"SERUM ALBUMIN AS A PROGNOSTIC MARKER IN CRITICALLY ILL PATIENTS ADMITTED TO MEDICAL ICU."

By:

DR.K.V. THANUJ REDDY. M.B.B.S

Dissertation submitted to the

Sri Devaraj Urs Academy of Higher Education and Research,

Tamaka, Kolar, Karnataka,

IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF

DOCTOR OF MEDICINE (M.D.)

IN

GENERAL MEDICINE

Under the Guidance Of

Dr. LAKSHMAIAH. V. M.B.B.S.,DCH, M.D(medicine).

Professor & Head Of the unit

DEPARTMENT OF MEDICINE

SRI DEVARAJ URS MEDICAL COLLEGE, TAMAKA, KOLAR, KARNATAKA.

April- 2018

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH TAMAKA, KOLAR, KARNATAKA.

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation / thesis entitled **"SERUM ALBUMIN AS A PROGNOSTIC MARKER IN CRITICALLY ILL PATIENTS ADMITTED TO MEDICAL ICU"** is a bonafide and genuine research work carried out by me under the guidance of **DR. LAKSHMAIAH.V**, Professor, Department of General Medicine, Sri Devaraj Urs Medical College, Kolar, Karnataka.

Date:

Place: Kolar **Dr. K. V. THANUJ REDDY.**

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH TAMAKA, KOLAR, KARNATAKA.

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"SERUM ALBUMIN AS A PROGNOSTIC MARKER IN CRITICALLY ILL PATIENTS ADMITTED TO MEDICAL ICU"** is a bonafide and genuine research work carried out by **Dr. K.V. THANUJ REDDY** in partial fulfillment of the requirement for the degree of **DOCTOR OF MEDICINE (M.D.)** in GENERAL MEDICINE.

Date

Place

Dr. LAKSHMAIAH. V. **M.B.B.S.,DCH, M.D(medicine).**

Professor

Department of General Medicine,
Sri Devaraj Urs Medical College,
Tamaka, Kolar.

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH TAMAKA, KOLAR, KARNATAKA.

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"SERUM ALBUMIN AS A PROGNOSTIC MARKER IN CRITICALLY ILL PATIENTS ADMITTED TO MEDICAL ICU"** is a bonafide research work done by **Dr. K.V. THANUJ REDDY** in partial fulfillment of the requirement for the **Degree of Doctor of Medicine (M.D.)** in General Medicine.

Date:

Place:

Dr. LAKSHMAIAH. V. **M.B.B.S.,DCH, M.D(medicine).**

Professor

Department of General Medicine,
Sri Devaraj Urs Medical College,
Tamaka, Kolar.

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH TAMAKA, KOLAR, KARNATAKA.

ENDORSEMENT

This is to certify that the dissertation entitled **"SERUM ALBUMIN AS A PROGNOSTIC MARKER IN CRITICALLY ILL PATIENTS ADMITTED TO MEDICAL ICU"** is a bonafide research work done by **Dr. K. V. THANUJ REDDY** under the guidance of **Dr. LAKSHMAIAH. V. M.B.B.S.,DCH, M.D(medicine)** Professor and HOU, Department of General Medicine, Sri Devaraj Urs Medical College, Kolar, PETER in partial fulfillment of the requirement for the degree of **M. D** in General Medicine.

DR Prabhakar.K
Professor & HOD
Department of Medicine,
Sri Devaraj Urs Medical College
Tamaka, Kolar

Date:
Place: Kolar

Dr. Harendra Kumar M.L
Principal
Sri Devaraj Urs Medical College
Tamaka, Kolar

Date:
Place: Kolar

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH TAMAKA, KOLAR, KARNATAKA.

ETHICAL COMMITTEE CERTIFICATE

This is to certify that the Ethical committee of Sri Devaraj Urs Medical College, Tamaka, Kolar, has unanimously approved **Dr. K.V. THANUJ REDDY** Post graduate student, in the department of General Medicine at Sri Devaraj Urs Medical College, Tamaka, Kolar, to take up the dissertation work titled **"SERUM ALBUMIN AS A PROGNOSTIC MARKER IN CRITICALLY ILL PATIENTS ADMITTED TO MEDICAL ICU"** to be submitted to the Sri Devaraj Urs Academy of Higher Education and Research, Kolar.

