ELEVATED RED CELL DISTRIBUTION WIDTH AS A PROGNOSTIC MARKER IN SEPSIS

DISSERTATION SUBMITTED FOR

MD DEGREE (BRANCH 1) GENERAL MEDICINE

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CHENNAI

CERTIFICATE FROM THE DEAN

This is to certify that this dissertation entitled " **ELEVATED RED CELL DISTRIBUTION WIDTH AS A PROGNOSTIC MARKER IN SEVERE SEPSIS** is the bonafide work of **Dr.G.KARUPPASAMY;**, in partial fulfilment of the university regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, for M.D General Medicine, Branch I examination to be held in April 2019.

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DECLARATION

I, **Dr.G.KARUPPASAMY,** solemnly declare that this dissertation titled "**Elevated Red cell distribution width (RDW) as a prognostic marker in severe SEPSIS** is a bonafide record of work done by me at the Department Of General Medicine, Government Rajaji Hospital, Madurai, under the guidance of **Dr. S. RAVINDRAN, MD.,** Professor, Department of General Medicine, Madurai Medical college , Madurai.

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INTRODUCTION

Sepsis is the term applied when an infectious etiology is suspected or proven .Initially sepsis is defined as systemic inflammatory response to infection and non infectious causes also elicit same response. In 2001 organ dysfunction parameters are included to define sepsis.

Currently available gold standard scoring system for assessment of SEPSIS is the Acute Physiology and Chronic Health Evaluation. It is useful in intensive care unit and is not widely adopted for patients with sepsis outside of the intensive care setting. Other scoring systems such as the Sequential Organ Failure Assessment developed but still suitable only in the intensive care setting and not for routine use in all patients presenting with sepsis .

These are not suitable for stratifying patients at the time of admission or shortly thereafter Simplified tests using serum marker such as procalcitonin is not readily available.

Red cell distribution width is an independent prognostic marker. it has been used in many pathological conditions such as Cardiovascular diseases respiratory diseases and other inflammatory conditions.The association was independent of covariable such as anaemia,nutritional status.

Inflammation and oxidative stress reduce RBC survival and suppress their maturation lead to release of premature RBC into circulation contributing Elevated RDW.

Complete blood count is done in almost all sepsis patients admitted to ICU by automated analysers. RDW is provided within CBC done by automated analyser. It is In expensive, routinely available and rapidly measurable prognostic tools.

YOUDEN'S INDEX

Optimal cut off value of red cell distribution width for predicting mortality defined by calculated youdens index.-Youdens idex of red cell distribution width for predicting 30 days mortality calculated to be 17.3%

APACHE SCORE

There are twelve parameters to calculate APACHE score.

Acute Physiology And Chronic Health Evaluation score. Rectal temperature, Mean arterial pressure, Heart rate, Respiratory rate, Oxegenation by pao2/fio2 ratio, Arterial Ph ,bicarbonate level, serum creatinine, serum potassium and sodium, PCV level,Total leucocyte level, Glasco Coma Score level and Finally patient age.

When APACHE score of 25 represent predicted mortality of 50% APACHE score of 35 represent predicted mortality of 85 % in ICU.

AIMS AND OBJECTIVES

- To assess the association of red cell distribution width with mortality in patients with severe sepsis.

REVIEW OF LITERATURE

SIRS definition

1.-FEVER > 38 degree celsiuos or HYPOTHERMIA

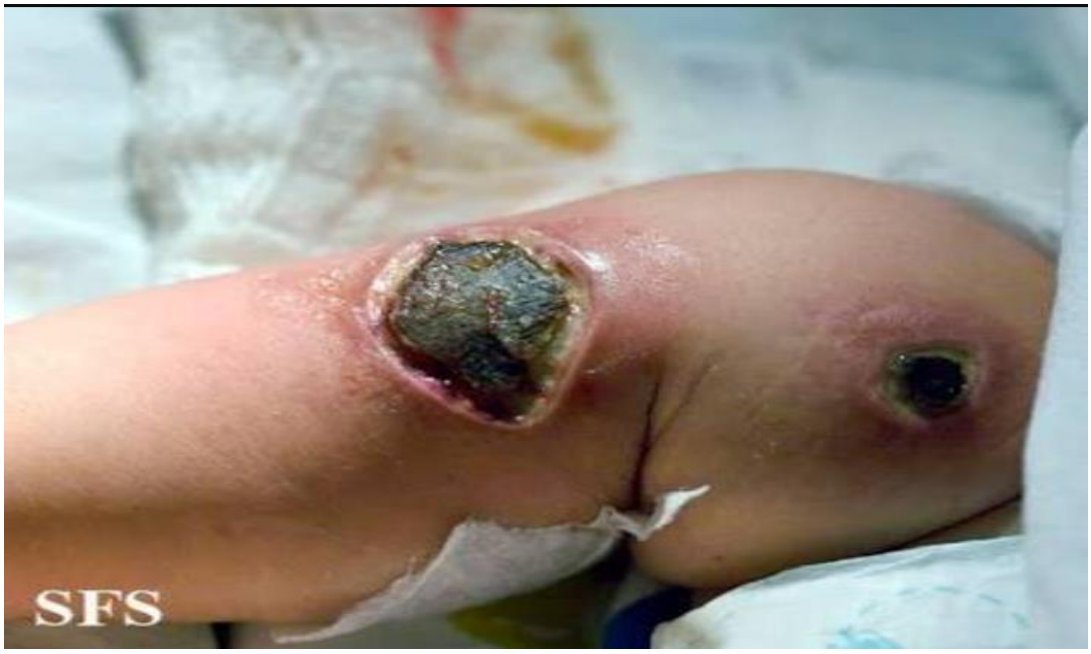
2.TACHYPNOEA > 24 breaths per minute

3.TACHYCARDIA HR > 90 per minute

4.LEUCOCYTOSIS > 12000 OR LEUCOPENIA <4000

SEPSIS

1. ***Cardiovascular:*** Arterial systolic blood pressure ≤90 mmHg or mean arterial pressure ≤70 mmHg .
2. ***Renal:*** Urine output <0.5 mL/kg per hour for 1 h despite adequate fluid resuscitation
3. ***Respiratory:*** Pao2/Fio2 ≤250
4. ***Hematologic:*** Platelet count <80,000/μL or 50% decrease in platelet count from highest value recorded over previous 3 days
5. ***Unexplained metabolic acidosis:*** A pH ≤7.30 or a base deficit ≥5.0 mEq/L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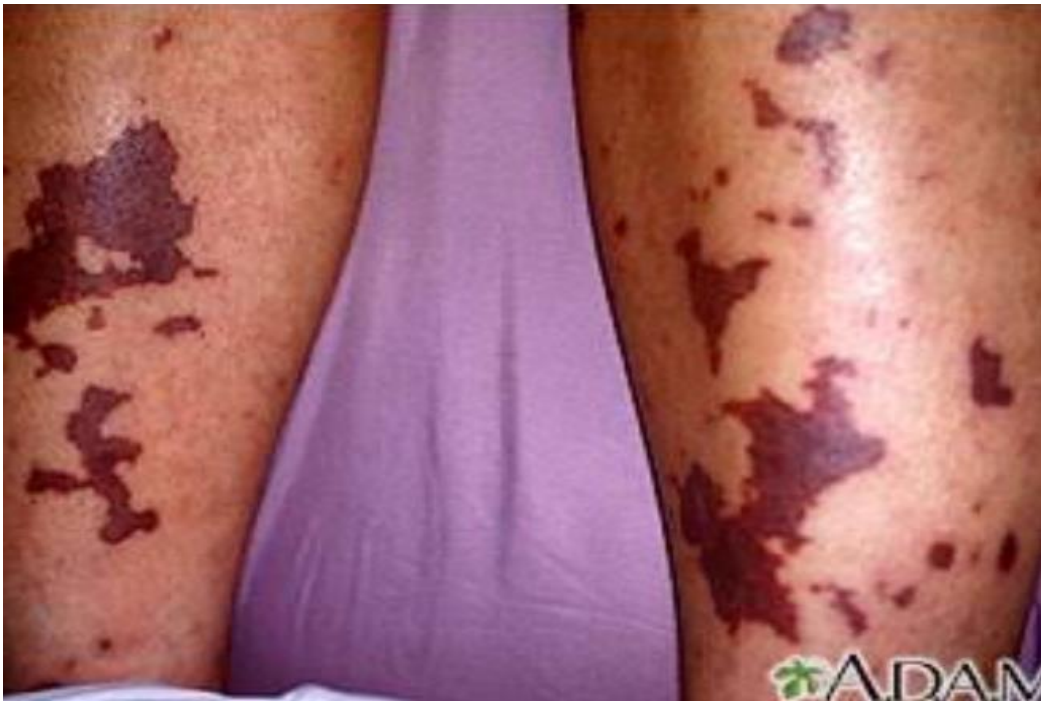
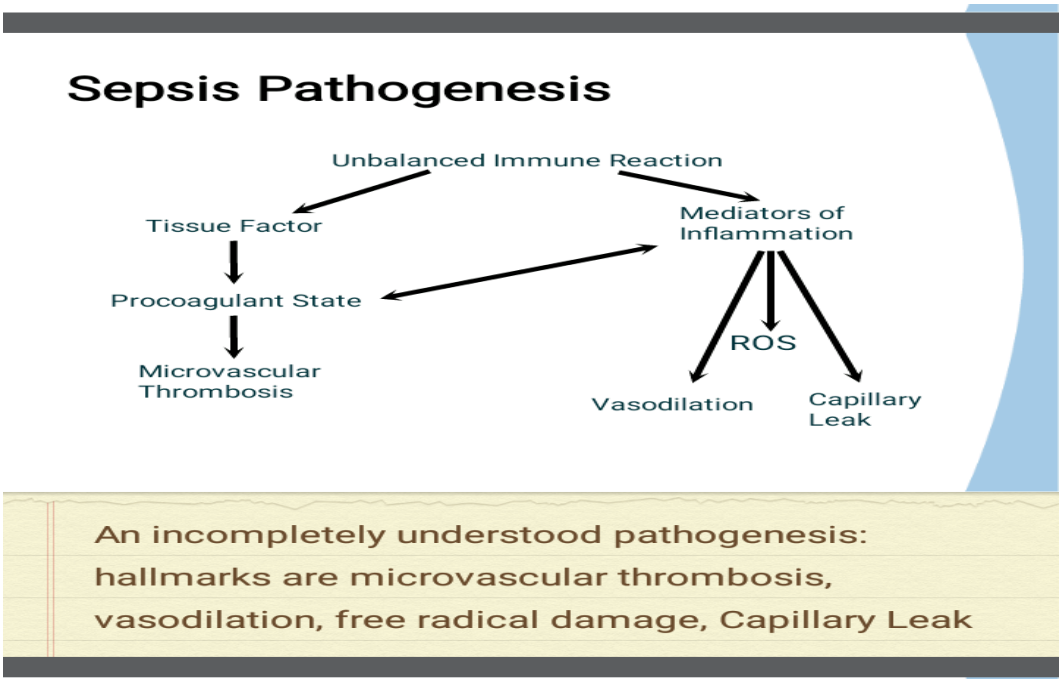

ADAM

Respiratory infections often induce severe sepsis followed by abdominal infections and urinary tract infections Severe sepsis caused by Neisseria meningitides and Streptococcus pyogenes.

Now a days sepsis is induced by commensal organism that infect the individuals whose epithelial barriers have been compromised by various illness.

Although gram negative organism isolated from severe sepsis the cases associated with gram positive infection has been steadily increasing. Candida spp now associated with severe sepsis.



Early host response to infection.

When a microbe breaches host epithelial barrier and enters underlying tissues it encounters macrophages ,mast cells,dendritic

cells.These cells sense the invader and stimulate local inflammatory response

Lipopolysaccharide which is present bacterial membranes attached to CD 14 which is expressed on phagocytes .This passes the LPS to transmemrane complex containing myeloid differentiation protein 2 and Toll Like receptor 4.This causes LPS recognition by cell interior.This causes signal transduction and gene transcription pathways activation promote secretion of inflammatory mediators.

Secretion of inflammatory mediators leads to increased vascular permeability and infiltration of neutrophils and induce the pain.

Fibrin deposition at local site stimulated by activated mavrophages and endothelial cells which helps wall off the infected tissue .Phagocytes release reactive oxygen species and prevent release of digestive enzymes into the circulation and limit the infection at local tissue.

Two inherited mechanism for killing microbes include mannose binding lectin and c reactive protein pathways .So invaded microbes eliminated by these phagocytes and complement pathway,antimicrobial peptides and invaded tissue become normal .This is called as Innate Immune system

Activation of innate immune system play an important role in pathogenesis of severe sepsis. Toll like receptor mobilze host response to invading microbes. In addition to this microbial endogenous ligands are

sensed by networks called as Neucleotide Oligomerization Domain.These stimulate the IL-1,IL-18.These induce the severe sepsis by stimulating various inflammatory cytokines.

Keeping infection and inflammation localized

The early systemic responses are controlled by BRAIN and LIVER.

CNS regulation of systemic response

Brain receives information about invading microbes by two mechanism.

1. Afferent impulses from nociceptive receptors from infected tissues reach hypothalamus where it activate HPA axis and thermoregulatory centre.
2. Blood borne mediators like TNF,IL 6,IFN reach the hypothalamus
3. Efferent from brain inhibits inflammation within the circulation.

LIVER essential role in systemic response to infection.

It remove all gut microbes and filter the endotoxins from microbes .kupfer cells extract LPS from microbes and inactivate it. Another most important mechanism of liver is that informs the brain about invading microbes.

Acute Phase Responses

Acute systemic responses to injury, infection, and other stresses in five categories :

Ant infective Anti-inflammator Procoagulant Metabolic Thermoregulator.;

Anti-infective Responses

Acute leucocytosis which largely reflects the demargination of neutrophils is brought about by epinephrine, cortisol, and possibly IL-10 and other mediators.;

- Enhanced surface expression of CD11b/CD18 on neutrophils may promote their adhesion to intercellular adhesion molecule on the surfaces of activated endothelial cells;. In addition to mobilizing neutrophils into the circulation and delivering them to sites of infection the acute-phase response also involves increased production of several proteins that bind conserved microbial molecules and assist in recognizing and killing microbes;
- Lactoferrin release from neutrophils and the production of hepcidin by the liver promote sequestration of iron in the reticuloendothelial system whereas zinc is retained within cells by binding to metallothionein..

