"EVALUATION OF CHANGES IN MEAN ARTERIAL PRESSURE AND PULSE PRESSURE FOLLOWING PASSIVE LEG RISING TEST AS INDEX AND PREDICTOR OF FLUID RESPONSIVENESS IN SEPTIC SHOCK PATIENTS"

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ABBREVIATIONS

SIPS	Sepsis in India Prevalence Study
PLR	Passive Leg Rising
ICU	Intensive Care Unit
HIV	Human Immuno Virus
GFR	Glomerular filtration rate
AKI	Acute Kidney Injury
IU	Interleukin
APR	Acute-phase reactants
SDG	Sustainable development goals
HR	Heart Rate
PR	Pulse rate
PP	Pulse pressure
MAP	Mean arterial pressure
SVI	Stroke volume index
CI	Cardiac index
MCVP	Mean central venous pressure
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
EVLW	Extravascular lung water
RVEDV	Right Ventricle end diastolic volume
WD	Wedge pressure
T2DM	Type 2 diabetes mellitus
IHD	Ischemic heart disease
COPD	Chronic obstructive pulmonary disease
CKD	Chronic kidney disease

EVALUATION OF CHANGES IN MEAN ARTERIAL PRESSURE AND PULSE PRESSURE FOLLOWING PASSIVE LEG RISING TEST AS INDEX AND PREDICTOR OF FLUID RESPONSIVENESS IN SEPTIC SHOCK PATIENTS

ABSTRACT

INTRODUCTION

Intravenous volume expansion is a fundamental aspect of hemodynamic therapy for individuals with life-threatening conditions who have hypoperfusion. In sepsis, resuscitation protocols in the beginning of the diagnosis which includes fluid therapy can reduce the mortality. In patients with right or left ventricular dysfunction, the volume expansion can stimulate the edema in the periphery and lungs and can negatively impact the microvascular perfusion and oxygen delivery. For patients who are in preload unresponsive condition, a significant amount of volume expansion can worsen the pulmonary edema, induce respiratory failure, increase the time on mechanical ventilation and develops intra-abdominal hypertension. Passive leg rising is recommended as a method to shift venous blood from the legs to intrathoracic region and hence increasing the intrathoracic volume and cardiac preload. The aim of the study was to determine if mean arterial pressure and pulse pressure as a measurement could be used in conjunction with PLR to predict the hemodynamic response to volume expansion. The objective of the study was to study the efficiency of changes in mean arterial pressure and pulse pressure as predictors of fluid resuscitation response following passive leg rising test as an indicator of fluid resuscitation in septic shock patients.

METHODOLOGY

Cross-sectional study conducted between January 2023 and December 2023 among patients admitted to Medical Intensive Care Unit in KLES Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi. In this cross-sectional study, all the consecutive patients fulfilling the inclusion criteria was included in the study.

RESULTS

The mean age of the study participants was 55.73 ± 18.5 years. Majority of the study participants were male (n=52, 62%). Almost half of the study patients were on support of ventilator (48.8%). The majority of the source of sepsis was respiratory. Presence of ischemic heart disease, is significantly associated with the status of ventilator support.

CONCLUSION

Almost half of the study participants were on invasive mechanical ventilator (48.8%). The ROC curve of MAP and PP showed unsatisfactory prediction of the tool. No significant correlation was observed between MAP changes with passive leg raising and fluid resuscitation when compared with various study variables.

INTRODUCTION

Definition of Septic Shock

Sepsis accompanied by hypotension and anomalies in perfusion even when appropriate volume resuscitation is provided is known as septic shock. Acute changes in mental status, oliguria, and lactic acidosis are examples of perfusion anomalies. Even in cases where hypotension is not present, patients in septic shock who are on inotropic or vasopressor medication may nevertheless show anomalies in perfusion. Septic shock is also defined as sepsis with hyperlactatemia and concurrent hypotension which requires vasopressor therapy and has a with-in hospital mortality rates of about 30% to 50%. Sepsis is defined as dysregulated systemic inflammatory response and immune response to microbial invasion which leads to injuries to the organs (Figure 1 and Figure 2). The mortality rate of sepsis is 15% to 25%. Severe sepsis is sepsis associated with organ dysfunction, hypotension or hyper fusion (1).

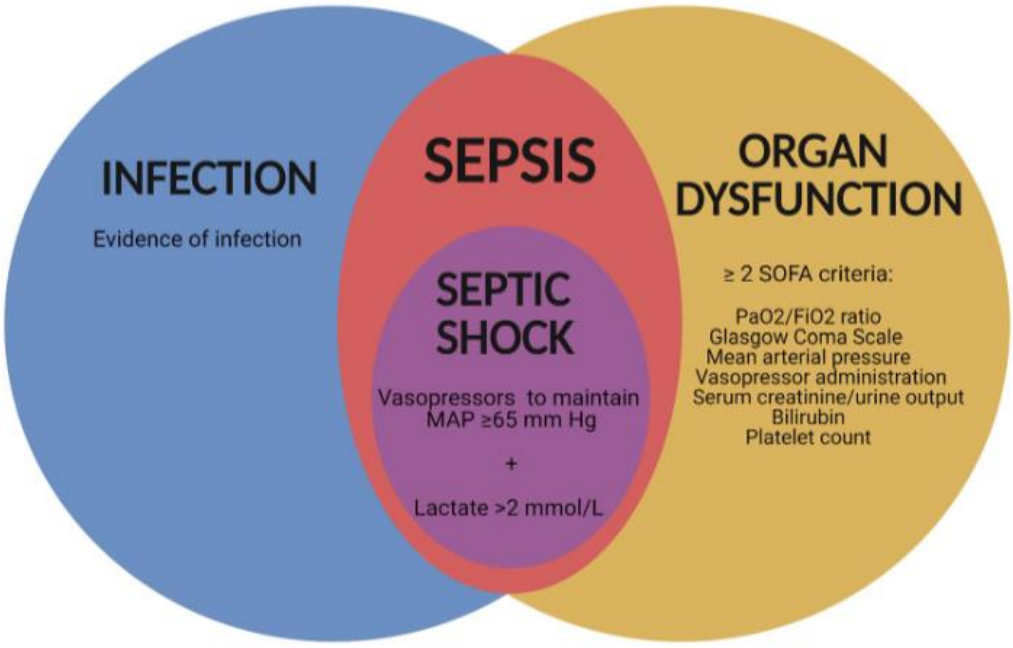

Figure 1: Sepsis

Table 1
Comparison of older and new definitions for the spectrum of sepsis and septic shock

	Sepsis-2 Definitions	Sepsis 3.0 Definitions
Sepsis	≥2 SIRS criteria AND Suspected infection	Increase in SOFA score ≥2 from baseline OR qSOFA ≥2 AND Suspected infection
Severe sepsis	Sepsis AND Organ dysfunction (change in SOFA ≥2 points)	(Not applicable)
Septic shock	Sepsis AND Hypotension despite fluid resuscitation OR Lactatemia despite fluid resuscitation	Sepsis AND Vasopressor requirement despite fluid resuscitation OR Lactate >2 mmol/L after resuscitation

Figure 2: Old and new definitions for sepsis and septic shock

Symptoms

Criteria for sepsis

Life-threatening organ dysfunction which leads to dysregulated host response to infection. Initiation of organ dysfunction away from the site of infection. At least two of the following factors will be involved in sepsis:

- Temperature more than 38º C or below 36º C.
- Heart rate more than 90 beats per minute
- Respiratory rate of more than 20 per minute or partial pressure of carbon dioxide of less than 32 mmHg
- White blood cell count of more than 12,000 per ml or less than 4000 per ml or more than 10% of immature cells.

Criteria for septic shock

The circulatory and cellular-metabolic abnormalities are to a level which considerably increases the mortality of the individual. Requires vasopressin therapy to maintain mean arterial pressure of more than 65 mmHg and increased plasma lactate level of more than 2 mmol/ L (1).

Septic shock is a severe complication of sepsis. The adverse outcomes like mortality rate of septic shock are higher (2).

Global and National Statistics

Sepsis is the frequent cause of death globally. In 2020, 48.9 million cases and 11 million sepsis-related mortality was recorded. This contributes to one-fifth of global deaths. Sepsis predominantly affects the low- and middle-income countries. Financial burden of the disease also is high (3). A retrospective study conducted in England showed 31.8% of overall hospital sepsis mortality rate and 55.5% of septic shock mortality rate (4). In India, in 2017, 11.3 million people were estimated to have sepsis with 2.9 million deaths. Around 10% of cases were considered as septic shock based on a cross-sectional study conducted by Sepsis in India Prevalence Study (SIPS) Investigator Network (5).

Rationale of the study

Intravenous volume expansion is a fundamental aspect of hemodynamic therapy for individuals with life-threatening conditions who have hypoperfusion. In sepsis, resuscitation protocols in the beginning of the diagnosis which includes fluid therapy can reduce the mortality. In patients with right or left ventricular dysfunction, the volume expansion can stimulate the edema in the periphery and lungs and can negatively impact the microvascular perfusion and oxygen delivery. For patients who are in preload unresponsive condition, a significant amount of volume expansion can worsen the pulmonary edema, induce respiratory failure, increase the time on mechanical ventilation and develops intra-abdominal hypertension. Passive leg rising is recommended as a method to shift venous blood from the legs to intrathoracic region and hence increasing the intrathoracic volume and cardiac preload. While stroke volume is the gold standard for volume responsiveness, many studies have been done to find other predictors for fluid responsiveness like pulse pressure, aortic blood flow and right atrial pressure. Of them pulse pressure was found to have good sensitivity and specificity, particularly when considering cost effectiveness. As pulse pressure is an easy to measure and calculate and doesn't require invasive monitoring/, special machinery or skill and can be applied in almost all Centre's without any difficulty. As mean arterial pressure can also be calculated easily, using it in conjunction with pulse pressure can help better identify fluid responsiveness. So we have set about to asses mean arterial pressure as predictor of fl;uid responsiveness. Very few studies are done in India regarding PLR in septic shock patients.

Study Aim and objectives

The aim of the study was to determine if mean arterial pressure and pulse pressure as a measurement could be used in conjunction with PLR to predict the hemodynamic response to volume expansion.

Objective: The objective of the study was to study the efficiency of changes in mean arterial pressure and pulse pressure as predictors of fluid resuscitation response following passive leg rising test as an indicator of fluid resuscitation in septic shock patients.

REVIEW OF LITERATURE

Sepsis is a life-threatening condition occurring when the immune system responds to an infection extremely. This leads to organ dysfunction. This reaction leads to shock, multiple organ failure and mortality if not identified and treated on time (3, 7) (Figure 3).

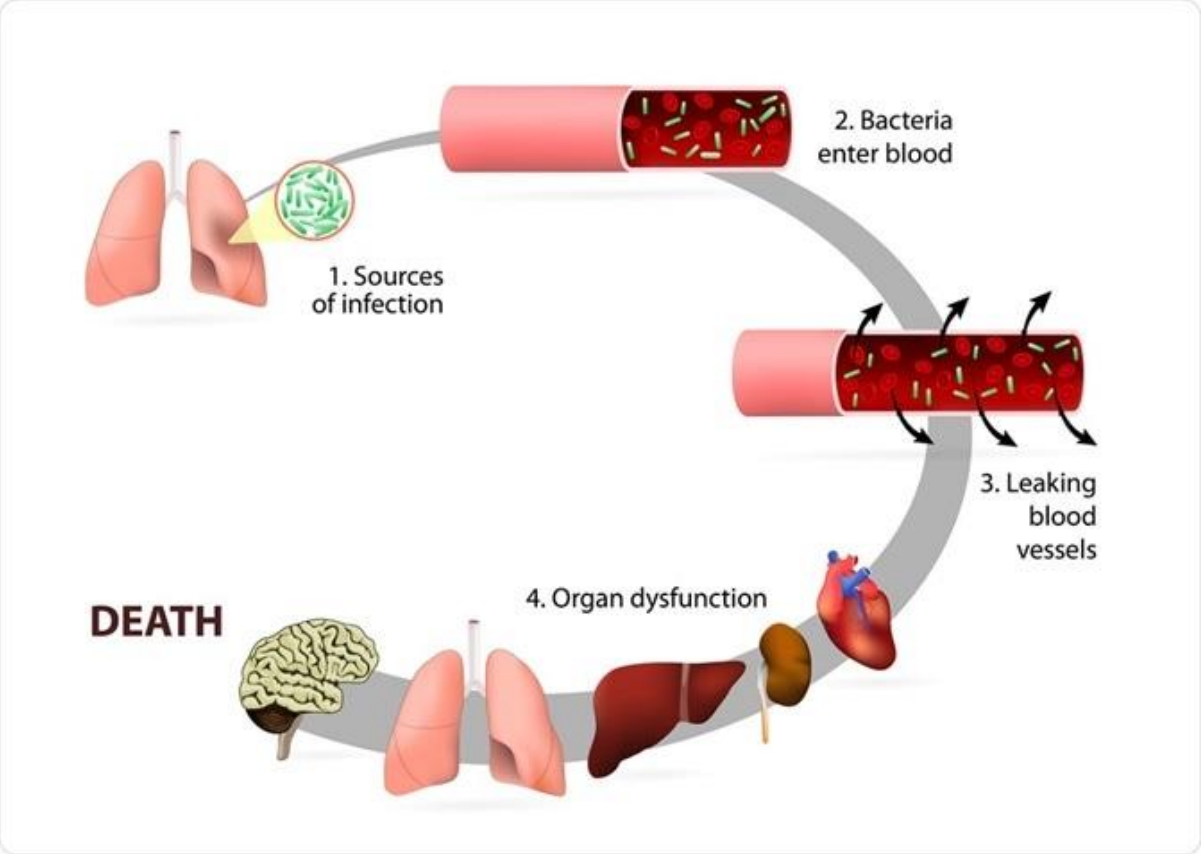

Figure 3: Stages of Sepsis

Signs and Symptoms

Common signs and symptoms of sepsis includes fever, higher heart rate, increased respiratory rate, confusion and body ache. This is followed by septic shock, multi-organ failure and death (3).