Date: Signature of Member Secretary

Place: Ethical Committee

SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION & RESEARCH TAMAKA, KOLAR, KARNATAKA.

COPYRIGHT

DECLARATION BY THE CANDIDATE

I hereby declare that the Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar, Karnataka shall have the rights to preserve, use and disseminate this dissertation / thesis in print or electronic format for academic / research purpose.

Date:

Place: Kolar **Dr. K.V. THANUJ REDDY**

ACKNOWLEDGEMENT

No academic work is single handedly accomplished. This work is no exception. Words fail me in expressing my heartfelt and humble gratitude to my guide ***Dr. LAKSHMAIAH V. ,*** *M.D., Professor, Department of General Medicine, for the guidance and encouragement all along in completing my study. His encouragement, sense of punctuality, research oriented approach, the painstaking effort to weed out errors and his affection during the entire course of study leaves me permanently indebted to him.*

It is with deep sense of gratitude and respect, I have taken an opportunity to thank my teacher ***Dr. PRABHAKAR K,*** *M.D, Professor and HOD, Department of General Medicine, Sri Devaraj Urs Medical College, Tamaka, Kolar, for his constant inspiration and valuable guidance at various stages of preparation of this dissertation.*

I express my deep sense of gratitude and humble thanks to ***Dr. B.N.Raghavendra Prasad, Dr.P.N.Venkatarathnamma****,* ***Dr.Raveesha, Dr.Vidyasagar*** *Professors for their advice and constant encouragement throughout the present study.*

I would like to thank all my teachers ***Dr.Srinivasa.S.V, Dr.Harish Kumar, Dr.Jagmohan, Dr.Reddy Prasad, Dr.Vishwanath Reddy, Dr.Niveditha, Dr.Prasanna, Dr.Anitha & Dr.Mahesh*** *from the Department of General Medicine for their heartfelt support at all times.*

I would like to acknowledge the opportune help and permission rendered by the Medical Director, Principal and Medical superintendent, SDUMC/RLJH, in conducting this study.

I humbly thank ***Dr. Sandeep Reddy, Dr. Sabari, Dr.Rahul, Dr.Uphar Gupta, Dr.Sridhar*** *my senior postgraduates for their help and guidance to complete my dissertation.*

I thank all my colleagues ***Dr.Rakesh,Dr. Vennala, Dr. Meena, Dr. Suhas, Dr. Pujitha, Dr. Raghvendra, Dr Hareen, Dr. Karthik*** *for their timely suggestion throughout the preparation of this manuscript.*

I thank ***Dr.Chethan,*** *Bio Statistician for his aid in Data interpretation & Statistical analysis of my Study which led to its successful completion.*

I am also thankful to all the Nursing Staff, Technical Staff and non-teaching staff for their invaluable help without which this study would not have been possible.

I thank my father ***Mr. K. Srinivasulu Reddy*** *my mother* ***Mrs. Parvathamma,*** *my sister* ***K. Neelima*** *and other family members for their constant source of encouragement, and support throughout the entire career.*

Last but not the least I am grateful to all those patients who were the subjects for the study, without whose cooperation this work would not have been possible.

Dr. K.V. THANUJ REDDY

ABSTRACT

BACKGROUND:

Albumin is the most abundant plasma protein in humans. It helps to maintain the colloid osmotic pressure, acts as a carrier protein, and is involved in metabolic, antioxidant and various other functions. Patients who are admitted in Medical Intensive Care Unit (M.I.C.U.) are at an increased risk of mortality due to the severity of their illness. It is thus, important to identify patients at the time of admission who are likely to have a poor outcome, so that such patients can be managed aggressively. Serum Albumin appears to be one such prognostic indicator. Hypoalbuminemia has been associated with increased hospital mortality and morbidity. It is known that serum albumin concentrations may decrease rapidly in critically ill patients with septic shock and after major surgery as well as in other illnesses.