Anti-inflammatory Responses

- The mechanisms that induce neutrophils to demarginate seem to inhibit their ability to adhere to noninflamed vascular endothelium thereby preventing unnecessary accumulation of neutrophils in uninfected tissues; Other responses that may prevent inflammation

within the systemic compartment include increase in the blood levels of cytokine antagonists IL-1Ra; soluble TNF receptors other anti-inflammatory mediators epinephrine, cortisol, adrenocorticotropic hormone ; IL-4, IL-6, IL-10, IL-13;

- A second exposure to the same or another microbial agonist fails to elicit the usual proinflammatory response whereas the production of some anti-inflammatory molecules IL-10 and IL-1Ra is maintained ;This adaptation which generally lasts a few days after the primary infection or exposure is thought to prevent untoward inflammation;
- At least in the case of LPS inactivation of the inciting ligand by a host enzyme acyloxyacyl hydrolase may be necessary to allow restoration of normal host defences ;adoptive transfer of CD34+ hematopoietic stem-progenitor cells enhanced bacterial clearance and improved long-term survival presumably by providing nontolerant immune cells;
- Inflammation induced procoagulant responses contribute to abscess formation and delayed hypersensitivity reactions in humans; In individuals sustained physical trauma activation of coagulation and inhibition of fibrinolysis occur roughly in proportion to the severity of injury;

- Inflammation-induced expression of tissue factor on the surfaces of monocytes and endothelial cells is thought to initiate the production of thrombin via factors VIIa and Xa whereas increased production of plasminogen activator inhibitor-1 (PAI-1) inhibits fibrinolysis
- Protein C is a natural anticoagulant that is converted to its activated form when thrombin binds thrombomodulin; Activated protein C then dissociates from its own receptor endothelial protein C receptor before binding soluble protein S to produce a complex that inactivates factors Va and VIIIa thereby blocking the activation of thrombin;
- During acute-phase responses, depletion of protein C and antithrombin III parallels the fall in serum albumin concentration; suggesting that these anticoagulants are negative acute-phase reactants. Protein C may also be degraded by elastase;

Thermoregulator responses

- Fever and the other elements of the acute-phase response are independently regulated; Because TNF, IL-6, and other putative pyrogens can be found in the blood in the absence of fever;
- It is possible that infection related thermogenesis is induced when local inflammation activates neural afferent signals to the thermoregulatory center either via nociceptive neurons or the vagus;

- The physiologic responses that increase body temperature include shivering and redirection of blood flow from the skin and extremities to internal organs by means of vasoconstriction; An increase in body temperature may favor host survival in several ways
- It may help inhibit bacterial growth and increase the bactericidal activities of neutrophils and macrophage;

Cytokines and Other Mediators

- Major proinflammatory cytokines TNF and IL-1 individually or in combination can induce severe sepsis and septic shock ; Blood of severely septic patients contains not only these and other proinflammatory mediators but also a broad array of anti-inflammatory molecules IL-4, IL-10, IL-1Ra, soluble TNF receptors; The dominant molecules in the plasma of septic patients are IL-10 and IL-4;
- IL-6 cytokine is proinflammatory can be produced by most cells in response to injury ;Epinephrine induces IL-6 production ; IL-6 is the most important activator of the HPA axis in response to stress and IL-6–deficient have exaggerated inflammatory responses to bacterial infections; IL-6 is the major procoagulant cytokine. ;Two proinflammatory mediators may become important late in the course of the response to severe infection;

- MIF is a product of T lymphocytes and macrophages that is induced by and opposes the actions of glucocorticoids. Although MIF normally circulates at a low basal level its plasma concentration increases during infection and stress and very high levels found in the plasma of patients with severe sepsis Second late proinflammatory molecule is a transcription factor HMGB-1 that appears in the blood several hours after infection begins and contributes to death;
- TNF and other proinflammatory mediators are produced at a local site of infection diffuse into the blood stream initiate systemic inflammation and are then opposed by a counterregulatory anti-inflammatory response ;An imbalance in these opposing forces cause severe sepsis;

Complement Activation

- The ability of normal human serum to kill bacteria is largely conferred by the complement system which can be activated by antigen-antibody complexes and CRP ;Then certain bacterial surface sugars mannose-binding lectin pathway or lipopolysaccharides alternative pathway.
- These pathways can be activated in the serum of patients with sepsis and at least two complement proteins may contribute to the septis;

- Activation of both the complement and the contact systems is regulated by C1-esterase inhibitor an acute-phase protein that undergoes proteolytic inactivation in patients with severe sepsis;
- Factor C5a is a potent chemo attractant that induce vasodilation increase vascular permeability and augment the release of granule enzymes from phagocytes. The blood neutrophils of humans with early sepsis may lose responsiveness to C5a. Antibody-mediated neutralization of C5a or its receptor may prevent death;

Coagulopathy;

- Activation of the coagulation cascade and inhibition of anticoagulation and fibrinolysis are commonly observed during sepsis ; These changes may be extensions of the normal acute phase response to infection . They may be triggered by vascular endothelial injury or dysfunction either at a local site of infection or more diffusely;
- The endothelium is pivotal in promoting coagulation via its expression of tissue factor and von Willebrand factor and its association with activated platelets; Key anticoagulant molecules antithrombin, protein C tissue factor pathway inhibitor also interact with the endothelial surface and can be compromised during activation of coagulation by inflammatory mediators;

- Cell fragments or microparticles derived from activated or apoptotic cells may express tissue factor and contribute to the procoagulant state. The extent to which coagulopathy contributes to organ dysfunction in septic humans is controversial.

Activation or Injury of the Vascular Endothelium;

- The vascular endothelium is involved in three processes that play major roles in sepsis pathophysiology:
- vascular tone ;- vascular permeability; - coagulation; Endothelial activation or injury contributes to abnormalities in blood pressure ,fluid extravasation, and coagulation is derived from endotoxin; Patients with severe sepsis and septic shock has higher concentrations of von Willebrand factor–positie endothelial cells in their plasma . There is also much interest in angiopoietin-2 which circulates in high levels in patients with severe sepsis and can disrupt the endothelial barrier;

Mitochondrial and Microcirculatory Dysfunction;

- Infection-associated abnormalities in organ function are often reversible. There is often little or no detectable evidence for cell death in the microscopic appearance of tissues of patients die from severe sepsis;

- Microcirculatory dysfunction and abnormal oxygen use and the long course of recovery and frequent occurrence of long-term sequelae common in sepsis;
- In septic patients the readily measurable indices of macrocirculatory function mean arterial pressure, cardiac output, mixed venous oxygen saturation often do not parallel the severity of organ dysfunction It is now widely believed that a critical cause of abnormal organ function in severe sepsis resides in the microcirculatory units arteriole, capillary bed, venule within tissues;
- Patients with severe sepsis has significantly lower vessel density and the proportion of perfused small vessels also below normal.. Mechanisms often invoked to account for changes in the microcirculation include reduced deformability of erythrocytes and activated neutrophils, neutrophil aggregation, and microthrombosis;
- Many phenomena might contribute, including diminished entry of pyruvate into the tricarboxylic acid cycl and uncoupling of oxidation from phosphorylation because of collapse of the proton gradient across the mitochondrial membrane;
- Nitric oxide (NO) and ROS are thought to play major roles in triggering mitochondrial loss and hypofunction. The ability of peroxynitrite and NO to activate polyadenosine diphosphate ribose polymerase (PARP) may also be important because PARP rapidly

polymerizes cellular ADP;It is likely that many influences intersect to alter mitochondrial function, including both cell-intrinsic mechanisms mitochondrial loss via autophagy;

Septic Shock

Septic shock may have two distinguishable phases. Vasoconstrictive shock characterized by low cardiac output and high peripheral resistance occurs in patients who are hypovolemic factors that contribute to decreased effective intravascular volume include redistribution of blood flow venous pooling, increased capillary permeability; increased insensible losses, and poor fluid intake;

- During this phase, the blood pressure is supported by peripheral vasoconstriction. Restoration of effective intravascular volume by the administration of fluids is usually followed by vasodilation. Vasodilation is not often seen with acute hemorrhagic shock or cardiogenic shock, and it does not usually occur in patients with shock caused by viral hemorrhagic fevers ;
- Tachyphylaxis to catecholamines, which diminishes the sensitivity of vascular smooth muscle to catecholamines administered as pressors.;
- The underproduction or peripheral resistance of glucocorticoids, which upregulate adrenergic receptor ;
- The underproduction or ineffectiveness of aldosterone ;

- The production of adrenomedullin, which has vasodilatory actions, increases renal blood flow, and inhibits aldosterone secretion;
- The release of NO from sites of inflammation and or distant vascular endothelium ;
- The absence of the normal baroreflex response that increases circulating vasopressin levels and depletion of neurohypophyseal vasopressin stores;
- The release of platelet activating factor ;
- The activation of potassium ATP channels in arteriolar smooth muscle cells by hypoxia and lactate ;
- The generation of bradykinin, a vasodilator that also increases capillary permeability ; The basic mechanisms that compromise essential cell function from hypoperfusion are alterations in cell membrane permeability and mitochondrial energy production. Hypoxic cells switch to anaerobic glycolysis and accumulate lactate, hydrogen ion, and inorganic phosphates;
- Cellular ATP stores decrease because of diminished synthesis, continued consumption, and the actions of ATPases.Energy-dependent sodium and calcium pumps in the plasma membrane are affected, resulting in the loss of cellular potassium and the accumulation of sodium, calcium, and water.This lead to cell death. In addition, protein synthesis is impeded, ribosomes detach from the

endoplasmic reticulum, and mitochondrial and lysosomal membranes are damaged.

- Protein misfolding further contributes to cell injury and death. High conductance, nonselective permeability channels develop in the mitochondrial inner membrane and the loss of membrane potential impedes oxidative phosphorylation and allows leakage of cytochrome C into the cytoplasm, compromising electron transport and serving as a major signal to initiate apoptosis;
- Increases in intracellular calcium may initiate cell injury and an imbalance between free-radical generation and radical-scavenging systems may enhance oxidative stress; Reactive oxygen species superoxide anion, hydrogen peroxide, and hydroxyl ions can accelerate cell injury via lipid peroxidation, damaging plasma and organelle membrane;

Infection Susceptibility and Outcome:

Genetic Influences

- A major obstacle to understanding the pathogenesis of severe sepsis is the striking heterogeneity of the patient population that experiences the syndrome; Patients may differ in age, sex, ethnic group, underlying disease, inciting microbe, medications, and numerous other variables;

- Genetic variation contributes to both susceptibility and outcome in infectious diseases ;Many polymorphisms associated with meningococcal disease and or pneumococcal disease;. single nucleotide polymorphism associations in small groups of critically ill patients with sepsis caused by diverse pathogens;

Microbial Triggers for Severe Sepsis

- The most commonly identified sites of primary infection in patients with severe sepsis are the lungs and the abdomen; Gram-positive lipoproteins, lipoteichoic acid and gram-negative lps bacterial molecules are recognized by distinct receptors on leukocytes; Downstream signaling pathways patients with severe sepsis caused by gram-positive and gram negative bacteria may have somewhat different cytokine responses
- IL-1β, IL-6, and IL-18 concentrations higher in the plasma of patients with sepsis caused by gram-positive bacteria. Higher levels of TNF or IL-6 in the plasma of patients with severe sepsis caused by gram-negative bacteria.
- In patients with severe sepsis and documented infection bacteremia has been associated with early mortality. Bloodstream infection with certain microorganisms such as Candida albicans,methicillin-resistant S. aureus and vancomycin-resistant Enterococcus faecium has also been associated with significant attributable mortality.

- First bacteremia is usually low grade . The body's innate immune mechanisms for clearing commensal bacteria and fungi from the bloodstream are evidently very effective.
- Second with some exceptions such as S. aureus bacteremia, meningococcemia, plagu and septicemic melioidosis the risk for developing severe sepsis has not correlated directly with the density of cultivatable bacteria in the blood.
- Third bacteremia has no distinctive clinical features at the bedside bacteremic patients with severe sepsis are indistinguishable from those whose cultures are negative a diagnostic algorithm that identified 88% of patients with bacteremia as a complication of community-acquired pneumonia .

The case-fatality rates for culture-positive and culture-negative patients with severe sepsis and septic shock have been very similar suggesting that bacteremia may contribute little to outcome.

Endotoxemia

- Bacterial endotoxin when it enters the bloodstream triggers systemic inflammation. ; There is no local inflammation to impede bacterial invasion or induce systemic responses. Meningococci can grow to very high density in the blood and shed membrane blebs that contain endotoxin and other molecules these particles may serve as

surfaces for activating complement and coagulation within the bloodstream.

- Limulus amebocyte lysate assay has been used to measure endotoxin in plasma ; The major site for the stimulatory action of endotoxin may be in an infected extravascular tissue not the circulating blood; It is also possible that endotoxin is more active in the blood of acutely infected previously healthy patients in whom the enhanced endotoxin-inactivating mechanisms cited previously have yet to be induced and in whom circulating endotoxin has been associated with poor outcome;.

CLINICAL MANIFESTATIONS

Patients with severe sepsis and septic shock experience derangements in both of the body's major communication networks.

Nervous and Neuroendocrine Systems

Patient may exhibit subtle abnormalities in cognitive performance . Confusion and other alterations in higher cerebral function are often early manifestations of severe sepsis particularly in older adult patients.

Sepsis-associated encephalopathy is defined as diffuse cerebral dysfunction that accompanies sepsis in the absence of direct CNS infection structural abnormalities or other types of encephalopathy.

Adrenal Insufficiency

Activation of the hypothalamic pituitary adrenal axis is essential for survival from severe stress. The most frequently implicated microbes are N. meningitidis, Mycobacterium tuberculosis, cytomegalovirus and Histoplasma capsulatum.