Risk factors

Sepsis affects any individual. Old age (Above 55 years), very young age (less than 2 years), pregnancy, hospitalized individuals, patients in ICU (Intensive Care Unit), compromised immune system or weak immune system (Example: due to HIV, transplantation, chemotherapy, radiation therapy, drug-mediated immune suppression, and blood transfusion) or history of chronic diseases (Example: Chronic Kidney disease, cancer, diabetes, chronic obstructive pulmonary disease, cirrhosis/ biliary obstruction, cystic fibrosis, collagen vascular disease and Obesity) are the risk factors of sepsis (1, 3).

Breach of natural barriers in case of trauma, surgical injury, catheterization/ intubation, burns and enterocolitis. Chronic infections incase of HIV, urinary tract infections, pneumonia, and decubitus or non-healing dermal wounds. Other diseases like protein calorie malnutrition (1).

Cause

Usually, sepsis is caused by bacterial infection. But infection due to virus, parasites or fungi can also cause sepsis. Sepsis can be acquired during hospital stay (3).

The most common site of infection of sepsis is lung (64%), abdomen (20%), bloodstream (15%) and renal & genitourinary tracts (14%). Gram-positive bacteria are slightly more common than Gram-negative bacteria for cause of infection. Staphylococcus aureus of Gram-positive bacteria and Pseudomonas species and Escherichia coli of Gram-negative bacteria groups are the most common organism for sepsis (7).

Pathophysiology of Septic Shock

A "cytokine storm" may arise from an increase in the innate immune system's production of proinflammatory cytokines. Changes in coagulation and endothelial damage are caused by this inflammatory condition. Heterogeneous organ perfusion, mitochondrial malfunction, cellular hypoxia, and organ dysfunction and failure are caused by inadequate blood flow. As a result, there is a higher capillary leak, which causes hypotension linked to a hyperdynamic cardiovascular condition. Additionally, bodily fluid levels rise, particularly during resuscitation. There may then be a period of immunosuppression that is unable to contain the infection. It is believed that these immunosuppressive and inflammatory states overlap, which makes disease monitoring even more difficult. Inflammation and coagulopathy ultimately result in organ failure and mortality as well as the vascular and organ damage that characterizes severe sepsis and septic shock (8) (Figure 4).

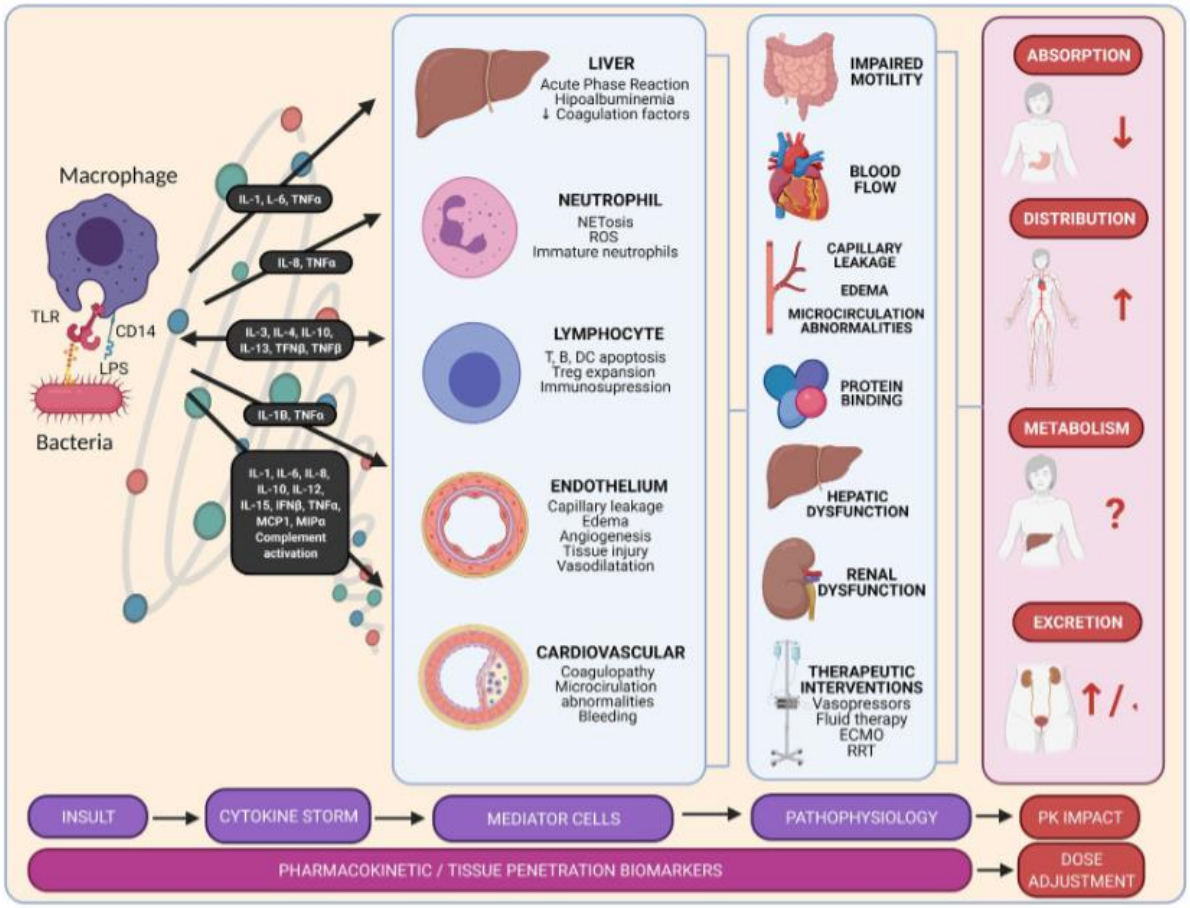

Figure 4: Bacteria to Sepsis and Septic Shock

Absorption

Patients in critical condition have variable oral bioavailability due to delayed and decreased absorption. Reduced gut motility results in delayed stomach emptying and decreased splanchnic blood flow. It takes longer for the antibiotic to reach its maximal concentration when there is a delay in stomach emptying. Additionally, subcutaneous and intramuscular injection absorption is compromised by a decrease in peripheral blood flow. Antibiotics in the ICU are typically first given intravenously due to these changes. Sepsis's proinflammatory condition damages endothelium and raises capillary permeability. Capillary leak syndrome is the consequence, leading to fluid extravasation and an increase in the volume of distribution of hydrophilic antibiotics. The volume of distribution can also be raised by therapeutic measures (such as drainages, extracorporeal circuits, and fluid resuscitation). Sepsis patients frequently have hypoalbuminemia, which lowers peripheral blood pressure and increases unbound medication concentrations that are vulnerable to enhanced clearance. The volume of distribution may be influenced by these increased unbound drug concentrations, resulting in subtherapeutic antibiotic concentrations

and inefficient microbial clearance. Critically sick individuals often have inadequate tissue perfusion and tissue hypoxia, with both low and high oxygenation and perfusion zones (8).

Metabolism

Patients in critical condition have impaired metabolism due to decreased hepatic blood flow, hepatic dysfunction, and altered enzyme activity. Hypothermia and reduced tissue blood flow both affect tissue metabolism. Since lipophilic antibiotics are typically highly metabolized, individuals with hepatic insufficiency may need to alter their dose (8).

Excretion

Critical illness can cause either elevated or impaired renal clearance, which can disrupt the elimination process. Although it is typically less compromised, biliary stasis and a reduced intestinal transit that results in recirculation can have an impact on biliary excretion. A hyperdynamic cardiovascular condition and subsequent vasodilatation in certain critically ill individuals lead to an increased glomerular filtration rate (GFR), which can be further improved with the administration of vasopressors and resuscitation fluid. This higher renal clearance causes hydrophilic medicines to be eliminated more frequently. Underdosage could result from this, as evidenced by a study with β-lactams. Conversely, some critically ill individuals require renal replacement therapy due to acute kidney injury. This will cause hydrophilic antibiotics to have a longer half-life, reduced antimicrobial clearance, and maybe even toxicity. Dosage modifications should therefore be taken into account when AKI or RRT are present (8).

Screening

No diagnostic tests are available for sepsis or septic shock. This is because both sepsis and septic shock are clinical syndromes which are defined by combination of signs, symptoms, pathological changes and laboratory abnormalities (1).

Sepsis Biomarkers can determine the type or prognosis of infection, gauge the response to treatment, and forecast the degree of sepsis and the onset of organ failure. Nevertheless, a thorough analysis of biomarkers' function in directing antibiotic dosage has not yet been conducted. Procalcitonin stewardship has been studied, although it might not be as effective as other biomarkers. Based on pathophysiology, we have categorized the putative biomarker predictors of pharmacokinetics into the following categories: coagulation, blood flow, endotheliopathy, inflammation, and hepatic and renal function. Some of these biomarkers have been shown to have diagnostic, prognostic, or therapeutic utility; however, the effect on medication pharmacokinetics is not well known. exhibits the critical biomarker attributes. To assess a biomarker's dependability during extracorporeal therapy, it is critical to understand its molecular weight. Because pathophysiological processes are dynamic and delayed

dynamics might result in delayed clinical choices, understanding biomarker kinetics is crucial (8) (Figure 5).

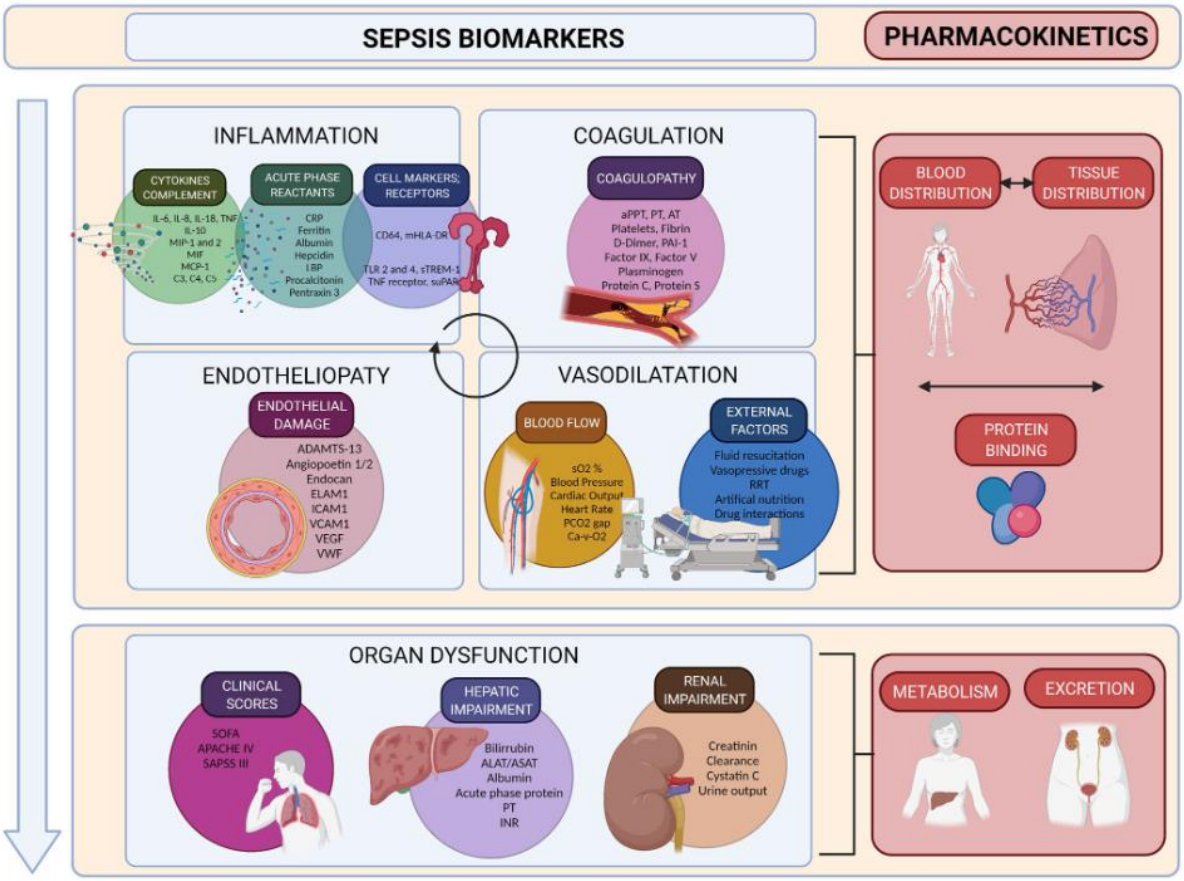

Figure 5: Biomarkers of sepsis

The "cytokine storm" syndrome is sepsis. Pathogen-associated chemical patterns, like lipopolysaccharide or peptidoglycan, bind to receptors that recognise patterns (PRRs), like toll-like receptors, and are enhanced by CD14 receptors during infections. The virus may cause the immune system to release proinflammatory cytokines, such as interleukin (IL)-1β, IL-6, IL-18, interferon, and tumour necrosis factor-α, in an excessive, uncontrollable, and overwhelming manner. The immune cells are constantly activated and proliferate from circulation to the infection as a result of this rise in cytokines. Additionally, the liver's synthesis of acute-phase reactants (APRs) is mediated by proinflammatory cytokines. Pro-calcitonin and C-reactive protein are two essential APRs that are frequently available for the detection and tracking of inflammatory conditions. On the other hand, in reaction to inflammation, the negative APRs, such albumin and transferrin, decrease (8).

