"ROLE OF RED CELL DISTRIBUTION WIDTH IN PREDICTING THE OUTCOME IN PATIENTS WITH SEVERE SEPSIS AND SEPTIC SHOCK"

By

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LIST OF CONTENTS

Sl No	Title	Page No
1	**INTRODUCTION**	11
2	**REVIEW OF LITERATURE**	14
3	**AIMS & OBJECTIVES**	21
4	**METHODOLOGY**	26
5	**RESULTS**	28
6	**DISCUSSION**	51
7	**STRENGTHS & LIMITATIONS**	56
8	**SUMMARY & CONCLUSION**	58
9	**BIBLIOGRAPHY**	59
10	**ANNEXURES** **I. ETHICAL CLEARANCE CERTIFICATE** **II. PATIENT CONSENT FORM** **III. PROFORMA** **IV. SOFA SCORE** **V. APACHE II SCORE**	 64 65 67 73 74

LIST OF TABLES

Sl. No.	TABLE	Page No.
1	WHO CUT-OFF VALUES OF HEMOGLOBIN (G/DL) TO DIAGNOSE ANAEMIA	14
2	DISTRIBUTION OF CASES BY AGE	28
3	DISTRIBUTION OF CASES BY GENDER	30
4	DISTRIBUTION OF CASES BY DURATION OF ADMISSION	31
5	DISTRIBUTION OF CASES BY SITE OF SEPSIS	32
6	DISTRIBUTION OF CASES BY NUMBER OF ORGAN FAILURES	34
7	DISTRIBUTION OF CASES BY COMORBIDITIES	35
8	COMPARISON OF DEMOGRAPHIC & CLINICAL DATA BETWEEN SURVIVORS AND NON-SURVIVORS	36
9	COMPARISON OF LABORATORY PARAMETERS BETWEEN SURVIVORS AND NON-SURVIVORS	37
10	MULTIVARIATE LOGISTIC REGRESSION ANALYSIS OF VARIABLES PREDICTIVE OF INHOSPITAL MORTALITY IN PATIENTS WITH SEVERE SEPSIS	50

LIST OF FIGURES

Sl No.	FIGURE	Page No.
1	DISTRIBUTION OF CASES BY AGE	29
2	DISTRIBUTION OF CASES BY GENDER	30
3	DISTRIBUTION OF CASES BY DURATION OF ADMISSION	31
4	DISTRIBUTION OF CASES BY SITE OF SEPSIS	32
5	DIAGRAMIC REPRESENTATION OF DISTRIBUTIONOF CASES BY SITE OF SEPSIS	33
6	DISTRIBUTION OF CASES BY NUMBER OF ORGAN FAILURES	34
7	DIAGRAMMATIC REPRESENTATION OF DISTRIBUTION OF CASES BY NUMBER OF ORGAN FAILURES	35
8	DISTRIBUTION OF CASES BY COMORBIDITIES	36
9	DIAGRAMMATIC REPRESENTATION OF SEX DISTRIBUTION BETWEEN SURVIVOR AND NON-SURVIVOR GROUPS	38
10	DIAGRAMMATIC REPRESENTATION OF SEX DISTRIBUTION BETWEEN SURVIVOR AND NON-SURVIVOR GROUPS	38
11	BOX PLOT SHOWING THE DIFFERENCE IN APACHE II SCORE AT ADMISSIONBETWEEN SURVIVORS AND NON-SURVIVORS	40
12	BOX PLOT SHOWING THE DIFFERENCE IN SOFA SCORE AT ADMISSION BETWEEN SURVIVORS AND NON-SURVIVORS	40
13	RECEIVER OPERATING CHARACTERISTIC CURVES FOR APACHE II SCORE, SOFASCORE AND RDW FOR PREDICTION OF INHOSPITAL MORTALITY IN PATIENTS WITH SEVERE SEPSIS	48
14	DIAGRAMMATIC REPRESENTATION OF CORRELATION BETWEEN RDW ANDAPACHE II SCORE AT ADMISSION IN THE STUDY POPULATION	49

ABBREVIATIONS

SS	Severe sepsis
SIRS	Systemic inflammatory response syndrome
RDW	Red cell distribution width
RDW - CV	Red cell distribution width – coefficient of variation
RDW - CV	Red cell distribution width – standard deviation
IL	Interleukin
TNF	Tumor necrosis factor
CBC	Complete blood count
APACHE II	Acute physiology and chronic health evaluation II
SOFA	Sequential organ failure assessment
SD	Standard deviation
IQR	Interquartile range
RAAS	Renin angiotensin aldosterone system
MCV	Mean corpuscular volume
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MAP	Mean arterial pressure
ScVO2	Central venous oxygen saturation
CVP	Central venous pressure
TLC	Total leucocyte count
DLC	Differential leucocyte count
ESR	Erythrocyte sedimentation rate

RBS	Random blood sugar
RPI	Reticulocyte production index
PT	Prothrombin time
PTI	Prothrombin time index
aPTT	Activated partial thromboplastin time
ECG	Electrocardiogram
SGOT	Serum glutamate oxaloacetate transaminase
SGPT	Serum glutamate pyruvate transaminase
ALP	Alkaline phosphatase
ROC	Receiver operating characteristic
AUC	Area under curve
ANOVA	Analysis of variance
CNS	Central nervous system
CVS	Cardiovascular system
CKD	Chronic kidney disease
CLD	Chronic liver disease

INTRODUCTION

In the twentieth century, the epidemiology of many diseases changed dramatically over the world. While the worldwide burden of lethal diseases such as smallpox, plague, and cholera has decreased substantially, non-communicable diseases have increased medical attention. The word sepsis" comes from the Greek word "sepo", meaning decay or putrefaction, which describes the decomposition of organic matter in a manner that results in decay and death (Geroulanos et al., 2006).

Sepsis is a severe life-threatening clinical condition that has cost humanity heavily since time immemorial, both in morbidity and mortality. Often described as a continuum, the clinical complex of sepsis, severe sepsis (SS), and septic shock has been found to have increased incidence throughout the world, especially in recent decades.[1,2]

In 1992, an international consensus panel defined sepsis as a systemic inflammatory response to infection, emphasising that sepsis can result from various infectious sources. The panel coined the term "severe sepsis" ("SS") to denote sepsis complicated by immediate organ failure. At the same time, "septic shock" was defined as sepsis complicated by either hypotension refractory to fluid resuscitation or hyperlactatemia. In 2003, a second consensus panel endorsed most of these concepts. The caveat is that signs of the systemic inflammatory response, such as tachycardia or an elevated white-cell count, occur in many infectious and non-infectious conditions. [3]

The severity of illness and the intrinsic mortality risk increase from systemic inflammatory response syndrome (SIRS) to multi-organ failure due to sepsis, severe sepsis, and septic shock. Estimates of mortality vary; however, Severe Sepsis and Septic Shock have actual fatality rates, maybe as high as 46%. Prognostication in severe sepsis may facilitate more aggressive management. Many prognostic factors such as age, sex, comorbidities,

biomarkers and severity of illness scores like Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE), etc., have been associated with the outcome in cases of severe sepsis.[4-6]

Red cell distribution width (RDW) is a measure of variability in the size of circulating RBCs and can be elevated in conditions where reticulocytes are released into the circulation. Besides its role in evaluating anaemia, recent studies have reported that RDW is also associated with prognosis in patients with congestive heart failure, acute myocardial infarction, pulmonary embolism, community-acquired pneumonia, critical illness, stroke, cardiac arrest, rheumatoid arthritis and metabolic syndrome.[2,7-13]

The association between RDW and adverse outcomes was shown to be independent of covariates such as nutritional status, anaemia, inflammatory markers, and significant comorbidities in these investigations. The exact mechanism of elevated RDW in these patients is unknown; however, a greater extent of the inflammation and oxidative stress has been suggested to reduce RBC survival and suppress maturation of RBCs resulting in the release of large premature RBCs into circulation to elevated levels of RBCs RDW.[14-16] The inflammatory process is essential in the pathophysiology of sepsis. A complete blood count (CBC) is a test performed on practically all sepsis patients admitted to emergency rooms worldwide. Most institutions now use automated haemocytometers to do CBCs. RDW is regularly included in automated haemocytometer CBCs and, hence, can predict outcomes in cases of sepsis/severe sepsis/septic shock in a timely and cost-effective manner.

Prognostication in acute cases when patients with sepsis/severe sepsis/septic shock are hospitalised has gained very little attention. In these scenarios, clinicians and researchers may find simple prognostic tools valuable, especially if they are affordable, quick to assess, and already frequently obtained in practice. RDW satisfies all of these standards. No recent studies have looked at the association between RDW and sepsis/severe sepsis/septic shock in India. Given the ever-increasing patient load and shortage of health resources, it is critical to implement enhanced prognostication approaches to allocate resources effectively. RDW has the potential to be a valuable tool in the prognostication of cases with sepsis/severe sepsis/septic shock.

REVIEW OF LITERATURE

Sepsis is a complex, dynamic and resource-demanding clinical entity frequently encountered in critical care settings. It has sparked widespread worry due to its complex, severe, and worldwide distribution. Sepsis was first mentioned in Hippocrates' writings and is derived from the Greek term "sepo," which means "I rot." The understanding of sepsis has advanced significantly in recent years. Medical research into coronary artery disease, stroke, and cancer has undoubtedly improved in recent decades, but the global increase in the frequency of sepsis has been enormous.

Sepsis may have been perceived with a humbler eye a couple of decades ago, but now the scenario has changed. Once easily treatable with antimicrobials, several common microorganisms have camouflaged themselves with a diverse armamentarium of antimicrobial resistance, belittling the available antibiotic arsenal. No longer being a local or regional public health problem, sepsis now demands a global perspective on an urgent basis. What makes the situation even worse in developing countries like India has limitations of resources (drugs, infrastructure and human resources). The high prevalence of HIV/AIDS and delayed referrals pose further challenges to healthcare providers in developing countries.

Early diagnosis and prompt institution of antibiotic therapy form the cornerstone of sepsis management. There is an urgent need for tools to assess the severity of sepsis for early identification and prognostication of sicker patients who warrant aggressive treatment and monitoring.

Sepsis has a high worldwide burden. Martin et al. evaluated the epidemiology of sepsis between 1979 and 2000 in the United States and showed an 8.7% annual increase in the incidence of sepsis. In the United States, approximately 750,000 cases of sepsis occur each year, about 50-90 patients per 1,00,000 population. Out of these, at least 225,000 succumb to their illnesses.[1] Sepsis has been reported to be the second leading cause of death in non-coronary intensive care units, and overall, it is the tenth leading cause of death. Roughly 9% of patients with sepsis progress to severe sepsis, and 3% of those with severe sepsis experience septic shock, accounting for 10% of admissions to intensive care units.[17] Organ failure occurs in 33.6% of the patients with sepsis. Severe sepsis carries estimated 30-50% mortality. 70% of the patients with three or more organ failures die. Those who survive sepsis have been found to have a lower quality of life compared to the general population.[1,18-22]

Changing demographics, the rise of antibiotic resistance, and the growing use of more potent and broader-spectrum antibiotics have been suggested as factors of rising sepsis rates worldwide. [22] By standardising terms, such as sepsis, the ability to compare protocols and evaluate therapeutic interventions have significantly improved. The systemic response to infection has been termed sepsis. It is apparent that a similar, or even identical, the response can arise in the absence of illness in conditions like burns, acute pancreatitis, etc. The term systemic inflammatory response syndrome (SIRS) describes this inflammatory process, independent of its cause. This systemic inflammatory response syndrome includes but is not limited to more than one of the

following clinical manifestations:

(i) a body temperature greater than 38.3 0C or less than 36 0C;

(ii) a heart rate greater than 90 beats per minute;

(iii) respiratory rate greater than 24 breaths per minute, and

(iv) an alteration in the white blood cell count, such as a count greater than 12,000/mm3, a count less than 4,000/mm3, or the presence of more than 10% immature neutrophils ("bands").

Sepsis and its sequelae represent a continuum of clinical and pathophysiologic severity. The severity of illness may independently affect prognosis. Severe sepsis is defined as sepsis associated with organ dysfunction, hypoperfusion abnormality, or sepsis-induced hypotension. Hypoperfusion abnormalities include lactic acidosis, oliguria, and acute alteration of mental status. Sepsis-induced hypotension is defined by the presence of systolic blood pressure of less than 90 mmHg or its reduction by 40 mm Hg or more from baseline in the absence of other causes for hypotension (e.g., cardiogenic shock).

The RDW is the coefficient of variation of the RBC volume distribution curve or the standard deviation. It represents the size variation of all the red blood cells in an individual patient. The RDW is ordered routinely as part of a complete blood count by automated analysers. RDW ranges typically between 11.5% and 14.5%. Elevated RDW can result from any disease process that causes the premature release of reticulocytes into the circulation. RDW is frequently high in ineffective red cell production (such as iron deficiency, B12 or folate deficiency, and hemoglobinopathies), increased red cell destruction (such as hemolysis), or after blood transfusion.

Elevations in RDW are associated with elevated inflammatory markers (tumour necrosis factor α, interleukin 6, interleukin 1β, etc.), affecting RBC survival and maturation.[16,23] Inflammation adversely affects erythropoiesis by various mechanisms, including direct suppression of erythroid precursors in bone marrow, promoting RBC apoptosis, reducing erythropoietin production, and reducing the bioavailability of iron and erythropoietin resistance in erythroid precursor cell lines.[14,24-27]

Increased oxidative stress has also been studied as a mediator of raised RDW.