OBJECTIVES:

1)To estimate serum albumin levels in critically ill patients

2)To evaluate the role of serum albumin level as a prognostic marker in critically ill patients

MATERIALS AND METHODS:

The present study was carried out at R.L. JALAPPA. Hospital and Medical Research Centre, Kolar over a period of Nineteen months during

APRIL 2016 to October 2017 among the patients admitted in MICU who needed invasive mechanical ventilatory support for at least 5 days or more.

The selected patient's informed consent was taken from the relative of the patient explaining the nature of the study. The study included patients with all etiologies who were intubated and were put on mechanical ventilation. Clinical and demographic profile at the time of admission to MICU including age, sex, smoking status, history of previous hospital admissions, associated chronic illnesses like hypertension, diabetes mellitus, chronic obstructive pulmonary disease were recorded. Number of days on ventilator, ICU stay, and hospital stay were recorded for all the patients. Duration of mechanical ventilation was defined as the time elapsed from the initiation of ventilatory support to the onset of weaning. The onset of weaning was the time that the physician in charge considered the patient likely to resume and sustain spontaneous breathing. Weaning was performed by either a reduction in the level of ventilator support or a trial of spontaneous breathing. Mechanical ventilation was delivered through an orotracheal tube. The patients were followed up till their stay in hospital. They qualified for the study if they were on mechanical ventilator for 5 days or more. They were excluded from the study if they were weaned from mechanical ventilation before 5

days or died within 5 days of being put on mechanical ventilator. For patients who were included in the study, serum albumin estimation was done on the day one of mechanical ventilator and subsequently on day three, day five and day 10. Serum albumin was assayed using an automated Bromo cresol purple (BCP) specific dye binding method. The outcome of the patient was recorded either as discharge of the patient from the hospital (survivor group) or patient's death in hospital (non-survivor group).

RESULTS:

A total of 64 cases were included in the study. Mean serum albumin level on day of admission (Day 1) for the study group was 3.3 g/dl (± 0.4 g/dl). In survivors, it was 3.4 g/dl (± 0.4 g/dl) and in non-survivors it was 3.1 g/dl (± 0.19 g/dl). It was significantly lower in non-survivors. In the survivor group, 43.9% patients have normal serum albumin levels on admission as compared to just 10.5% in the non-survivor group, suggesting hypoalbuminemia at admission indicates a poorer prognosis in terms of increased mortality. More non-survivors were hypoalbuminemic at admission than survivors suggesting that a low serum albumin at admission indicates a poor prognosis. Our study indicates that the strongest predictor of outcome of the patient is low serum albumin level on day three.

CONCLUSION:

Patients who have normal serum albumin level at admission are more likely to survive as compared to patients who have hypoalbuminemia at admission. Patients who have a steep decline in serum albumin level have a poor prognosis in terms of increased mortality. Serial serum albumin levels also suggest that there are other factors associated with prognosis of the patients. The strongest predictor of adverse outcome of the patient is low serum albumin level on day three.

KEY WORDS:

Critical illness, Serum Albumin, Invasive Ventilator, Adverse Outcome.

LIST OF ABBREVIATIONS USED

α	-	*Alpha*
Å	-	*Armstrong unit*
APACHE	-	*Acute Physiology and Chronic Health Evaluation*
ARDS	-	*Acute Respiratory Distress Syndrome*
ARF	-	*Acute Renal Failure*
ATP	-	*Adenosine Triphosphate*
BCG	-	*Bromo cresol green*
BCP	-	*Bromo cresol purple*
COP	-	*Colloid Osmotic Pressure/colloid oncotic pressure*
COPD	-	*Chronic Obstructive Pulmonary Disease*
CRP	-	*C-Reactive Protein*
Da	-	*Dalton*
dl	-	*Deciliter*
ECF	-	*Extracellular Fluid*
FDR	-	*Fractional Degradation Rate*
Fi O2	-	*Fraction on inspired Oxygen*
GTP	-	*Guanosine Triphosphate*
G	-	*Gram*
HOCl	-	*Hypochlorous Acid*
ICU	-	*Intensive Care Unit*
IL	-	*Interleukine*
Kg	-	*Kilogram*
mg	-	*Milligram*