Severe endothelial cell dysfunction and glycocalyx degradation are linked to sepsis, which can cause tissue oedema, dysregulation of vascular reactivity, and haemostasis. Interstitial oedema is caused by

this endotheliopathy's increased microvascular permeability to the extravascular space. Components including hyaluronan, heparan sulphate, and syndecan-1 are released into the plasma during glycocalyx breakdown. Human endothelial cells respond to proinflammatory cytokines by expressing endocan, which enhances microvascular permeability. It has previously been demonstrated that these endothelial glycocalyx biomarkers are indicators of mortality and/or organ failure in sepsis. The angiopoietin protein family has been studied as a key modulator of glycocalyx breakdown because endothelial cells triggered by angiopoietin-2 express more vascular cell adhesion molecule-1 and intercellular adhesion molecule-1. Endothelial cell–cell connections change as a result, causing microvascular leakage. It has been discovered that in sepsis patients, the angiopoietin-2/1 ratio is a reliable indicator of 28-day death. Endothelial development, proliferation, and permeability are stimulated by serum vascular endothelial growth factor and its receptor. Higher values can be used to predict prognosis because they are present in sepsis. As a result, these endotheliopathy indicators predict the capillary leakage that causes the pharmacokinetic variability in the tissues of sepsis patients; however, further research is required to determine the relative importance of each sign (8).

Prevention and Treatment

Preventive measures to be followed to reduce the invasion of microbial organisms. Following proper hygiene, vaccination programs, improvement of sanitation, quality of water, and other infection prevention and control measures in hospital set-up and in the community set-up (3).

Anti-microbials, intravenous fluids are used to treat the sepsis. Other management of symptoms are also followed to treat the patient. Early diagnosis or identification of sepsis during the hospital stay will be beneficial. This ensures timely management or treatment of sepsis and preventing septic shock by using anti-microbial and fluid resuscitation. This reduces the mortality (3). Treatment includes three parts: infection control, hemodynamic stabilization and modulation of septic response.

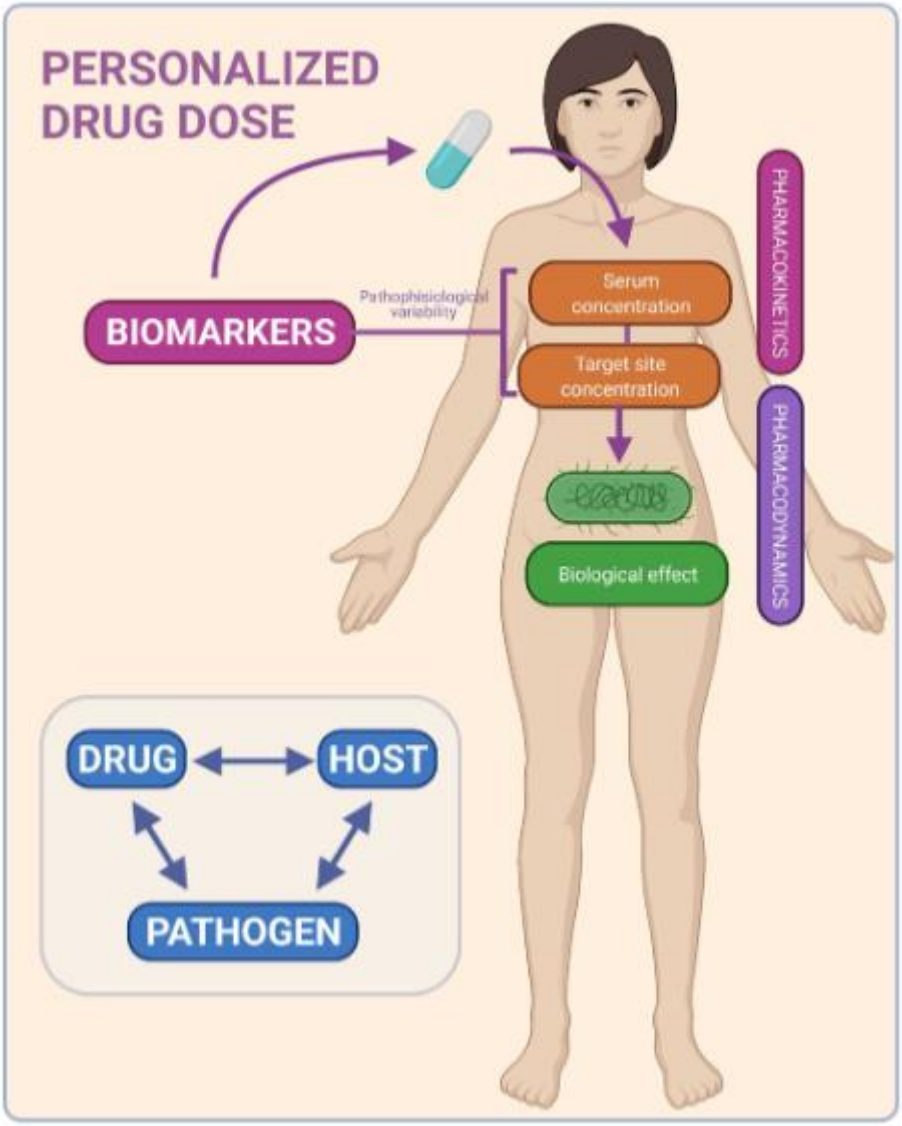

Figure 6: Personalized drug dose

In infection control section, the treatment is providing early and adequate anti-microbial administration and control of the source of infection. When sepsis is diagnosed, a comprehensive investigation is needed to identify a likely source. Appropriate imaging techniques, clinical symptoms and signs, and the right microbiological cultures should all be employed to attempt and identify the infectious source. The initial administration of anti-microbial as soon as possible without waiting for the culture report is important. This substantially reduces the risk of death. As the culture report will be unavailable while initiating the antimicrobial treatment, selection of broad-spectrum antimicrobial is encouraged. This selection can be done using few factors like likely source of infection, local microbiological flora, its resistance pattern, recently administered antimicrobial therapy, and ecology of the heath care facility. Two or multiple drug administration can also be initiated. After obtaining culture report, re-evaluate the antimicrobials administered. If possible, narrow down the spectrum of the antimicrobial when possible.

This reduces the toxicity, increases the medication efficiency, prevents drug resistance, and reduces the cost. Understand that, in few cases, the culture report can be negative. Hence, the broad spectrum provided may not be reduced. By this step, removal of source of infection is possible.

Hemodynamic stabilization of an individual is done in four stages. The stages are salvage, optimization, stabilization and de-escalation. These stages provide the hemodynamic support to prevent the organ injury and shock. The amount of fluid administration depends up on the phase of shock (Figure 6). In salvage or rescue phase, generous amount of fluid can be administered. In optimization phase, as the name suggests, individual approach is required. In a mechanically ventilated patient, passive leg rising may be helpful. After stabilization period, in the de-escalation phase, the fluid balance should be negative (1).

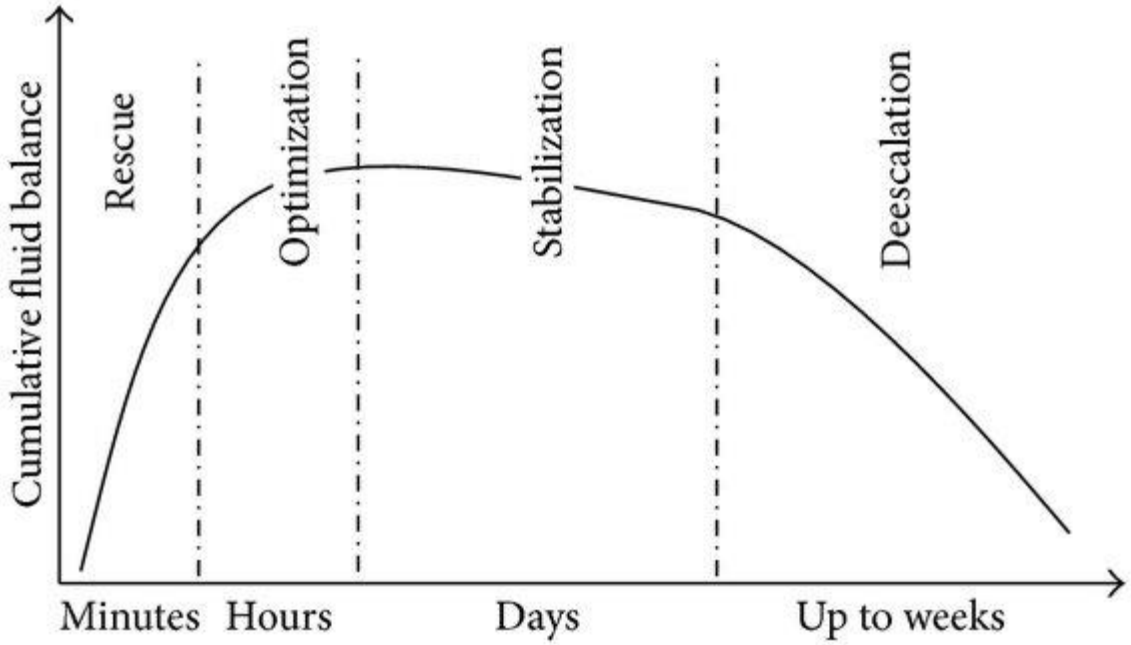

Figure 7: Fluid balance in various stages of Hemodynamic stabilization

Modulation of septic response stage is an increased early inflammatory response in order to target early intervention using biological response modifiers in septic shock or severe sepsis. No trials show effectiveness (1).

Antibiotic concentration fluctuation is seen at the infection site, both within and between patients. Although they cannot be utilised regularly, a variety of techniques may be utilised to evaluate penetration at the target site in critically ill patients. Alternatively, as they may anticipate target-site concentrations, biomarkers correlated with pharmacokinetic abnormalities could be used to augment

antibiotic dosage methods. Clinical and microbiological components may be utilised in pharmacometric models to optimise dosing in critically ill patients through model-informed precision dosing. The discovered biomarkers can be included as covariates in model-informed precision dosing (Figure 7) (8).

Sustainable development goals (SDG)

As sepsis leads to death of pregnant women and newborns, SDG goal 3.8 focus on quality of care and SDG goals 3.1 and 3.2 focus on improving mortality rates in these vulnerable population. SDG goal of 3.3 focus on deaths of individuals with pre-existing diseases like HIV, tuberculosis, malaria, etc., (3).

Passive Leg Rising

Used to determine whether giving fluids may improve heart function, the PLR test can be utilized (Figure 8).

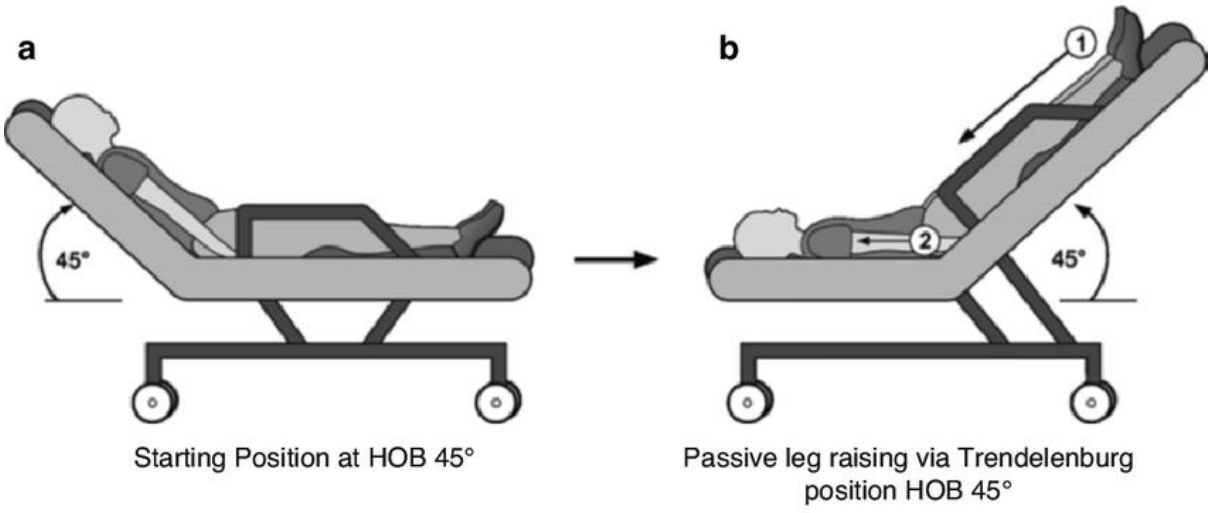

Figure 8: Passive Leg Rising

PLR is regarded as a fluid challenge since it involves autotransfusion of 150–300 mL of blood from the peripheral to the central circulation. Because no additional volume is administered and the cardiovascular response is quickly reversible, this test is safe and avoids the problems associated with volume overload (9).