High oxidative stress is present in sepsis through the generation of reactive oxygen species by activated leucocytes.[28] High oxidative stress contributes to elevated RDW by decreasing RBC survival and promoting the release of large premature RBCs into the peripheral circulation.[29] In addition, sepsis alters RBC membrane glycoproteins and ion channels which contribute to a change of RBC morphology. Patel KV et al. showed that RDW predicted mortality in adults more than 44 years old in the general population.[34]

Bazick HS et al. investigated the association between RDW and all-cause mortality in a large group of critically ill patients. This study analysed results from more than fifty thousand sick critically patients, including 13.5% of patients who had sepsis at admission. This study demonstrated a significant graded relationship between RDW and all-cause mortality and between RDW and bloodstream infection. Authors have quoted it as the first study to show a significant association between RDW and mortality in patients with sepsis. RDW was demonstrated to be a significant predictor of 30-, 90-, and 365-day mortality, in-hospital mortality, and bloodstream infection.

In addition to inflammation and oxidative stress, the RDW–mortality association in this study was also attributed to neurohumoral response due to arterial underfilling, which involves arginine vasopressin renin-angiotensin-aldosterone system (RAAS), and the sympathetic nervous system. Activation of the renin-angiotensin system triggers an acceleration of erythrocyte production resulting in an increased RDW through macrocytosis related to skipped cell divisions. Such arterial underfilling is common in cardiac failure and sepsis. This study had a retrospective observational design with its inherent biases, and it also did not include physiological data. APACHE (Acute Physiology and Chronic Health Evaluation) and other physiological-based scoring systems are strong predictors of mortality in the critically ill. Despite multivariable adjustment of potential confounders, the absence of physiological data remains a limitation of this study.[15, 30,31]

Jo et al. studied the association of RDW with 28-day mortality in patients with severe sepsis and septic shock.[32] They compared demographic, clinical and laboratory parameters including RDW at admission and APACHE II score between 28-day survivors and non-survivors. A total of 566 patients were consecutively included, and overall mortality was 29%. "Surviving Sepsis Campaign: international protocols for the management of severe sepsis and septic shock" were used to treat patients with severe sepsis and septic shock. RDW was measured initially at admission to the emergency department irrespective of diagnosis and severity, so the measurement time of RDW was uniform. In addition to mortality, the APACHE II score and the outcomes of patients were also evaluated in the study. RDW was significantly higher in non-survivors as compared to survivors. Moreover, they demonstrated a significant graded relationship between RDW and 28-day mortality across the RDW tertiles ($P<.001$). [(32)]

They also observed that age, presence of urinary tract infection, history of chronic liver disease, pH, blood urea nitrogen, creatinine, albumin, and APACHE II score were independent predictors on multivariate analyses. This study had a retrospective design, and it was done in a single institution. Iron, folate, and vitamin B12 levels were not measured, which could have influenced RDW. Owing to its retrospective design, history regarding blood transfusion before inclusion in the study was not available, which is considered to be a significant confounder of raised RDW.[32]

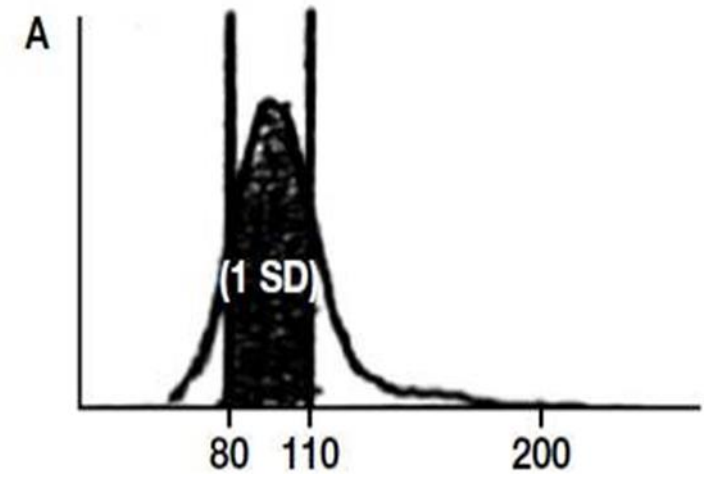
Red cell distribution width (RDW) estimation – methodological details

RDW is essentially the most commonly used parameter of a degree of anisocytosis of the red blood cell population and is available on most of the automated haematology analysers. It can be expressed either as RDW-coefficient of variation (RDW-CV), which is reported as a percentage (%) or RDW- standard deviation (RDWSD), which is reported in femtolitres (fL). RDW-CV and RDW-SD measure the dispersion of data around the mean. The standard deviation increases as the data become more dispersed (SD). Both approaches employ standard deviation (SD) to calculate the degree of anisocytosis, but they do it differently.

RDW-CV

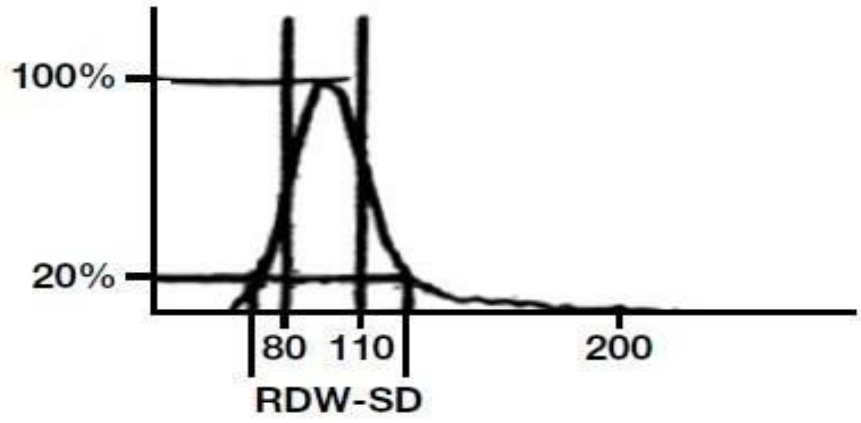
It measures dispersion through a ratio of SD (Standard deviation) to MCV (Mean corpuscular size), Hence, it is expressed as a percentage, and both SD and MCV influence it.

$$\textbf{RDW-CV} = \frac{\textbf{Standard deviation (SD)}}{\textbf{Mean corpuscular volume (MCV)}} \times 100$$



RDW-SD

It is a direct measure of RDW, measured as the arithmetic width of the red cell distribution curve (RBC histogram) at a 20% frequency level. To eliminate interference in the computation of RDW, information or particles below the 20% frequency threshold are removed. On the right side of the curve, these include aperture artefacts, cell coincidence, doublets, triplets, and agglutinates, while on the left side, they include electrical interference, platelet clumping, and megathrombocytes.



AIMS AND OBJECTIVES OF THE STUDY

1. To study the role of red cell distribution width in predicting the outcome in patients with severe sepsis and septic shock during hospital stay.
2. To assess the correlation between RDW and the need for life-saving procedures like vasopressor usage, mechanical ventilation, renal replacement therapy in patients with severe sepsis and septic shock.

MATERIALS AND METHODS

Study site

The study was conducted in Patients with Severe Sepsis admitted to BLDE (DU) Shri BM. Patil Medical College Hospital and Research Centre, Vijayapura, from November 2019 to April 2021.

Study design

It was a single center prospective observational study.

Study population

Ninety-six adult (≥18 years old) medical patients admitted for more than 24 hours with an admission diagnosis of severe sepsis/septic shock fulfilling all inclusion criteria were included in the study.

Inclusion criteria

The study included following patients:

a) Age 18 years or more;

b) Intensive care stay for more than 24 hours;

c) Two or more of the following conditions:

- Fever (oral temperature >38.3°C) or hypothermia (<36°C);
- Tachypnea (>24 breaths/min);
- Tachycardia (heart rate >90 beats/min);
- Leucocytosis (>12000/mm^3), leukopenia (<4000/mm^3), or >10% bands;

- Altered mental status [Glasgow coma scale (GCS) <9]
- Significant edema or positive fluid balance (>20 mL/kg over 24 hours)
- Hyperglycaemia (glucose >140 mg/dl) in the absence of diabetes

d) Documented source of infection anywhere, either clinically or by laboratory/ radiological investigation/s

e) With concurrent evidence of acute organ dysfunction (33) defined as follows:

- **Cardiovascular system**: Arterial systolic blood pressure ≤90mmHg or mean arterial pressure ≤70 mmHg that responds to administration of intravenous fluid
- **Pulmonary system**: with Pao_2/Fio_2 less than 250 in the absence of pneumonia as infection source, Pao_2/Fio_2 < 200 in the presence of pneumonia as infection source
- **Renal system**: Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation or creatinine > 2.0 mg/dL
- **Hematologic system**: platelet count less than 100,000/mm^3 or 50% decrease in platelet count from the highest value recorded over previous 3 days
- **Unexplained metabolic acidosis**: A pH ≤7.30 or a base deficit 5.0 mEq/L and a plasma lactate level above upper limits oflaboratory normal
- **Central nervous system**: Altered mental status [Glasgow coma scale (GCS) <9]

- **Gastrointestinal system**: presence of at least one of the following gastrointestinal problems documented inpatient data during their stay: food intolerance, gastrointestinal haemorrhage, and ileus. Food intolerance is the inability to feed the patient via nasogastric tube due to vomiting or nasogastric aspirate volumes more significant than those previously given enterally. Gastrointestinal haemorrhage is defined as the visual presence of blood in nasogastric tube aspirates or stool. Ileus is definedas intestinal obstruction due to inhibition of bowel motility.

Exclusion Criteria:

a) Who did not give consent for the study (refusal of informed consent)

b) Patients younger than 18 years

c) Pregnancy

d) Packed red blood cells transfusion in the previous week

e) Medical history of haematological disorders such as leukaemia, myelodysplastic syndrome, neoplastic metastases to the marrow

f) Recent chemotherapy

g) Chronically immunosuppressed (defined as immunosuppression for solid organ transplantation, post-splenectomy, receiving ≥10 mg/d prednisolone or equivalent for ≥30 days, treatment with other immunosuppressive agents, or neutropenia [neutrophils $\leq 1.0 \times 10^9$/L])

METHODOLOGY

Ninety-six adult (≥18 years old) medical patients admitted for more than 24 hours with an admission diagnosis of severe sepsis/septic shock fulfilling all inclusion criteria and exclusion criteria were evaluated. Various demographic, clinical and laboratory parameters of patients were recorded in a predesigned proforma.

Informed consent was obtained from patients or next of kin.

A. After admission to the intensive care unit, each patient was evaluated, and the following parameters were recorded in a predesigned instrument:
B. Demographic data, clinical history and physical examination findings
C. Underlying or concomitant diseases
D. Main diagnostic categories leading to intensive care unit admission
E. Chest X-ray
F. 12 lead ECG
G. Arterial blood gas
H. Hemogram (Hemoglobin, TLC, DLC, ESR, platelet count, RDW, MCV, MCH, MCHC and peripheral blood smear). RDW was measured as a part of the automated complete blood count (CBC) using Sysmex XN1000, and the reference range of our institution is 11.5%to 14.5%
I. Random blood sugar, serum electrolytes
J. Renal function test (blood urea and creatinine)
K. Liver function test (SGOT, SGPT, ALP, total protein, albumin, total and indirect bilirubin)

L. Patients found to have anaemia (as per WHO criteria to diagnose anaemia) were further classified based on RBC indices (MCV, MCH, MCHC) and peripheral blood smear into either of the following

- microcytic (< 80 fL), normocytic or macrocytic (MCV > 96 fL).

Table No. 1. WHO cut-off values of haemoglobin (g/dL) to diagnose anaemia

Population	**Non -Anaemia**	**Anaemia**		
		Mild	**Moderate**	**Severe**
Non-pregnant women (15 years of age and above)	12.0 or higher	11.0-11.9	8.0-10.9	lower than 8.0
Pregnant women	11.0 or higher	10.0-10.9	7.0-9.9	lower than 7.0
Men (15 years of age and above)	13.0 or higher	11.0-12.9	8.0-10.9	lower than 8.0

M. The severity of illness was assessed by calculation of sequential organ failure assessment (SOFA) score and Acute physiology and chronic health evaluation (APACHE II) score from data collected during the first 24 hrs following admission

N. Need of inotrope/vasopressor therapy

O. Need of mechanical ventilation,

P. Development and details of organ failure

Q. Total duration of hospital stay

STATISTICAL ANALYSIS

- Numerical variables will be presented as Mean ±SD, and categorical variables will be presented as frequency (%) and diagrams
- Comparison of numerical variables between groups will be found using unpaired t-test/ Anova test and categorical variables by Chi-square or Fisher's Exact test.
- For predicting ROC curve will be used.
- Furthermore, the association between variables will be found using the chi-square test/Fisher's Exact test, and Quantitative data will be compared using independent t-test/ Anova test.
- Data will be collected using a pretested proforma meeting the objectives of the study. Detailed history, physical examination and necessary investigations will be undertaken. The purpose of the study will be explained to the patient, and informed consent will be obtained.

