ROLE OF RED BLOOD CELL DISTRIBUTION WIDTH AS A PROGNOSTIC MARKER IN PATIENTS WITH SEVERE SEPSIS AND SEPTIC SHOCK

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ABSTRACT

BACKGROUND

Red Cell Distribution Width (RDW) is widely available to clinicians, because it is routinely reported as part of complete blood count. Several studies have reported that RDW is closely related to outcome in critically ill patients. Severe sepsis and septic shock are increasing in incidence and contributing significantly to mortality. Prediction of outcome for patients with sepsis using easily available and reliable marker may facilitate more aggressive interventions made at appropriate time. We studied this correlation and whether changes in Red cell distribution width reflects acute changes in disease progression.

METHODS

We studied 150 patients who were admitted to ICU and wards of Medicine Department in tertiary care center with diagnosis of sepsis, severe sepsis and septic shock; 75 patients were selected in each group based on outcome, i.e. those who died and those who were discharged. Clinical data was collected for all patients. Various haematological and biochemical parameters on admission and after 72 hours were compared among two groups using appropriate statistical methods.

RESULTS

Mean RDW was significantly higher in non-survivors than in survivors. Median baseline RDW in discharged group was 15.5±2.33 and 18.0±3.84 in death group (P<0.001). Patients with greater change in RDW (After 72 hours) from baseline exhibited greater mortality. Mortality rate in patients with change in RDW >0.2 from baseline was 74.16% (66 patients died out of 89) and 14.75% (9 patients died out of 61) in patients where change in RDW was less than or equal to 0.2 from baseline (P=0.001).

CONCLUSION

We found that not only baseline red cell distribution width (RDW), but RDW after 72 hours of hospitalization was strongly associated with outcome in patients with sepsis, severe sepsis and septic shock. RDW also varied significantly according to severity of sepsis. Change in RDW from baseline to 72 hours after hospitalization was strongly associated with outcome. This shows that RDW can be used as dynamic marker, which will predict acute changes in disease states.

KEYWORDS

Sepsis, Severe Sepsis, Septic Shock, Red Blood Cell Distribution Width, RDW, Sepsis Markers, Sepsis Prognosis.

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INTRODUCTION

Septic response is a leading contributory factor for morbidity and mortality, especially in intensive care settings. Incidence of sepsis is on the rise worldwide and at the same time the mortality rate remained high despite ongoing advances in the management of sepsis. Partly this is attributable to the aging of the population, increased awareness of public regarding health related issues, advanced management protocols for patients with chronic diseases increasing their longevity and in turn increased number of predisposed population for sepsis, various sources of infection in hospital setup such as indwelling catheters, misuse of antimicrobials and mechanical devices.

The established biological markers of inflammation (Leukocytes, C-reactive protein, procalcitonin) may be influenced by parameters other than infection and often do not reflect disease progression on quantifiable scale. Also scoring systems such as APACHE, SOFA and SAPS are not always available to assess patient's condition because of non-availability of facilities to obtain parameters needed to calculate such scores.

The prediction of outcome for patients with sepsis using easily available and reliable marker may facilitate more aggressive interventions made at appropriate time. Recent studies have shown that Red Cell Distribution Width (RDW), which is widely available to physicians since it is reported as part of complete blood count, a routine haematological investigation done in all hospitalized patients, can be effectively used as a prognostic marker for critically ill patients. Various pathophysiological mechanisms though not

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studied thoroughly are likely to be responsible for this association. Systemic inflammation response impacts bone marrow function and iron metabolism.[1] also proinflammatory cytokines have been found to inhibit erythropoietin-induced erythrocyte maturation and proliferation and to down-regulate erythropoietin receptor expression, which are associated with increase in RDW.[2] Oxidative stress may also be a contributing factor of the association between RDW and mortality. High oxidative stress is present in sepsis through the generation of reactive oxygen species by activated leukocytes. Moreover, it has been proposed that oxidative stress induces an increase in RDW by reducing RBC survival and increasing the release of large premature RBCs into the peripheral circulation.[2] Also renal dysfunction, which is common in septic patients have direct and indirect effect on erythropoiesis.[3] In our study, we have evaluated this correlation and also studied whether changes in Red cell distribution width reflects acute changes in disease progression.