To estimate the changes in the SVI (stroke volume index) due to passive leg rising was studied among individuals diagnosed with severe sepsis. The study duration was between 2010 to 2011, one year. A total of 32 patients with severe sepsis were included in the study. Heart rate (HR), systolic and diastolic blood pressure (SBP and DBP), mean central venous pressure (MCVP) and cardiac index (CI) were recorded and compared. 68.8% of the individuals were responders in the study. MAP, DBP, SBP,

MCVP were statistically significant among responders group. SVI and MCVP predicts the changes in the fluid response among patients with severe sepsis who were mechanically ventilated (10).

In a 1000-patient randomized experiment, Weidmann et al. contrasted liberal and conservative fluid regimens in patients with acute respiratory distress syndrome. The mortality rates after 60 days were the main result. They discovered that, at the conclusion of the specified period, the death rates in the conservative group were 25.5%, while those in the liberal fluid group were 28.4%. P=0.3 indicates that there was no statistically significant difference. The liberal fluid arm had a mean fluid balance of 6992+/-502 ml, while the conservative group's mean fluid balance was -136+/-491 ml. However, the oxygenation index and lung damage score were found to be statistically and clinically significant (14.6+/-0.5 vs. 12.1+/-0.5, P<0.001) by the researchers. They also observed that the conservative fluid arm had a higher percentage of ventilator-free days (11).

In an alternate randomized trial with patients with pulmonary edema, Mitchel et al. aimed to assess how fluid management affected pulmonary mechanics. They postulated that a fluid management regimen that prioritizes diuretics and fluid restriction will reduce extravascular lung water (EVLW), which would reduce the need for ventilator days. Due to their severe illnesses, every patient needed a pulmonary artery catheter. They discovered that the group given the restricted fluid arm had more ventilator-free days and substantially lower EVLW (12).

RV end diastolic volume (RVEDV) measurement has been investigated by Diebel et al. as a surrogate marker for fluid status assessment. He had contrasted it with the wedge pressure of the pulmonary artery (WP). A regression study involving 131 hemodynamic investigations revealed that the cardiac index had a stronger correlation (r20.61) with RVEDV than did WP (r20.42). However, the specificity and sensitivity were insufficiently strong for clinical application. These so-called "dynamic indices" cause a cardiac response without the requirement for a fluid bolus. Rather, it makes use of how the patient's posture and the cardiopulmonary changes that occur during mechanical ventilation interact to replicate the effects of a fluid bolus. These interactions would reveal how the fluid bolus alters the volume of the stroke. They are separated into three categories: pulse pressure alterations, oximetric waveform changes, and stroke volume variations during mechanical breathing. They are all predicated on the cyclical variations in cardiac output that are listed below. Fully sedated patients on mechanical ventilation have cyclical changes in both left and right heart pressure due to changes in intrathoracic pressure during breathing; they do not exhibit spontaneous respiratory effort. The positive pressure nature of mechanical ventilation during the inspiration phase causes an increase in intrapleural pressure. In addition to compressing the heart itself, this pressure also compresses the venous inflow and the pulmonary vasculature (13).

The assessment of fluid responsiveness through the use of stroke volume variation was made possible by the 2000 evaluation of 40 patients in septic shock who were on mechanical ventilation. They observed that pulse pressure variation (Pp) during the respiratory cycle was greater than 13% in volume-responsive individuals (responders), and that following a fluid bolus, cardiac output rose by more than 15% in those patients. The researchers discovered that stroke volume fluctuation could be utilized to assess fluid responsiveness since pulse pressure served as a stand-in signal for stroke volume. Before volume expansion, there was a strong correlation between Pp and VE-induced changes in CI ($r2 = 0.85$, $p < 0.001$) (14).

In their analysis of met analysis, Marik et al. examined a number of studies that examined SVV from pulse contour analysis and PPV from arterial waveform analysis. They accurately predicted the intravascular volume status and the degree of change in cardiac output following volume expansion. Every study revealed a threshold between 11 and 13%, and they were all rather consistent (15).

A study published in 2021 in the Journal of South East Asian medical research, PLR at early resuscitation significantly increased CO (3.57 ± 0.27 Vs 2.2 ± 0.8 L/min, p=0.037), MAP (22.48 ± 5.6 Vs 10.83 ± 4 mmHg, p<0.001), DBP (19 ± 0.20 Vs 1.23 ± 0.12 mmHg, p=0.001) and CVP (4.52 ± 0.19 Vs 2.18 ± 0.13 mmHg, p=0.002). However, no differences were observed in HR, SVR, pulmonary complications of chest X-ray (2(10%) Vs 1(5%), p=0.23) as well as survival at hospital admission (16 (80%) Vs 13 (65%), p=0.48) between two groups (16).

A study published in society of critical care medicine and Lippincott Williams & Wilkins. The stroke volume >10% predicted fluid responsiveness with sensitivity of 86% and specificity of 90%. The pulse pressure >9% predicted fluid responsiveness with sensitivity of 79% and specificity of 85%. The velocity of femoral artery flow >8% predicted fluid responsiveness with sensitivity of 86% and specificity of 80% (17).

A study published by Monnet X and et al. (25) in 2006 found that an increase in pulse pressure by ≥ 12 % on passive leg raising had a sensitivity of 60 % and specificity of 86% in their study when compared to aortic blood flow as predictor of fluid responsiveness in mechanically ventilated patients without arrythmias.

METHODOLOGY

Source of data

Patients admitted to Medical Intensive Care Unit in KLES Dr Prabhakar Kore Hospital and Medical Research Centre, Belagavi.

Study Design

Cross-sectional study

Study Period

The data was collected for over one year between January 2023 to December 2023.

Sample Size

Formula used for sample size calculation was:

$$N = \frac{Z^2_{\alpha/2} * P\ (1-P)}{E^2}$$

Where, n is the sample size required,

P is the proportion or prevalence,

E is the error,

Z is the value corresponding to level of confidence required.

From the study conducted in China by Zhou-Zhou dong et al., it was observed that out of 32 cases with sepsis 22 were responders, that is proportion of respondent was 68.75%. That is, p =0.6875, the absolute error was taken as 10% with 95% confidence interval. Hence the sample size was:

$$N= \frac{1.96^2 * 0.6875\ (1-0.6875)}{0.1^2}$$

$$N=82.53$$

Hence, n=83.

Sampling technique

In this cross-sectional study, all the consecutive patients fulfilling the inclusion criteria was included in the study.

Inclusion criteria

- Age >18 years
- Acute circulatory failure consisting of at least 1 of the following, SBP less than 90 mmHg (or more than 40 mmHg in known hypertensives); vasopressor requirement to maintain SBP more than 90 mmHg (dopamine more than 5 µg per Kg per minute or norepinephrine more than 0.1 µg per Kg per minute); less than 0.5 ml per kg per hour of urine output for minimum of one hour; and increased heart rate of more than 100 per minute.

Exclusion criteria

- Central nervous system pathology
- Amputated leg
- Intra-abdominal hypertension
- Cardiac arrhythmias
- Diuretic treatment
- Uncontrolled hemorrhage, leg amputation, phlebitis, compression stockings
- Intra-aortic balloon pump support
- PaO2/ FiO2 of less than 70 mmHg or high risk of pulmonary edema.
- Pregnant women
- Hypertensives on antihypertensive drugs
- Adrenal insufficiency

Statistical analysis

Statistical analysis was done via IBM SPSS using descriptive analysis and Chi-square test. All the categorical variables were expressed in number and percentage. All the continuous variables were expressed in mean and standard deviation. MAP and PP changes with passive leg raising and fluid resuscitation were plotted in ROC curve to evaluate the efficiency of MAP as predictor for fluid responsiveness.

RESULTS

Table 1: Distribution of patients age wise

AGE DISTRIBUTION	NUMBER (%)
18 – 30 Years	12 (14.3%)
31-40 Years	9 (10.7%)
41 – 50 Years	10 (12%)
51 – 60 Years	12 (14.3%)
61 – 70 Years	17 (20.2%)
71 – 80 Years	18 (21.4%)
80 – 90 Years	6 (7.1%)

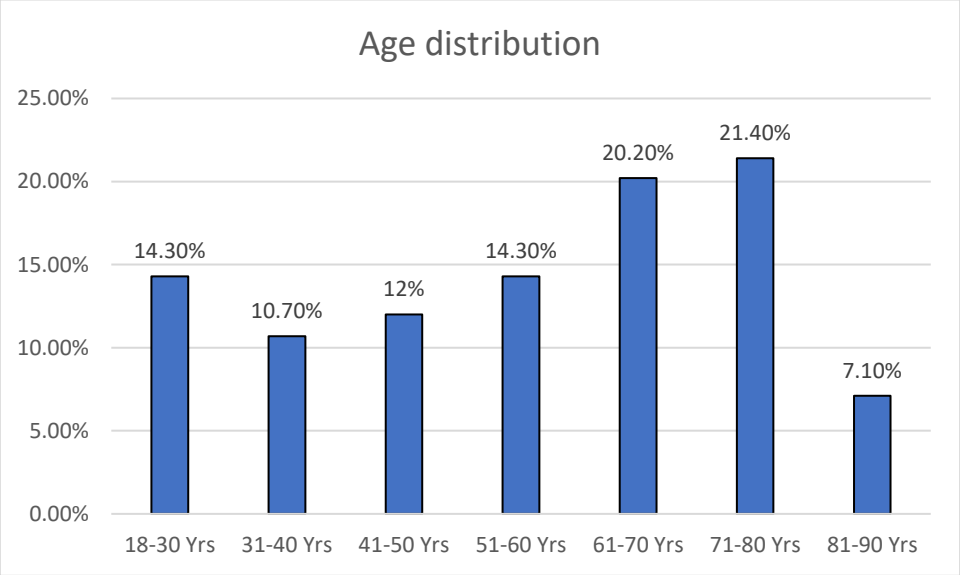

Figure 9: Age distribution of study participants

In our present study of 84 participants, the maximum number of patients were in age group 71-80 years, that is 18 patients (21.4%) in the group, followed by 17 patients in the group of 61-70 years (20.2%), 12 in each group of age between 18-30 years and 51-60 years (14.3%), 10 in 41-50 years group (12%), 9 in group of 31-40 years group (10.7%) and 6 in 81-90 years group (7.1). The mean age of the study participants was 55.73 ± 18.5 years (Table 1 and Figure 9).

Table 2: Distribution of patients gender wise

GENDER	NUMBER (%)
Male	52 (62%)
Female	32 (38%)

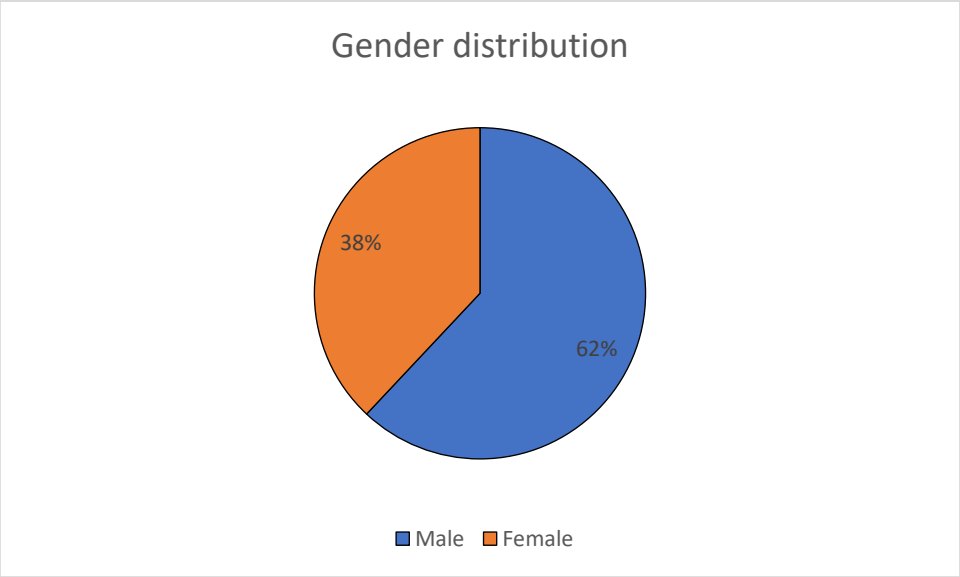

Figure 10: Gender distribution among study participants

There were 52 (62%) male participants and 32 (38%) female participants in our study (Table 2 and Figure 10). There was male preponderance observed ratio is 1.625 with ratio of male to female 1.6:1.