- CMV-related adrenalitis has been common in patients with end-stage human immunodeficiency virus infection ;Among the other factors that may contribute to hypoadrenalism in septic patients are hypoperfusion, cytokine-induced dysfunction of the adrenals, drug-induced steroid hypermetabolism or inhibition of steroidogenesis and desensitization to glucocorticoid responsiveness at the cellular level ; Secondary adrenal insufficiency caused by pituitary infection or apoplexy is quite rare; Adrenal insufficiency diagnosed if the plasma cortisol level less than 10 µg/dL in the setting of significant stress or if the level did not increase more than 9 µg/dL in response to ACTH stimulation (250 µg synthetic ACTH [cosyntropin];.
- A clinical entity critical illness related corticosteroid insufficiency reflects inadequate cellular corticosteroid activity resulting from adrenal insufficiency, tissue corticosteroid resistance or both; CIRCI is associated with exaggerated and prolonged inflammatory responses to infection;

- The aldosterone response to exogenous ACTH seems to be maintained in most patients with severe sepsis . A state of hyperreninemic hypoaldosteronism has been described in critically ill individuals most of whom have been hypotensive.

Autonomic Dysfunction

Heart rate variability is influenced by the balance of vagal and sympathetic inputs to the sinoatrial node; Autonomic reflexes can modulate these inputs as can the central vasomotor and respiratory centers and peripheral arterial pressure and respiratory movement oscillators;

Blood Compartment Blood Cells

A neutrophilic leukocytosis is the normal response to bacterial or fungal infection ;It is produced by mobilizing neutrophils from the marginal pool as well as the marrow Failure to mount a neutrophilic leukocytosis has been associated with a poor outcome;

At the onset of sepsis peripheral blood lymphopenia occurs reflecting diminished numbers of T, B, and NK cells. At least in part the reduction in circulating CD4+ cells may be due to apoptosis. In contrast the numbers of circulating B-lymphocytes may increase despite apoptotic cell death.

- The percentage of T-helper lymphocytes producing IL-17 increases and the fraction that produces IFN-γ decreases at the onset of sepsis

this pattern may reverse after 1 week. NK-cell absolute numbers fall and their IFN-γ production is reduced;

- Monocyte numbers do not change substantially but their cellular function is altered ; Decreased cytokine responses and cell-surface expression of HLA-DR are common and have been used as biomarkers of immunosuppression in severely ill patients.;
- Increased expression of CD163 and CD206 markers of alternative activation phenotypes occurs within the first week of severe sepsis. Although thrombocytopenia often accompanies DIC it may be the only routinely measured clotting parameter that is abnormal on the other hand many patients with low-grade DIC do not have thrombocytopenia; The basis for isolated thrombocytopenia in septic patients is probably multifactorial with peripheral nonimmune destruction hemophagocytic histiocytosis and marrow suppression playing variable roles;

Lipid Metabolism;

- Striking changes occur in the circulating lipids and lipoproteins .High-density lipoprotein and low-density lipoprotein levels decrease whereas triglyceride, free fatty acid and very low density lipoprotein levels increase; The decrease in serum cholesterol is almost entirely accounted for by lower concentrations of cholesterol esters in circulating HDL and LDL;

Glucose Metabolism

Hypoglycemia is a relatively uncommon manifestation of sepsis. The pathogenesis of hypoglycemia is not well understood but adrenal insufficiency should be considered in such patients. Moderate or severe hypoglycemia associated with an increased risk of death .The body's acute metabolic responses to infection maintain the blood sugar concentration through gluconeogenesis, glycogenolysis, and insulin resistence ;

Coagulopathy

The prevalence of DIC increases as the inflammatory response intensifies reaching approximately 30% to 50% in patients with severe sepsis. The patient's underlying condition like infection, solid cancers, hematologic malignancies, obstetric diseases, trauma, liver disease can influence diagnostic laboratory tests; In addition all of these conditions can be complicated by the development of sepsis making the diagnosis and treatment of DIC dependent on the clinical context rather than on any one specific laboratory parameter;

Commonly used screening assays for DIC include

1. A reduced or downward trend in the platelet count usually < 100,000/mm3
2. The presence of fibrin-related markers including fibrin degradation products, D-dimers, or soluble fibrin in plasma

3. Prolongation of the prothrombin time or the activated partial thromboplastin time (>1.2 times the upper limit of normal
4. Low plasma levels of endogenous anticoagulants antithrombin III , protein C ; Reduced levels of ADAMTS13 activity and elevation of soluble thrombomodulin, plasminogen activator inhibitor, von Willebrand factor, and von Willebrand factor propeptide may be seen;

Respiratory system involvement;

ARDS is classified as Mild 200 mm Hg < partial pressure of arterial oxygen / fractional inspired oxygen < 300 mm Hg),

Moderate (100 mm Hg < Pao2/Fio2 ≤ 200 mm Hg)

Severe (Pao2/Fio2 ≤ 100 mm Hg).

The underlying pathology is diffuse alveolar epithelial injury with increased barrier permeability and exudation of protein-rich fluid into the interstitial and airspace compartments

- Neutrophils and monocytes accumulate in the lungs and may form cellular aggregates in pulmonary vessels .Significant right-to-left shunting occurs;
- Dead space volume increases and compliance decreases, augmenting the work of breathing and often necessitating mechanical ventilation;

- Indeed a common indication for mechanical ventilation is respiratory muscle fatigue in patients who are obtunded or have impaired gag reflexes;
- Intubation may also be used to prevent aspiration of oropharyngeal or gastric contents;

Renal Dysfunction

- Severe sepsis is often accompanied by azotemia and oliguria. The renal abnormalities range from minimal proteinuria to profound renal failure. Acute tubular injury and minimal glomerular damage may be manifestation;
- The pathogenetic mechanisms include hypovolemia, hypotension, renal vasoconstriction, and toxic drugs .
- Sepsis-induced renal injury is largely reversible. On the other hand sepsis can also occur in patients who have acute kidney injury of other etiologies and then acquire nosocomial infection;
- Predictors of sepsis after acute kidney injury included oliguria , higher fluid accumulation, higher severity of illness score;

Hepatic Dysfunction

The principal sepsis-associated abnormality is cholestatic jaundice characterized by elevations in conjugated and unconjugated bilirubin ;. These changes occur in patients with and without preexisting liver disease and may precede recognition of infection;

In patients with severe sepsis, elevated alkaline phosphatase, bilirubin, and amino transferase levels are common, but frank hepatic failure is unusual; If the duration of septic shock is prolonged however, a massive rise in serum transaminases leads to hypoxic necrosis of centrilobular liver cells.

Immune Dysfunction Reactivation;

Latent CMV infections occurs in approximately 35% of critically ill patients. CMV viremia has been described in a similar fraction of patients with severe sepsis; The extent to which CMV contributes to immunosuppression in these patients is not known, yet patients with CMV antigenemia have had higher rates of nosocomial infection, prolonged hospitalization and mortality.

Cutaneous Manifestations;

A wide range of skin lesions may occur in patients with severe sepsis . Pustule and eschar lesions that appear at sites of hematogenous seeding of the skin or underlying soft tissue.

Petechiae, pustules, ecthyma gangrenosum, cellulitis diffuse eruptions caused by bloodborne toxins and hemorrhagic or necrotic lesions Recognition of certain characteristic lesions can greatly assist etiologic diagnosis.

- Cellulitis and thrombophlebitis are associated with intense local inflammation. Bacteria implicated include Campylobacter fetus , Vibrio species, and Aeromonas hydrophila
- When the inflammatory response is impaired usually by neutropenia, ecthyma gangrenosum or bullous lesions may occur
- Pseudomonas aeruginosa is the most commonly isolated microorganism..
- In symmetrical peripheral gangrene associated with DIC fibrin thrombi are seen in small vessels but neither inflammatory cells nor bacteria are found

DIAGNOSIS

- No bedside or laboratory test provides a definitive diagnos. There is also considerable inter-individual and time-dependent variability in the expression of the body's responses to infection so a diagnostically useful profile of laboratory tests is not possible;.
- In addition to the signs that comprised SIRS tachycardia; tachypnea, leukocytosis ;or leukopenia; and fever; or hypothermia ; findings such as altered mental status; unexplained hyperbilirubinemia; lactatemia; metabolic acidosis or respiratory alkalosis; and thrombocytopenia can be useful clues.

- The appearance of new lesions on the skin or mucosae may also be suggestive. One normal response to infection is a neutrophilic leukocytosis in the peripheral blood.
- Fever is also a normal response to infection, and an increase in body temperature above a certain level (usually 38.0° or 38.3° C) is often the trigger for initiating a diagnostic evaluation;

Some septic patients may be euthermic or hypothermic.

Differential Diagnosis

- Numerous noninfectious conditions can mimic sepsis by presenting with hypotension or organ failure.
- Burns, trauma, adrenal insufficiency, pancreatitis, pulmonary embolism, dissecting or ruptured aortic aneurysm, myocardial infarction, occult hemorrhage, cardiac tamponade, and drug overdose;
- Fever and hypotension can also be caused by a number of noninfectious processes, including adrenal insufficiency;
- Thyroid storm, pancreatitis, drug hypersensitivity reactions, malignant hyperthermia, serotonin syndrome, and heatstroke;
- Vasodilatory shock can be a manifestation of anaphylaxis;

Cultures

- Cultures are essential for identifying the likely microbial invaders and ascertaining antimicrobial susceptibility patterns;
- For optimal sensitivity and specificity blood cultures should be drawn from two or three different venipuncture sites;
- The volume of blood drawn adults 20 to 30 mL/venipuncture, children no more than 1% of total blood volume is the most important variable in detecting bacteremia;
- Bacteremia categorized as transient, intermittent, or continuous;
- Transient bacteremia lasts minutes to hours and may occur with manipulation of either anatomic sites colonized by normal flora;
- Intermittent bacteremia is associated with closed-space infections or focal infections ;
- Persistent low-grade bacteremia is associated with an intravascular focus, such as endocarditis or vascular graft infection;
- Careful preparation of the skin is essential to avoid false positive cultures from skin contaminants.

Chlorhexidine (2%) has a short drying time compared with 10% povidone-iodine or 1% to 2% tincture of iodine cleansing with 2% chlorhexidine in 70% alcohol was superior to 10% aqueous povidone-iodine for preventing culture contamination.

Cultures and microscopic examination of urine, sputum including tracheal aspirate if done within a few hours of intubation likely infected fluids, purulent wound drainage, and skin lesions should also be obtained.

Gram-stained material obtained from biopsies or needle aspirates of petechial lesions can provide a rapid diagnosis in patients with meningococcemia.

Imaging Axial tomography is an important complement to routine chest and abdominal radiography to assess for unrecognized sources of infection in the sinuses, lungs, liver, and abdomen.

Ultrasonography and cholescintigraphy (hepatobiliary iminodiacetic acid [HIDA] scanning) may be useful for evaluating gallbladder function

Adrenal Insufficiency in Patients with Septis

The clinical and laboratory diagnoses of sepsis-associated relative adrenal insufficiency are very difficult. .

To measure free cortisol the diagnostic significance of cortisol-binding proteins, the utility of salivary cortisol levels and the quantitation of tissue glucocorticoid resistance.

The most useful clinical definition of relative adrenal insufficiency is based simply upon the response to hydrocortisone administration .

The presence of “pressor-dependent hypotension that responds to the administration of 50 to 100 mg hydrocortisone every 6 hours strongly support the diagnosis.

Obtaining a baseline serum cortisol level before initiating hydrocortisone therapy. A value less than 15 µg/dL in a patient with septiS should encourage careful evaluation for adrenal insufficiency after recovery from the septic episode.

Antimicrobial Drugs

A drug is considered appropriate if it is able to inhibit the patient’s microbial isolate in vitro and is administered within 24 to 48 hours of the onset of bacteremia or severe sepsis.

Antimicrobial Chemotherapy Severe Sepsis;

- In patients with suspected or proven streptococcal myositis/fasciitis or toxic shock syndrome clindamycin should be given in addition to penicillin G to reduce toxin production.
- If staphylococcal toxic shock syndrome is considered, clindamycin should be given with either oxacillin ; vancomycin;, or linezolid.;

IMMUNOCOMPETENT PATIENTS;

- Pipercillin-tazobactum;
- Imipenam cilastin;
- Cefepime;

If the patient allergic to beta lactams use ciprofloxacin, levofloxacin plus clindamycin and vancomycin.

NEUTROPENIA;

Regimens include

- 1-Imipenam –cilastin or Meropenam;
- 2-.Pipercillin –tazobactum plus Tobramycin;
- 3-.Vancomycin should be added;
- 4.-Empirical antifungal therapy echinocandin or Voricanozole to be added;

SPLENECTOMY PATIENT;

Cefotaxim plus vancomycin

If the patient allergic to beta lactam vancomycin plus levofloxacin to be used.

Fluid resuscitation in severe sepsis

- A reasonable goal in general is maintenance of mean arterial pressure greater than 65 mm Hg although in some patients with long-standing hypertension a higher MAP may be required; In most patients 15 to 30 mL/kg or up to 4 to 6 L of crystalloid required in the early phases of resuscitation.
- Too little fluid may cause tissue hypoperfusion and worsen organ function, whereas excessive fluid administration may impair organ function resulting from tissue edema; Dopamine is considered the

drug of choice for restoring normotension in patients with septis; Noradrenaline is alternative to dopamine in fliud resuscitation

Glucocorticoid

- In patients with septic shock who have not responded to fluid and vasopressor resuscitation hydrocortisone treatment should be initiated 50 mg IV every 6 hours or with a loading dose of 100 mg followed by a continuous infusion of 10 mg/hr continued for 7 days and then slowly tapered over 5 to 6 days.

Anti-inflammatory Drugs

- Immunomodulatory drugs to improve survival in patients with severe sepsis; Large doses of glucocorticoids ; Antiendotoxin agents , Antibodies to TNF , TNF-immunoglobulin fusion proteins that trap TNF; IL-1 receptor antagonist ;Antagonists to PAF, bradykinin, phospholipase A2, NO synthase, cyclooxygenase, bradykinin,

Anticoagulants

- Administration of heparin is associated with a reduction in mortality; The basis for these results is not clear because most ICU patients receive low-dose heparin as prophylaxis for deep venous thrombosis unless there is a contraindication to its use.