OBSERVATIONS AND RESULTS

Ninety-six patients who fulfilled the criteria for severe sepsis admitted to the intensive care unit were enrolled and prospectively evaluated in the study period from NOV 2019 to APR 2021.

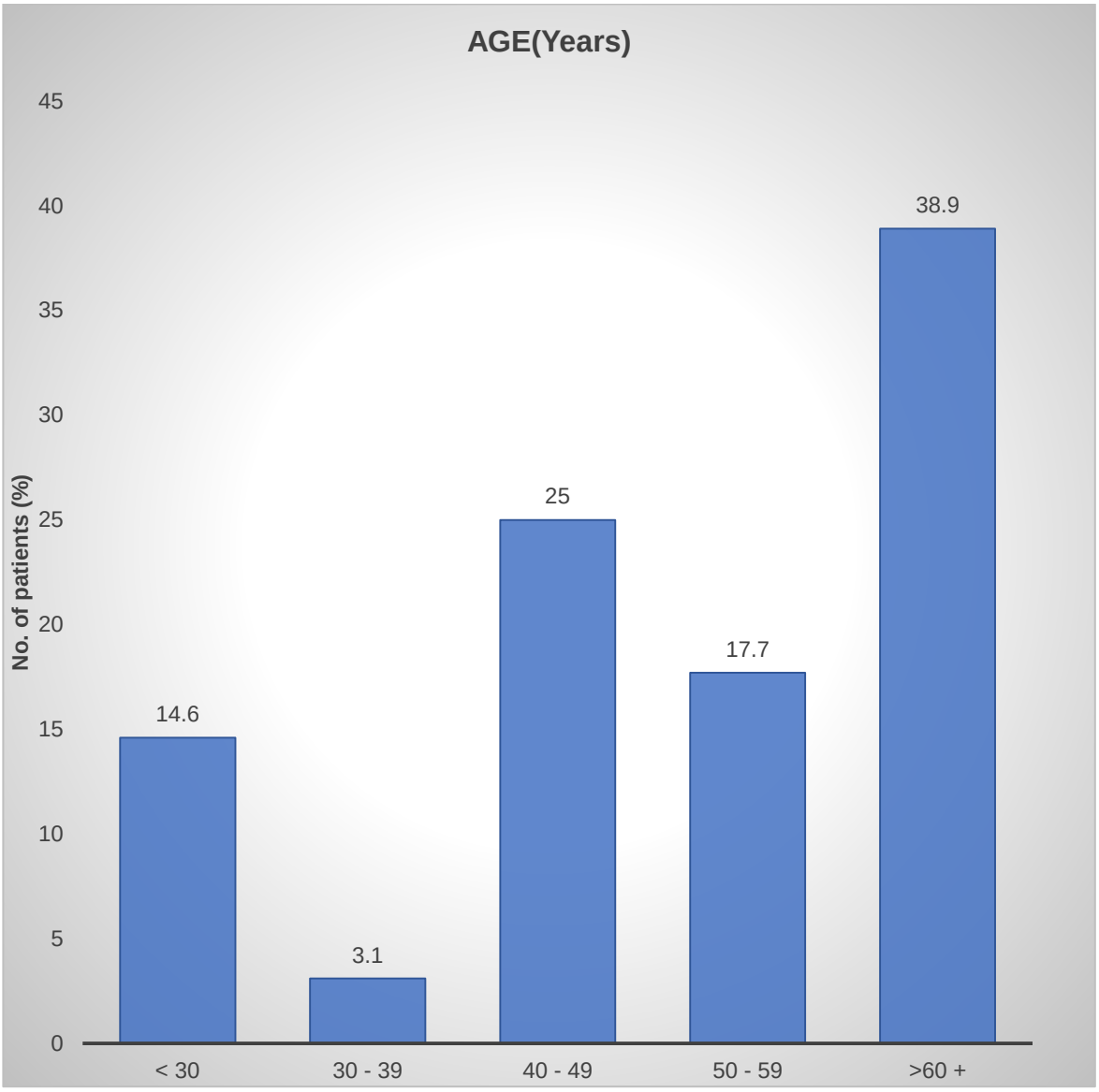
DISTRIBUTION OF CASES BY AGE

Among Ninety-six patients, the Mean age of the study population was 52.99 ± 16.9 years (range 22 -80 years), and most of the patients are greater than 60 years.

TABLE 2: DISTRIBUTION OF CASES BY AGE

Age (Years)	No. Of patients	Percentage
< 30	14	14.6
30 – 39	3	3.1
40 – 49	24	25.0
50 – 59	17	17.7
60+	38	39.6
Total	96	100.0

FIGURE 1: DISTRIBUTION OF CASES BY AGE



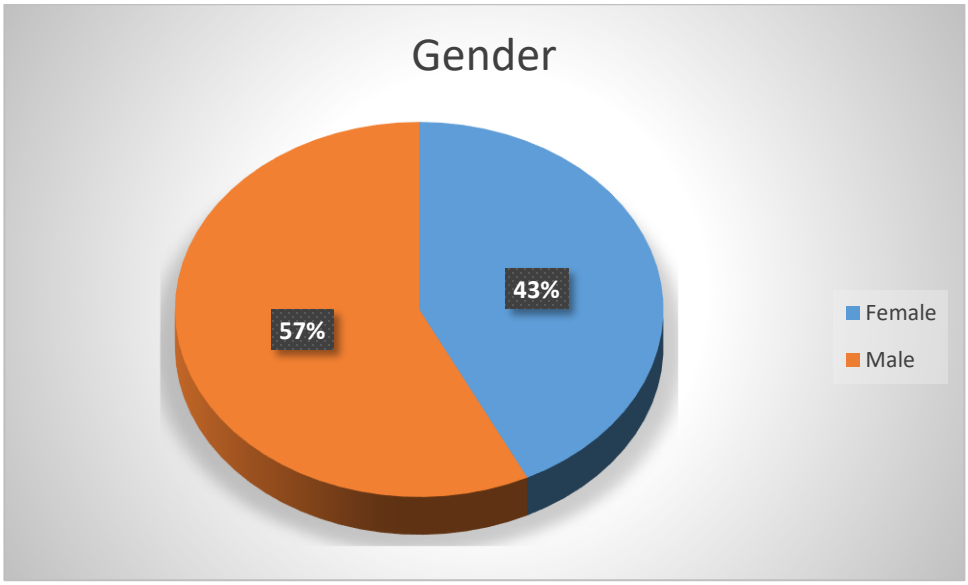
DISTRIBUTION OF CASES BY GENDER

In this study, the number of male and female case distribution in total 96 cases are found to be 55 males (57.3%) and 41 females (42.7%).

TABLE 3: DISTRIBUTION OF CASES BY GENDER

SEX	No. of patients	Percentage
Male	55	57.3
Female	41	42.7
Total	96	100.0

FIGURE 2: DISTRIBUTION OF CASES BY GENDER

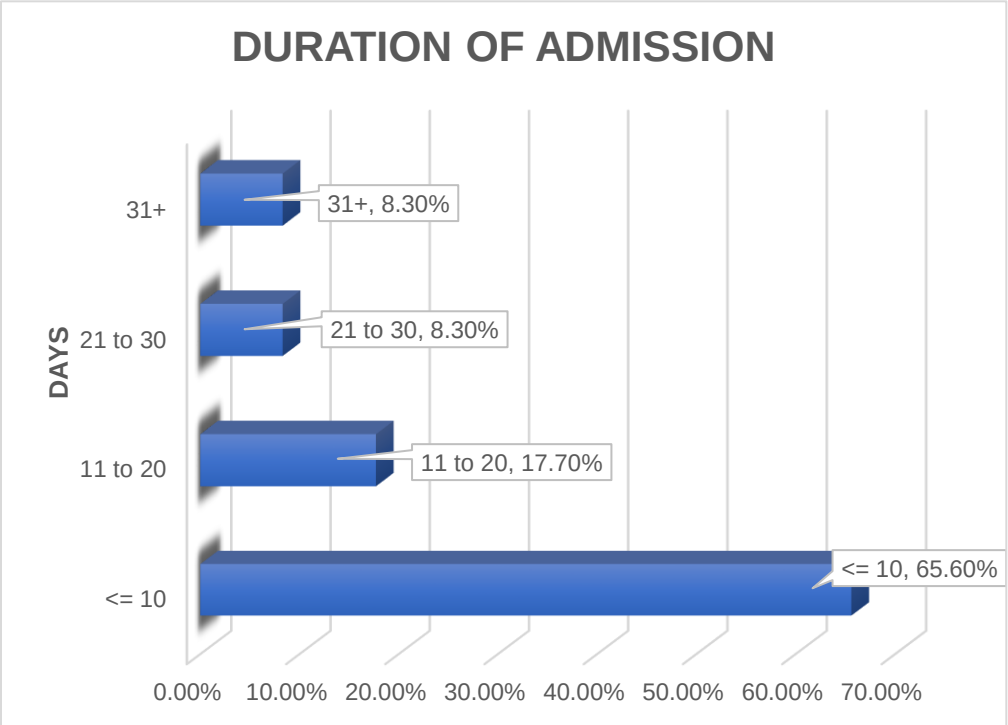


DISTRIBUTION OF CASES BY DURATION OF ADMISSION

Table 4: DISTRIBUTION OF CASES BY DURATION OF ADMISSION

DURATION OF ADMISSION	No. of patients	Percentage
<= 10	63	65.6
11 – 20	17	17.7
21 – 30	8	8.3
31+	8	8.3
Total	96	100.0

FIGURE 3: DISTRIBUTION OF CASES BY DURATION OF ADMISSION



The mean duration of hospital stay was 11.4±10.02 days with a minimum of 2 days and a maximum of 45 days. Non-survivors had spent a lesser number of days in hospital when compared to survivors.

DISTRIBUTION OF CASES BY SITE OF SEPSIS

Table 5: DISTRIBUTION OF CASES BY SITE OF SEPSIS

Site of sepsis	No. of patients	Percentage
Respiratory	35	36.5
Urogenital Tract	52	54.2
Abdominal	50	52.1
Skin And Soft Tissue	9	9.4
CVS	2	2.1
CNS	38	39.6

FIGURE 4: DISTRIBUTION OF CASES BY SITE OF SEPSIS

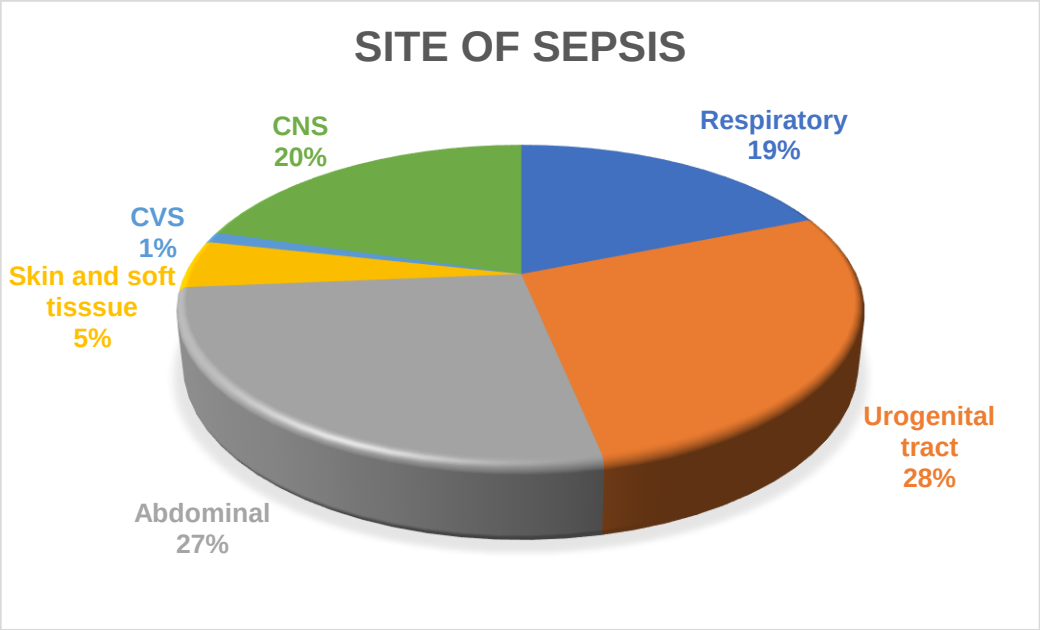
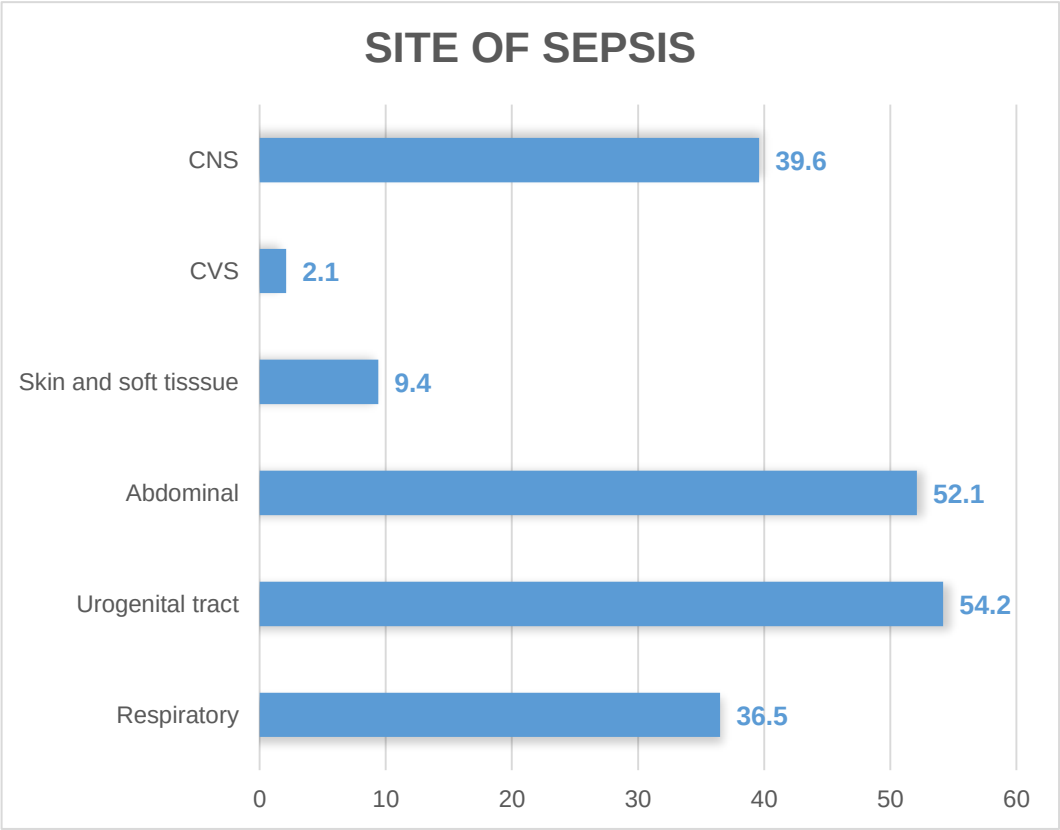