MICU	-	*Medical Intensive Care Unit*
Min	-	*Minute*
ml	-	*Milliliter*
L	-	*LITRE*
mm Hg	-	*Millimeters of Mercury*
Mmol	-	*Millimoles*
Mrna	-	*Messenger Ribonucleic Acid*
NO	-	*Nitric Oxide*
PaO2	-	*Arterial Oxygen Tension*
RNA	-	*Ribonucleic Acid*
Rrna	-	*Ribosomal Ribonucleic Acid*
SA	-	*Serum Albumin*
TER	-	*Trans capillary Exchange Rate*
TNF	-	*Tumor Necrosis Factor*
Trna	-	*Transfer Ribonucleic Acid*

TABLE OF CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

INTRODUCTION

INTRODUCTION

Albumin is the most abundant plasma protein in humans. It has been the subject of extensive studies. We now know the amino acid sequences of albumin, the complete gene sequence of human albumin, and the location of mutations in the gene sequence[1].

It helps to maintain the colloid osmotic pressure, acts as a carrier protein, and is involved in metabolic, antioxidant and various other functions.

Patients who are admitted in Medical Intensive Care Unit (M.I.C.U.) are at an increased risk of mortality due to the severity of their illness. It is thus, important to identify patients at the time of admission who are likely to have a poor outcome, so that such patients can be managed aggressively[2].

Serum Albumin appears to be one such prognostic indicator. Its utility as a prognostic indicator has been studied in various contexts including critically ill patients. A low serum albumin (SA) concentration correlates with increase in length of stay in ICU, increase the risk of death and readmission to hospital sooner and more frequently. The daily trend of SA can be useful tool in predicting the weaning capability of patients

needing mechanical ventilation. It has been used by many investigators as an index of the nutritional and metabolic status of the patients.

Hypoalbuminemia has been associated with increased hospital mortality and morbidity. It is known that serum albumin concentrations may decrease rapidly in critically ill patients with septic shock and after major surgery as well as in other illnesses[3].

A recent review reports an estimated increase in the death from 24% to 56% for each 2.5gm/litre decrement in SA concentration over the range of studies reviewed[4].

It has also been shown that there is a significant difference between SA concentration of non-survivors and survivors of prolonged critical illness. Patients who were in the ICU for 7 days or more and survived had higher mean SA concentration than non-survivors[1].

Hypoalbuminemia is also shown to be a potent independent predictor of poor outcome. Each 10gm/litre decrease in SA concentration significantly increased the mortality by 137%, morbidity by 89%, prolonged ICU stay by 28%, hospital stay by 71% and increased resource utilization by 66%[5].

It was also noticed that non-survivors had lower SA concentration on admission to the ICU and their SA concentration decreased more rapidly in the first 24 to 48 hours[3].

In view of the above facts, this study intends to determine the acute changes in the serum albumin concentrations that occur following admission to the ICU and evaluate the role of serial SA measurement as an independent prognostic indicator.

OBJECTIVES

OBJECTIVES

1)To estimate serum albumin levels in critically ill patients

2)To evaluate the role of serum albumin level as a prognostic marker in critically ill patients

REVIEW OF LITERATURE

REVIEW OF LITERATURE

The last 25 years have seen major advances in our understanding of albumin. We now know the amino acid sequences of human albumin, the complete gene sequence of human albumin, and the location of mutations in the gene sequence[1,6].

STRUCTURE OF ALBUMIN

Albumin being the most abundant plasma protein in human's accounts for 55–60% of the measured serum protein[7]. It consists of a single polypeptide chain of 585 amino acids with a molecular weight of 66,500 Da[1]. The polypeptide chain lacks a carbohydrate moiety and is characterized by a low content of tryptophan (1 to 2 residues) and methionine[8].

The mature, circulating molecule is arranged in a series of -helices, folded and held by 17 disulphide bridges[1,9]. The in-folding of the molecule and its hydrophilic regions permit its excellent binding properties[8].

The tertiary structure of human albumin crystal is seen as a heart-shaped molecule 80 x 30 Å[10]. In solution, the shape is quite different. The three domains appear to be arranged in an ellipsoid pattern, giving the molecule low viscosity. It has a strong negative charge of -17[1]. The molecule is very flexible and changes shape readily with variations in environmental conditions and with binding of ligands[11].