Nutrition and Other Supportive Measures

- Use of enteral instead of intravenous nutrition in critically ill patients. Prophylaxis for GI bleeding, deep venous thrombosis, and

decubitus ulcers should be followed ;Decubitus ulcers prevented by avoiding prolonged skin exposure to stool and urine and by frequent repositioning and by adequate nutrition;

Preventing SecondaryInfections;

- Patients with severe sepsis are immunosuppressed and subjected to invasive procedures they may be at risk for secondary infections; Hand washing and the use of barrier precautions when examining patients colonized with resistant bacteri ; Semirecumbent body position reduces the risk for nosocomial pneumonia, especially in patients who receive enteral nutrition.;

RED BLOOD CELLS;

- The red blood cells carry hemoglobin in the circulation; The RBC are biconcave disks that are manufactured in the bone marrow. In humans they survive in the circulation for an average of 120 days;
- The average normal red blood cell count is 5.4 million/μL in men and 4.8 million/μL in women. Each human red blood cell is about 7.5 μm in diameter and 2 μm thick and each contains approximately 29 pg of haemoglobin;

ROLE OF THE SPLEEN

The spleen is an important blood filter that removes aged or abnormal red cells ;It also contains many platelets and plays a significant role in the immune system. Abnormal red cells are removed by spleen.;

HEMOGLOBIN

The red oxygen-carrying pigment in the red blood cells of vertebrates is haemoglobin; Heme is an iron-containing porphyrin derivative.

ERYTHROID PROGENITORS

Burst-Forming Unit–Erythroid;

The earliest identifiable progenitor committed to the erythroid lineage is the BFU-E; A BFU-E is defined by its ability to create a "burst" on semisolid medium that is; a colony consisting of several hundred to thousands of cells by 10 to 14 days of growth ;during which time smaller satellite clusters of cells form around a larger central group of erythroid cells giving rise to the designation of a burst;

Colony-Forming Unit–Erythroid

- As erythroid maturation progresses a later progenitor the CFU-E; derived from the BFU-E . The CFU-E is dependent on erythropoietin for its development .Thus the CFU-E forms a smaller colony of morphologically recognizable erythroid cells in 5 to 7 days ; Adhesion between erythroid cells and macrophages occurs at the CFU-E stage of maturation;
- In erythropoiesis, the earliest precursor is the proerythroblast.
- Erythroid progenitor cells are identified as marrow cells capable of forming erythroid colonies ;

Proerythroblasts

On stained films the proerythroblast appears as a large cell, irregularly rounded or slightly oval;

Basophilic Erythroblasts

Basophilic erythroblasts are smaller than pro erythroblasts. The nucleus occupies three-fourths of the cell area and is composed of characteristic dark violet heterochromatin interspersed with pink staining clumps of euchromatin ;

Polychromatophilic Erythroblasts

Following the mitotic division of the basophilic erythroblast the cytoplasm changes from deep blue to gray as haemoglobin dilutes the polyribosome content.

Maturation

Following nuclear extrusion, the reticulocyte retains mitochondria, small numbers of ribosomes, the centriole, and remnants of the Golgi apparatus. It contains no endoplasmic reticulum.

Erythropoietin

The principal hormone regulating erythropoiesis is EPO which is produced principally in the kidney. Erythroid progenitors express their own EPO. Different levels of kidney-produced EPO are optimal for various stages of erythroid maturation;

Erythropoietin Receptor;

Interaction of EPO with its receptor EPOR results in stimulation of erythroid cell division; erythroid differentiation by induction of erythroid specific protein expression prevention of erythroid progenitor apoptosis.

Hypoxia-Inducible Factors;

EPO production is mediated by decreased oxygen saturation of hemoglobin, that is hypoxemia. Hypoxia is an important factor in development, energy metabolism, vasculogenesis, iron metabolism, tumor promotion and is the principal regulator of erythropoiesis.

Measurement of red cell mass;

The red cell mass is maintained and regulated by the kidney and marrow The kinetics of red cell production and destruction helps establish their pathogenesis. A number of tests have been developed to measure the three main components of red cell kinetics:

HEMATOCRIT

Packed red cell volume is commonly referred as the haematocrit. It is measured as the percentage of the volume of whole blood that is made up by red blood cells; Hct indirectly based on red cell count and the mean red cell volume. Total-body Hct is the volume of red cells in the body divided by the total blood volume;

EFFECTIVE RED CELL PRODUCTION

Effective erythropoiesis is most simply estimated by determining the reticulocyte count. Most modern automated counters measure reticulocytes by nucleic acid binding dyes such as thiazole orange using flow Cytometry;.Absolute reticulocyte count =%reticulocytes × red cell count/100

Total erythropoiesis

- Total erythropoiesis which is the sum of effective and ineffective red cell production, can be estimated from a marrow examination.
- A differential count then is performed determining the ratio between granulocytic and erythroid precursors. In a normal adult, the ratio is approximately 3:1 to 5:1.

Red Cell Distribution Width;

- The RDW is an estimation of the variance in volume within the population of red cells expressed as 1 SD of red cell volume measurements divided by the MCV.
- Instrument manufacturers calculate RDW using different algorithms, so that reference ranges vary according to analyzer model; The RDW can be used in the laboratory as a flag to select those samples that should have manual review of blood films for red cell morphology;

- More significantly, a large literature has now developed around the evidence that the RDW is a biomarker predicting morbidity and mortality in a broad variety of clinical settings such as angina/myocardial infarction heart failure; trauma; pneumonia; sepsis; intensive care treatment;renal and liver disease; and in the general population.
- Most of these studies are retrospective, observational, or cohort-based studies, often using databases of routinely collected data gathered for other purposes but prospectively designed studies have arrived at similar conclusions.
- The RDW retains its association with poor clinical outcomes whether or not anemia is present and it adds predictive power to more established predictive risk models;
- RDW may be a surrogate for systemic inflammation;oxidative stress; but the predictive value of RDW is independent of other inflammatory markers suggesting that this biomarker is tracking other mechanistic processes as well.
- Identification of physiologic mechanisms linking RDW to adverse clinical outcomes will be important in using this predictive biomarker to inform therapeutic decisions

RED CELL DISTRIBUTION WIDTH;

It measure variation in red cell volume and size;

ANISOCYTOSIS

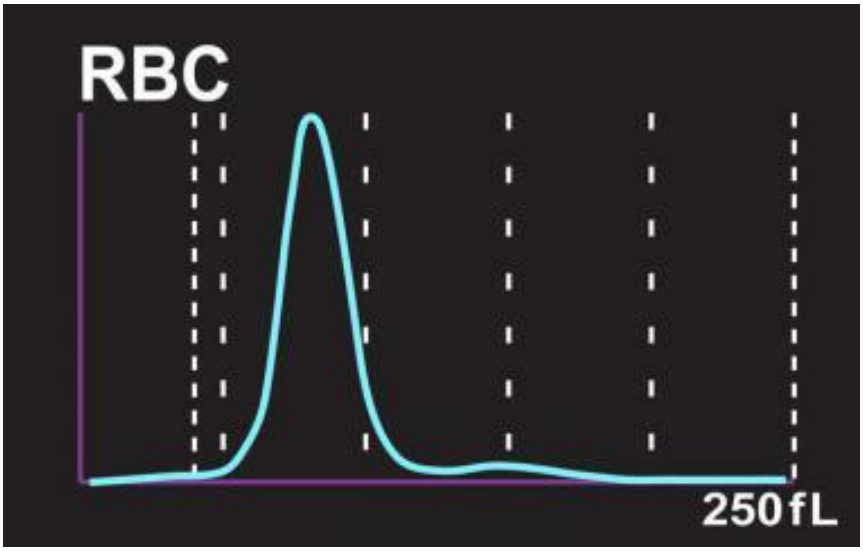
Coefficient of variation of RBC volume and is representation of RBC size heterogeneity;

It means variation in cell size.variation in red blood cell size is expected when elevated red cell distribution width present.

Normal range of Red cell distribution width;

RDW –SD =39-46 femtolitre.

RDW –CV=11.6 -14.6%

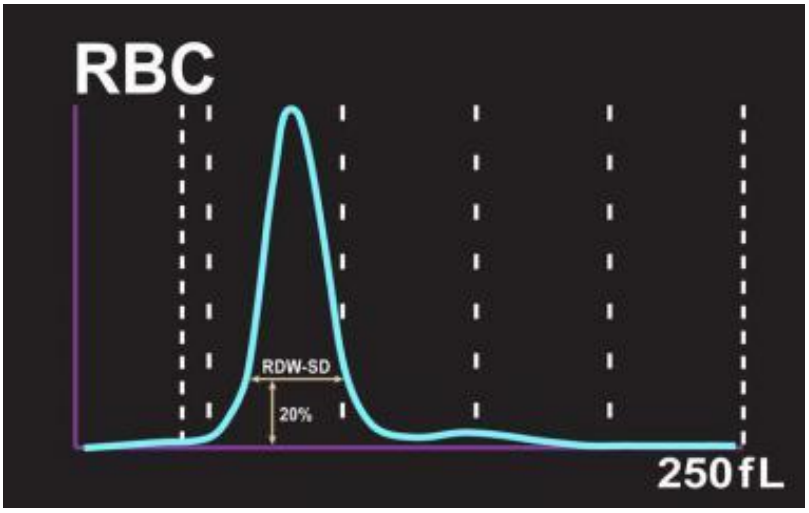


Sysmex SE-2100 analyzer- RBC size distribution histogram ;

Here MCV of 81.4 fL; RDW-SD of 38.2 fL; & RDW-CV of 12.8%.

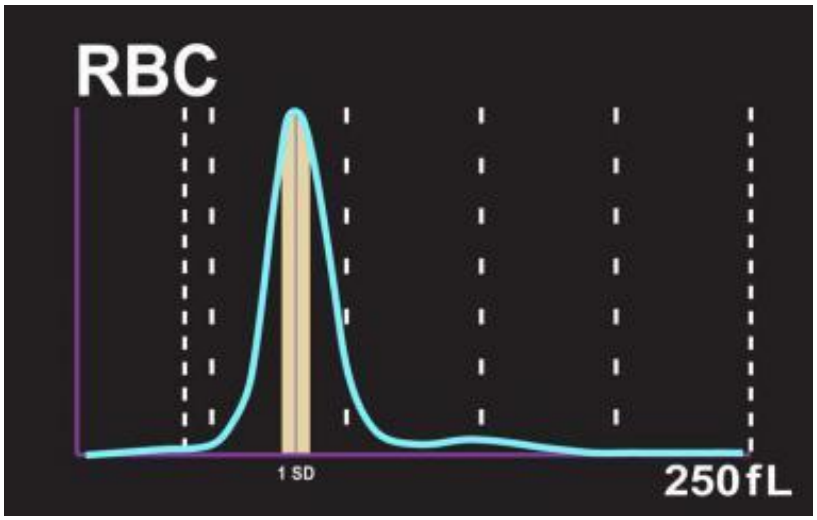
Determination of RDW-SD measurement;

Here RDW -38 fl



Determination of RDW-SD measurement;

In this example; RDW-SD is 38.1 fL



Calculation of RDW-CV measurement which is derived from 1SD divided by MCV times 100%.

- In this example RDW-CV is 12.8%.;

RDW –SD

- It is expressed in femtolitre;
- It is a measurement of variation of red blood cell size;
- It is measured by distribution histogram;
- Calculating width of RBC in fl at 20% ht level of

RBC

This is not influenced by mean corpuscular volume;

RDW-CV

- It is expressed in percentage ; It is calculated from standard deviation and mean corpuscular volume - RDW-CV %=one std deviation of RBC volume /MCV

RDW USES

- In nutritional deficiency like iron, folate, vit B12 deficiency RDW is elevated earlier than other red cell indices ; Useful in differentiate various anaemia by using both RDW and MC ; It indirectly gives information about red cell fragmentation ;agglutination.

Elevated RDW and LOW MCV causes;

- Sickle cell anaemia;
- Iron deficiency anaemia;

NORMAL RDW and high MCV

- Aplastic anaemia
- Chronic liver disease

Elevated RDW and High MCV

- Folate and B12 def
- Immune haemolytic anaemia
- Chronic liver disease
- Myelo dysplastic syndrome

Normal RDW and low MCV

- Anaemia of chronic disease
-Heterozygous thalassemia
- Haemoglobin E trait

Elevated RDW mechanism

Proinflammatory cytokines like CRP;ESR;IL-6;TNF aipha. have been shown to suppress maturation of red blood cells and variable maturation of RBC leads to elevated RDW.

The RBC in the acute critical setting is afflicted by significant stress.the erythrocyte survival time is decreased in response to

proinflammatory cytokines.this results in rapid clearing of RBC.Shorter RBC survival leads to variation in size of RBC

STUDY METHODS

Study will be conducted on 100 adult patients [greater than 18 years old] with diagnosis of severe sepsis for greater than 24 hrs in GOVERNMENT RAJAJI HOSPITAL & MADURAI MEDICAL COLLEGE during the study period

Design of study

- PROSPECTIVE OBSERVATIONAL

Period of study

- 6 months

INCLUSION CRITERIA

- Patients with diagnosis of severe sepsis for greater than 24 hours

EXCLUSION CRITERIA

- Patients who denied formal consent,
- Pregnant Females,
- History Of Packed Cell Transfusion,
- Known Haematological Disorders,
- Recent Chemotherapy,

- Immunosuppression
- For Solid Organ Transplantation,
- Post Splenectomy Patients,
- Drugs

Which Induce Changes In Morphology And Rheology Of RBC

INVESTIGATIONS

- Complete blood count
- Renal function test
- Liver function test
- Complete haemogram with peripheral smear with red cell indices
- Random Blood Sugar level
- Arterial blood Gas

MATERIALS AND METHODS

Patient received in ICU – Collect Blood for Culture and red cell distribution width

Compare clinical and lab investigations. severity of Illness duration of hospital stay ,requirement vasoactive agents with patients having high Red cell distribution width against low red cell distribution width;

Compare number of patients who died having High/Normal red cell distribution width as against their acute physiology and chronic health evaluation score for sepsis;

Compare number of patients who survived having Normal/ High red cell distribution width as against their Acute physiology and chronic health evaluation score for sepsis;

ANTICIPATED OUTCOME

Patients with elevated red cell distribution width has higher mortality which co-relates with APACHE scoring system;

A diagnosis of severe sepsis required following features;

1. Cardivascular; systolic blood pressure <90 mmHg
2. Renal;Urine output <0.5 ml /kg /hr for one hr despite adequate fluid resuscitation.