FIGURE 5: DIAGRAMMATIC REPRESENTATION OF DISTRIBUTION OF CASES BY SITE OF SEPSIS



In this study, the most commonsite of sepsis at presentation was urogenital tract (54.2%), followed by abdomen (52%), CNS (39.6%), respiratory tract (36.5%) skin and soft tissue (9.4%) and the least being cardiovascular system (2.1%) at presentation.

Forty-three (44.79%) patients were chronic alcohol consumers, and 55 patients (57.29%) were smokers.

DISTRIBUTION OF CASES BY NUMBER OF ORGAN FAILURES

Table 6: DISTRIBUTION OF CASES BY NUMBER OF ORGAN FAILURES

NUMBER OF ORGAN FAILURES	No. of patients	Percentage
1	20	20.8
2	45	46.9
3	24	25.0
≥4	7	7.3
Total	96	100.0

FIGURE 6: DISTRIBUTION OF CASES BY NUMBER OF ORGAN FAILURES

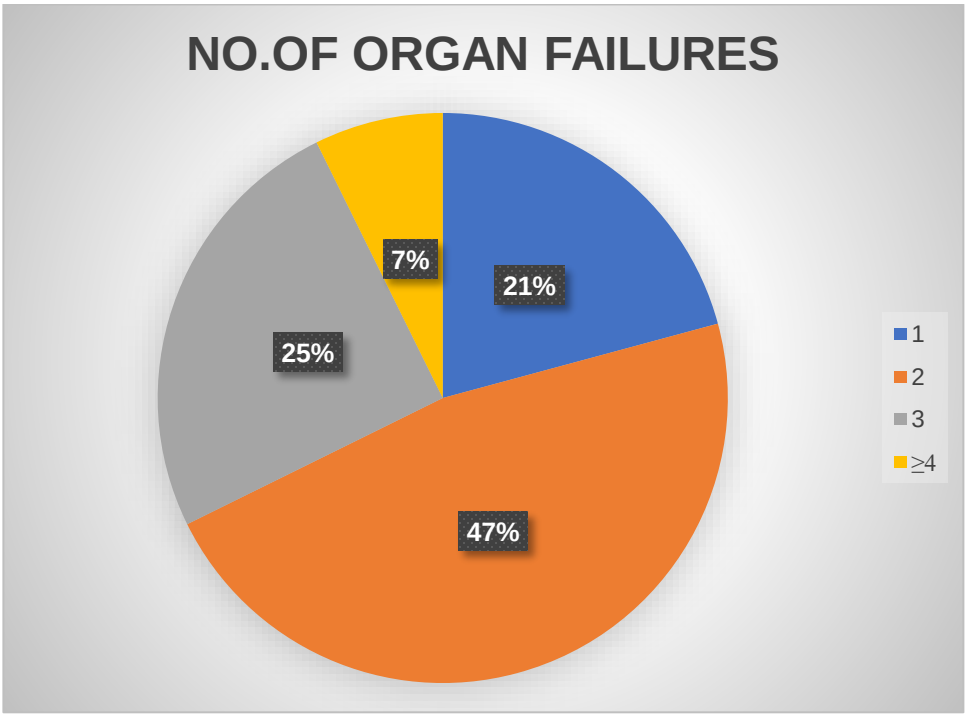
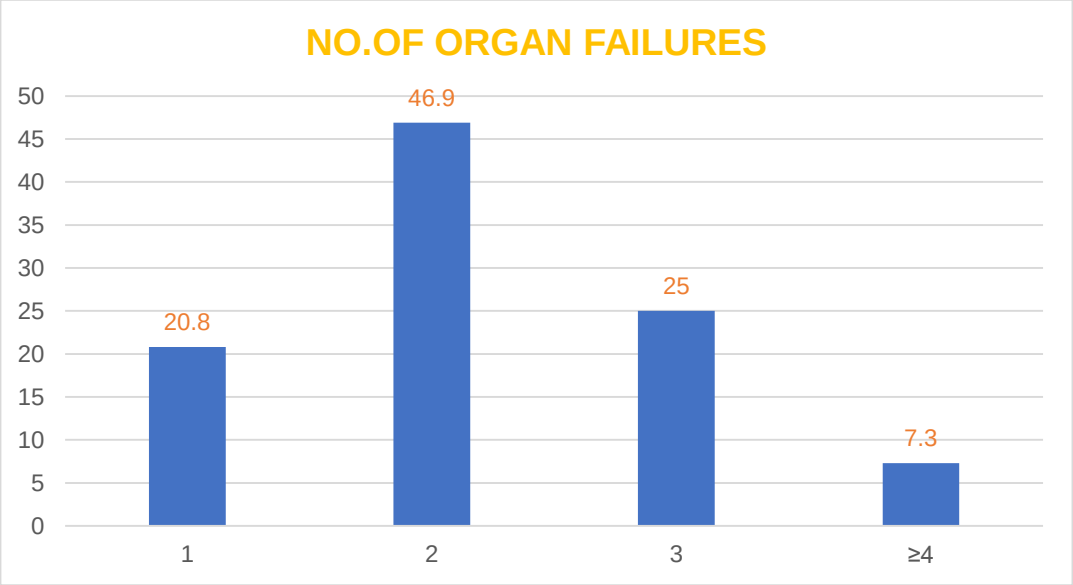


FIGURE 7: DIAGRAMMATIC REPRESENTATION OF DISTRIBUTION OF CASES BY NUMBER OF ORGAN FAILURES



Among the study cohort, twenty (20.8%) patients had one organ failure, forty- five (46.9%) had two organ failures, twenty-four (25.0%) had three organ failures, and the rest (7.3%) had four or more than four organ failures. Further elaboration of the number of organ dysfunction has been done in Figure 7.

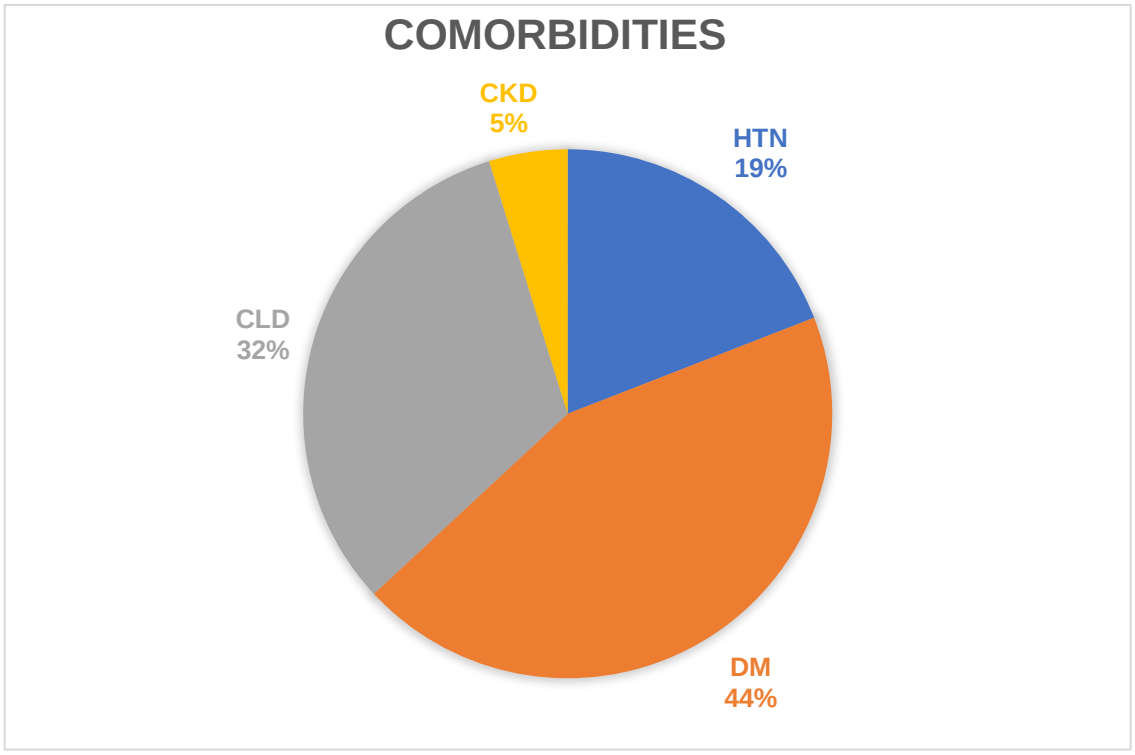
During the hospital stay follow-up period, 62 (64.58%) patients died, out of which were 40 males and 22 females.

DISTRUBUTION OF CASES BY COMORBIDITIES

Table 7: DISTRIBUTION OF CASES BY COMORBIDITIES

COMORBIDITIES	No. of patients	Percentage
HTN	16	16.7
DM	37	38.5
CLD	27	28.1
CKD	4	4.2

FIGURE 8: DISTRIBUTION OF CASES BY COMORBIDITIES



In this study, most of the patients are 37 (38.5%) belonging to type 2 diabetic mellitus, followed by 27 (28.1%) chronic liver disease, 16 (16.7%) hypertensives and the least being 4 (4.2%) chronic kidney disease patients.

The mean APACHE II score of study population at admission was 22.54±5.7 .

The mean SOFA score at admission was 8.4±3.0

Seventy-seven (80%) patients had anaemia (as per WHO classification) at presentation.

Iron profile could not be studied for many patients due to financial constraints.

Mean RDW at presentation was 17.19 ± 3.71%. Mean highest RDW and lowest RDW during hospital stay was higher 19.45± 3.80 and 15.71 ± 3.71%, respectively

During follow up period, the primary outcome, i.e., mortality prediction 62 (64.58%) patients died & Mean duration of hospital stay was 11.4±10.02 days. Sixty-nine patients (71.9%) required vasoactive agents support & 49 (51.04) patients required mechanical ventilation, and 23 (24%) patients required renal replacement therapy during the hospital stay.