Table 3: Distribution of patients with comorbidities

COMORBIDITY	NUMBER (%)
T2DM	29 (34.5%)
IHD	12 (14%)
COPD	5 (6%)
CKD	1 (1.2%)
Ca-Lung	1 (1.2%)

(T2DM-Type 2 diabetes mellitus; IHD-Ischemic heart disease, COPD-Chronic obstructive pulmonary disease; CKD-chronic kidney disease and Ca-Lung- Lung Cancer)

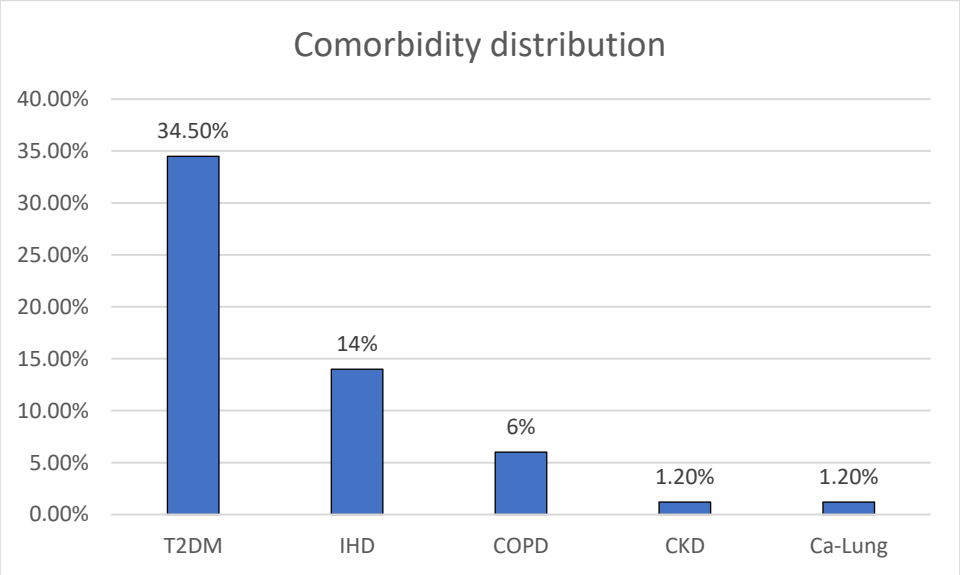

Figure 11: Distribution of comorbidities

We studied all our 84 patients for their associated comorbidities and found to have 29 (34.5%) patients had type 2 diabetes mellitus, 12 (14%) had ischemic heart disease, 5 chronic obstructive pulmonary disease (6%) patients, 1 (1.2%) each in CKD and cancer of lung (Table 3 and figure 11).

Table 4: Distribution of patients according to source of infection for sepsis

SOURCE	NUMBER (%)
Respiratory	29 (34.5%)
Urogenital	24 (28.6%)
Abdominal	13 (15.5%)
Skin	9 (10.7%)
Gastrointestinal	6 (7.2%)
Undetermined	3 (3.5%)

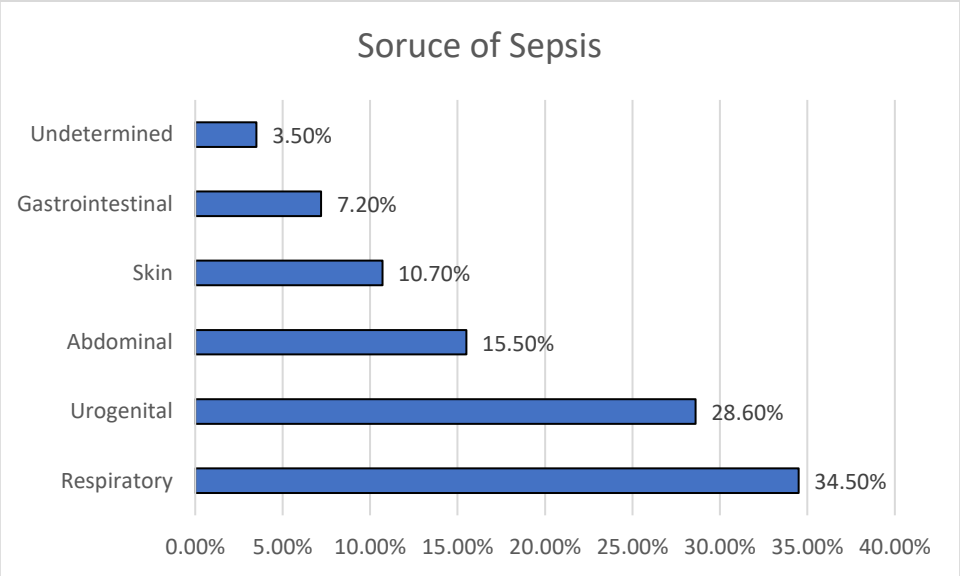

Figure 12: Source of sepsis

We observed in our study 29 (34.5%) patients had respiratory infection as source of sepsis, 24 (28.6%) urogenital, 13 (15.5%) abdominal, 9 (10.7%) skin, 6 (7.2%) gastrointestinal tract and 3 (3.5%) unknown sources (Table 4) (Figure 12).

Table 5: Distribution of patients according to the heart rate in basal, passive leg rising and fluid resuscitation

	RANGE	BASELINE	PASSIVE LEG RAISING	POST FLUID RESUSCITATION
Heart rate	<100	1 (1.2%)	3 (3.5%)	3 (3.5%)
	100-110	24 (28.5%)	31 (37%)	33 (40%)
	111-120	29 (34.5%)	28 (33.3%)	30 (36%)
	121-130	20 (23.8%)	16 (19%)	11 (13%)
	131-140	9 (10.8%)	5 (6%)	6 (7.14%)
	<140	1 (1.2%)	1 (1.2%)	1 (1.2%)
Mean		118.98	114.97	113.88
Standard Deviation		9.95	10.85	10.80
Minimum		94	92	95
Maximum		142	144	146

Majority of the study participants had heart rate between 111 to 120 (n=29, 34.5%) in supine position. Mean heart rate of study participants in supine position was 118.98 ± 9.95. Majority of the study participants had heart rate between 100 to 110 (n=31, 37%) in passive leg rising position. Mean heart rate of study participants in passive leg rising position was 114.97 ± 10.85. Majority of the study participants had heart rate between 100 to 110 (n=33, 39.2%) in post-fluid resuscitation. Mean heart rate of study participants in post-fluid resuscitation was 113.88 ± 10.8 (Table 5).

Table 6: Distribution of patients according to Systolic blood pressure in basal, passive leg rising and fluid resuscitation

	RANGE	BASELINE	PASSIVE LEG RAISING	POST FLUID RESUSCITATION
Systolic blood pressure	60-70	39 (46.4%)	15 (17.85%)	8 (9.5%)
	71-80	35 (41.6%)	29 (34.5%)	21 (25%)
	81-90	10 (12%)	36 (42.85%)	50 (59.5%)
	<90	0 (0%)	4 (4.8%)	5 (6%)
Mean		74.59	80.52	82.08
Standard Deviation		6.36	7.61	7.39
Minimum		60	62	60
Maximum		86	94	96

Majority of the study participants had Systolic blood pressure between 60 to 70 (n=39, 46.4%) in supine position. Mean Systolic blood pressure of study participants in supine position was 74.59 ± 6.36. Majority of the study participants had Systolic blood pressure between 81 to 90 (n=36, 42.85%) in passive leg rising position. Mean Systolic blood pressure of study participants in passive leg rising position was 80.52 ± 7.61. Majority of the study participants had Systolic blood pressure between 81 to 90 (n=50, 59.5%) in post-fluid resuscitation. Mean Systolic blood pressure of study participants in post-fluid resuscitation was 82.08 ± 7.39 (Table 6).

Table 7: Distribution of patients according to Diastolic blood pressure in basal, passive leg rising and fluid resuscitation

Diastolic blood pressure	**RANGE**	**BASELINE**	**PASSIVE LEG RAISING**	**POST FLUID RESUSCITATION**
	40-50	61 (72.5%)	22 (26.2%)	21 (25%)
	51-60	20 (24%)	58 (69%)	50 (59.5%)
	61-70	3 (3.5%)	4 (4.8%)	13 (15.5%)
Mean		50.59	54.76	55.78
Standard Deviation		4.92	5.40	5.52
Minimum		40	42	44
Maximum		64	64	66

Majority of the study participants had diastolic blood pressure between 40 to 50 (n=61, 72.5 %) in supine position. Mean diastolic blood pressure of study participants in supine position was 50.59 ± 4.92. Majority of the study participants had diastolic blood pressure between 51 to 60 (n=58, 69 %) in passive leg rising position. Mean diastolic blood pressure of study participants in passive leg rising position was 54.76 ± 5.4. Majority of the study participants had diastolic blood pressure between 51 to 60 (n=50, 59.5 %) in post-fluid resuscitation. Mean diastolic blood pressure of study participants in post-fluid resuscitation was 55.78 ± 5.52 (Table 7).

Table 8: Distribution of patients according to Mean arterial blood pressure in basal, passive leg rising and fluid resuscitation

	RANGE	BASELINE	PASSIVE LEG RAISING	POST FLUID RESUSCITATION
Mean Arterial Pressure	45-50	1 (1.2%)	0 (0%)	1 (1.2%)
	51-55	22 (26.1%)	11 (13%)	8 (9.5%)
	56-60	37 (44%)	12 (14.2%)	11 (13%)
	61-65	20 (24%)	31 (37%)	23 (27.3%)
	66-70	4 (4.7%)	25 (29.8%)	31 (37%)
	71-75	0 (0%)	5 (6%)	10 (12%)
Mean		58.46	63.32	64.25
Standard Deviation		4.24	5.41	5.41
Minimum		47	52	50
Maximum		68	71	72

Similarly, attempt was made to look for baseline MAP, passive leg rising and with fluid resuscitation. The below table depicts various findings in our population (Table 8). Majority of the study participants had mean arterial pressure between 56 to 60 (n=37, 44 %) in supine position. Mean value of mean arterial pressure of study participants in supine position was 58.46 ± 4.24. Majority of the study participants had mean arterial pressure between 61 to 65 (n=31, 37 %) in passive leg rising position. Mean value of mean arterial pressure of study participants in passive leg rising position was 63.32 ± 5.42. Majority of the study participants had mean arterial pressure between 66 to 70 (n=31, 37 %) in post-fluid resuscitation. Mean value of mean arterial pressure of study participants in post-fluid resuscitation was 64.25 ± 5.41.

Table 9: Distribution of patients according to pulse pressure in basal, passive leg rising and fluid resuscitation

	RANGE	BASELINE	PASSIVE LEG RAISING	POST FLUID RESUSCITATION
Pulse Pressure	10-15	2 (2.3%)	1 (1.2%)	1 (1.2%)
	16-20	30 (35.7%)	12 (14.3%)	9 (10.7%)
	21-25	15 (18%)	24 (28.6%)	20 (23.8%)
	26-30	30 (35.7%)	39 (46.5%)	43 (51.2%)
	31-35	5 (6%)	6 (7.1%)	8 (9.5%)
	36-40	2 (2.3%)	2 (2.3%)	3 (3.6%)
Mean		23.92	25.71	26.28
Standard Deviation		5.33	4.8	4.44
Minimum		14	14	14
Maximum		36	38	36

Similarly, we looked for mean pulse pressure for basal, passive leg rising and fluid resuscitation pulse pressure. Majority of the study participants had pulse pressure between 16 to 20 and 26 to 30 (Each n=30, 35.7 %) in supine position. Mean pulse pressure of study participants in supine position was 23.92 ± 5.33. Majority of the study participants had pulse pressure between 26 to 30 (n=39, 46.5 %) in passive leg rising position. Mean pulse pressure of study participants in passive leg rising position was 25.71 ± 4.8. Majority of the study participants had pulse pressure between 26 to 30 (n=43, 51.2 %) in post-fluid resuscitation. Mean pulse pressure of study participants in post-fluid resuscitation was 26.28 ± 4.44 (Table 9).