3. Respiratory;PaO2 /FiO2 ratio <250
4. Unexplained metabolic acidosis;Ph<7.30
5. Sepsis is defined as systemic inflammatory response to proven or suspected infection.

- The Red cell distribution width (RDW) is to be analyzed on day zero correlated with severity
- Sensitivity, specificity, Positive predictive value, negative predictive value, diagnostic accuracy of both tests are calculated.
- DESIGN OF STUDY: Prospective analytical study
- PERIOD OF STUDY: March 2018 to September 2018
- COLLABORATING DEPARTMENTS:

Department of Medicine, Department of Pathology, Biochemistry, Microbilogy.

CONSENT: Individual written and informed consent.

ANALYSIS: Statistical analysis

CONFLICT OF INTEREST: Nil

PARTICIPANTS: patients with acute pancreatitis attending the Department of Medicine & Department of Medical gastroenterology, Govt. Rajaji Hospital, Madurai.

Method of study

This study was conducted in Govt. Rajaji Hospital, Madurai which is affiliated to Madurai Medical College. This study subjects were selected from the patients admitted in Department of Medicine and Department of medical gastroenterology, Govt. Rajaji Hospital Madurai.

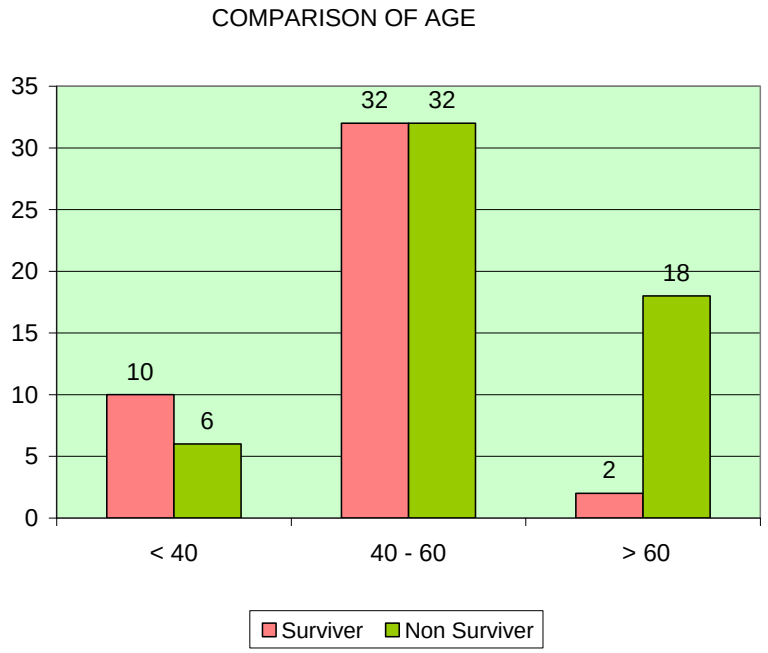
The study was conducted in 100 patients; the patients had severe sepsis diagnosed by clinical background and further evaluated and confirmed with biochemical investigations. The patients are examined clinically with the following parameters and only 100 patients are taken for study.

Study protocol

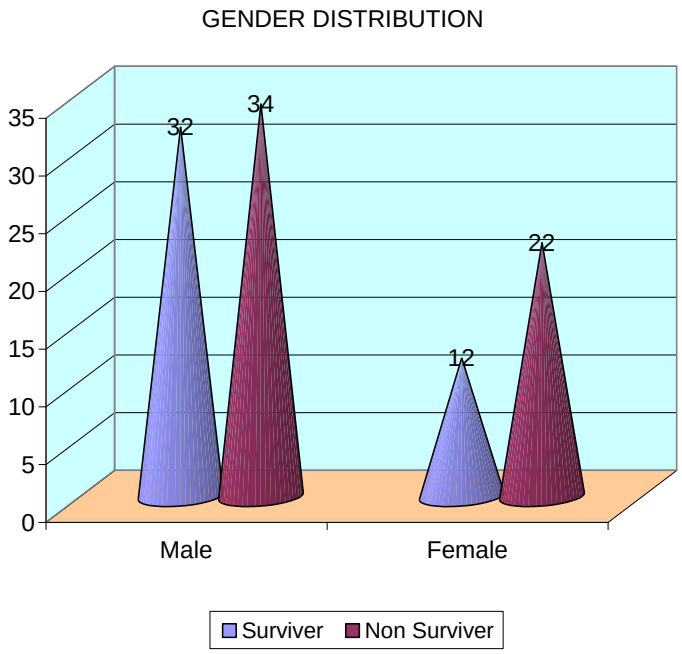
Patients with clinical, biochemical evidence of severe sepsis that fulfilling above criteria are included in this study.

OBSERVATION OF RESULTS

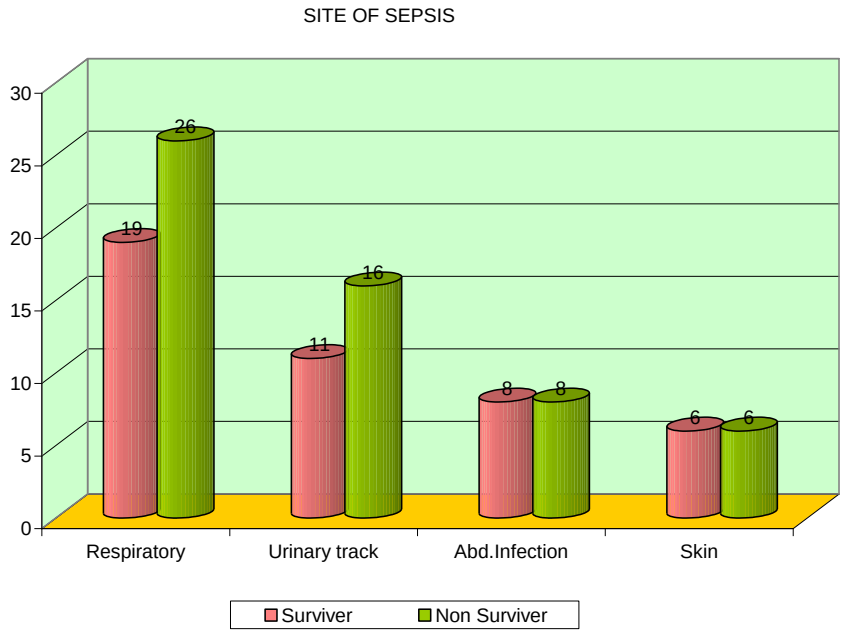
Age	Surviver	Non Surviver	Total
< 40	10	6	16
40 - 60	32	32	64
> 60	2	18	20
Total	44	56	100
Mean	47.07	55.96	
SD	8.56	11.25	
p value	0.005 Significant		



Sex	Surviver	Non Surviver	Total
Male	32	34	66
Female	12	22	34
Total	44	56	100
p value	0.265	Not significant	



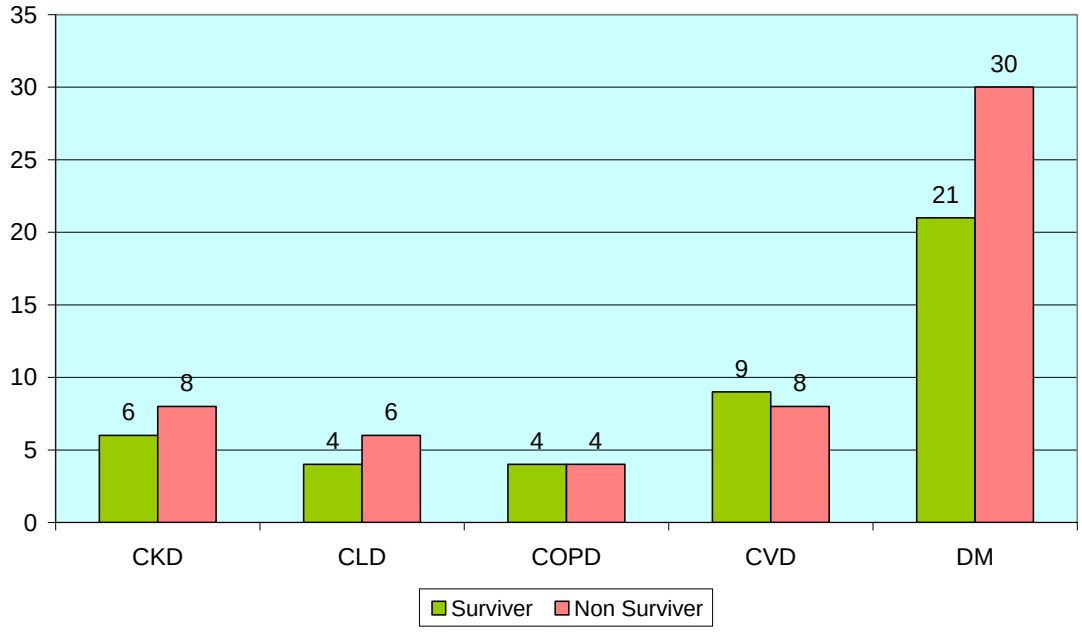
Site Of Sepsis	Surviver	Non Surviver	Total
Respiratory	19	26	45
Urinary track	11	16	27
Abd.Infection	8	8	16
Skin	6	6	12
Total	44	56	100



Source Of Sepsis	Surviver	Non Surviver	Total
Community	39	47	86
Hospital	5	9	14
Total	44	56	100
P value			

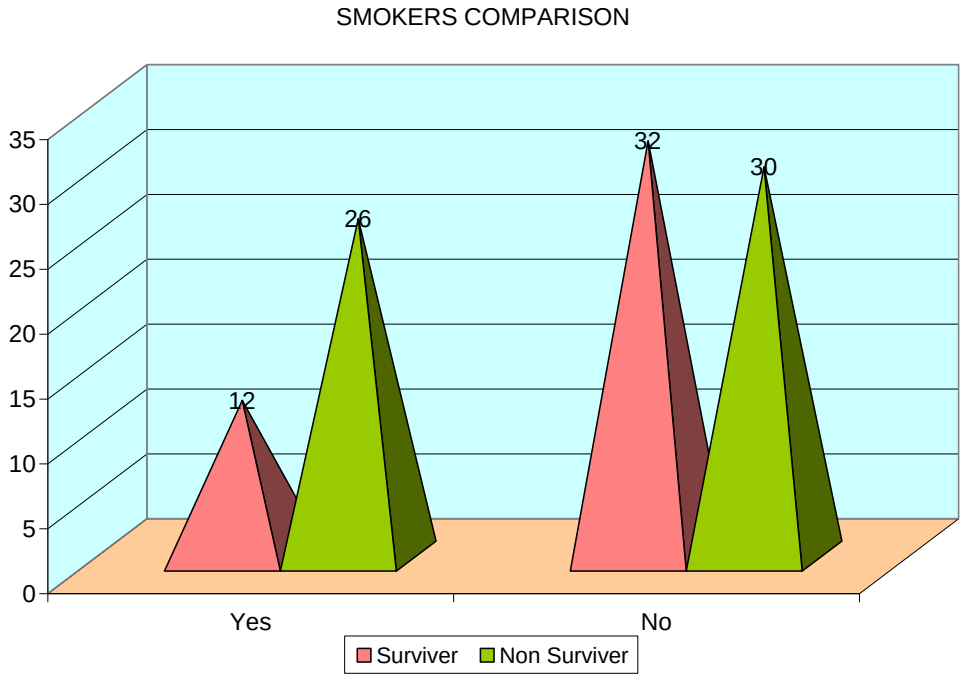
Comorbidities	Surviver	Non Surviver	Total
CKD	6	8	14
CLD	4	6	10
COPD	4	4	8
CVD	9	8	17
DM	21	30	51
Total	44	56	100