FIGURE 9: DIAGRAMMATIC REPRESENTATION OF AGE DISTRIBUTION BETWEEN SURVIVOR AND NON-SURVIVOR GROUPS

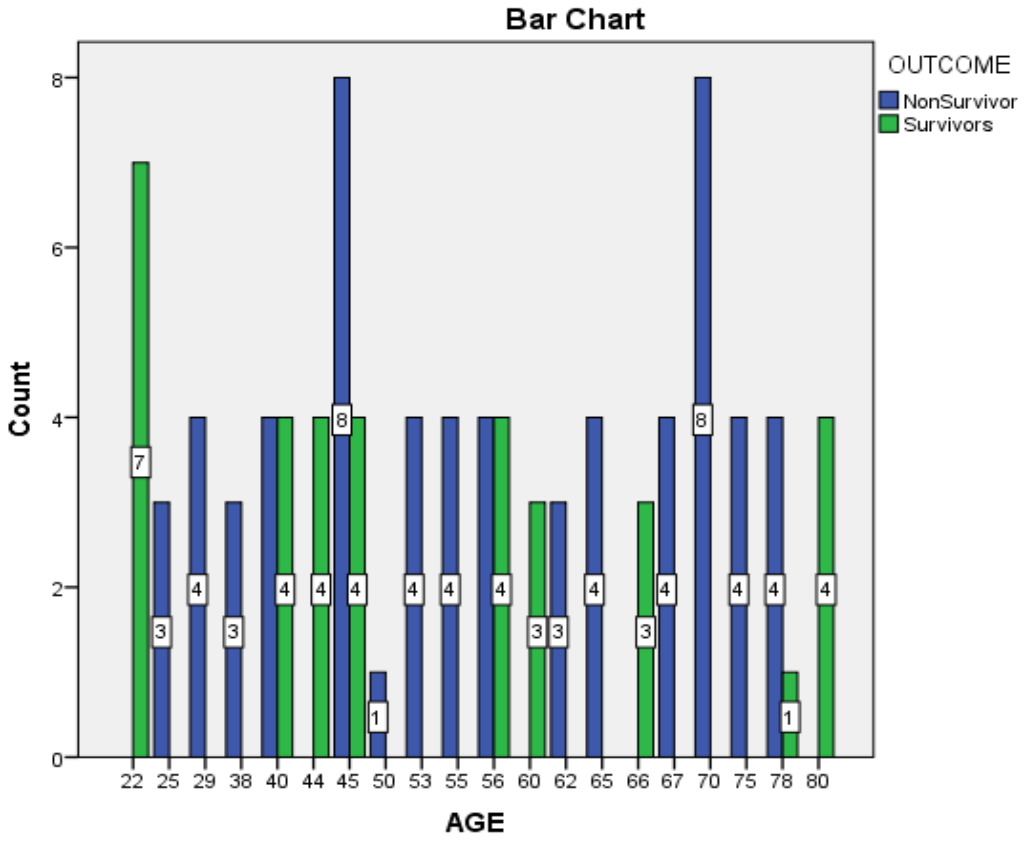
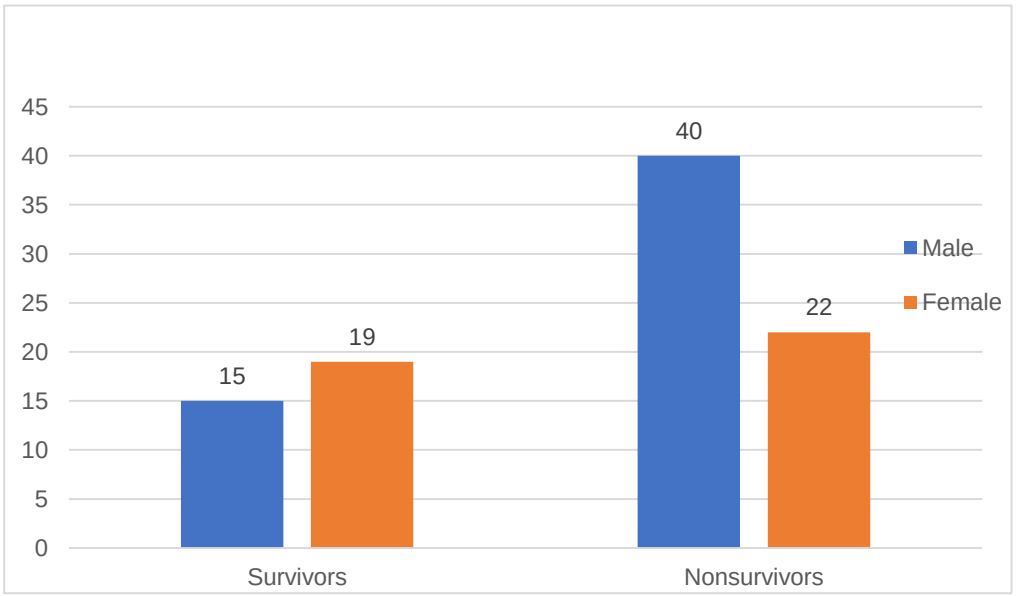


FIGURE 10: DIAGRAMMATIC REPRESENTATION OF SEX DISTRIBUTION BETWEEN SURVIVOR AND NON-SURVIVOR GROUPS



UNIVARIATE ANALYSIS OF VARIABLES BETWEEN SURVIVORS AND NONSURVIVORS: As mentioned previously, patients included in the study were followed from the day of admission. After the recording of demographic details and baseline laboratory values at admission, the patients were prospectively evaluated for development of organ failures, highest and lowest laboratory values during the hospital stay, need for renal replacement therapy, vasoactive agents' requirement, and usage of invasive mechanical ventilation and duration of stay in hospital stay was also recorded. For the patients who died during the hospital stay, the cause of death was recorded.

We did univariate analysis initially and compared various demographic, clinical, laboratory variables, organ dysfunction scores and length of hospital stay between survivors and non-survivors. Non-survivors had significantly higher mean age [55.72$\pm$15.34years] as compared to survivors [48.23 years ($\pm$18.26)], P = 0.036. Mean arterial pressure (MAP) at admission was also significantly lower in non-survivors [73.6 mmHg ($\pm$23.83)] as compared to survivors [80.51 mmHg ($\pm$16.13)], P = 0.001. In addition, systolic and blood pressure recordings were also significantly lower in non-survivors than survivors (P <0.05).

APACHE II score at admission was significantly higher in non-survivors [25.2 ($\pm$5.2)] as compared to survivors [18.9 ($\pm$4.1)], P<0.001. SOFA score at admission was also significantly higher in non-survivors [9.6 ($\pm$2.9)] as compared to survivors [6.8 ($\pm$2.5)], P <0.001. These observations were also corroborated by the higher number of organ failures in non-survivors than survivors, P <0.001.

FIGURE 11. BOX PLOT SHOWING THE DIFFERENCE IN APACHE II SCORE AT ADMISSIONBETWEEN SURVIVORS AND NON-SURVIVORS

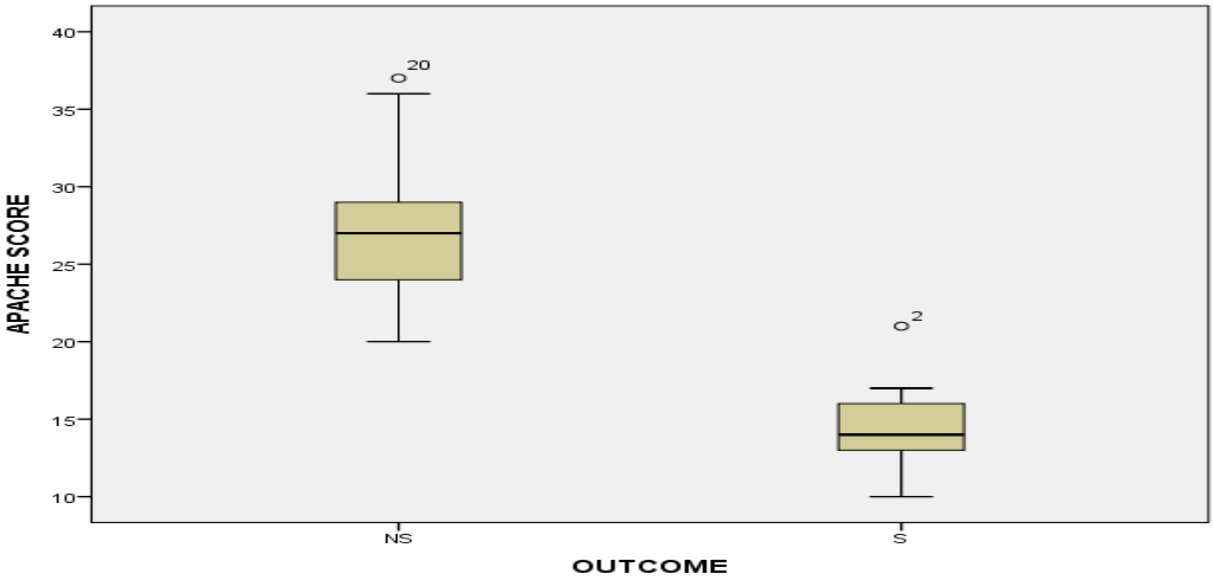
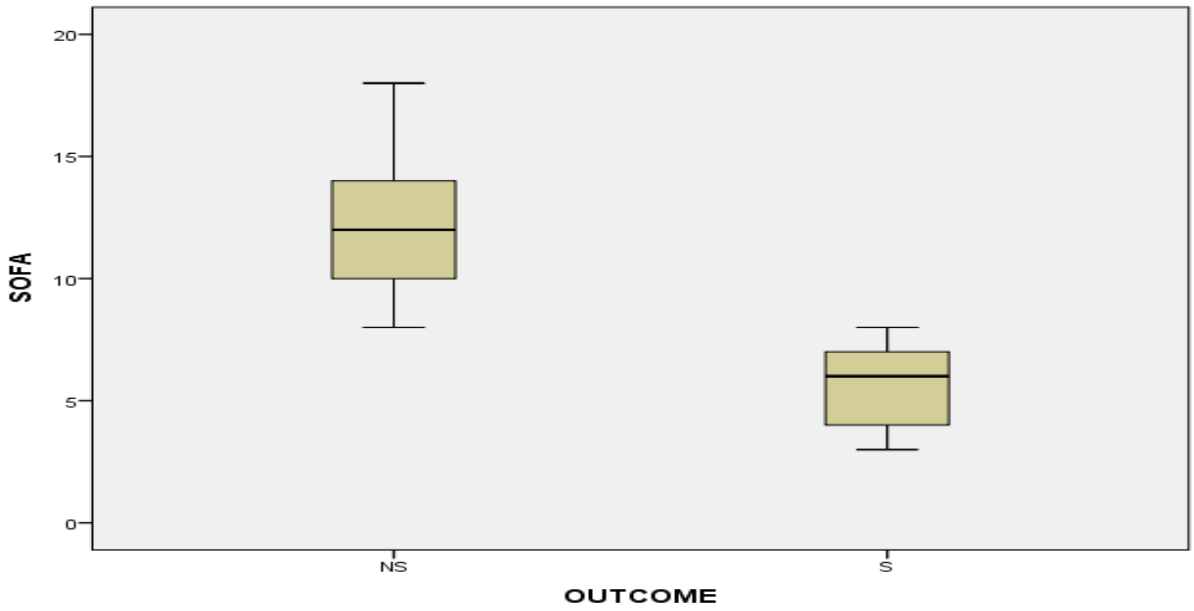


FIGURE 12. BOX PLOT SHOWING THE DIFFERENCE IN SOFA SCORE AT ADMISSION BETWEEN SURVIVORS AND NON-SURVIVORS



The non-survivors had significantly higher vasoactive agent requirements (71.9%) than survivors (28.1%), P <0.003. The requirement for renal replacement therapy was not significantly higher in non-survivors (26.2%) than survivors (32.4%), P = 0.942.

The mean duration of hospital stay was significantly higher in survivors [17.94 days (±14.61 days)] as compared to non-survivors [7.64 days (±5.68 days)], P <0.001. The mean duration of hospital stay was statistically different between survivors and non-survivors, P = <0.001. Further elaboration of baseline characteristics of study cohort along-with details of univariate analysis of various demographic and clinical parameters between survivors and non-survivors has been done in Table 89.

Mean RDW at admission was significantly higher in non-survivors [17.8 (±4.34)] as compared to survivors [15.92 (±1.54)], P = 0.013. The mean highest RDW during hospital stay was also significantly higher in non-survivors [20.26(±4.38)] as compared to survivors [17.97 (±3.2)], P = 0.001.

Table 8: COMPARISON OF DEMOGRAPHIC & CLINICAL DATA BETWEEN SURVIVORS AND NON-SURVIVORS

VARIABLE	All(n=96)		Survivors (n=34)		NonSurvivors (n= 62)		P value
	Mean	±SD	Mean	±SD	Mean	±SD	
AGE	52.99	16.91	48.23	18.61	55.72	15.348	**0.036***
Female/Male	41/55		19/15		22/40		0.860
ANEMIA AT ADMISSION	77	80%	30	35.06%	47	64.9%	0.231
APACHE II SCORE	22.54	5.7	18.9	4.1	25.2	5.2	**<0.001***
SOFA SCORE	8.4	3.0	6.8	2.5	9.6	2.9	**<0.001***

HOSPITAL STAY	11.40	10.02	17.94	14.61	7.64	5.68	**<0.001***
PR	111.36	12.41	114.77	8.95	109.41	13.69	**0.041***
SBP	103.69	32.44	106.80	27.72	101.90	34.94	**0.047***
DBP	64.58	18.69	69.43	14.94	61.80	20.12	**0.054***
MAP	76.16	21.51	80.51	16.13	73.66	23.83	**0.004***
SPO2	90.09	11.18	95.83	2.88	86.80	12.77	**<0.001***
ESR	48.47	29.18	56.91	37.53	43.62	22.01	**0.031***
RBS	128.77	71.56	169.97	80.29	105.13	53.82	**<0.001***
Hypertension	16	16.7%	8	23.5%	8	12.9%	0.186
Diabetes Mellitus	37	38.5%	13	38.2%	21	61.8%	0.964
CKD	4	4.2%	4	11.8	0	0	**0.006***
CLD	27	28.1	4	11.8	23	37.1	0.008
ALCOHOL	43	44.8%	11	32.4	32	51.6	0.070
SMOKER	55	57.3	17	50	38	61.3	0.285
IONOTROPES USAGE	69	71.9	12	35.3	57	91.9	**0.001***
MECHANICAL VENTILATION	55	57.2	18	18.75	37	38.54	**0.003***
RRT	23	24.05	8	23.5	15	24.2	0.942

N, number of patients; SD, standard deviation; CNS, Central nervous system; BP, blood pressure; MAP, Mean arterial pressure; PR, pulse rate; RR, respiratory rate; APACHE II, Acute Physiology and Chronic Health Evaluation score; SOFA, Sequential Organ Failure Assessment score

There was no statistical difference in the proportion of patients with anaemia at admission among survivors and non-survivors, P = 0.231. Baseline and lowest haemoglobin values during the hospital stay were lower in non-survivors than survivors but were not statistically significant (P > 0.05).