Table 10: Distribution of patients according to requirement of Inotropes

NUMBER OF INOTROPIC AGENTS INTAKEN	NUMBER (%)
One	54 (64.3%)
Two	21 (25%)
Three	9 (10.7%)

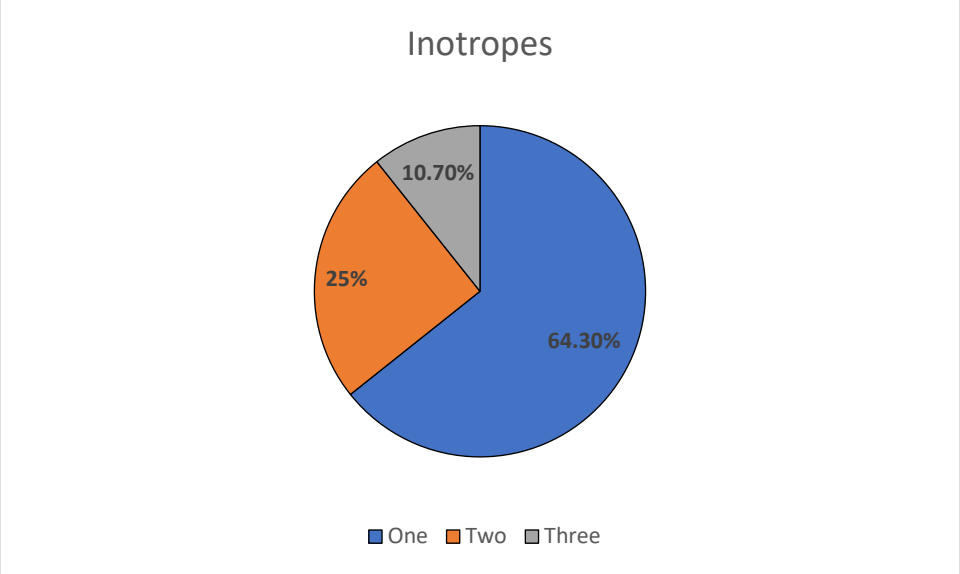

Figure 13: Distribution of patients according to requirement of Inotropes

We observed in our 84 patients who required pressure support for maintenance of BP, a total number of 54 (64.3%) patients required only 1 inotrope, that is, noradrenaline, 21 (25%) patients required 2 inotropes (noradrenaline and vasopressin), 9 (10.7%) patients required 3 inotropes (Noradrenaline, vasopressin and dobutamine) (Table 10). (Figure 13).

Table 11: Distribution of patients according to Ventilator Support

Invasive Ventilation	Number (Percentage)
Yes	41 (48.8%)
No	43 (51.2%)

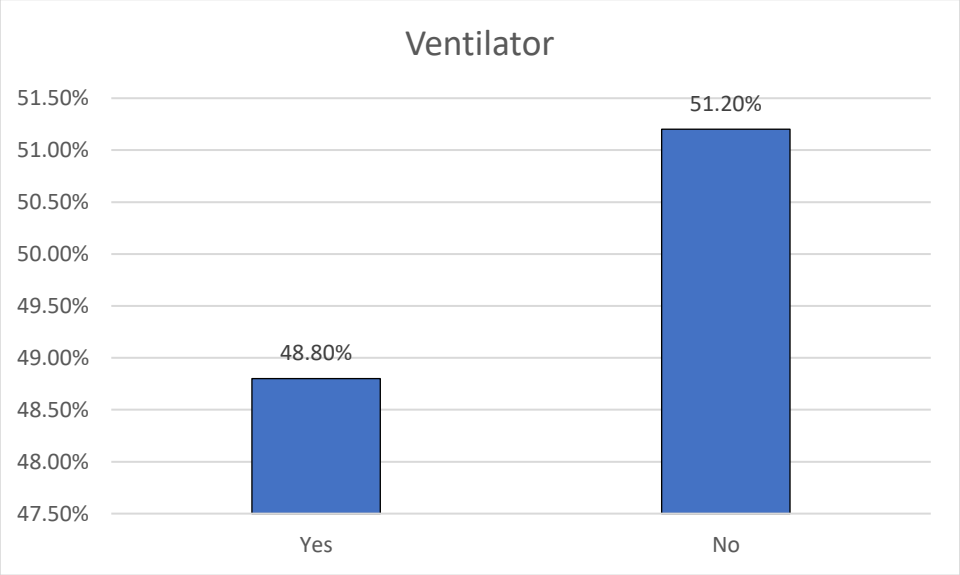

Figure 14: Study participants on ventilator support

Similarly, we attempted to categorize our patients based on need for ventilator support and observed that a total of 41 patients required invasive ventilator support and remaining 43 patients did not require invasive ventilator support but were on non-invasive ventilator support. (Table 11 and Figure 14).

Table 12: Comparison of study participants based on invasive ventilator support and non-invasive ventilator support

VARIABLES	INVASIVE VENTILATOR		P value
	YES (n=41)	NO (n=43)	
Age	62.04 ± 17	49.72 ± 18.37	0.380
Gender			
Male	29 (70.7%)	23 (53.5%)	0.098
Female	12 (29.3%)	20 (46.5%)	
Presence of comorbidity			
Yes	26 (63.4%)	22 (51.2%)	0.098
No	15 (36.6%)	21 (48.8%)	
T2DM			
Yes	15 (36.6%)	14 (32.6%)	0.382
No	26 (63.4%)	29 (67.4%)	
CKD			
Yes	0 (0%)	2 (4.7%)	0.235
NO	41 (100%)	41 (95.3%)	
Hypothyroidism			
Yes	5 (12.2%)	5 (11.6%)	0.600
No	36 (87.8%)	38 (88.4%)	
Hypertension			
Yes	15 (36.5%)	14 (32.5%)	0.488
No	26 (63.5%)	29 (67.5%)	
IHD			
Yes	10 (24.4%)	2 (4.7%)	**0.016**
No	31 (75.6%)	41 (95.3%)	
COPD			
Yes	3 (7.3%)	2 (4.7%)	0.195
No	38 (92.7%)	41 (95.3%)	
Cancer			
Yes	1 (2.4%)	0 (0%)	0.512

No	40 (97.6%)	43 (100%)	
Sepsis focus			
Abdomen	4 (9.6%)	9 (20.9%)	
GIT	2 (4.9%)	4 (9.3%)	
Respiratory	20 (49%)	9 (20.9%)	
Skin	4 (9.6%)	5 (11.6%)	**0.031**
Urogenital	9 (22%)	15 (35%)	
Undetermined	2 (4.9%)	1 (2.3%)	
Inotropes			
One	22 (53.7%)	32 (74.4%)	
Two	11 (26.8%)	10 (23.3%)	**0.047**
Three	8 (19.5%)	1 (2.3%)	

Similarly, we attempted taking age, gender, comorbidities, source of infection for sepsis and inotrope support in patients on ventilatory support.

We observed when these variables were compared with above factors there was no statistical difference observed with age, gender etc.

Table 13: Comparison of patients with Mean Arterial Pressure (Age, gender, comorbidities etc.)

Variables	MAP Changes				P value
	Increased and sustained (n=56)	Increased and not sustained (n=12)	Decreased/ No change and sustained (n=7)	Decreased/ No change and not sustained (n=9)	
Age	55.03 ± 18.86	61.91 ± 14.75	54.85 ± 20.73	52.55 ± 16.53	0.198
Gender Male Female	 36 (64.3%) 20 (35.7%)	 7 (58.3%) 5 (41.7%)	 4 (57.1%) 3 (42.9%)	 5 (55.6%) 4 (44.4%)	0.936
Comorbidities	32 (57.1%)	7 (58.3%)	4 (57.1%)	5 (55.6%)	0.999
T2DM	20 (35.7%)	3 (25%)	3 (42.9%)	3 (33.3%)	0.864
CKD	2 (3.6%)	0 (0%)	0 (0%)	0 (0%)	0.795
Hypothyroidism	6 (10.7%)	2 (16.7%)	2 (28.6%)	0 (0%)	0.333
HTN	15	7	4	5	0.918
IHD	8 (14.3%)	2 (16.7%)	2 (28.6%)	0 (0%)	0.436
COPD	2 (3.6%)	1 (8.3%)	0 (0%)	2 (22.2%)	0.146
Ca	1 (1.8%)	0 (0%)	0 (0%)	0 (0%)	0.918
Ventilator Yes No	 28 (50%) 28 (50%)	 6 (50%) 6 (50%)	 5 (71.4%) 2 (28.6%)	 4 (44.4%) 5 (55.6%)	0.717
Sepsis Abdominal GIT Respiratory Skin Urogenital Undetermined	 10 (17.9%) 2 (3.6%) 18 (32.1%) 6 (10.7%) 17 (30.3%) 3 (5.4%)	 1 (8.3%) 2 (16.7%) 3 (25%) 1 (8.3%) 5 (41.7%) 0 (0%)	 2 (28.6%) 2 (28.6%) 3 (42.9%) 0 (0%) 0 (0%) 0 (0%)	 0 (0%) 0 (0%) 5 55.6%) 2 (22.2%) 2 (22.2%) 0 (0%)	0.239
Inotropes 1 2 3	 42 (75%) 10 (17.9%) 4 (7.1%)	 4 (33.3%) 7 (58.3%) 1 (8.3%)	 2 (28.6%) 1 (14.3%) 4 (57.1%)	 6 (66.7%) 3 (33.3%) 0 (0%)	**0.02**

When various factors were compared with mean arterial pressure the observations made are tabulated in above tableno.13

There was no statistical significance observed when compared with these factors in Mean arterial pressure.

Table 14: Comparison of mean arterial pressure and Pulse pressure values, values, passive leg rising with fluid resuscitation

Variables	Increased and sustained	Increased and not sustained	Decreased/ No change and sustained	Decreased/ No change and not sustained
MAP	56 (66.7%)	12 (14.3%)	7 (8.3%)	9 (10.7%)
PP	35 (41.7%)	14 (16.7%)	18 (21.4%)	17 (20.2%)

Above observations were made as depicted in table no.14.

There was a change in mean arterial pressure and pulse pressure (56 pts (66.7%) and 35 pts (41.7%)). Though initially there was increase in Mean Arterial Pressure and Pulse pressure, but it was not sustained (12 (14.3%) and 14 (16.7%).

In some patients there was decrease/no change in Mean Arterial Pressure and Pulse pressure but it was sustained (7 (8.3%) and 18 (21.4%))

In some patients there was decrease/no change and was not sustained also in Mean Arterial Pressure and Pulse pressure (9 (10.7%) and 17 (20.2%).

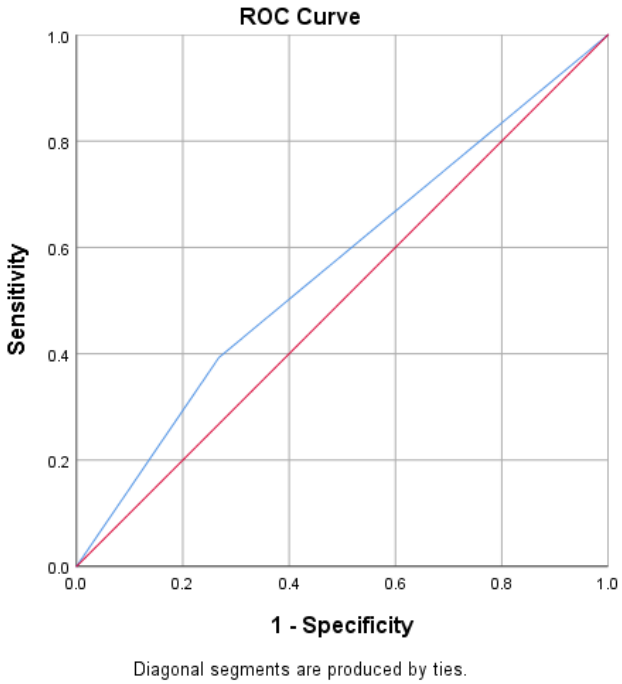

Figure 15: Distribution of patients according to ROC curve plotting for mean arterial pressure and pulse pressure with passive leg raising and fluid challenge compared with baseline

When we subjected all our study population i.e. n=84 (100%) to ROC curve and found no direct correlation. Applying ROC curve to see effect of passive leg raising and fluid challenge there should be a increased response of ≥ 12% in mean arterial pressure which can be compared to pulse pressure, this observation was not found in our study. The cut off value is 0.6, to be considered satisfactory. we observed in our study the ROC curve of 0.56, which has no direct corelation with mean arterial pressure and pulse pressure (Figure 15). Though there is a negative corelation with Roc curve. The possible mechanism for this is, with passive leg raising and fluid challenge has effect on preload of heart, but no effect on peripheral vascular system. This is because in patients of septic shock there is a vasodilatation instead of vasoconstriction. Hence mean arterial pressure is not going to get altered with these two methods i.e. passive leg raising and fluid challenge.

DISCUSSION

In present study of 84 patients the mean arterial pressure and pulse pressure with passive leg raising and with fluid resuscitation the response in patients of septic shock was studied and compared with various factors.

All our 84 patients presented with various sources of sepsis, were in shock and their age ranged between 18 patients in age group of 71-80 years (21.4%), 17 in 61-70 years (20.2%), 12 in 51-60 years as well as in 18-30 years (14.3 % each), 10 in 41-50 years (12%), 9 in 31-40 years (10.7%) and only 6 patients in 80-90 years. Mean age of our study was 55.73± 18.5 years.

Youngest was 18 years old and oldest was 90 years old.

A study by Dina Zidan and Ahmed Nabil., (9) have found mean age of their patients almost similar to ours though the sample size of their study was 30 patients. To a sharp contrast, a study by Boontoterm P et al., (16) in a study population of 40 patients the mean age observed was 68±17.23. A study by Mallat J et al., (23) in their study population of 270 patients the maximum patients were in age group of 59-74 years i.e. 68 patients. The difference could be because of more number of patients in their study population.

In our study there were 52 (62%) males and 32 (38%) females with male to female ratio of 1.6:1.

A study by Lakhal K et al. (24) in a study population of 102 patients they also observed male to female preponderance with male to female ratio of 2.4:1. Another study by Mallat J et al., (23) in their study population of 270 patients they also observed male preponderance with 1.7:1.