Although it is flexible, under physiological conditions albumin regains shape easily as it has disulphide bridges which provide strength[12]. After their rupture, the molecule can re-establish these bridges and regain its structure[1].

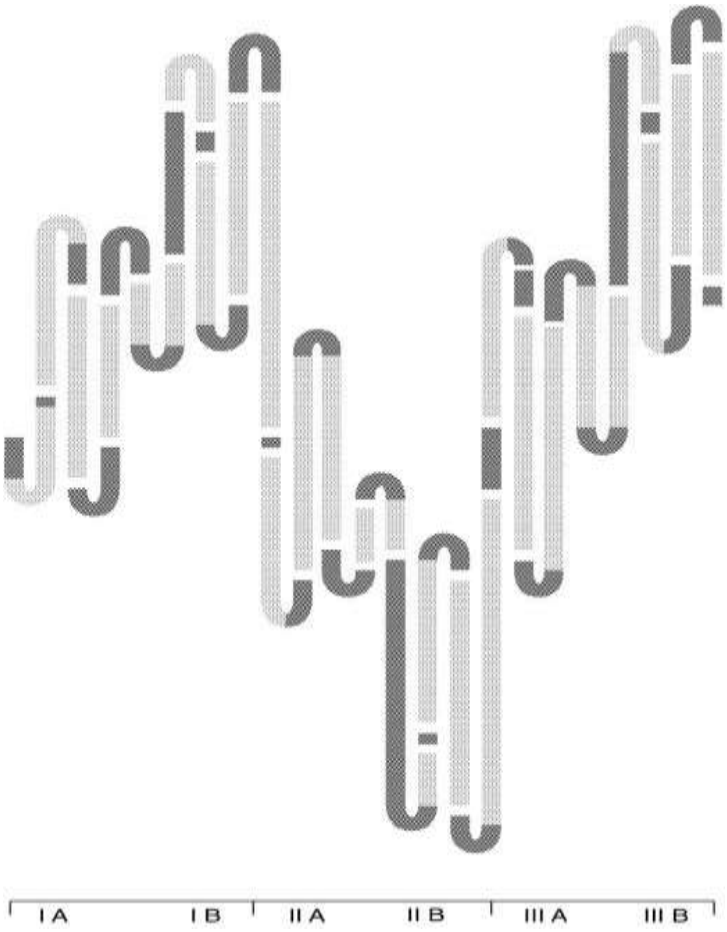


Fig No I: **Two-dimensional representation of the albumin molecule reflecting the heart-shaped structure. The regions of the molecule that are normally in the -helix configuration are shown in dark grey. The seventeen disulphide bridges are depicted in light grey. The three domains, separated into A and B subdomains, are shown along the bottom axis.**