COMORBIDITIES

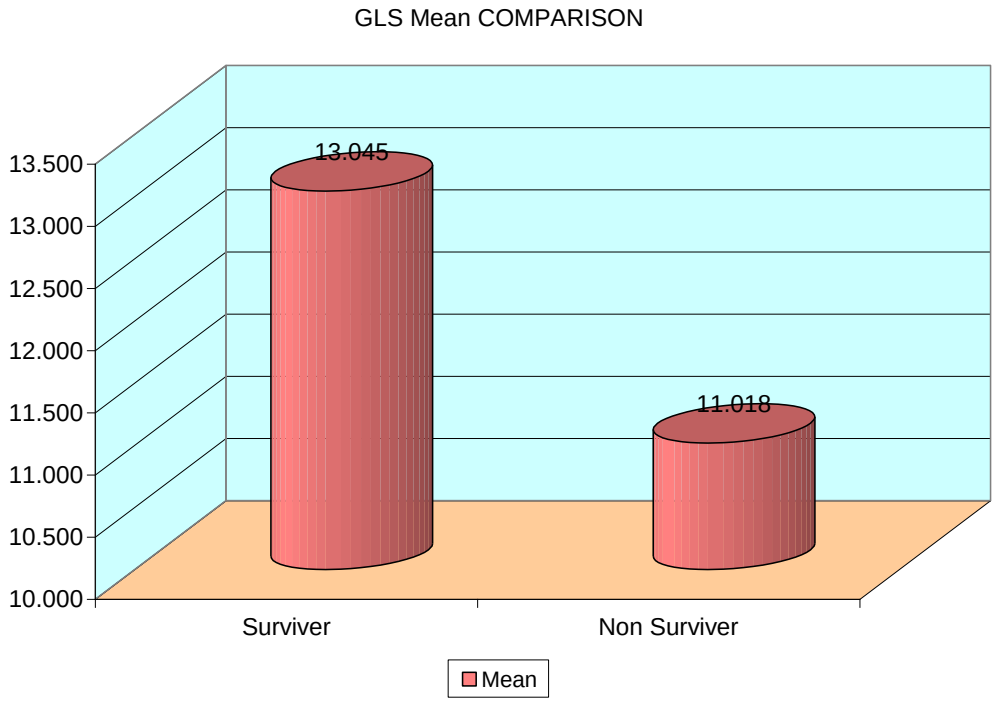


Smokers	Surviver	Non Surviver	Total
Yes	12	26	38
No	32	30	62
Total	44	56	100

P value	0	Not Significant

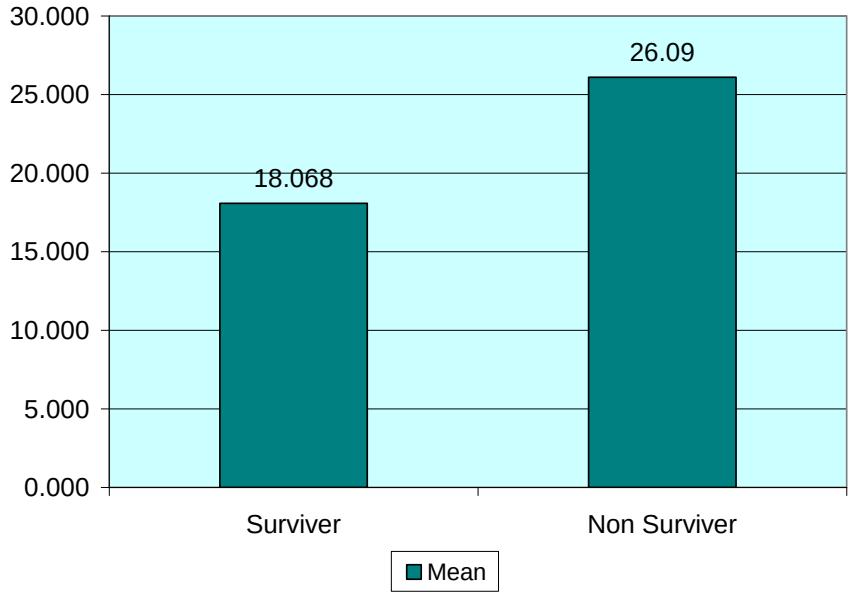


GCS	Surviver	Non Surviver	Total
< 13	17	42	59
≥ 13	27	14	41
Total	44	56	100
Mean	13.045	11.018	
S.D	1.363	1.959	
P'	<0.001	Significant	

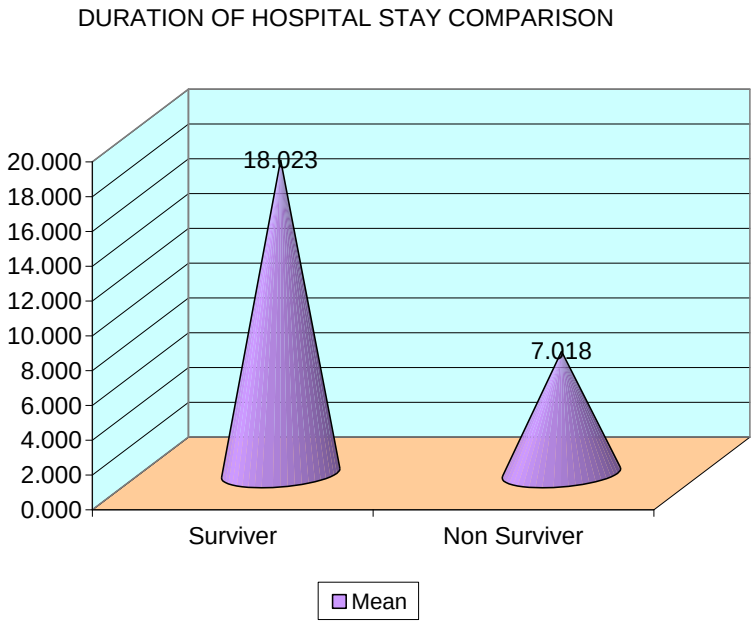


Apache	Surviver	Non Surviver	Total
≤ 20	36	3	39
> 20	8	53	61
Total	44	56	100
Mean	18.068	26.09	
S.D	2.723	3.71	
P'	<0.001	Significant	

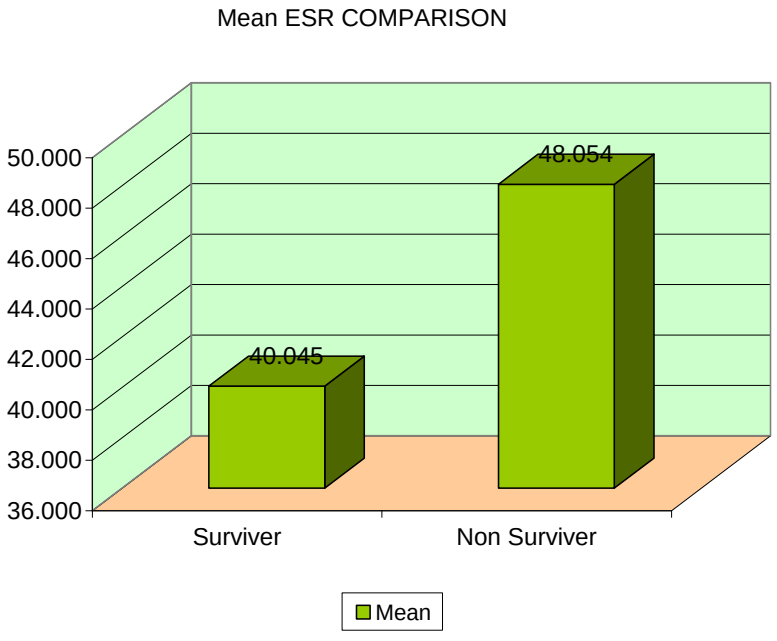
APACHE Mean COMPARISON



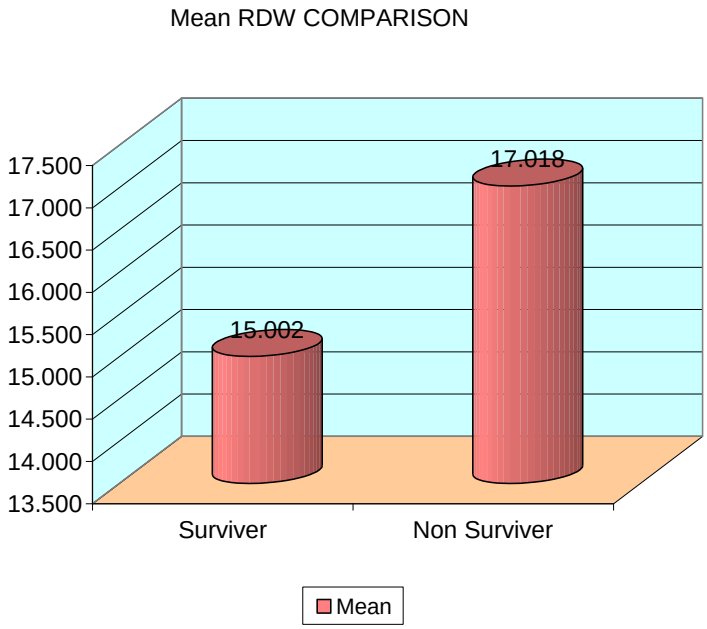
Hosp.Stay	Surviver	Non Surviver	Total
≤ 15	21	56	77
> 15	23	0	23
Total	44	56	100
Mean	18.023	7.018	
S.D	4.49	1.42	
P'	<0.001	Significant	



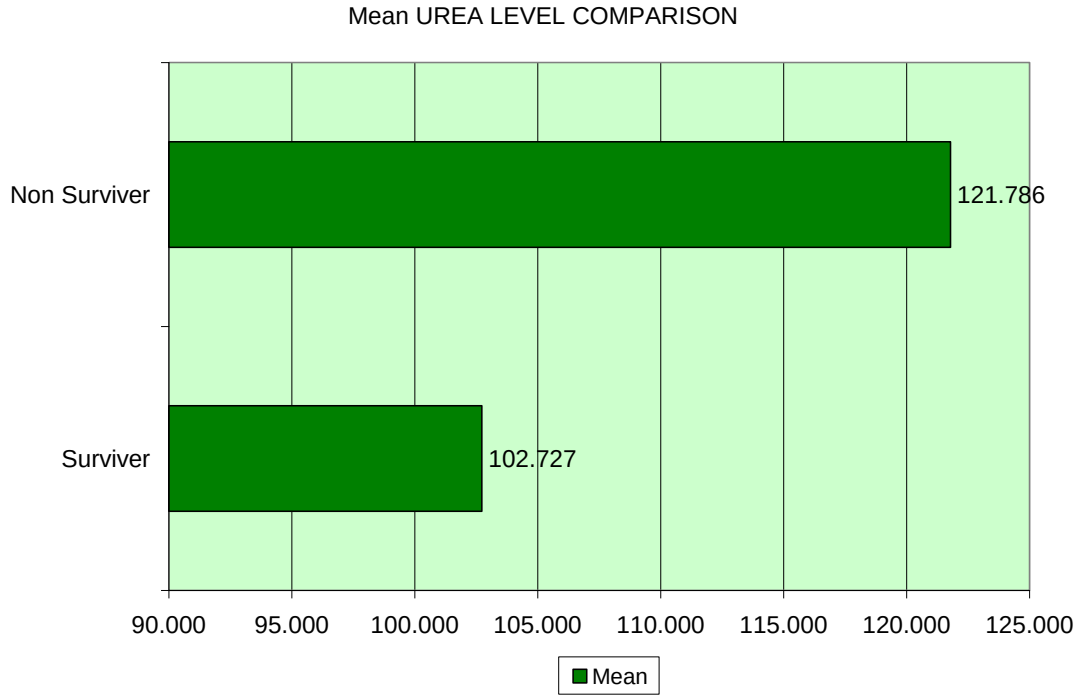
ESR	Surviver	Non Surviver	Total
≤ 45	35	22	57
> 45	9	34	43
Total	44	56	100
Mean	40.045	48.054	
S.D	5.344	5.492	
P'	<0.001	Significant	



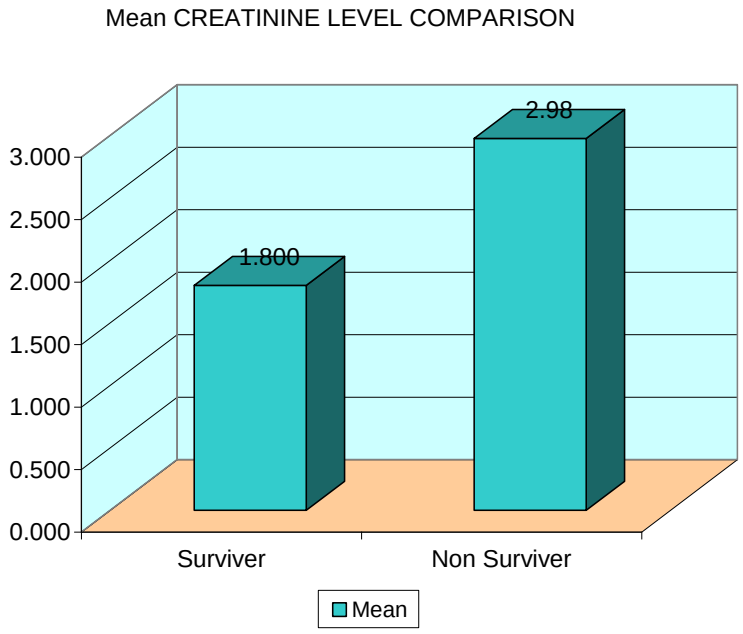
RDW	Surviver	Non Surviver	Total
≤ 15	18	0	18
> 15	26	56	82
Total	44	56	100
Mean	15.002	17.018	
S.D	0.675	0.820	
P'	<0.001	Significant	



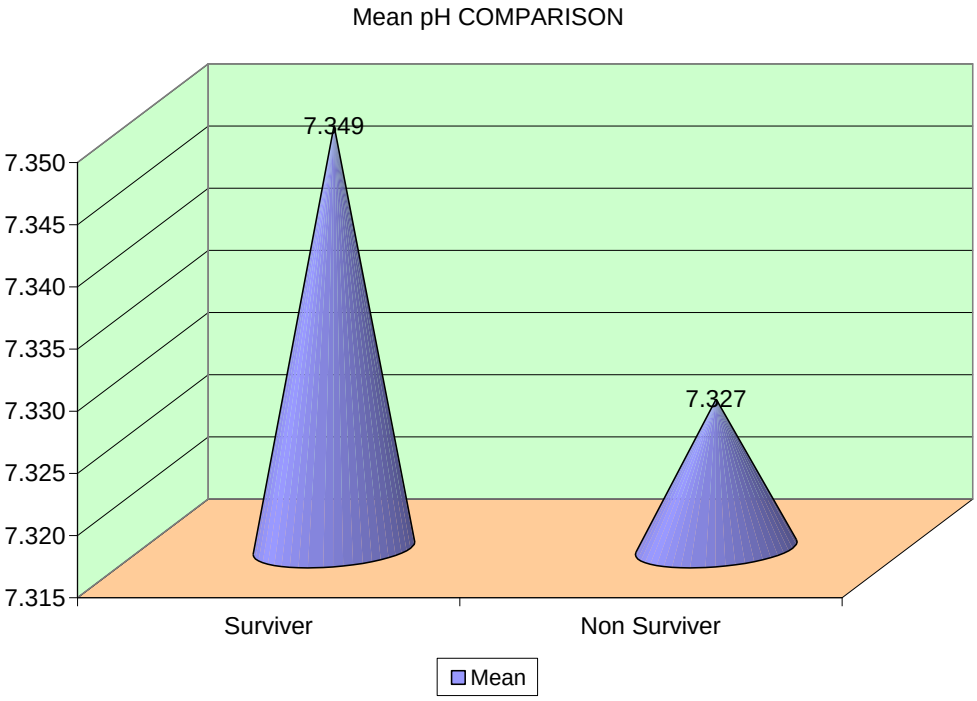
UREA	Surviver	Non Surviver	Total
≤ 150	40	43	83
> 150	4	13	17
Total	44	56	100
Mean	102.727	121.786	
S.D	36.111	36.590	
P'	0.011	Significant	