MATERIALS AND METHODS

This study was prospective observational study, where continuous data was enumerated of cases who fulfilled the inclusion criteria. However, at the end equal cases were taken for study in two groups based on outcome (75 in Death group and 75 in Discharged group). Study was conducted from October 2014-September 2015, at tertiary care center, NSCB Medical College, Jabalpur. All patients admitted to Intensive Care Units (ICU) and Wards who fulfilled the criteria of sepsis, severe sepsis and septic shock according to ACCP/SCCM consensus conference committee guidelines (1992), modified in 2001 [Table 1] were enrolled for study. Patients with blood product transfusion in previous week of admission, bleeding >10% blood volume, previous history of diseases primarily affecting Red Blood Cells, recent Chemotherapy, use of any other drugs known to significantly change Morphology and Rheology of Red Blood Cells were excluded.

A detailed history was taken from patients, general physical examination and systemic examination was done. Complete Blood Count (CBC), routine urine analysis, renal function tests, random blood sugar, liver function tests, serum electrolytes, fasting lipid profile, chest X-ray, ECG, sputum Gram's/AFB staining, cultures-blood/sputum/urine, etc. were done wherever indicated. CBC was done on admission and after 72 hours of admission. Red blood cell distribution width (RDW reported as part of CBC) on admission (RDW0) and after 72 hours (RDW72) and also change between two values (Delta RDW) were calculated for each patient. All other CBC parameters were also noted.

Acute cardiac dysfunction was defined as Systolic Blood Pressure <90 mmHg or MAP<70 mmHg that responded to fluid administration, in the absence of cardiac tamponade or pulmonary embolism; myocardial infarction or severe arrhythmias. Respiratory failure was defined as failure to maintain PaO2/FiO2 ratio at 200 or above. Acute renal dysfunction was defined as urine output <0.5 mL/kg/Hour for at least 1 hour despite adequate fluid resuscitation or creatinine increase >0.5 mg% from admission value or a doubling of the admission creatinine level in case of pre-existing renal disease. Liver dysfunction was defined as a total bilirubin level >4 mg% or coagulation abnormalities, INR >1.5 or aPTT >60 seconds. Haematological dysfunction was defined as Platelet count <80000/uL OR 50% less than highest value recorded over last 3 days. Neurological dysfunction was defined as central nervous system impairment with a Glasgow Coma Scale (GCS) of <7/15.

STATISTICAL ANALYSIS

Qualitative data was represented in the form of frequency and percentage. Association between qualitative variables was assessed by Chi square test with continuity correction for all 2X2 tables and Fisher's exact test for all 2X2 tables, where p-value of Chi square test was not valid due to small counts. Quantitative data was represented using Mean±SD and Median and IQR (Interquartile Range). Analysis of Quantitative data between the two groups was done using unpaired t-test if data passes 'Normality test' and by Mann-Whitney Test (or Kruscal Wallies Test for more than 2 variables) if data fails 'Normality test.' SPSS software Version 20 was used for analysis.

RESULTS

We enrolled 150 patients in our study, out of which 113 were males and 37 were females. Out of 113 males 55 died and 58 survived with mortality of 48.67% and out of 37 females 20 died with mortality of 54.05%. There was no statistically significant difference for mortality rates among two groups (p value >0.05). Most patients in study population were in the age group of 46 to 65 years followed by 31 to 45 years. Hypertension (16%), CVA (13.33%), Diabetes Mellitus (12.67%) were common comorbid conditions in patients. Most common presenting symptom was Fever (58.00%) followed by Cough (30.67%) and Altered sensorium (28.00%). Most common source of sepsis was Respiratory tract (36.7%), Unknown Source (22.7%) followed by Nervous system infections (16.7%). Only 39 patients (26%) had positive blood (And other fluid) cultures. Escherichia coli was the most common organism isolated followed by Klebsiella spp. and Staphylococci.