In our present study of 84 patients type 2 diabetes mellitus and hypertension was the associated comorbidity 29 patients each (34.5%), followed by ischemic heart disease 12 patients (14%) Chronic obstructive pulmonary disease 5 patients (6%), chronic kidney disease and carcinoma lung 1 each. A study by Boontoterm P et al., (16) in their study population hypertension was the most common comorbidity associated in their study followed by diabetes and dyslipidaemia, chronic kidney disease was seen in 10 patients in their study and 9 chronic liver disease patients. A study by Hofer CK et al., (22) in their study population majority were hypertension followed by Chronic obstructive pulmonary disease.

In our present study the commonest source of infection was respiratory 29 (34.5%), urogenital 24 (28.6%), abdominal13 (15.5%), skin 9 (10.7%), gastrointestinal tract 6 (7.2%) and unknown sources was 3 (3.5%). A study by Rameau A et al., (21) in their study population majority had gastrointestinal as source of infection / sepsis followed by respiratory infection. A study by Douglas is (20) et al., in

their study they have analysed their patients based on infection whether bacterial/ viral/ fungal and found to have bacterial cause as highest followed by viral least fungal.

The source of infection in our study as well as in our quoted study and many other studies by various authors have not found any corelation with the parameters we studied in our patients (mean arterial pressure and pulse pressure).

In our study the mean heart rate was 118.98 (basal), with passive leg raising 117.47 and with fluid resuscitation 113.88. minimum heart rate was 94,92 and 95 respectively in basal with passive leg raising and fluid resuscitation. Where as maximum was 142,142 & 146 in basal with passive leg raising and fluid resuscitation.

A study by Boulain T et al., (19) in their study population the basal heart rate, passive leg raising and fluid resuscitation was on lower side maybe this is because majority of our patients had profound hypotension requiring more than one inotrope support, where as in their study they were on one inotrope support. This could be the cause of increased heart rate at basal, with passive leg raising & with fluid resuscitation. In our study most of our patients had blood pressure below 90/60 mm Hg as compared to other study whose baseline Blood pressure was >90/60 mm Hg. A study by Monnet X et al., (25) observed heart rate response was on lower side (basal, passive leg raising & with fluid resuscitation) when compared to our study all the 3 heart rates i.e. with basal, passive leg raising & with fluid resuscitation Was more.

In our patients the mean systolic blood pressure was 74.59, with passive leg raising 80.52 and with fluid resuscitation 82.08. Minimum being 60, 62 and 60 i.e. basal, with passive leg raising & with fluid resuscitation. Maximum was 86, 94 and 96 i.e. basal, with passive leg raising & with fluid resuscitation. Though the raise of systolic blood pressure from mean systolic blood pressure with passive leg raising and fluid resuscitation was seen it was not significant raise.

A study by Monnet X et al., (25) have also observed this similar observation, the raise of systolic blood pressure with passive leg raising and fluid resuscitation.

A study by Boulain T et al., (19) had similar observation of raise of systolic blood pressure with passive leg raising and fluid resuscitation was observed. They have used stroke volume in their study population as another parameter. We did not use stroke volume to asses heart rate, systolic blood pressure with passive leg raising and fluid resuscitation in our study.

The response of diastolic blood pressure was also a raising trend with passive leg raising and fluid resuscitation minimum being 40, 42 and 44 (basal, passive leg raising & with fluid resuscitation). Maximum was 60, 64 and 66 (basal, passive leg raising & with fluid resuscitation). A study by Monnet x et al., (25) and Boulain T et al. (19) observed similar response as far as diastolic blood pressure was

observed in their study population. They have used stroke volume in their study population to compare the basal heart rate/systolic blood pressure/diastolic blood pressure. The increase in systolic blood pressure and diastolic blood pressure from baseline to passive leg raising and fluid resuscitation is explained on basis of stroke volume with passive leg raising and fluid resuscitation is the explanation offered. Though there was response observed in heart rate with systolic blood pressure and diastolic blood pressure, we did not address stroke volume in all our patients.

When attempted to calculate mean arterial pressure, there was a response observed with both tests i.e. passive leg raising & fluid resuscitation in our patients. A study by Monnet x et al., (25) and Boulain T et al., (19) observed similar as far as mean arterial pressure was observed in their study.

Similarly pulse pressure was taken into account with both tests i.e. passive leg raising and fluid resuscitation. Though there was a raise in pulse pressure the raise was minimal. A study by Monnet x et al,(25) and Boulain T et al.,(19) the raise was significant we are of opinion this difference is because for pulse pressure their basal mean pulse pressure was more in their patients where as in our study the basal pulse pressure was lower, so response with passive leg raising and fluid resuscitation was also minimal.

In our patients there were 54 patients who were on single inotropes (64.3%), 21 with 2 inotropes (25%) and 9 were with three inotropes (10.7%) for their maintenance of blood pressure with sepsis. Majority of studies by various authors have used single inotrope in their study population. Almost 30 % of our patients were on more than one inotrope support this probably explains the severity of sepsis and its sequelae were concerned as, expected decrease in heart rate, increase in systolic/diastolic blood pressure, MAP and PP did not increase satisfactorily with these two measures i.e. passive leg raising and fluid challenge. Though some amount of response was observed especially raise in blood pressure, MAP and PP it was not significant statistically. Whereas studies by other authors did find a significant changes in their study population. In our study we have not looked for stroke volume to calculate all these parameters to see the effect of passive leg raising and fluid resuscitation. In 84 patients of our study 41 patients (48.8%) required invasive ventilatory support whereas 43 (51.2%) were on non-invasive mode of ventilatory support. The same was compared with various factors like e.g. age, sex, comorbidities and source of infection. The significant corelation was observed with ischemic heart disease. In ischemic heart disease group, a greater number of patients were on invasive ventilatory support which was statistically significant.

Mean arterial pressure was compared with various factors (age, sex, comorbidities and source of sepsis) and there was no significant relation.

Similarly comparing mean arterial pressure and pulse pressure with passive leg raising and fluid resuscitation (table 14) was not compared by other authors.

We subjected all our patients i.e. n=84 (100%) to ROC curve, found no direct corelation. The cut off value for ROC curve 0.6 is considered satisfactory. The ROC curve of our study is 0.56, which is not significant and has no direct corelation. Though there is a negative corelation with Roc curve. Applying ROC curve to see effect of passive leg raising and fluid challenge there should be a increased response of $\geq$ 12% in mean arterial pressure which can be compared to pulse pressure, this observation was not found in our study. The possible mechanism for this with passive leg raising and fluid challenge has effect on preload of heart, but no effect on peripheral vascular system. This is because in patients of septic shock there is a vasodilatation instead of vasoconstriction. Hence mean arterial pressure is not going to get altered with these two methods i.e. passive leg raising and fluid challenge.

We feel it is worthwhile taking a greater number of patients in the study and seeing the response with passive leg raising and fluid challenge in patient presenting with sepsis and shock. There are not many studies done in India. If it is applied to large population, it is simple tool to apply in these patients. A simple passive leg raising and fluid challenge and observe pulse rate, blood pressure response, mean arterial pressure and pulse pressure which may guide us to treat our patients in the initial management of the patients with sepsis and shock.

CONCLUSION

In our present study, the evaluation of changes in mean arterial pressure and pulse pressure following passive leg rising test as index and predictor of fluid responsiveness in septic shock patients admitted in medical intensive care unit of KLE Dr Prabhakar Kore Hospital and research Centre, Belagavi. We conclude that.

- In our present study of 84 patients with sepsis in shock the most number of patients were in the age group of 61-70 years followed by 18-30 years and 51-60 years.
- There was a male preponderance observed in our study with a male to female ratio of 1.6:1.
- Hypertension and type 2 diabetes were the most common comorbidities present in our patient.
- The respiratory source of infection was the most common source of infection for sepsis.
- Almost half of our study population was on invasive ventilatory support (48.8%).
- Almost 30 percent of our study population were on more than one inotrope support for their maintenance of blood pressure.
- Patients with ischemic heart disease required more invasive ventilator support in our study which was statistically significant in our study population.
- When all clinical parameters like heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure and pulse pressure were compared to baseline, with passive leg raising and fluid resuscitation, the changes observed were not significant.
- When mean arterial pressure was compared with various study variables we found no significant correlation.
- We found mean arterial pressure is a poor predictor of fluid responsiveness in our present study.

SUMMARY

In our present study of the evaluation of changes in mean arterial pressure and pulse pressure following passive leg rising test as index and predictor of fluid responsiveness in septic shock patients admitted in medical intensive care unit at KLE Dr Prabhakar Kore Hospital and research Centre, Belagavi during study period from January 2023 to December 2023 with study population of 84 patients.

- Ischemic heart disease is associated with increased need of invasive ventilation in our study.
- When comparing the mean arterial pressure response on passive leg raising and fluid resuscitation with various factors like age, gender, comorbidities, sources of infection for sepsis etc. there is no significant correlation between any factor and outcome.
- The results observed on subjecting the patients to passive leg raising and fluid resuscitation showed that mean arterial pressure is a poor indicator of fluid resuscitation and is not an ideal tool for evaluating fluid responsiveness.

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ANNEXURE-I-INFORMED CONSENT FORM

Title Of Research Study: "EVALUATION OF CHANGES IN MEAN ARTERIAL PRESSURE AND PULSE PRESSURE FOLLOWING PASSIVE LEG RISING TEST AS INDEX OF FLUID RESPONSIVENESS IN CRITICALLY ILL PATIENTS".

Introduction and Purpose:- It is essential to know the status of volume expansion in patients of circulatory failure.PLR is an noninvasive, quick and painless procedure and MAP and PP values are noninvasive methods with zero cost , discomfort and pain to patient.

Procedure:

● If you agree to be part of the research study, you will be asked the relevant history and will be subjected to rising of your lower limbs passively for a brief time followed by set of measurements of MAP and PP before and Post fluid resuscitation

-Risk and Benefits:

The only risk and possible discomfort you might get is during PLR in the form of abdominal discomfort. You may not be benefitted by these investigations but you will be part of this study which is going to be useful to others in the future.

Alternatives:

Taking part in this study is voluntary. You may choose not to take part in this study.
If you decide to take part you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive.
The study doctor or sponsor may stop your participation in this study at any time. If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality:

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy:

Does not apply to this research

Financial incentives for participation:

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results:

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

CONSENT FORM

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read this consent form, or it has Been read to me, this consent form and have had all the questions answered

Signature / Left Thumb print of the Participant or legally authorized representative

Participant's name :……...

Signature / Left thumb impression:……...

of the participant

Name of the legally authorized :……...

representative / guardian

Signature / Left thumb impression :……...

Witness' name :……...

Signature / Left thumb impression :……...

Investigator's name and signature :……...

Date:

Place:

ANNEXURE II -PROFORMA

CASE NO	
NAME	
IP NO	
AGE	**YEARS**
SEX	**MALE FEMALE**
ADDRESS	
OCCUPATION	

Complaints at presentation and diagnosis	
Past history	
Family history	
Personal history	
Treatment history	

Vitals :

Temperature	
Pulse	
Respiratory rate	
Blood pressure	

PHYSICAL EXAMINATION:

	Yes	**No**
Pallor		
Icterus		
Lymphadenopathy		
Cyanosis		
Clubbing		
Edema		

SYSTEMIC EXAMINATION:

C.V.S	
R.S.	
C.N.S	
PER ABDOMEN	

INVESTIGATIONS:

PARAMETERS	SUPINE POSITION	PASSIVE LEG RISING	POST FLUID RESUSCITATION
HEART RATE			
SYSTOLIC BLOOD PRESSURE			
DIASTOLIC BLOOD PRESSURE			
MEAN ARTERIAL PRESSURE			
PULSE PRESSURE			

ANNEXURE III- KEY TO MASTER CHART

PLR	Passive Leg Rising
HR	Heart Rate
PR	Pulse rate
PP	Pulse pressure
MAP	Mean arterial pressure
DOBUT	dobutamine
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
VASO	vasopressin
NORAD	noradrenalinme
HTN	hypertension
T2DM	Type 2 diabetes mellitus
IHD	Ischemic heart disease
COPD	Chronic obstructive pulmonary disease
CKD	Chronic kidney disease