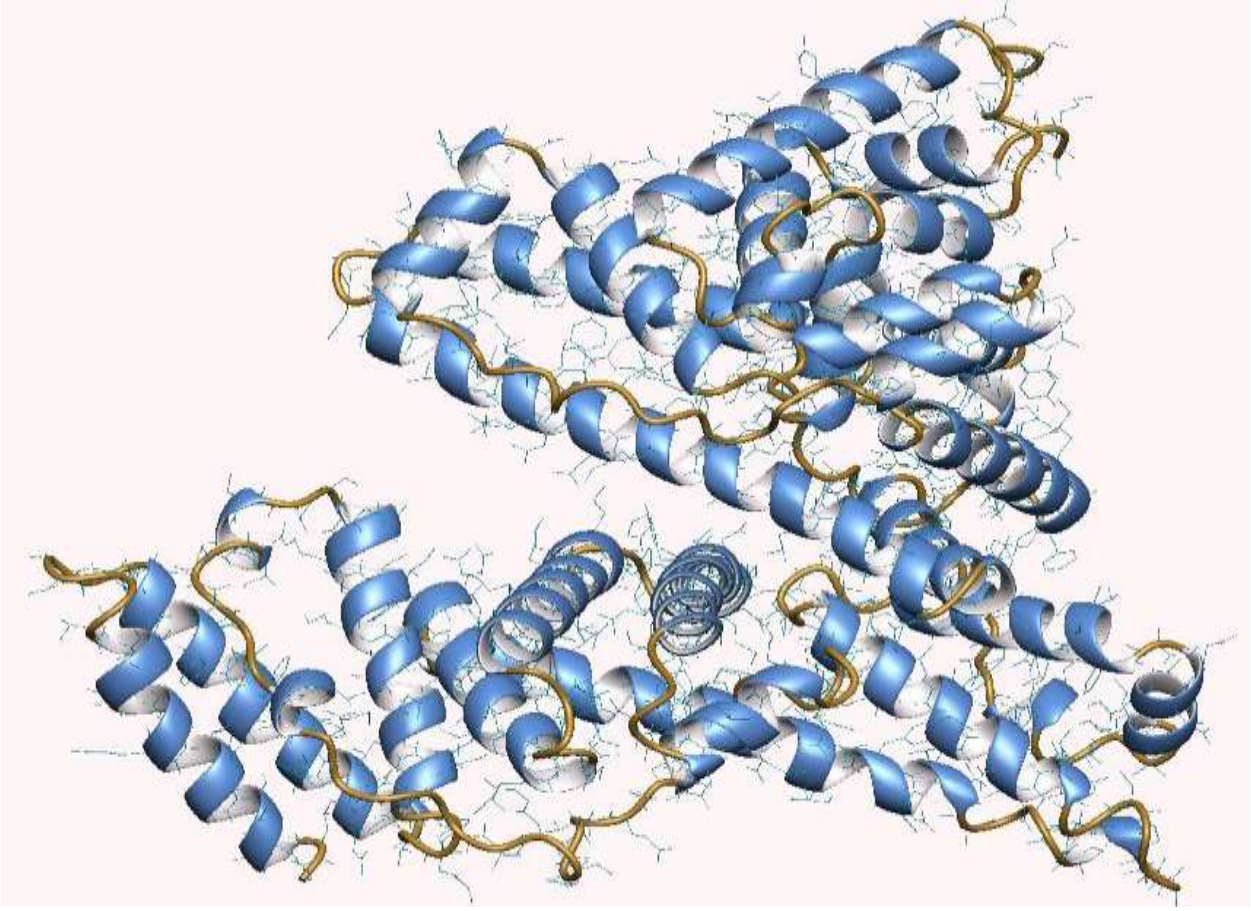


Fig No II: Three-dimensional structure of albumin molecule

ALBUMIN METABOLISM

The plasma albumin concentration is, determined by the intravascular albumin mass divided by the plasma volume[13].

It is a function of its rates of synthesis and degradation and its distribution between the intravascular and extravascular compartments. The total amount of albumin pool constitutes to 3.5–5.0 g kg^{-1} body weight (250–300 g for a healthy 70 kg adult). The plasma compartment holds about 42% of this pool, the rest being in extravascular compartments[1]. Some of this albumin is easily mobilized from the loose interstitial tissues whilst some is bound particularly in the skin[13].

SYNTHESIS

Albumin synthesis in humans takes place in liver only[14,15]. As soon as albumin is manufactured in body it is not stored in liver but secreted into portal circulation. In healthy young adults, the rate of synthesis is 194 (SD 37) mg/kg/day[1], or about 12–25 g of albumin per day[16]. The rate of synthesis varies with nutritional and disease states. The liver can increase albumin synthesis to only 2–2.7 times of its normal capacity because most of the liver's synthetic machinery is already devoted to albumin at rest[1].

The newly synthesized molecule is not stored in the hepatocyte but is rapidly secreted. The time of appearance of a de novo

molecule of albumin outside the hepatocyte has been estimated at about 20 minutes from the onset of its synthesis. Albumin is not a high priority protein (i.e. a protein necessary for the organism to protect itself from an immediate threat to its survival or homeostasis). It is synthesized during periods of inadequate nutrition, exposure to hepatotoxins or if the hepatocyte is exposed to an increased colloid osmotic pressure[8].

The colloid osmotic pressure (COP) of the interstitial fluid bathing the hepatocyte is the most important regulator of albumin synthesis[8,17,18].