Based on the definition given by ACCP patients were classified as sepsis, severe sepsis and septic shock. Accordingly, 61 patients (40.67%) were in the group of sepsis; 42 patients (28%) were in the group of severe sepsis and 47 patients (31.33%) were in the group of septic shock. In sepsis group out of 61 patients, 23 died and 38 were discharged (Mortality 37.70%), in severe sepsis group mortality was 47.61% and in septic shock group mortality was 68.08%. So as the severity of sepsis increased mortality also increased and there was statistically significant difference between mortality rates among these groups (p=0.007). Tachycardia (Heart rate >90/min) and tachypnea (Respiratory rate >24/min) were the most common SIRS parameters found in 136 patients out of 150 patients (90.67%), followed by Leucocytosis or Leucopenia (TLC <4000 or >12000) which was found in 93 patients (62%) patients, (4%) had hypothermia (Temperature <36^{0}C) and 81 patients (54%) had hyperthermia (Temperature >38^{0}C).

Median baseline RDW in sepsis group (n=61) was 15.5±2.38, in severe sepsis group (n=42) was 16.4±3.20 and in septic shock group (n=47) 18.1±4.06. RDW after 72 hours of hospitalization was 16.1%, 17.3% and 19.6% respectively in these groups. Both parameters showed strong statistically significant difference (p value 0.001 for baseline RDW and 0.002 for RDW after 72 hours of hospitalization). Median

baseline RDW in discharged group was 15.5±2.33 and 18.0±3.84 in death group. Median RDW after 72 hours in discharged group was 15.6±2.10 and 19.4±4.14 in death group. Median change in RDW from baseline to 72 hours of hospitalization was 0.00±1.55 in discharged group and 1.8±1.21 in death group. All these parameters had statistically significant difference among both groups (p value <0.001). Considering cut-off RDW value of 15%, mortality rate in patients with baseline RDW greater than 15 was 59.18% (58 patients died out of 98 patients) and in patients with baseline RDW less than 15 was 32.69% (17 patients died out of 52 patients), statistically significant difference between mortality rates was observed among two groups (p value=0.002).

Mortality rate in patients with change in RDW >0.2 from baseline was 74.16% (66 patients died out of 89) and 14.75% (9 patients died out of 61) in patients, where change in RDW was less than or equal to 0.2 from baseline, statistically significant difference between mortality rates was observed among two groups (p value 0.001). Renal dysfunction occurred in 48 patients (32%), out of which only 20 patients survived, inferring a mortality rate of 41.67%. There was no statistically significant association between renal dysfunction and outcome (p value >0.05). Other Haematological and Biochemical Parameters did not show any significant difference between "Death" and "Discharged" groups, Except Serum creatinine level on admission, which showed statistically significant difference (P value=0.006).

DISCUSSION

The present study is prospective observational study to evaluate prognostic value of baseline RDW and changes in RDW in patients with sepsis, severe sepsis and septic shock. With gathered data we also had opportunity to study clinical profile of these patients.