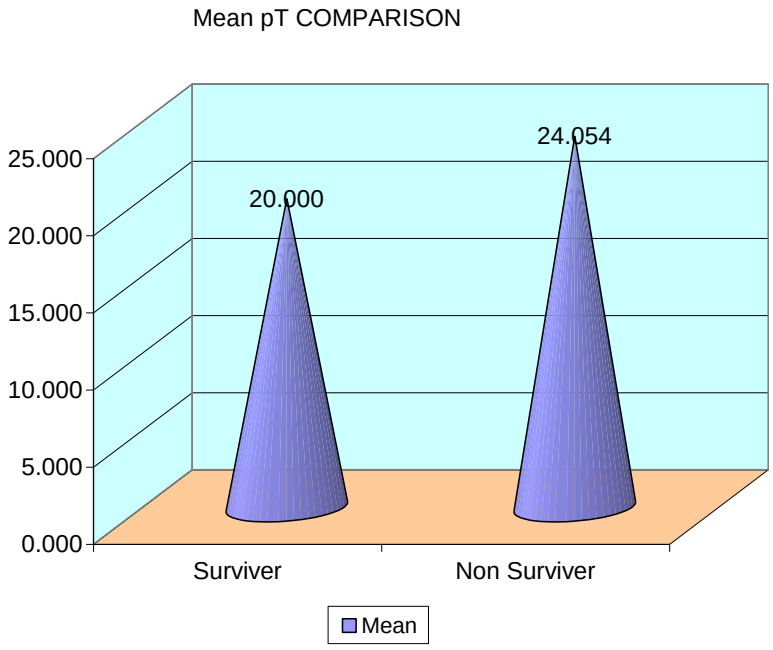
CREATININE	Surviver	Non Surviver	Total
≤ 2.5	44	12	56
> 2.5	0	44	44
Total	44	56	100
Mean	1.800	2.98	
S.D	0.278	0.53	
P'	<0.001	Significant	



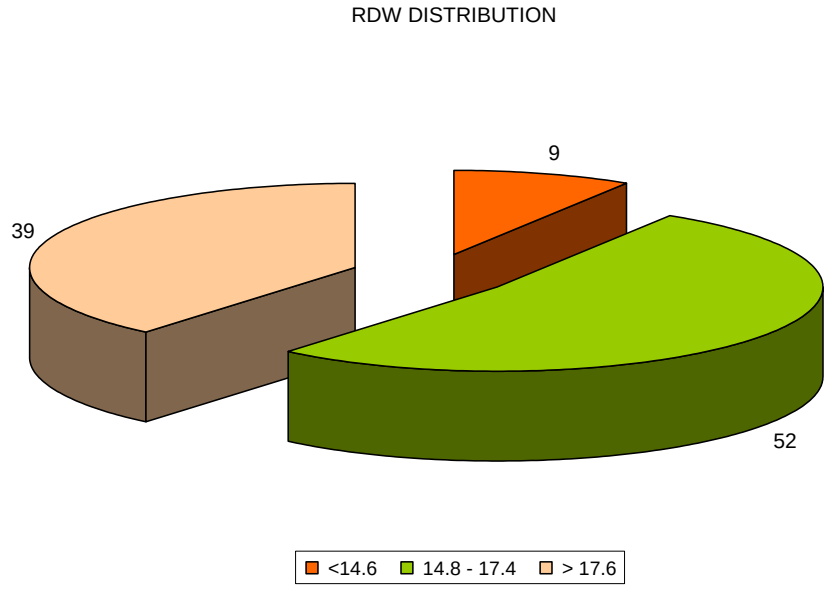
pH	Surviver	Non Surviver	Total
≤ 7.32	7	31	38
> 7.32	37	25	62
Total	44	56	100
Mean	7.349	7.327	
S.D	0.026	0.100	
P'	0.148	Not sig	



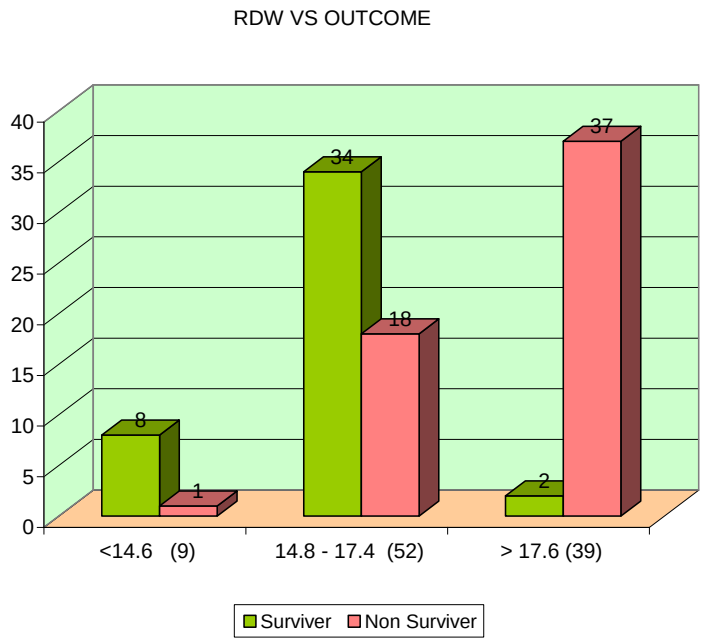
Surviver	pT	Non Surviver	Total
36	≤ 24	25	61
8	> 24	31	39
44	Total	56	100
20.000	Mean	24.054	
3.959	S.D	6.890	
<0.001	P'	Significant	



RDW	No.of cases
<14.6	9
14.8 - 17.4	52
> 17.6	39
Total	100



RDW	Surviver	Non Surviver
<14.6 (9)	8	1
14.8 - 17.4 (52)	34	18
> 17.6 (39)	2	37
Total	44	56



Age	Group I	Group II	Group III
< 40	2	8	6
40 - 60	5	37	22
> 60	2	7	11
Total	9	52	39

Sex	Group I	Group II	Group III
Male	7	37	22
Female	2	15	17
Total	9	52	39

Source Of Sepsis	Group I	Group II	Group III
Community	9	44	33
Hospital	0	8	6
Total	9	52	39

Site Of Sepsis	Group I	Group II	Group III
Respiratory	3	28	14
Urinary track	2	11	14
Abd.Infection	4	8	4
Skin	0	5	7
Total	9	52	39

Comorbidities	Group I	Group II	Group III
CKD	0	8	6
CLD	0	5	5
COPD	2	4	2
CVD	6	7	4
DM	1	28	22
Total	9	52	39

GCS	Group I	Group II	Group III
< 13	3	29	27
> 13	6	23	12
Total	9	52	39
Mean	12.778	12.327	11.154
S.D	2.333	1.712	2.059
P'	0.007 Significant		

Apache	Group I	Group II	Group III
< 20	7	28	4
> 20	2	24	35
Total	9	52	39
Mean	17.444	21.096	25.692
S.D	2.833	4.864	4.169
P'	<0.001 Significant		

Hosp.Stay	Group I	Group II	Group III
< 15	6	33	38
> 15	3	19	1
Total	9	52	39
Mean	16.778	14.288	7.487
S.D	5.380	6.628	2.394
P'	<0.001 Significant		

RDW	Group I	Group II	Group III
≤ 15	2	15	1
> 15	7	37	38
Total	9	52	39
Mean	15.533	15.687	16.862
S.D	1.168	1.246	0.921
P'	<0.001 Significant		

UREA	Group I	Group II	Group III
≤ 150	7	43	33
> 150	2	9	6
Total	9	52	39
Mean	126.444	108.038	117.538
S.D	38.455	39.384	34.039
P'	0.27 Not significant		

CREATININE	Group I	Group II	Group III
≤ 2.5	8	38	10
> 2.5	1	14	29
Total	9	52	39
Mean	2.000	2.219	2.882
S.D	0.819	0.693	0.536
P'	<0.001 Significant		

pH	Group I	Group II	Group III
≤ 7.32	2	16	20
> 7.32	7	36	19
Total	9	52	39
Mean	7.349	7.339	7.331
S.D	0.046	0.062	0.099
P'	0.792 Not significant		

Inotrope requirement	Group I	Group II	Group III
Required	2	36	30
Not required	7	16	9
Total	9	52	39
P'	<0.001 Significant		

pT	Group I	Group II	Group III
≤ 24	5	35	21
> 24	4	17	18
Total	9	52	39
Mean	22.444	21.942	22.667
S.D	4.157	5.903	6.811
P'	0.854 Not significant		

Renal replacement therapy	Group I	Group II	Group III
Replacement	1	18	19
Nil	8	34	20
Total	9	52	39
P'	<0.001 Significant		

30 days Mortality	Group I	Group II	Group III	Total
Death	1	18	37	56
Survived	8	34	2	44
Total	9	52	39	100
P'	<0.001 Significant			

Results

Hundred and TWO patients were enrolled during the study period. Out of them TWO patients had either missing data or were lost to follow- up and 100 patient were included in the final analysis.

Divided the patients into survivor and non survivor with elevated RDW and normal RDW.

Male preponderance 34 % was noted among non survivor compared to non survivor in female 22%.

- Most common Source of sepsis at presentation was 47% through community acquired among non survivor compared to survivor 39 % through community acquired.9% through community acquired among non survivor compared to 5% among survivor.
- Site of sepsis respiratory system often increased in frequency among survivor 26 persons compared to non survivor 15 persons.urinary tract infections increase in non survivor compared to survivor.Abdomen and skin infections equally present in both survivor and non survivor.

Comorbidities like chronic kidney disease, chronic liver disease , chronic obstructive pulmonary disease, cardiovascular disease and diabetes present in both survivor and non survivor. But diabetes was most common among non survivor;.

Smoking didn't have any impact on mortality among both survivor and non survivor.

Glsscow Coma Scale at presentation was 11.01% among non survivor compared to survivor which was 13.04 % .

Red Cell Distribution Width among non survivor was 17.04% compared to survivor 15.00

APACHE score among non survivor was 26.09% compared to 18.08% in survivor.

Duration of stay among non survivor 7.01% compared to 18.02in % in survivor.And ESR was increased among non survivor compared to survivor.

Renal function test like urea was 121.78% among non survivor compared to survivor it was 102.72%.And serum creatinine level 2.98 % among non survivor compared to survivor.Mean total protein was decreased among non survivor compared to survivor.

Mean pH was 7.32 among non survivor compared to survivor 7.349.Mean prothrombin time among non survivor was 24.054 compared to 20.00 in survivor.

Study population was divided into two groups based on RDW at admission – normal RDW group (RDW ≤14.5%) and raised RDW group (RDW >14.5%). Ten patients in the study population had normal RDW and remainng had raised RDW at presentation. Demographic, clinical,

and laboratory parameters were compared between these groups.. Mean erythrocyte sedimentation rate (ESR) at baseline was higher in patient group with raised RDW .But it did not reach the statistical significance. This patient group also had significantly higher proportion of patients with renal failure . Mean serum albumin at admission was significantly lower in high RDW group, while mean APACHE II score at admission was significantly higher in raised RDW group. 30- day mortality was significantly higher in raised RDW group

We further subdivided the study group into three groups using RDW values 14.5%.and 17.3% Group one: ≤14.5%,Group two14.6%–17.3%, and Group three >17.3%.; RDW was also found to have significant graded association with APACHE II score at admission showing progressively increasing score along with rising RDW;. Thirty- day mortality showed a significant graded relationship with RDW at admission across these three groups.

Various parameters including demographic,clinical, laboratory and other variables such as organ dysfunction, severity of illness scores, and length of hospital stay were compared between survivors and nonsurvivors. Mean age, APACHE II score; (PaO2/FiO2 ratio and duration of hospital stay were significantly lower in nonsurvivors as compared to survivors.

In this prospective observational study, we evaluated the role of RDW as a prognostic marker of 30- day mortality in patients with severe sepsis . RDW was significantly associated with 30- day mortality in patients with severe sepsis across all age groups .

DISCUSSION

Sepsis syndrome influences erythropoiesis through various mechanisms. Elevated inflammatory markers affect the RBC survival and maturation. Early release of immature, larger RBCs into the circulation results in elevated RDW;

Pro- inflammatory state in sepsis syndrome also leads to decreased erythropoietin production ;resistance to its effect; as well as decreased iron bioavailability. Erythroid precursor activity is thus suppressed in the bone marrow; Oxidative stress may also be a contributor for RDW- mortality association in sepsis. Elevated RDW is seen in states of high oxidative stress. It occurs by decreased RBC survival and release of large premature RBCs into circulation;

SUMMARY OF PRIOR PUBLICATIONS

Elevated red cell distribution width as a prognostic marker in severe sepsis: A prospective observational study

Indian Journal of critical care medicine Oct 2, 2017

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Sepsis is a dysregulated host response to infection resulting in potentially life-threatening organ dysfunction. Elevation in red cell distribution width (RDW), a simple routinely done investigation, could be a prognostic marker in these patients.

In severe sepsis patients, RDW though showed a graded relationship with 30-day mortality was not found to be an independent predictor of 30-day mortality.

Red Blood Cell Distribution Width during the First Week Is Associated with Severity and Mortality in Septic Patients

Public library of science one published online August 25 2014

Although the mechanism of elevated RDW in these patients is yet to be elucidated, an association of inflammation and oxidative stress with elevated RDW has been suggested.14 The inflammatory response is important in the pathophysiology of sepsis. Besides, aging is also a powerful prognostic factor of severe sepsis and septic shock.

Initial RDW values were significantly associated with 30-day mortality in older patients hospitalized with severe sepsis and septic shock.

4. An increase in red blood cell distribution width from baseline predicts mortality in patients with severe sepsis or septic shock Critical Care 2013 17:R282.