S.NO.	IP NO.	AGE	SEX	COMORBIDITIES	SEPSIS FOCI	INVASIVE VENTILATION	HR (BPM)	SBP (mm Hg)	DBP (mm Hg)	MAP (mm Hg)	PP (mm Hg)	INOTROPES
							BASAL/PLR/POST	BASAL/PLR/POST	BASAL/PLR/POST	BASAL/PLR/POST	BASAL/PLR/POST	
1	10025577	75	M	T2DM,IHD HTN	UROGENITAL	YES	124/120/116	80/86/88	60/60/62	67/69/71	20/26/26	1,NORAD
2	1200786	74	F	T2DM HTN	RESPIRATORY	NO	130/120/118	80/94/96	50/60/60	60/71/72	30/34/36	1, NORAD
3	100078577	38	M	NONE	UROGENITAL	YES	106/102/106	80/78/80	50/50/52	60/59/61	30/32/28	2, NORAD & VASOPRESSIN
4	10027984	55	M	COPD, HTN	RESPIRATORY	YES	112/110/110	86/84/84	50/50/50	62/60/62	36/34/34	1, NORAD
5	10006751	58	F	T2DM HTN	SKIN	YES	120/115/112	84/90/90	50/56/56	60/66/66	34/34/32	1, NORAD
6	10019994	80	M	COPD	RESPIRATORY	YES	94/92/96	80/90/80	50/60/50	60/70/60	30/30/30	1,NORAD
7	1192158	65	M	NONE	GIT	YES	106/102/106	60/72/62	40/50/44	47/57/50	20/18/18	1,NORAD
8	1183508	54	M	T2DM	SKIN	NO	106/102/100	64/70/60	46/50/48	52/60/60	18/20/20	1,NORAD
9	10027953	58	M	T2DM, HYPOTHYROIDISM	UROGENITAL	NO	108/104/108	64/76/66	50/56/50	54/63/55	14/20/16	1, NORAD
10	10023753	30	M	NONE	RESPIRATORY	YES	136/130/128	78/84/88	50/54/60	59/64/69	28/30/28	1, NORAS
11	1171870	19	M	NONE	RESPIRATORY	NO	116/112/108	70/70/84	44/42/60	53/52/68	26/28/24	1, NORAD
12	1178742	62	M	T2DM HTN	SKIN	NO	116/116/112	80/78/90	50/50/60	60/59/70	30/28/30	1, NORAD
13	1171870	55	F	T2DM, HYPOTHYROIDISM	ABDOMEN	NO	124/119/110	70/70/84	44/46/58	53/54/67	26/24/26	1, NORAD
14	1171846	20	F	NONE	ABDOMEN	NO	120/109/110	80/86/86	44/56/56	53/66/66	26/30/30	1, VASOP
15	10028795	55	M	CKD HTN	UROGENITAL	NO	120/120/118	80/86/86	64/64/66	64/71/72	16/22/20	1, NORAD
16	1195550	81	M	T2DM IHD HTN	RESPIRATORY	YES	104/96/95	86/94/96	50/56/60	62/69/72	30/38/36	1, NORAD
17	10027526	90	F	T2DM, COPD	RESPIRATORY	YES	126/128/128	64/62/66	48/48/46	52/53/53	16/14/20	3, NORAD, VASO, DOPA
18	1192158	64	M	HTN	SKIN	NO	140/132/136	74/80/84	50/54/58	58/63/67	24/26/26	1,NORAD
19	10026003	68	F	CA LUNG	RESPIRATORY	YES	116/114/116	80/84/84	50/56/58	60/65/66	30/28/26	1, NORAD
20	1195823	52	M	NONE	UROGENITAL	NO	132/128/126	78/80/84	52/54/58	61/63/67	26/24/26	1, NORAD
21	10024468	64	M	T2DM,IHD , HTN	UNDETERMINED	NO	104/106/102	70/84/83	50/54/52	59/64/63	26/30/32	1, NORAD
22	10024540	72	F	NONE	UROGENITAL	NO	108/106/100	66/66/84	48/48/54	54/54/63	18/18/30	1,NORAD
23	1171845	58	M	COPD	RESPIRATORY	YES	106/105/102	70/70/86	44/44/50	54/54/62	26/26/36	1,NORAD
24	1204597	64	F	T2DM HTN	SKIN	YES	134/138/120	68/68/80	46/44/50	53/52/60	22/24/30	2, NORAD &VASO
25	10018508	67	F	HYPOTHYROID	ABDOMEN	NO	109/112/106	70/84/86	50/56/56	57/63/66	20/28/30	1,NORAD

26	1205027	20	M	NONE	ABDOMEN	YES	136/140/138	80/80/80	54/54/54	63/63/63	24/24/24	3,NORAD, VASO& DOBUT
27	1205275	71	M	HYPOTHYROID	SKIN	YES	126/124/126	84/94/94	50/56/56	61/69/69	34/28/28	1,NORAD
28	1193640	69	M	T2DM, HTN	UNDETERMINED	YES	101/96/96	70/84/86	50/56/56	57/63/66	20/28/30	1, NORAD
29	10023018	36	M	NONE	ABDOMEN	NO	120/112/116	70/80/72	46/54/44	54/63/54	24/26/28	2, NORAD DOPA
30	10021105	46	F	HTN	RESPIRATORY	YES	110/108/109	80/80/80	60/60/62	67/67/68	20/20/18	1, NORAD
31	10028888	73	M	T2DM HTN	RESPIRATORY	YES	106/102/106	74/80/84	50/54/58	58/63/64	24/24/26	1, DOBUT
32	10025577	75	M	NONE	UROGENITAL	YES	120/106/103	70/80/80	50/60/60	59/62/62	20/30/30	1, NORAD
33	10006564	45	F	T2DM, HYPOTHYROID	GIT	NO	120/124/126	70/72/70	50/50/50	59/58/58	20/18/20	2, NORAD & DOBUT
34	10024392	77	M	T2DM HTN	RESPIRATORY	YES	110/106/102	80/90/92	50/60/60	60/70/70	30/30/28	2, NORAD & VASOPRESSIN
35	10020479	24	M	NONE	UROGENITAL	NO	120/116/112	78/80/84	52/54/58	58/63/67	14/26/26	1, NORAD
36	10029197	85	M	T2DM	GIT	YES	126/128/130	70/70/70	44/46/44	54/54/54	26/24/26	3, NORAD, VASO & DOBUT
37	10029011	71	M	HYPOTHYROID	UROGENITAL	YES	110/108/104	70/80/72	46/54/44	54/63/52	24/26/28	2,NORAD & VASOPRESSIN
38	10025596	82	M	IHD HTN	UTI	NO	126/124/126	84/84/84	60/60/62	68/69/68	24/22/24	2, NORAD & VASOPRESSIN
39	1200963	36	F	T2DM	GIT	NO	110/106/102	70/84/84	50/54/52	59/64/63	26/30/32	1, NORAD
40	10023753	33	M	NONE	RESPI	NO	124/118/110	70/70/84	44/46/58	58/63/67	24/24/26	1, NORAD
41	10022990	24	F	NONE	ABDOMEN	NO	120/110/110	80/90/90	50/60/62	60/70/71	30/30/28	1, NORAD
42	10020828	48	M	NONE	RESPI	YES	110/112/106	70/70/84	44/42/60	52/53/65	26/28/24	2, NORAD & VASOPRESSIN
43	10008476	61	F	NONE	RESPI	YES	128/130/132	80/80/78	54/54/52	63/63/61	26/26/28	3, NORAD, VASOPRESSIN & DOBUT
44	10014895	72	F	T2DM HTN	ABDOMEN	NO	124/118/110	70/84/84	50/60/62	62/70/72	20/24/22	1, NORAD
45	10017578	50	F	NONE	RESPI	YES	120/110/112	74/80/82	50/56/58	58/64/66	24/24/24	1, NORAD
46	10018065	43	M	NONE	UROGENITAL	NO	126/118/116	70/84/84	50/60/60	57/68/68	20/24/24	1, NORAD
47	10018268	63	M	NONE	RESPI	NO	136/130/126	70/70/72	50/54/50	57/59/57	20/16/22	2, NORAD & VASOPRESSIN
48	10018303	52	M	T2DM, HTN	BLOOD	YES	120/120/118	80/86/80	64/64/60	64/71/60	16/22/20	2 NORAD & VASOPRESSIN
49	10018508	67	F	NONE	UROGENITAL	YES	110/102/104	84/90/90	50/60/62	61/70/71	34/30/28	1, NORAD

50	10019872	72	M	COPD,	RESPI	NO	108/100/100	70/84/84	50/56/56	57/65/65	20/28/28	1, NORAD
51	10017222	61	M	HTN	UROGENITAL	YES	106/106/102	80/86/86	50/60/60	60/69/69	30/26/26	1,NORAD
52	10019784	79	M	T2DM IHD HTN	RESPI	YES	120/110/120	80/80/80	60/60/62	63/63/63	24/24/22	3, NORAD, VASOPRESSIN & DOBUT
53	10019784	76	F	NONE	UROGENITAL	NO	126/120/116	64/72/74	46/52/50	52/59/58	18/20/24	2, NORAD & VASOPRESSIN
54	10019752	71	M	T2DM	ABDOMEN	NO	134/128/128	70/80/80	44/52/52	54/64/64	26/28/28	2,NORAD & VASOPRESSIN
55	10020149	25	F	NONE	UROGENITAL	NO	126/120/116	64/62/86	46/46/54	52/53/64	18/16/22	1, NORAD
56	10020888	72	M	T2DM HTN	GIT	NO	110/104/102	74/80/82	52/58/60	59/65/67	22/22/22	2,NORAD & VASOPRESSIN
57	10020501	49	M	T2DM HTN	GIT	NO	112/106/102	76/84/86	54/60/60	61/68/69	18/24/26	1, NORAD
58	10027526	65	F	HYPOTHYROID	UROGENITAL	YES	124/123/122	70/80/80	50/56/56/	57/64/64	20/24/24	2, NORAD &VASO
59	10004587	58	F	T2DM IHD HTN	RESPIRATORY	YES	126/122/120	84/90/90	56/60/60	65/70/70	28/30/30	2, NORAD & VASOPRESSIN
60	10004365	50	M	NONE	SKIN	NO	116/111/112	70/80/82	50/56/56	57/64/65	20/24/26	1, NORAD
61	10004489	72	M	T2DM HTN	RESPIRATORY	YES	142/144/146	66/66/64	48/50/50	54/55/55	18/16/14	3, NORAD, VASOPRESSIN & DOBUT
62	10004226	30	F	NONE	UROGENITAL	NO	120/1114/114	80/88/88	54/58/58	63/68/68	26/30/30	1, NORAD
63	10005421	67	M	NONE	RESPIRATORY	YES	126/124/118	70/70/84	44/42/60	52/53/65	26/28/24	1, NORAD
64	10005310	56	F	IHD HTN	ABDOMEN	YES	110/108/112	70/80/74	44/52/46	53/61/56	26/28/28	2,NORAD & VASOPRESSIN
65	10005938	72	F	HYPOTHYROID	UROGENITAL	NO	120/117/115	80/86/88	54/60/62	63/69/71	26/26/26	1, NORAD
66	10006304	26	F	NONE	UROGENITAL	NO	117/110/109	86/94/92	50/58/60	62/69/68	36/36/32	1, NORAD
67	10006332	29	F	NONE	UROGENITAL	NO	111/102/103	70/84/84	50/56/56	58/63/64	20/28/28	2, NORAD & VASOPRESSIN
68	10006326	62	M	T2DM IHD HTN	RESPI	YES	126/118/116	70/84/84	50/60/60	57/68/68	20/24/24	1, NORAD
69	10006386	62	F	T2DM	RESPI	NO	136/138/135	74/72/76	52/50/50	59/57/59	22/22/26	2, NORAD & VASOPRESSIN
70	10006174	40	F	NONE	ABDOMEN	NO	120/115/112	84/90/90	50/56/56	60/66/66	34/34/32	1, NORAD
71	10006276	87	M	IHD HTN	RESPIRATORY	YES	120/110/112	80/86/86	64/64/62	64/71/70	16/22/24	1, NORAD
72	10006717	52	F	HYPOTHYROID	UROGENITAL	YES	110/103/102	80/86/88	60/60/62	67/69/71	20/26/26	2, NORAD & VASOPRESSIN

73	10006747	23	F	NONE	SKIN	NO	126/121/119	76/86/88	60/64/64	65/71/72	20/22/24	2, NORAD & VASOPRESSIN
74	10006676	32	M	NONE	UNDETERMINED	YES	108/101/103	80/88/86	54/60/60	63/69/69	26/28/26	1,NORAD
75	10006554	82	M	IHD,T2DM	RESPIRATORY	YES	130/125/124	74/82/82	50/60/60	58/67/67	24/22/22	3, NORAD, VASOPRESSIN & DOBUT
76	10007022	34	M	NONE	ABDOMEN	YES	116/111/109	70/82/84	52/56/56	58/65/65	18/26/28	1,NORAD
77	10007267	34	F	NONE	UROGENITAL	NO	120/115/112	84/90/90	50/56/56	60/66/66	34/34/32	1, NORAD
78	10007272	43	M	NONE	RESPIRATORY	NO	116/120/118	78/78/80	50/50/50	59/59/60	28/28/30	1, NORAD
79	10007444	36	M	NONE	ABDOMEN	NO	130/130/131	76/74/74	48/48/46	57/57/55	28/26/28	1, NORAD
80	10007902	49	M	CKD HTN	UROGENITAL	NO	137/133/136	66/68/68	50/50/50	55/56/56	16/18/18	3, NORAD, VASOPRESSIN & DOBUT
81	10007709	50	M	T2DM	RESPIRATORY	NO	110/106/102	70/84/84	50/54/52	59/64/63	26/30/32	1, NORAD
82	10004673	63	M	IHD HTN	UROGENITAL	YES	120/112/116	70/80/72	46/54/44	54/63/54	24/26/28	2, NORAD DOPA
83	10007888	73	F	HYPOTHYROID, IHD	RESPIRATORY	YES	120/110/120	80/80/80	60/60/62	63/63/63	24/24/22	3, NORAD, VASOPRESSIN & DOBUT
84	10008038	30	M	NONE	ABDOMEN	YES	120/115/113	70/80/82	54/60/60	54/63/64	16/20/22	1, NORAD