Most of the patients in our study were in the age group of 46 to 65 years followed by 31 to 45 years. This probably infers the occurrence of sepsis, mostly in the older age group. However, this might be a case selection bias and not necessarily has any inference on the severity of the illness. The age distribution is similar to studies done around the world. Out of 150 patients, 113 (75.33%) were males and 37 patients (24.67%) were females [Table 2]. This finding can be correlated with the fact that in general admission rates in our hospital were higher for males than females, also in Indian rural setup exposure to environmental and other factors which will directly or indirectly facilitate sepsis process is more for males than females. However, there can be other factors responsible for this such as relatively more prevalence of comorbid conditions in males and other immunological factors that need to be studied. In the study of Padkin et al. there was a predominance of men (58.8%) in their cohort of patients with severe sepsis. Similarly, there were 59.6% men in the Australian and New Zealand study.[4] In a study by Sinha M, et al. male patients were more with male-female ratio of 28:12.[5] Hypertension (16%), CVA (13.33%), Diabetes Mellitus (12.67%) were common comorbid conditions in patients. These comorbidities lie on a common spectrum, hence their prevalence in this study is more or less equal. Out of 150 patients, 106 had one or more comorbidities and 44 patients had no comorbidities. This shows that people with comorbidities are more predisposed for sepsis. Study done by Lai et al. had diabetes (38%) as most common comorbid condition.[6]

Most common presenting symptom was Fever (58.00%) followed by Cough (30.67%) and Altered sensorium (28.00%). Further fever is the most common presenting symptom in all the three groups of patients classified on the basis of severity. While "Altered sensorium" is the second most common presenting symptom after "fever" in septic shock group. The most common source of sepsis was Respiratory tract (36.7%), Unknown Source (22.7%) followed by Nervous system infections (16.7%). Respiratory infections included pneumonitis, COPD patients with secondary infections, pyothorax and lung abscess. Some patients had ARDS due to aspiration and other direct lung injury. This finding is consistent with most previous studies, which have reported respiratory infections (64%) as a most common focus for sepsis.[7] Based on the definition given by ACCP patients were classified as sepsis, severe sepsis and septic shock. Accordingly, 61 patients (40.67%) were in the group of sepsis; 42 patients (28%) in severe sepsis group and 47 patients (31.33%) in septic shock group. Most previous studies had relatively lesser number of cases in septic shock group, but in our study more number of patients in this group might be because of patients reporting late to tertiary care center after advanced stage of infective process only when their symptoms affected their routine activities. Outcome was not statistically related to source of infection. Though data regarding outcome with respect to source of sepsis is not available in previous studies, respiratory infections being the most common source, mortality is more because of sepsis from these infections. A larger study shall establish relation between source of sepsis and outcome.

Median baseline RDW in sepsis group (n=61) was 15.5±2.38, in severe sepsis group (n=42) was 16.4±3.20 and in septic shock group (n=47) 18.1±4.06. RDW after 72 hours of hospitalization was 16.1%, 17.3% and 19.6% respectively in these groups. Both parameters showed strong statistically significant difference (p value 0.001 for baseline RDW and 0.002 for RDW after 72 hours of hospitalization) [Table 3].

Median change in RDW from baseline to after 72 hours of hospitalization was 0.3±1.38 in sepsis group, 0.4±2.15 in severe sepsis group and 1.4±1.44 in septic shock group. No statistically significant difference was observed among these group as far as change in RDW from baseline to 72 hours of hospitalization is concerned (p value 0.197). So as the severity of sepsis increased, RDW also increased significantly. Median baseline RDW in discharged group was 15.5±2.33 and 18.0±3.84 in death group. Median RDW after 72 hours in discharged group was 15.6±2.10 and 19.4±4.14 in death group. Median change in RDW from baseline to 72 hours of hospitalization was 0.00±1.55 in discharged group and 1.8±1.21 in death group. All these parameters showed strong statistically significant difference among both groups (p value <0.001). Hence, RDW is not only strongly associated with severity of sepsis but also can be used as reliable prognostic marker in patients with sepsis as seen in our study. Also RDW correlates with acute changes in disease states, as change in RDW from baseline to 72 hours of hospitalization was strongly associated with outcome.