Synthesis requires:

- mRNA for translation;
- An adequate supply of amino acids, activated by binding to tRNA;
- Ribosomal machinery for assembly;
- Energy in the form of ATP and/or GTP.

The mRNA concentration available for action on ribosomes is an important factor controlling the rate of albumin synthesis. Trauma and disease processes will affect the mRNA content[19,20]. A reduction in albumin mRNA concentration, caused by a decrease in gene transcription, is seen in

the acute-phase reaction mediated by cytokines, mainly interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α)[21,22,23].

Insulin is required for adequate albumin synthesis[24]. It is necessary for the maintenance of endoplasmic reticulum. Corticosteroids have complex effects on albumin synthesis. There is increased albumin synthesis with combinations of steroids and insulin, and of steroids with amino acids[16,25]. Steroids also increase albumin catabolism[26].

Albumin synthesis has been shown to be stimulated by cortisone and thyroid hormones in vivo in man[27,28,29,30,31]. Thyroid hormone stimulates mRNA and rRNA synthesis, and hypothyroidism results in the opposite effects[32.33.34]. Further there is an increase in the endoplasmic membrane bound RNA and a stimulus to the rate of peptide elongation. Cortisone likewise stimulates the synthesis of hepatic RNA[35,36,37,38,39,40]. Hypophysectomy results in a decreased level of protein synthesis, and growth hormone administration stimulates amino acid transport and albumin production by stimulating gene transcription[8].

Albumin production is reduced by fasting, but specifically omitting protein from the diet causes a greater reduction in synthesis[1]. Malnutrition or decrease in protein intake in vivo results in a rapid loss of cellular RNA, a disaggregation of the endoplasmic membrane bound polysomes and a decrease in albumin synthesis. This change occurs rapidly so that a 24 – or 48-hour fast results in a decrease in albumin synthesis by at

least one third. Refeeding within 15 to 30 minutes restores the ability of the liver cell to synthesize albumin[41-53]. Two amino acids are particularly effective, tryptophan and ornithine[54].Protein deprivation for a longer time leads to a 50 to 60% decrease in the activity and concentration of the mRNA, presumably through increased breakdown, as gene transcription is not slowed in rats on a 0 to 4% protein diet[55].Calories are important, however. There is a reduction in synthesis in starved rats, and polysomes will reaggregate with glucose feeding alone[56].

Ninety-nine percent of the synthesized albumin reaches the plasma pool directly, and only a small fraction is directly picked up by hepatic lymph because of the high plasma flow rate of 0.9 ml per gm of liver per min compared to the much smaller lymph flow rate of 0.0005 ml per gm liver per minute[57]. In healthy individuals, average flow rates in the major lymphatics have been estimated to be 120 ml/hour with a protein content of about 80% of plasma[13].

Tracer studies utilizing iodinated albumin demonstrated that albumin leaks from the vascular pool at about 4% per hour and this rate is not significantly altered in oedematous states, although it would be increased in situations with direct losses of albumin such as nephrosis, protein losing enteropathy, severe skin disases, trauma and burns[58,59,60].

DEGRADATION

Total albumin degradation is around 14 g/day or 5% of daily whole-body protein turnover in a 70-kg man. Albumin is broken down in most organs of the body. Muscle and skin break down 40–60% of a dose of labelled albumin[61]. The liver, despite its high rate of protein metabolism, degrades 15% or less of the total. The kidneys are responsible for about 10%, while another 10% leaks through the stomach wall into the gastrointestinal tract. Albumin is not catabolised in starvation[1].Half-life of Serum Albumin is approximately 20 days.

Each day, 120–145 g of albumin is lost into the extravascular space. Most of this is recovered back into the circulation by lymphatic drainage. In intestinal tract about 1 g each day is digested and releases amino acids and peptides, which are reabsorbed. There is minimal urinary loss of albumin in healthy subjects. Of the 70 kg of albumin that passes through the kidneys each day, only a few grams pass through the glomerular membrane. Nearly all of this is reabsorbed, and urinary loss is usually no more than 10–20 mg/ day. There is a rapid phase of disappearance from the plasma over the first two days[1].