An increase in RDW from baseline during the first 72 hours after hospitalization is significantly associated with adverse clinical outcomes. Therefore, a combination of baseline RDW value and an increase in RDW can be a promising independent prognostic marker in patients with severe sepsis or septic shock.

Red cell distribution width and early mortality in elderly patients with severe sepsis and septic shock Sejin Kim1, Kyoungmi Lee1, Inbyung Kim1, Siyoung Jung1, Moon-Jung Kim2 Departments of 1Emergency Medicine and 2Laboratory Medicine, Myongji Hospital, Goyang, Korea

In this study, initial RDW values were significantly associated with 30-day mortality in older patients hospitalized with severe sepsis and septic shock

CONCLUSION

RDW was relatively found to be an independent predictor of 30- days mortality. At admission APACHE II score PaO2/FiO2 ratio were observed to be independent predictors of 30- day mortality in cohort of severe sepsis patients admitted to emergency medical services.

SUMMARY

Even though many prognostic criteria's and markers are widely available in severe sepsis for predicting outcome they all are not suitable for diagnosing patients at the time of admission. Some of investigations like procalcitonin is expensive ;non-validated in the clinical arena; and not readily available;

So simplified investigations like complete hemogram that are routinely done in all patients and easily available investigation; Through this we can easily derive RDW as a routine workup. This give clue to predicting the outcome of severe sepsis & they serve as important mortality indicator;

So we can change the treatment plan and managing protocol according to the RDW values; it will help to categorize the patients & predict the outcome even before developing clinical and other biochemical abnormalities.

LIMITATIONS OF THIS STUDY

Single centre study conducted in large tertiary care centre Patients included admitted in Intensive Medical Care unit only other patients not included small sample size.

Further recommendations

A longer duration of study in larger population should be considered in the future, Combination of RDW along with other haematological parameters must be included in the prognostic criteria Treatment details such as antibiotics and other specific managements that alter inflammation should be consider in future.

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PROFORMA

Name:

Age/Sex

Occupation:

Presenting complaints:

H/o Fever,chills,abdominal pain.

Past history:

H/o Tuberculosis, Chronic liver disease, coronary artery disease, chronic kidney disease

Clinical examination:

General examination:

Consciousness, Pallor, jaundice, Clubbing, Lymphadenopathy,

Vitals: PR, BP, RR, SpO2, Temperature

Systemic examination:

CVS:

RS:

Abdomen:

CNS:

LABORATORY INVESTIGATIONS:

1. Complete Haemogram

2.Artereial Blood Gas analysis

S.No	Outcome	Group	RDW	Age	Sex	Source Of Sepsis	Site Of Sepsis	Comorbidities	Smokers	GCS	Apache	Hos.Stay	ESR	RDW	UREA
1	S	II	15.6	49	M	Community	Skin	DM		12	19	16	46	14.4	110
2	NS	III	17.90	42	M	Community	Respiratory	DM		10	20	5	53	18	201
3	NS	III	17.70	59	F	Community	Urinary track	CVD	Yes	9	30	10	43	16	103
4	S	I	13.5	61	M	Community	Respiratory	CVD	Yes	14	15	24	41	15.7	150
5	NS	II	16.4	67	M	Community	Abd.Infection	COPD		12	29	6	48	17	134
6	NS	III	18.70	58	M	Community	Skin	CKD	Yes	8	20	7	55	17	145
7	NS	III	19.60	63	F	Community	Respiratory	DM		13	31	8	40	17	160
8	S	II	15.4	57	F	Community	Urinary track	CKD		11	22	17	32	15.8	160
9	NS	III	17.90	72	M	Hospital	Urinary track	CLD	Yes	11	30	6	40	16	131
10	NS	II	16.7	43	F	Community	Respiratory	DM	Yes	8	21	5	55	16	161
11	S	II	16.7	48	F	Community	Urinary track	DM		13	14	23	47	14.9	60
12	NS	III	19.50	66	M	Community	Respiratory	CVD	Yes	14	25	8	47	18	127
13	NS	III	18.30	57	F	Community	Abd.Infection	DM		11	27	7	54	16	114
14	S	II	15.4	39	M	Hospital	Respiratory	DM	Yes	11	21	15	50	14.3	140
15	S	I	14.5	47	M	Community	Abd.Infection	COPD		15	21	18	40	15.8	170
16	S	I	13.7	55	M	Community	Urinary track	CVD	Yes	14	15	15	49	15.6	100
17	NS	III	17.80	47	M	Community	Urinary track	CKD	Yes	8	30	8	42	17	131
18	NS	III	20.10	74	M	Community	Skin	DM		9	24	6	42	17	39
19	NS	II	15.1	52	F	Community	Respiratory	CVD	Yes	12	30	9	60	18	96
20	NS	III	18.60	72	F	Hospital	Urinary track	DM		10	27	7	41	18	46
21	NS	III	19.30	39	M	Community	Abd.Infection	COPD		13	31	5	53	18	116
22	NS	III	20.20	44	F	Community	Respiratory	DM	Yes	11	32	8	47	17	87
23	S	II	15.6	38	F	Community	Respiratory	DM		12	18	15	46	15.8	70
24	NS	III	17.80	53	M	Community	Skin	DM		14	29	6	55	16	121
25	NS	II	15.6	75	M	Hospital	Urinary track	CLD		12	31	7	41	17	92
26	NS	II	17.10	43	F	Community	Respiratory	CKD	Yes	8	27	8	42	18	87
27	NS	III	20.00	56	M	Community	Urinary track	CVD		8	25	6	43	18	55
28	S	II	16.9	50	M	Community	Urinary track	CLD		15	16	20	39	15.7	140
29	S	II	15.2	44	M	Community	Urinary track	DM	Yes	13	13	16	30	15.4	90
30	NS	II	16.2	39	F	Community	Abd.Infection	DM		12	21	6	53	16	165
31	S	I	12.9	32	F	Community	Respiratory	CVD	Yes	13	17	15	45	15.1	130
32	NS	II	16.3	71	M	Community	Respiratory	DM	Yes	11	21	5	45	17	68
33	NS	III	18.60	51	F	Community	Urinary track	DM		14	26	5	41	16	88
34	NS	II	16.1	76	M	Hospital	Skin	CVD	Yes	13	22	7	43	16	83
35	S	II	14.9	55	M	Hospital	Urinary track	CKD		14	23	15	33	15.3	50
36	NS	III	17.70	59	F	Community	Respiratory	DM		12	31	6	51	17	108
37	S	II	15.4	31	M	Community	Respiratory	DM		15	20	22	40	13.8	80
38	NS	III	17.90	39	M	Community	Urinary track	DM	Yes	9	22	10	47	18	61

39	S	II	17.1	46	M	Community	Abd.Infection	CVD		12	18	30	41	15.6	120
40	NS	III	18.00	55	F	Community	Abd.Infection	CLD	Yes	9	22	6	52	17	146
41	S	II	15.6	50	F	Community	Skin	COPD	Yes	14	15	15	44	15.2	90
42	NS	II	15	46	M	Hospital	Respiratory	DM		12	30	8	55	16	144
43	NS	III	17.90	45	F	Community	Skin	COPD		11	29	7	53	18	85
44	S	II	16.7	49	M	Community	Respiratory	DM		13	22	29	45	13.5	70
45	NS	III	18.80	39	M	Community	Urinary track	CKD	Yes	14	26	9	48	17	152
46	S	I	14.5	44	M	Community	Abd.Infection	DM		15	20	26	48	14.2	150
47	NS	II	17	77	M	Community	Respiratory	DM		13	32	6	46	16	143
48	S	II	14.9	55	M	Community	Respiratory	DM		13	14	16	33	15.1	100
49	NS	III	17.60	70	F	Community	Urinary track	DM		11	29	6	44	18	101
50	NS	III	18.60	38	M	Community	Abd.Infection	CLD	Yes	12	31	8	54	18	160
51	S	II	15.4	53	M	Community	Respiratory	CKD	Yes	12	19	15	46	14.1	60
52	NS	III	19.10	54	F	Community	Respiratory	DM		10	28	5	43	18	89
53	S	II	16.40	44	F	Community	Urinary track	CVD		14	17	15	43	15.1	140
54	NS	II	17.2	45	M	Community	Respiratory	DM		11	23	7	56	18	83
55	NS	III	20.20	51	M	Hospital	Urinary track	CKD	Yes	14	27	10	54	17	117
56	NS	III	17.70	46	F	Community	Respiratory	DM	Yes	12	21	6	45	16	153
57	S	II	15.20	42	M	Community	Abd.Infection	DM		12	19	15	32	15.8	120
58	S	II	16.30	50	M	Community	Respiratory	DM		15	20	27	40	14.3	70
59	S	II	15.70	32	M	Community	Skin	DM		13	18	17	42	15.3	60
60	S	II	16.80	55	F	Community	Respiratory	CKD	Yes	11	20	19	49	15.6	160
61	NS	II	16.5	42	F	Community	Abd.Infection	CVD		13	27	7	51	18	163
62	NS	II	16.6	76	M	Community	Respiratory	DM		11	32	8	49	17	148
63	S	I	13.6	63	M	Community	Abd.Infection	CVD		14	15	15	41	15.8	110
64	NS	III	18.40	53	F	Community	Respiratory	DM	Yes	9	25	6	50	17	118
65	NS	III	17.80	72	M	Hospital	Skin	DM		11	22	6	53	16	91
66	S	II	15.70	45	M	Hospital	Urinary track	CLD		12	18	16	39	15.8	70
67	NS	II	16.6	49	M	Community	Respiratory	DM		12	26	7	46	18	169
68	NS	III	19.30	39	F	Community	Urinary track	CKD	Yes	9	23	9	45	16	146
69	S	II	16.80	59	M	Community	Respiratory	COPD		15	19	15	38	13.9	40
70	S	III	19.40	47	M	Community	Skin	DM	Yes	14	13	15	42	15.2	120
71	NS	III	20.10	67	M	Community	Respiratory	DM		9	24	8	57	17	137
72	NS	III	17.60	52	M	Community	Urinary track	CLD		8	28	8	49	18	152
73	S	II	15.20	51	F	Community	Respiratory	DM		13	20	28	31	15.5	100
74	NS	II	16.5	58	M	Community	Respiratory	DM	Yes	13	23	5	42	16	99
75	S	I	13.7	55	M	Community	Urinary track	CVD		11	15	15	40	15.7	50
76	S	II	16.10	50	M	Community	Abd.Infection	CKD		12	17	15	38	14.2	140
77	S	II	14.9	41	M	Community	Respiratory	DM	Yes	14	16	15	34	15.1	90
78	NS	III	17.90	47	F	Community	Urinary track	CVD	Yes	14	28	7	50	17	116
79	S	III	18.30	33	M	Hospital	Skin	DM		13	19	16	34	14.4	120

80	S	II	15.70	43	F	Community	Urinary track	CLD		15	23	21	41	15.6	90
81	NS	III	19.50	73	M	Community	Respiratory	DM		12	22	7	47	16	148
82	NS	II	17.1	49	M	Hospital	Abd.Infection	CKD	Yes	8	25	6	42	18	106
83	S	II	16.20	59	M	Community	Respiratory	CVD		14	22	18	35	15.1	100
84	S	II	15.90	55	M	Community	Respiratory	DM		12	19	18	48	14.6	160
85	NS	II	16.4	71	M	Community	Respiratory	COPD	Yes	9	20	9	52	17	201
86	NS	III	17.60	57	F	Community	Respiratory	DM		10	23	7	44	16	119
87	S	I	13.2	38	F	Community	Abd.Infection	COPD	Yes	11	17	15	36	13.9	110
88	NS	III	17.90	42	M	Community	Respiratory	DM	Yes	13	24	10	59	17	148
89	NS	II	17.3	48	M	Community	Urinary track	DM		11	29	8	48	18	166
90	S	II	15.70	51	M	Community	Urinary track	DM		12	21	15	37	15.0	30
91	NS	III	20.10	74	M	Hospital	Respiratory	CKD		14	23	5	51	16	89
92	S	II	16.40	50	F	Community	Respiratory	DM		15	20	25	40	14.8	120
93	S	II	15.30	38	M	Community	Skin	CKD		14	17	15	35	14.0	80
94	NS	III	17.60	55	F	Community	Respiratory	CLD		12	25	7	43	17	138
95	NS	I	14.5	54	M	Community	Respiratory	CVD	Yes	8	22	8	40	18	168
96	S	II	16.70	41	M	Hospital	Respiratory	DM		11	14	15	37	15.1	130
97	NS	III	17.90	73	M	Community	Urinary track	DM	Yes	10	30	6	42	16	106
98	S	II	15.20	35	F	Community	Respiratory	CLD	Yes	12	16	16	41	14.7	60
99	S	II	16.30	59	M	Community	Abd.Infection	DM		11	18	15	36	15.8	120
100	S	II	15.70	32	M	Community	Respiratory	CVD		13	20	15	38	14.5	90

MADURAI MEDICAL COLLEGE
MADURAI, TAMILNADU, INDIA -625 020
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Chennai, Tamil Nadu)

ETHICS COMMITTEE CERTIFICATE

Name of the Candidate	:	Dr.G.Karuppasamy
Course	:	PG in MD., General Medicine
Period of Study	:	2016-2019
College	:	MADURAI MEDICAL COLLEGE
Research Topic	:	Elevated red cell distribution width as a prognostic marker in severe sepsis
Ethical Committee as on	:	10.07.2018

The Ethics Committee, Madurai Medical College has decided to inform that your Research proposal is accepted.

Member Secretary Chairman Dean / Convenor

Prof Dr V Nagaraajan
M.D., MNAMS, D.M., Dsc.,(Neuro), Dsc (Hon)
CHAIRMAN
IEC - Madurai Medical College
Madurai

DEAN
Madurai Medical College
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20 JUL 2018

Urkund Analysis Result

Analysed Document: karupasamy thesis (Autosaved).docx (D42411911)
Submitted: 10/11/2018 11:09:00 AM
Submitted By: karups.gk80@gmail.com
Significance: 15 %

Sources included in the report:

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