These results can be further enforced by comparing outcome in groups based on cut-off baseline RDW value. We divided patients in two groups based on baseline RDW, in one

group patients with baseline RDW <=15% and in other patients with baseline RDW >15% were kept. Mortality rate in patients with baseline RDW greater than 15 was 59.18% (58 patients died out of 98 patients) and in patients with baseline RDW less than 15 is 32.69% (17 patients died out of 52 patients) [Figure 1]. Statistically significant difference between mortality rates was observed among two groups (p value=0.002). We also divided patients based on mean change in RDW value from baseline to 72 hours after hospitalization. In one previous study done by Chan Ho Kim et al. in 2013, patients were grouped as those having change in RDW <=0.2% and those having change in RDW >0.2%.[8] In our study mortality rate in patients with change in RDW >0.2 from baseline was 74.16% (66 patients died out of 89) and 14.75% (9 patients died out of 61) in patients where change in RDW was less than or equal to 0.2 from baseline [Figure 2]. Statistically significant difference between mortality rates was observed among two groups (p value 0.001). This finding is consistent with the study of Chan Ho Kim et al. who found more mortality in patients who had change in RDW >0.2%.[8]

In one study done by Eyal Braun et al. in 2014, where 3815 patients of community acquired pneumonia were studied, they found 16.9% (32.69% in our study) mortality in patients with RDW <=15% and 21.7% (59.18% in our study) mortality in patients with RDW >15%.[9] In another study done by Nader A Mahmood et al. in 2014 RDW ≥16% was independently associated with an APACHE II score of ≥15. This suggests that septic patients with an RDW ≥16% may have a higher severity of illness.[10] In study done by Jo YH, et al. in 2013 red cell distribution width was significantly higher in non-survivors than in survivors and the corresponding mortality of patients with an RDW of 14% or less, 14.1% to 15.7% and 15.8% or greater was 13.1%, 30.1% and 44.9%, respectively (P <0.001).[11] In another study by Raúl Carrillo Esper et al. done in 2008, median RDW in discharged group was 15.9% (15% in our study) and 16.8% (16.4% in our study) in death group.[12] Other Haematological and Biochemical Parameters did not show any significant difference between "death" and "discharged" groups [Table 4], except Serum creatinine level on admission which showed statistically significant difference among two groups (P value=0.006). This might be because of our definition of renal dysfunction, which had considered patients with urine output less than 0.5 mL/kg/hour, so though renal dysfunction and outcome was not statistically related, serum creatinine level on admission was independently associated with outcome. Some of the limitations of our study were relatively small sample size and sudden death of patients with sepsis due to some other cause such as cardiac arrhythmias, acute decompensation of heart failure, etc. which might have affected outcome in these patients. However, number of such patients was negligible. Study with larger sample size and exclusion of such cases will establish association of RDW with outcome more precisely.

CONCLUSION

Based on these results, we recommend that Physicians must remain watchful of RDW in patients with sepsis. Any increase in baseline RDW should be viewed as marker of worsening patient's condition. Aggressive therapy (e.g. switching over to broad spectrum antibiotics or selecting antibiotics based on culture and sensitivity) and vitals monitoring should be done in such patients. RDW can be considered as a proxy marker for assessing patient's condition in such setups where facilities (e.g. Arterial Blood Gas Analysis) to calculate APACHE (Acute Physiology and Chronic Health Evaluation), SOFA (Sequential Organ Failure Assessment), SAPS (Simplified Acute Physiology Score) scores are not available.

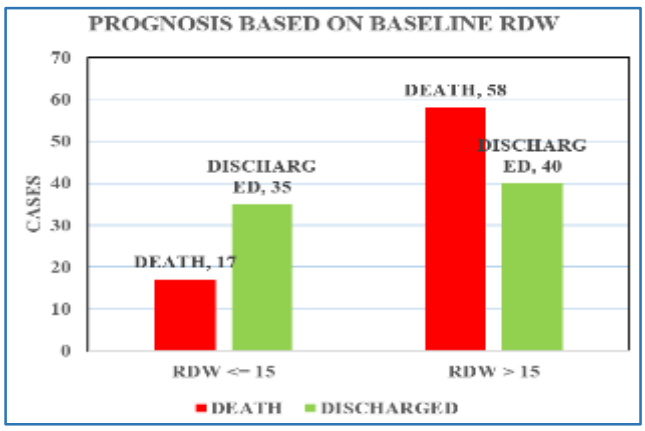

Fig. 1: Prognosis based on Baseline RDW

(RDW–Red cell distribution width expressed in percentage)