Baseline and highest Total leucocyte count were higher in non-survivors than survivors but were not statistically different P >0.05. Baseline, highest, lowest platelet counts were lower in non-survivors than survivors but were statistically different, P <0.001

Baseline and highest urea values during the hospital stay were higher in non-survivors than survivors and statistically significantly higher in non-survivors, P = 0.020. Similarly, baseline and highest serum creatinine values during the hospital stay were higher in non-survivors than survivors but did not reach statistical significance. Baseline and highest total bilirubin values during the hospital stay were higher in non-survivors than survivors, highest values being statistically significant,P = 0.001.

Mean baseline and highest values of SGOT and SGPT during the hospital stay were higher in non-survivors than survivors and are statistically significant (P < 0.05).

Mean baseline, highest and lowest serum albumin values during the hospital stay were significantly lower in non-survivors, P <0.05.

Mean baseline and lowest pH values during the hospital stay were lower in non-survivors, P <0.01. Nonsurvivors also had significantly lower PaO_2/FiO_2 values, P <0.01.

Non-survivors had a greater magnitude of coagulopathy as observed in the form of significantly lower prothrombin time index (P <0.01) and prolonged aPTT (P<0.01).

Serum lactate at admission, was significantly higher in non-survivors [2.56 mmol/L ($\pm$1.0)] as compared to survivors [2.1 mmol/L ($\pm$1.0)], P = 0.001. Further details of univariate analysis of various laboratory parameters among survivors and non-survivors have been provided in Table 10.

Table 9: COMPARISON OF LABORATORY PARAMETERS BETWEEN SURVIVORS AND NON-SURVIVORS

Variables	All(n=96)		Survivors (n=34)		NonSurvivors (n= 62)		P value
	Mean	±SD	Mean	±SD	Mean	±SD	
HB(g/dl)							
BASELINE	10.46	2.86	10.97	2.68	9.93	2.92	0.231
HIGHEST	11.45	2.49	11.00	2.37	11.72	2.53	0.254
LOWEST	9.39	2.83	9.57	2.58	9.29	2.97	0.552
TLC(/µL)							
BASELINE	14274.3	7646.6	12731.8	7147.8	15120.2	7833.8	0.144
HIGHEST	20175.7	8842.74	16722.4	6710.18	22069.5	93341.6	**0.004***
LOWEST	8095.9	4350.00	7765.9	3955.65	8276.9	4.572.81	0.585
ESR	48.47	29.179	56.91	37.534	43.62	22.006	**0.031***
PLATELETS ($x10^3$xµL)							
BASELINE	217.14	181.15	321.65	199.32	157.18	139.31	**<0.001***
HIGHEST	246.76	174.06	367.45	177.07	177.50	129.74	**<0.001***
LOWEST	155.50	132.56	254.74	147.23	98.55	80.66	**<0.001***
RDW (%)							
BASELINE	17.19	3.71	15.92	1.54	17.88	4.34	**0.013***
HIGHEST	19.45	3.80	17.97	1.62	20.26	4.38	**0.004***
LOWEST	15.79	3.71	14.52	1.54	16.48	4.34	**0.013***
MCV (fL)							
BASELINE	86.45	9.44	85.97	12.40	85.70	13.89	0.777
HIGHEST	87.67	9.42	87.57	9.23	87.73	9.60	0.934
LOWEST	84.88	9.89	85.17	8.40	84.72	10.72	0.831
MCH (pg)							
BASELINE	27.92	4.31	28.17	3.76	27.78	4.63	0.677

HIGHEST	28.58	4.11	28.68	3.67	28.52	4.36	0.854
LOWEST	27.45	4.26	27.57	3.64	27.39	4.61	0.845
MCHC (%)							
BASELINE	32.16	1.79	32.60	1.14	31.91	2.05	0.074
HIGHEST	32.69	1.80	32.91	1.19	32.57	2.06	0.375
LOWEST	31.60	1.94	31.77	1.57	31.50	2.14	0.527
UREA (mg/dl)							
BASELINE	81.83	62.91	63.57	49.51	91.64	67.35	**0.020***
HIGHEST	111.95	76.43	68.14	54.15	137.57	74.98	**0.008***
CREATININE (mg/dl)							
BASELINE	2.44	2.51	2.34	3.11	2.41	2.23	0.903
HIGHEST	3.22	2.83	2.80	3.74	3.62	2.31	0.187
NA (mEq/L)							
BASELINE	132.47	9.52	131.79	6.89	132.85	10.73	0.605
HIGHEST	140.17	10.26	136.55	5.69	142.16	11.62	**0.010***
LOWEST	129.69	9.19	129.85	11.11	129.61	8.05	0.903
K (mEq/L)							
BASELINE	4.16	0.87	4.30	0.85	4.09	0.88	0.269
HIGHEST	4.75	1.12	4.61	0.62	4.84	1.32	0.345
LOWEST	3.29	0.90	3.58	0.59	3.12	0.99	**0.016***
TB (mg/dl)							
BASELINE	3.82	5.06	0.62	0.80	5.24	5.50	**0.001***
HIGHEST	6.25	11.05	0.72	0.61	6.86	7.48	**0.001***
SGOT(U/L)							
BASELINE	115.40	140.15	61.82	50.37	145.65	164.47	**<0.001***
HIGHEST	152.15	306.65	61.82	50.37	223.19	419.57	**<0.001***
SGPT(U/L)							
BASELINE	61.19	61.34	37.14	22.48	74.91	72.22	**<0.001***

HIGHEST	160.67	513.95	37.14	22.48	274.45	726.86	**0.002***
ALP(U/L)							
BASELINE	162.42	73.42	180.82	68.54	151.88	74.24	0.627
HIGHEST	171.55	64.80	180.82	68.54	165.70	62.05	0.034
PROTEIN (g/dl)							
BASELINE	5.67	0.94	5.87	0.97	5.55	0.92	0.119
HIGHEST	5.8160	0.99	5.93	0.93	5.74	1.03	0.372
LOWEST	5.5740	0.93	5.87	0.97	5.41	0.87	**0.020***
ALBUMIN (g/dl)							
BASELINE	2.50	0.64	2.84	0.621	2.44	0.57	**0.002***
HIGHEST	2.58	0.64	2.92	0.632	2.53	0.53	**0.001***
LOWEST	2.41	0.57	2.60	0.53	2.31	0.59	**0.017***
GLOBULIN(g/dl)							
BASELINE	3.18	0.78	3.34	1.02	3.09	0.59	0.143
HIGHEST	3.36	0.82	3.46	0.88	3.29	0.78	0.277
LOWEST	3.09	0.85	3.31	1.05	2.96	0.70	0.098
PH							
BASELINE	7.29	0.14	7.40	0.08	7.23	0.14	**<0.001***
HIGHEST	7.40	0.11	7.42	0.08	7.38	0.17	**0.066**
LOWEST	7.25	0.16	7.36	0.13	7.19	0.14	**0.002***
PaO2(mmHg)							
BASELINE	88.61	41.18	84.82	25.38	90.06	48.99	**0.001***
HIGHEST	123.03	51.74	102.20	19.84	134.98	60.13	0**.002***
LOWEST	64.86	26.31	81.60	25.00	55.26	22.02	**0.0001***
PaCO2 (mmHg)							
BASELINE	32.47	14.76	25.62	5.20	36.41	16.92	**<0.001***
HIGHEST	42.38	19.12	34.48	18.07	46.91	18.34	**0.002***

LOWEST	25.13	7.06	24.88	5.04	25.27	8.03	0.795
HCO3 (mmol/L)							
BASELINE	14.62	4.02	16.00	4.37	13.79	3.58	**0.010***
HIGHEST	18.94	5.87	19.08	5.04	19.03	5.32	0.903
LOWEST	13.66	4.02	15.48	4.63	12.62	3.22	**0.001***
PaO2/FIO2							
BASELINE	302.86	96.57	292.56	84.33	247.33	103.33	**0.001***
HIGHEST	353.43	72.92	376.47	33.10	340.80	85.03	**0.021***
LOWEST	239.58	111.90	302.95	84.33	204.83	110.40	**<0.001***
PT (sec)							
BASELINE	25.95	19.91	17.45	6.32	30.83	23.21	**0.001***
HIGHEST	30.16	24.58	17.45	6.29	37.45	28.04	**<0.001***
LOWEST	20.30	11.71	18.20	6.00	21.50	13.88	0.184*
aPTT(sec)							
BASELINE	42.11	19.42	33.68	7.85	46.95	22.30	**0.001***
HIGHEST	42.15	19.40	33.68	7.85	47.01	22.26	**0.001***
LOWEST	37.59	12.72	33.40	8.09	40.00	14.25	**0.014***
LACTATE	2.36	1.623	2.11	1.2	2.56	1.46	**0.001***

N, number of patients; SD, Standard deviation; TLC, Total leucocyte count; ESR, erythrocyte sedimentation rate; MCV, Mean corpuscular volume; MCH, Mean corpuscular haemoglobin; MCHC, Mean corpuscular haemoglobin concentration;SGOT, Serum glutamate oxaloacetate transaminase; SGPT, Serum glutamate pyruvate transaminase; ALP, Alkaline phosphatase; RBS, Random blood sugar; PaO_2, partial pressure of oxygen; PaO2/FIO2, pressure of arterial oxygen/fraction of inspired oxygen; $PaCO_2$, partial pressure of carbon dioxide; SpO_2, oxygen saturation; PT, Prothrombin time; aPTT, Activated partial thromboplastin time. [#]unpaired t-test

ROC CURVE ANALYSIS: Receiver operating characteristic curve analysis was performed to assess the diagnostic accuracy for predicting in-hospital mortality, and the area under the curve (AUC) was calculated. The area under curve (AUC) for APACHE II score at admission was 0.812 (95% confidence interval, 0.762-0.836), P<0.001; whereas AUC for SOFA score at admission was 0.710 (95% confidence interval, 0.636-0.782),P <0.001. AUC for RDW at admission was 0.606 (95% confidence interval, 0.527-0.685), P <0.001.

Figure 13. Receiver operating characteristic curves for APACHE II score, SOFAscore and RDW for prediction of inhospital mortality in patients with Severe sepsis

