh/mm^3) 159 (62.11%) were non-survivors. Whereas 47 (13.9%) were survivors. The findings correlated with our study.

It was seen that RDW to platelet ratio (RPR) was higher in non-survivors as compared to survivors. ROC curve analysis demonstrated 100% sensitivity at a cut off value of 0.136 for RPR. The area under the ROC curve is 0.998. (95% CI, 0.945-1.000) (Table 2). In our study RPR values proved to be a significant risk factor of mortality according to univariate cox regression curve. RPR values were not statistically significant independent prognostic factors based on multivariate Cox regression curve (Table 3, Table 4). According to Kaplan- Mier survival curves on day 5,7,10 and 20 mortality was 0% in the low RPR group. Whereas on the same day's mortality was 59.3%, 88.6%, 74.3% and 90.5% respectively in high RPR group (Figure 16 and 19).

According to study RPR is an independent risk factor on both unilabiate as well as multivariate Cox regression curve.[2] Our study showed that RPR was not an independent risk factor in multivariate cox regression curve. We observed that the mean platelet value of >10.4 optimal cut off point had 0.809 (0.717-0.881) area under the ROC curve with the sensitivity of 87.5% on day 5. It was a statistically significant predictor of mortality (Table 2, Figure 2).

It was seen that in non-survivors the blood urea and serum creatinine values gradually increased. By day 20 mean values of blood urea and serum creatinine were 72.68 mg/dl and 1.45 mg/dl respectively. Whereas in survivors the mean values of blood urea and serum creatinine were 33.36 mg/dl and 0.46 mg/dl by day 20 (p=0.0001) (Table 1). On the Kaplan Meier curve, it was observed that patients with blood urea levels of more than 41 mg/dl had increased risk of mortality. Blood urea and serum creatinine values proved to be statistically significant independent mortality predictors and risk factors of mortality according to unilabiate and multivariate cox regression curve (Table 2, Figure 8, Figure 11).

The significant cut off values for serum creatinine for predicting early acute kidney injury and thereby increased risk of mortality ranged from 0.85mg/dl – 1.15 mg/dl.[28] It was a significant biomarker predicting acute kidney injury. Area under ROC curve for blood urea was 0.541 (p= 0.523).[29] It was not a significant biomarker for predicting acute kidney injury, unlike our study. Our study revealed both blood urea as well as serum creatinine as statistically significant independent risk factors for mortality in burn patients.

CONCLUSION

The results indicated that parameters like haemoglobin, RDW, blood urea and serum creatinine and % of burns are statistically significant independent mortality predictors in burn patients. Whereas; RPR did not prove to be a statistically significant independent mortality predictor. It is suggested that future randomized studies using common and clinically relevant endpoints to evaluate and look for a new, reliable, effective and readily available prognostic factors.

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