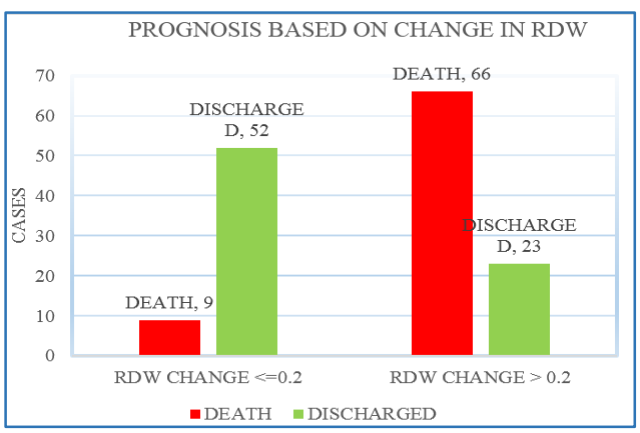

Fig. 2: Prognosis based on Change in RDW

(RDW CHANGE–Absolute difference between baseline and 72 hours' post-hospitalization red cell distribution width, RDW expressed as percentage).

SIRS	**Two or more of the following:** 1. Fever (oral temperature >38°C) or Hypothermia (<36°C). 2. Tachypnea (>24 breaths/min). 3. Tachycardia (heart rate >90 beats/min). 4. Leucocytosis (>12,000/uL), Leucopenia (<4,000/uL) or >10% bands.
SEPSIS	SIRS that has proven or suspected microbiological aetiology.
SEVERE SEPSIS	Sepsis with one or more signs of organ dysfunction.
SEPTIC SHOCK	Sepsis with Hypotension, arterial blood pressure <90 mmHg or 40 mmHg less than patient's normal value for at least 1 hour despite adequate fluid resuscitation or need of vasopressors to maintain SBP >90 mmHg.

Table 1: ACCP/SCCM Consensus Conference Committee Guidelines (1992) Modified in 2001. (SIRS–Systemic Inflammatory Response Syndrome, SBP–Systolic Blood Pressure)

Variable		Discharged (n=75)	Death (n =75)
Age Group	15 – 30	25	13
	31 – 45	20	27
	46 – 60	20	21
	61 – 75	9	9
	76 – 90	1	5
Sex	Male	58	55
	Female	17	20
Comorbid conditions	HTN	13	11
	DM	11	08
	CVA	06	14
	COPD/BA	04	04
	IHD	03	02
	CKD	03	03
	Malignancy	01	00
	Cirrhosis	01	05
Source of sepsis	Respiratory	29	26
	Urinary tract	06	00
	Gastrointestinal tract	11	09
	Cellulitis	06	03
	Neuro infection	11	14
	Puerperal	00	01
	Unknown	12	22
Severity of sepsis	Sepsis	38	23
	Severe Sepsis	22	20
	Septic Shock	15	32
Median RDW (%)	Baseline	15.5 (± 2.33)	18.0 (±3.84)
	After 72 Hours	15.6 (± 2.10)	19.4 (±4.14)
	Mean change	0.0 (±1.55)	1.8 (±1.21)
Baseline RDW	≤ 15	35	17
	> 15	40	58
Change in RDW	≤ 0.2	52	09
	> 0.2	23	66

Table 2: Comparison of epidemiological, clinical and biochemical variables in study groups. (HTN – Hypertension, DM–Diabetes Mellitus, CVA – Cerebrovascular Accidents, COPD–Chronic Obstructive Pulmonary Diseases, BA–Bronchial Asthma, IHD – Ischemic Heart Diseases, CKD – Chronic Kidney diseases, RDW – Red Blood Cell Distribution Width)