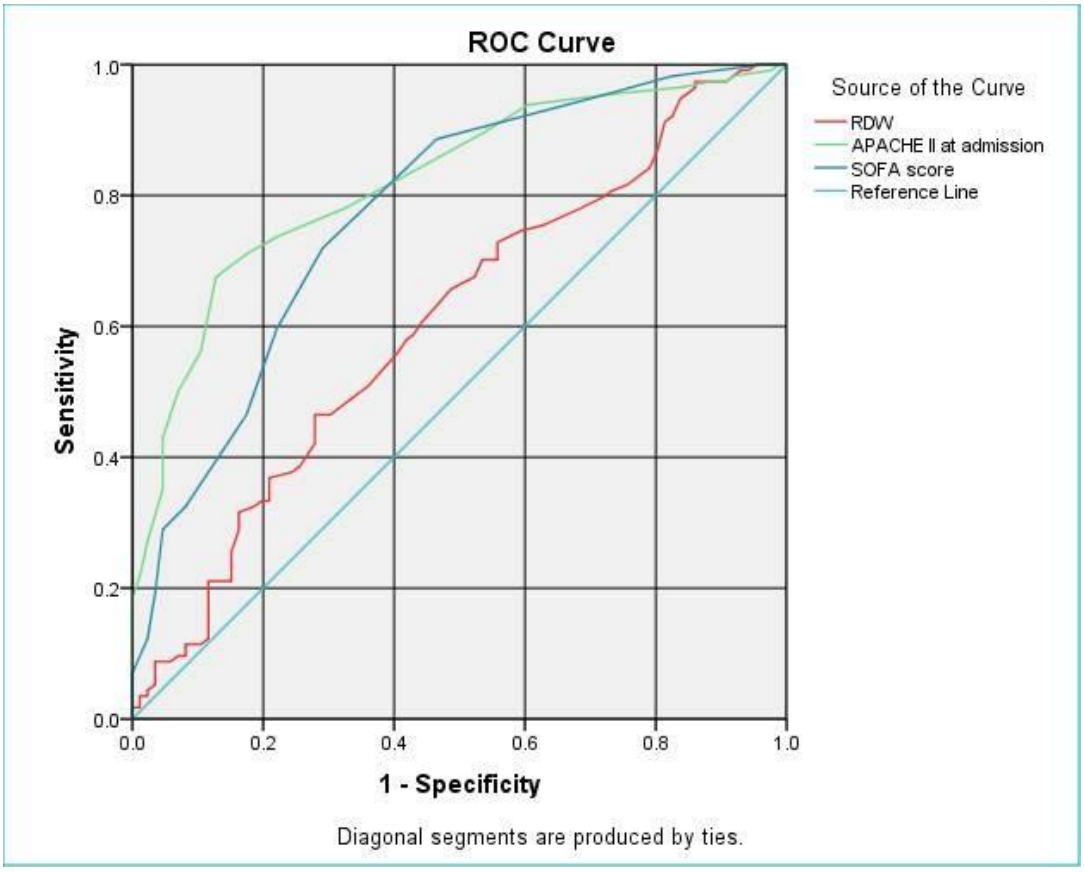
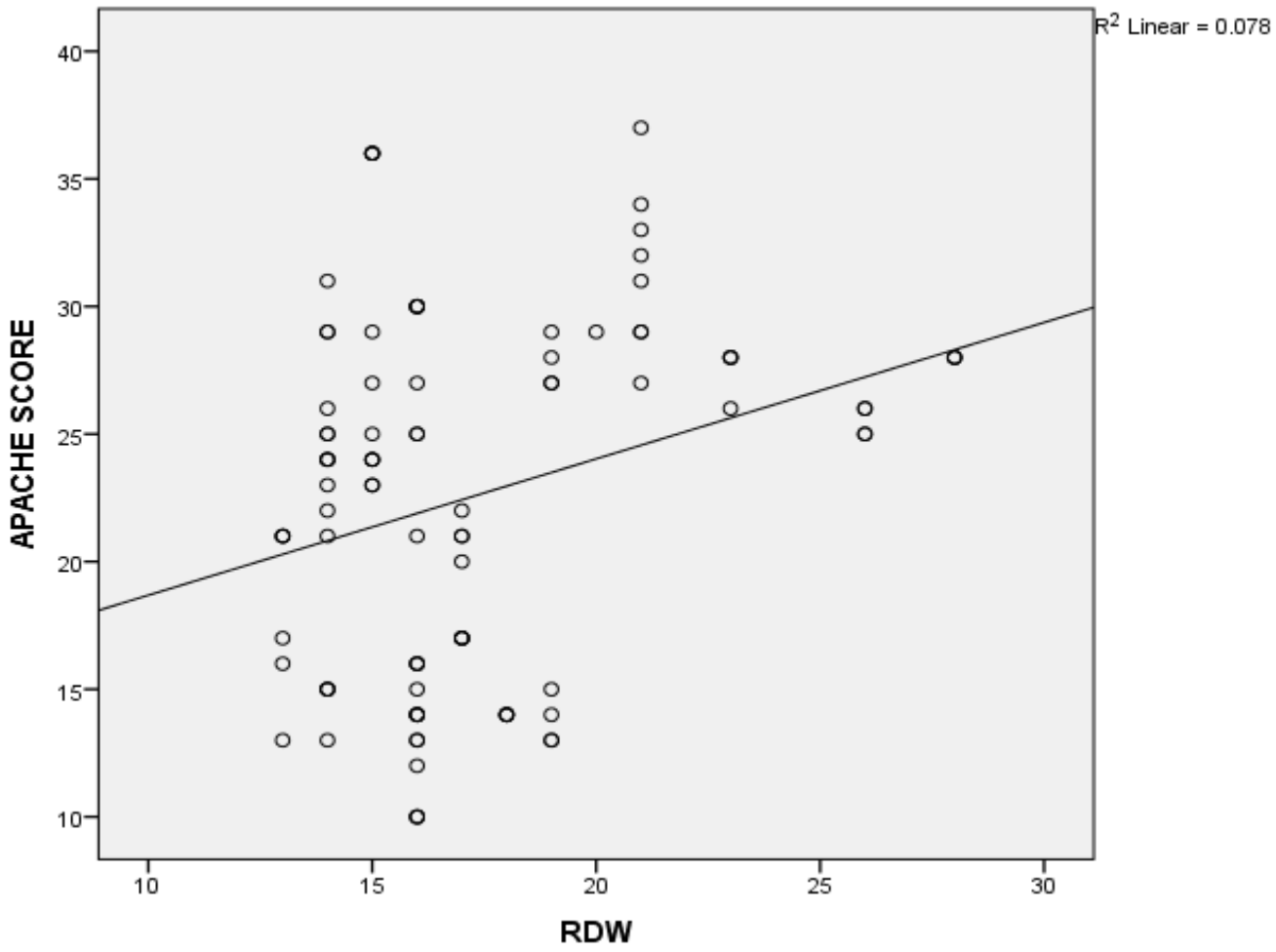


Figure 14. Diagrammatic representation of the correlation between RDW and APACHE II score at admission in the study population



MULTIVARIATE LOGISTIC REGRESSION ANALYSIS FOR INHOSPITAL MORTALITY : Multivariate logistic regression was performed to determine the independent factors of mortality during the hospital stay, and the results were expressed as odds ratio and 95% confidence intervals (CI). Variables that had a P value less than 0.1 in univariate analyses between survivors and non-survivors and the variables known to confound RDW such as age, sex, total leucocyte count, ESR, mean corpuscular volume (MCV), mean corpuscular haemoglobin, blood urea nitrogen, and creatinine were included in the analysis.

In multivariate logistic regression analyses, APACHE II score at admission, serum albumin at admission, PaO2/FiO2 ratio, and serum fibrinogen at admission were independent predictors of inhospital mortality (P <0.05). APACHE II score showed a significant positive correlation with inhospital mortality, whereas albumin, PaO2/FiO2 ratio and fibrinogen showed a significant negative correlation with inhospital mortality.

Table No. 10. Multivariate logistic regression analysis of variables predictive of inhospital mortality in patients with severe sepsis

Variable	Regression Coefficient	Oddsratio	95% Confidence intervals	P value
APACHE II score at admission	0.241	1.27	1.16-1.38	< **0.001**
Serum Albumin at admission	-0.820	0.441	0.194 - 0.999	0.050
PaO2/FiO2 ratio at admission	-0.006	0.994	0.994 - 0.989	0.008

DISCUSSION

In this prospective observational study, we tried to look into the role of RDW as a prognostic marker of in-hospital mortality in patients presenting in BLDE(DU Shri BM Patil Medical College, a large tertiary care Centre with severe sepsis/septic shock, was admitted to the intensive care unit for more than 24 hours.

In recent studies, RDW has emerged as a potentially robust prognostic marker of the burden of inflammation. Its role as a prognostic marker has been well studied in cardiovascular diseases[7], pulmonary embolism[8], stroke[11], rheumatoid arthritis[12], and many other conditions having inflammation as the cornerstone of their pathophysiology.Raised RDW has also been found to be associated with all-cause mortality in adults more than 45 years.[34] In critical care settings, increased RDW has been particularly associated with high in-hospital and ICU mortality.[35]

In the present study, the primary outcome, i.e., in-hospital mortality, was 64.58 %. GS Martin et al. studied the epidemiology of sepsis in the United States from 1979 for 22 years and reported the mortality associated with severe sepsis and septic shock ranging from 35 to 70%. (1) Esper et al. studied the prognostic significance of red cell distribution width in septic patients and found 31.03% mortality in the sepsis group during hospitalisation. (42)

We demonstrated that RDW at admission was significantly associated with in-hospital mortality in univariate analysis**.** However, in multivariate logistic regression, APACHE II score at admission,albumin, PaO_2/FiO_2 ratio were the independent predictors of in-hospital mortality.

In this study, the mean age of the study population was 52.99 ± 16.91 years (range 22 - 80 years). Our study included patients belonging to all age groups starting from 18 years. It demonstrated that older age was significantly associated with inhospital mortality in univariate analysis but was not an independent predictor in multivariate analysis. Patel et al. showed that RDW was significantly associated with all-cause mortality in outpatients older than 44 years.[34]

Jo et al. evaluated RDW in an older population (mean age 70.0 ± 13.4 years), which included five hundred sixty-six patients and found that age was an independent predictor of 28-day mortality.[32] Similarly, Bazick et al. studied RDW in more than fifty thousand critically ill patients (mean age 67.7 years), which included nearly seven thousand (13.5%) septic patients The higher mean age in these studies per se could have been the more potent determinant of mortality which was observed in our study.

Our study included patients with a wide variety of comorbidities and showed that their distribution was not significantly between survivors and non-survivors. Neither the comorbidities were significantly different between survivors and non-survivors, nor were they found to be independent predictors of mortality in multivariate analyses. Thus, the significant association between RDW and in-hospital mortality holds true across a diverse variety of comorbidities. These findings are consistent with the results of Jo et al. except for chronic kidney disease, which was found to be significantly associated with mortality in that study.[32]

In the index study, we observed a significantly higher mean APACHE II score at admission in non-survivors. This finding is consistent with previous studies that analysed and validated APACHE II score as the severity of disease classification system. APACHE II score includes physiological variables and therapeutic interventions into consideration. It provides a composite score reflecting the severity of illness in critically ill patients.[37] Similarly, mean SOFA score at admission was also significantly higher in non-survivors. Our finding is consistent with the results of Vincent et al., who found significantly higher SOFA score for each organ in septic patients.[38] SOFA score has been well studied as a simple yet effective tool for the description of organ dysfunction in critically ill patients.[39]

Mean RDW at admission was 17.19 ± 3.712% with a very wide range, from 13.48% to 20.9%. Esper et al. found a similar mean RDW (18.2 ± 2.2%) in the sepsis group.[42] However, other studies reported a lower mean RDW. Jo et al. reporteda lower mean RDW in their study population (15.8% in non-survivors Vs 14.4% in survivors).[32] Though seventy-seven (63%) patients in our study population had anaemia at admission, anaemia distribution was not significantly different between survivors and non-survivors. Moreover, anaemia was not found to be a significant variable in multivariate logistic regression analysis for in-hospital mortality

We observed a similar distribution of organ failures in the study population as reported by Sadaka et al., who studied prognostic significance of RDW in patients with septic shock.[40] The number of patients with four or more organ failures was significantly higher in the non-survivor group. This finding corroborates with significantly higher mean APACHE II and SOFA scores in non-survivors.

Non-survivors had significantly lower serum albumin levels and higher RDW values than survivors at baseline and during the hospital stay despite having a similar distribution of source of sepsis, site of sepsis, comorbidities and addictions. Though not statistically significant, the non-survivors also had higher TLC and higher ESR. These findings are consistent with previous studies.[32,40]. The mean duration of mechanical ventilation was also higher in non-survivors. These findings are consistent with previous studies.[24,35,40]

The non-survivor's group was found to have significantly lower MAP, lower platelets, & a higher proportion of patients with CNS. Nonsurvivors also had a lower PaO_2/FiO_2 ratio and poorer coagulation parameters (PTI and aPTT) at presentation as compared to survivors.

They also had a significantly higher requirement for vasoactive agents. The mean duration of mechanical ventilation was also higher in non-survivors. These findings are consistent with previous studies.[24,35,40]

This study found that RDW correlated significantly with albumin, ESR, lactate, bilirubin, and serum urea. Moreover, serum albumin was found to be an independent predictor of in-hospital mortality. As serum albumin is a negative acute phase reactant, this finding might also illustrate the relationship between RDW and the extent of inflammation.

To assess the discriminatory ability of RDW for in-hospital mortality, we studied the receiver operating characteristic curve analyses, which found marginal discriminatory power (AUC 0.606) compared to APACHE II (AUC 0.812) and SOFA score (AUC 0.710). Similar results were demonstrated by Lorente et al., who showed the marginal discriminatory ability of RDW (AUC 0.606) during the first week of hospitalisation.

However, they demonstrated a significant association of RDW with malondialdehyde (as a marker of oxidative stress) and TNF α levels (as a marker of inflammatory load).[41] Sadaka et al. showed significantly high discriminatory power of RDW in septic shock patients (AUC 0.74) for in-hospital mortality as compared to APACHE II score (AUC 0.69) and SOFA score (0.69).[40]

STRENGTHS & LIMITATIONS

This study had a prospective design and patients were prospectively enrolled. All patients were managed under similar settings with uniform institutional management protocol based on surviving sepsis guidelines. We included patients having a wide range of comorbidities and a variety of illnesses. There was uniformity in the time of measurement of RDW, i.e., at admission in the intensive care unit. So, baseline RDW was not affected by medical management during hospitalisation. Patients with a history of transfusion of blood products were not included by reviewing transfusion records prior to admission. Blood transfusion is an important confounder for raised RDW. Because of their retrospective design, earlier studies did not address this important aspect.

However, the present study also had certain limitations. As it is a single-centre study conducted in a tertiary care institution, results may not be generalizable to other health care institutions. This study included ninety-six patients, a sample size that may not seem as robust as earlier studies. It included only patients admitted in medical intensive care unit results may not be extrapolated to surgical patients with severe sepsis. Though RDW was significantly associated with in-hospital mortality, it was not an independent predictor of inhospital mortality. Therefore, a causal association between raised RDW and mortality cannot be considered.

Iron profile and Vitamin B12/Folic acid levels, which are well-known confounders of raised RDW, were not studied for many patients due to financial constraints. The primary outcome of the study, i.e., in-hospital mortality, is an objective, clinically relevant and well-accepted outcome in studies about critical care which is present in our study, whereas many other studies have evaluated for 28 day and 30-day mortality

Baseline, highest and lowest values of RDW and other laboratory variables were not measured dynamically; they often depended on the number of times the treating team repeated these investigations. This study did not include the estimation of inflammatory cytokine levels. Though the association of raised RDW with laboratory variables considered markers of inflammation might illustrate RDW–inflammation association, this cannot be established with certainty. We have not studied the association between normal and raised RDW levels predicting mortality

.

SUMMARY AND CONCLUSIONS

In this prospective observational study, ninety-six critically ill adult medical patients admitted to the Intensive care unit for more than 24 hours with an admission diagnosis of severe sepsis/septic shock fulfilling all inclusion and exclusion criteria were evaluated, and an attempt was made to determine the association between RDW at admission and inhospital mortality in these patients. The salient findings of this study are:

- RDW is significantly associated with in-hospital mortality in patients with severe sepsis/septic shock across all age groups and various comorbidities. However, it is not an independent predictor of in-hospital mortality.
- APACHE II score at admission, albumin, PaO_2/FiO_2 ratio are the independent predictors of in-hospital mortality
- RDW showed significant graded relationship with severity of illness i.e. APACHE II score at admission.
- RDW is strongly correlated with the duration of hospital stay in the survivors.
- RDW showed a graded relationship with laboratory markers of inflammation i.e., serum albumin, ESR and TLC.

In conclusion, RDW is significantly associated with inhospital mortality in patients with severe sepsis/septic shock across all age groups and a variety of comorbidities in univariate analysis; but it is not an independent predictor of inhospital mortality

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ANNEXURE I

ETHICAL CLEARANCE CERTIFICATE

IEC/MD-131/2019
22-11-19

B.L.D.E. (DEEMED TO BE UNIVERSITY)
(Declared vide notification No. F.9-37/2007-U.3 (A) Dated. 29-2-2008 of the MHRD, Government of India under Section 3 of the UGC Act, 1956)
The Constituent College
SHRI. B. M. PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The ethical committee of this college met on 13-11-2019 at 3-15 pm to scrutinize the synopsis of Postgraduate students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has been accorded Ethical Clearance

Title: A study of red cell distribution width and its correlation in severe sepsis.

Name of PG student: Dr Pallavali Janardhana Reddy. Department of General Medicine

Name of Guide/Co-investigator: Dr Siddanagouda M Biradar, *Associate Prof* Department of General Medicine

DR RAGHVENDRA KULKARNI
CHAIRMAN
Institutional Ethical Committee
BLDEU's Shri B.M. Patil
Medical College,BIJAPUR-586103

Following documents were placed before Ethical Committee for Scrutinization:

1. Copy of Synopsis / Research project
2. Copy of informed consent form
3. Any other relevant documents.

12

ANNEXURE-II

INFORMED CONSENT FORM

TITLE OF RESEARCH:

"ROLE OF RED CELL DISTRIBUTION WIDTH IN PREDICTING THE OUTCOME IN PATIENTS WITH SEVERE SEPSIS AND SEPTIC SHOCK"

GUIDE : DR SIDDANAGOUDA M BIRADAR

PG STUDENT : DR PALLAVALI JANARDHANA REDDY

PURPOSE OF RESEARCH:

I have been informed that the purpose of this study is to access ROLE OF RED CELL DISTRIBUTION WIDTH IN PREDICTING THE OUTCOME IN PATIENTS WITH SEVERE SEPSIS AND SEPTIC SHOCK

PROCEDURE:

I understand that I will undergo a detailed history and clinical examination and investigations.

RISKS AND DISCOMFORTS:

I understand that there is no risk involved in this study, and I may experience mild pain during the above-mentioned procedures.

BENEFITS:

I understand that my participation in this study will help to early

Diagnose pulmonary tuberculosis in HIV infection

CONFIDENTIALITY:

I understand that the medical information produced by the study will become a part of hospital records and will be subjected to confidentiality and privacy regulation of the hospital. If the data is used for publication, the identity will not be revealed

REQUEST FOR MORE INFORMATION:

I understand that I may ask for more information about the study at any time.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary, and I may refuse to participate or withdraw from the study at any time.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me during the study, I will get medical treatment but no further medical compensation.

_____ _____

(Signature of Guardian) (Signature of patient)

STUDY SUBJECT CONSENT FORM:

I confirm that DR PALLAVALI JANARDHANA REDDY has explained the purpose of this research, the study procedure that I will undergo and the possible discomforts and benefits that I may experience in my own language.

I have been explained all the above in detail in my own language, and I understand the same. I agree to give my consent to participate as a subject in this research project.

SIGNATURE OF PARTICIPANT DATE

SIGNATURE OF WITNESS DATE

ANNEXURE III

PROFORMA

Name: CASE NO

Age: IP NO:

Sex: DOA

Present Occupation:

Residence:

Chief complaints:

History of present illness:

Past history:

Family history:

Personal history Family history:

General physical examination:

Systemic examination:

Cvs

Rs-

Per abdomen-

Central nervous system –

Provisional diagnosis –

	Within 24 hoursof emergency services presentation	Highest throughout hospital stay	Lowest throughout hospital stay
Hb g/dL			
TLC/µL			
DLC		NA	NA
ESR			
Platelet count/µL			
Red cell distribution width			
MCV (fl)			
MCH (pg)			
MCHC %			

Biochemical Parameters

	Within 24 hours of emergency services presentation	Highest throughout hospital stay	Lowest throughout hospital stay
Na+ (mEq/L)			
K+ (mEq/L)			
Blood urea (mg/dL)			
S.Creatinine (mg/dL)			
SGOT (U/L)			
SGPT (U/L)			
ALP (U/L)			
Total protein (g/dL)			
Albumin (g/dL)			
Globulin (g/dL)			
Bilirubin total (mg/dL)			
Unconjugated (mg/dL)			
Conjugated (mg/dL)			
Random blood sugar(mg/dL)			
pH			
PaO_2 (mmHg)			
$PaCO_2$ (mmHg)			
HCO^3 (mmol/L)			
PaO_2/FiO_2			
PT (sec)			
APTT (sec)			

SOFA Score at the time of presentation

APACHE II Score at the time of presentation

Outcome at hospital discharge:

- Died
- Recovered

Immediate cause of death:

- 1. Complete blood count
- 2. Urine examination
- 3. Random blood sugar
- 4. Renal function tests
- 5. Electrocardiogram
- 6. Arterial blood gas analysis
- 7. Liver function test
- 8. Serum lactate (arterial sample)
- 9. Ultrasound abdomen
- 10.chest x-ray

FINAL DIAGONOSIS:

TREATMENT

Sepsis definitions

A. Sepsis is defined as documented or suspected infection with one or more of thefollowing:

General variables

- Fever (core temperature >38.3 ^{0}C)
- Hypothermia (core temperature <36 ^{0}C)
- Heart rate >90 beats/min
- Tachypnea (RR >24)
- Altered mental status(GCS <9)
- Significant edema or positive fluid balance (>20 mL/kg over24 hours)
- Hyperglycemia (plasma glucose >110 mg/dL or 7.7 mmol/L)in the absence of diabetes

- Inflammatory variables
  - Leukocytosis (white blood cell [WBC] count >12,000/mL)
  - Leukopenia (WBC count <4000/mL)
  - Normal WBC count with >10% immature forms

B. Severe sepsis is defined as sepsis associated with organ dysfunction, hypoperfusion, or hypotension.

Organ dysfunction variables are:

- Cardiovascular system: Arterial systolic blood pressure ≤90 mmHg or mean arterial pressure ≤70 mmHg that responds to the administration of intravenous fluid;

- Pulmonary system: with Pao_2/Fio_2 less than 250 in the absence of pneumonia asinfection source, Pao_2/Fio_2 < 200 in the presence of pneumonia as infection source;
- Renal system: Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation or Creatinine > 2.0 mg/dL;
- Hematologic system: with platelet count less than 80 000/mm3 or 50% decrease in platelet count from the highest value recorded over previous 3 days;
- Unexplained metabolic acidosis: A pH 7.30 or a base deficit 5.0 mEq/L and a plasma lactate level above upper limits laboratory normal;
- Central nervous system: Altered mental status [Glasgow coma scale (GCS) <9];
- Gastrointestinal system: Presence of at least one of the following gastrointestinal problems documented in inpatient data during their stay: food intolerance, gastrointestinal haemorrhage, and ileus. Food intolerance is the inability to feed the patient via nasogastric tube due to vomiting or nasogastric aspirate volumes larger than those previously given enterally. Gastrointestinal haemorrhage is defined as visual presence of blood in nasogastric tube aspirates or in stool. Ileus is defined as intestinal obstruction due to inhibitionof bowel motility.

C. Septic shock is defined as acute circulatory failure unexplained by other causes.

- Hypotension [arterial blood pressure <90 mmHg systolic, a mean arterial pressure (MAP) <70 or a reduction in systolic blood pressure of 40 mm Hg from patient's baseline] for at least 1 h despite adequate fluid resuscitation; *or* Need for vasopressors to maintain systolic blood pressure ≥90 mmHg *or* MAP≥70.

ANNEXURE IV
SOFA SCORE

Organ system	0	1	2	3	4
Respiratory PaO2/FiO2	>400	≤400	≤300	≤200	≤100
Renal creatinine (mg/dl) or urine output (mL/d)	<1.2	1.2 – 1.9	2.0–3.4	3.5–4.9 or <500	>5.0 or <200
Coagulation Platelets $10^3/mm^3$	>150	<150	<100	<50	<20
Liver Bilirubin (mg/dL)	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
Cardiovascular Hypotension (µg/kg/min)	No hypotension	MAP <70	Dopamine </=5 ordobutamine (any)	Dopamine or >5 norepinephrine </=0.1	Dopamine or >15 norepinephrine >0.1
CNS Glasgow Coma Score	15	13–14	10–12	6–9	<6

ANNEXURE V
APACHE II -- Severity of Disease Classification System

	HIGH ABNORMAL RANGE					LOW ABNORMAL RANGE			
Physiological variable	**+4**	**+3**	**+2**	**+1**	**0**	**+1**	**+2**	**+3**	**+4**
TEMPERATURE (° C)	> 41°	39 ° - 40.8 °		35.5 ° - 38.9 °	36 ° - 38.4 °	34 ° - 35.8 °	32 ° - 33.9 °	30 ° - 31.9 °	< 29.9 °
MEAN ARTERIAL PRESSURE (mm Hg)	> 160	130 - 159	110 – 129		70 - 109		50-69		< 49
HEART RATE (ventricular response)	> 180	140 - 178	110 – 139		70 - 109		55-69		< 39
RESPIRATORY RATE (non ventilated or ventilated)	> 50	35 - 49		25 - 34	12 - 24	10 - 11	6 - 9		< 5
OXYGENATION **If FiO2 > 0.5, Use (A-a) Do2** **If Fio2 ≤ 0.5 Use Pao2**	> 500	350 - 498	200 - 349		< 200 ..... PO, > 70	..... PO, 61 - 70	.....	..... PO, 55-60	..... PO, < 55
ARTERIAL pH	> 7.7	7.6 - 7.69		7.5 - 7.59	7.33 - 7.49		7.15 - 7.32	7.15 - 7.24	< 7.15
SERUM SODIUM (meg/dl)	> 180	160 - 179	155 - 159	150-154	130 - 149		120 - 129	111 - 119	< 110
SERUM POTASSIUM (meg/dl)	> 7	6 - 6.9		5.5 - 5.9	3.5 - 5.4	3 - 3.4	2.5 - 2.9		< 2.5
SERUM CREATININE (mg/100 ml)	> 3.5	2 - 3.4	1.5 - 1.9		0.6 - 1.4		< 0.6		
HEMATOCRIT (%)	> 60		50 - 59.9	48 - 49.9	30 - 45.9		20-29.9		< 20
WHITE BLOOD COUNT (total/mm3) (in 1000s)	> 40		20 - 39.9	15 - 19.9	3 - 14.9		1-2.9		< 1
GLASGOW COMA SCORE (GCS) (score 15 minus actual GCS)									
Total ACUTE PHYSIOLOGY SCORE (APS) Sum of the 12 individual variable points									
SERUM HCO3	> 52	41 - 51.9		32 - 40.9	22 - 31.9		18 - 21.9	15 - 17.9	< 15

AGE POINTS

Assign points to age as follows:

AGE (yrs)	POINTS
< 44	0
45 - 54	2
55 - 64	3
65 - 74	5
> 75	6

CHRONIC HEALTH POINTS

If the patient has a history of severe organ system deficiency or is immuno - compromised, assign points as follows:

a. For non-operative or emergency postoperative patients (5 points)

b. for elective postoperative patients
(2 points)

DEFINITIONS:
Organ insufficiency or immuno-compromised state must have been evident prior to the hospital admission and conform to the following criteria.

LIVER:
Biopsy proven cirrhosis and documented portal hypertension episodes of past upper GI bleeding attributed to portal hypertension: prior episodes of hepatic failure/encephalopathy/coma.

RESPIRATORY:
Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction.

Unable to climb stairs or perform household duties: documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (> 40mmHg), or respirator dependency.

RENAL:
Recurring chronic dialysis

IMMUNO-COMPROMISED:
The patient has received therapy that suppresses resistance to infection [e.g.immuno-suppression, chemotherapy, radiation, long-term or recent high dose steroids] or has a disease that is sufficiently advanced to suppress resistance to infection [e.g. leukaemia, lymphoma, AIDS]

APACHE SCORE

[sum of A+B+C]

A. APS points

B. Age points

C. Chronic health points

TOTAL APACHE SCORE