	SEPSIS (61)	SEVERE SEPSIS (42)	SEPTIC SHOCK (47)	P VALUE
MEDIAN RDW (BASELINE)	15.5 (±2.38)	16.4 (±3.20)	18.1 (±4.06)	0.001
MEDIAN RDW AFTER 72 HOURS	16.1 (±2.64)	17.3 (±3.74)	19.6 (±4.68)	0.002
MEDIAN CHANGE IN RDW	0.3 (±1.38)	0.4 (±2.15)	1.4 (±1.44)	0.197

Table 3: RDW Changes with Severity of Sepsis

(RDW–Red blood cell distribution width in percentage).

Parameter	Median among Discharged	Median among Death	P value
WBC COUNT	13200	13600	0.479
RBC COUNT	4.3	4.11	0.416
HAEMOGLOBIN	10.7	10.5	0.321
MCV	84.10	85.10	0.452
MCH	26.5	26.7	0.569
MCHC	29.5	29.1	0.060
PLATELET COUNT	206000	176000	0.068
MPV	9.3	9.8	0.053
RBS	104.5	92	0.071
SERUM CREATININE	0.89	1.21	0.006

Table 4: Comparison of various parameters for prognosis. (Haematological parameters expressed in standard units, RBS–Random blood sugar in mg%, Serum creatinine values in mg%)

REFERENCES

1. Chiari MM, Bagnoli R, De Luca PD, et al. Influence of acute inflammation on iron and nutritional status indexes in older inpatients. J Am Geriatr Soc 1995;43(7):767–71.
2. Pierce CN, Larson DF. Inflammatory cytokine inhibition of erythropoiesis in patients implanted with a mechanical circulatory assist device. Perfusion 2005;20(2):83–90.
3. Ujszaszi A, Molnar MZ, Czira ME, et al. Renal function is independently associated with red cell distribution width in kidney transplant recipients: a potential new auxiliary parameter for the clinical evaluation of patients with chronic kidney disease. Br J Haematol 2013;161(5):715–25.
4. Padkin A, Goldfrad C, Brady A. Epidemiology of severe sepsis occurring in the first 24 hrs in intensive care units in England, Wales and Northern Ireland. Crit care 2003;31:2332-8.
5. Sinha M, Desai S, Mantri S, et al. Procalcitonin as an adjunctive biomarker in sepsis. Medknow Publications and Media Pvt. Ltd. Indian J Anaesth 2011;55(3):266–70.
6. Lai CC, Chen SY, Wang CY, et al. Diagnostic value of procalcitonin for bacterial infection in elderly patients in the emergency department. J Am Geriatr Soc 2010;58(3):518–22.
7. Kasper, Fauci, Longo, et al. Harrison's principles of internal medicine. McGraw Hill. 2015;19th ed:1751-1759.
8. Kim CH, Park JT, Kim EJ, et al. An increase in red blood cell distribution width from baseline predicts mortality in patients with severe sepsis or septic shock. Crit Care 2013;17(6):R282.
9. Braun E, Kheir J, Mashiach T, et al. Is elevated red cell distribution width a prognostic predictor in adult patients with community acquired pneumonia? BMC Infect Dis 2014;14(1):129.
10. Mahmood NA, Mathew J, Kang B, et al. Broadening of the red blood cell distribution width is associated with increased severity of illness in patients with sepsis. Int J Crit Illn Inj Sci 2015;4(4):278–82.
11. Jo YH, Kim K, Lee JH, et al. Red cell distribution width is a prognostic factor in severe sepsis and septic shock. Am J Emerg Med 2013;31(3):545–8.
12. Raúl Carrillo Esper, Vladimir Contreras Domínguez, Luis. Red blood cell distribution width changes in septic patients. Med Crit y Ter Int 2008;22(1):20–5.