Four to 5% of total intravascular albumin extravasates per hour, this rate of movement is known as the Trans capillary Escape Rate (TER), and this is determined by[62]:

1. Capillary and interstitial free albumin concentration.

2. Capillary permeability to albumin.

3. Movements of solvent / solute.

4. Electrical charges across the capillary wall.

5. Lymph protein content is 80% that of plasma.

This trans capillary exchange rate of 4-5% per hour gives a distribution half-time of about 15 hours. Then there is a slower exponential decay, representing the fractional degradation rate (FDR), of about 3.7% per day with an elimination half time of about 19 days[1].

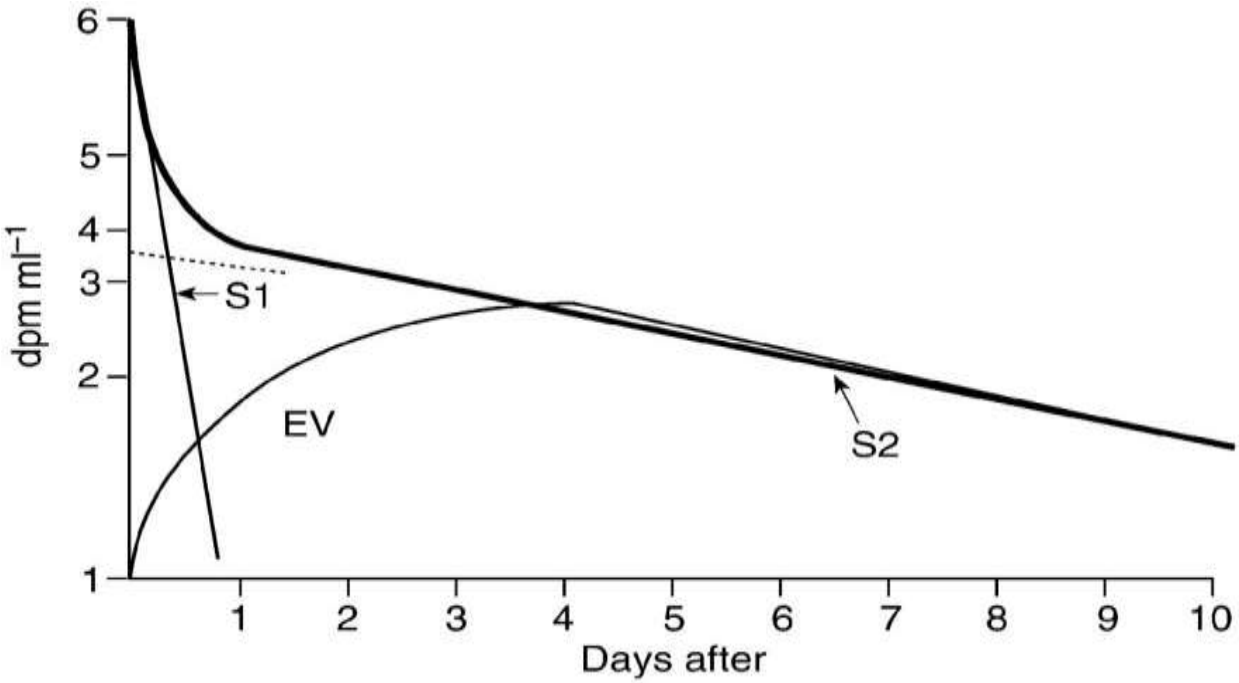


Fig No III: Decay pattern of labelled albumin versus time after i.v. injection of a tracer dose of 125I-labelled human serum albumin (thick line). Slope 1 (S1) is the trans capillary escape rate, which equals about 4-5% per hr . Slope 2 (S2) is the fractional degradation rate, which is about 3.7% per hour. EV is the calculated increase in extravascular labelled albumin concentration. Note that the activity of extravascular albumin is greater than that of intravascular albumin from about day 3 onwards. This suggests that degradation occurs directly from the vascular compartment.

The mechanism of the escape of albumin into the extravascular compartment has come under review recently. Albumin must cross capillaries. Most organs in the body have continuous capillaries, but in some there are wide-open sinusoids (liver, bone marrow) or fenestrated capillaries (small intestine, pancreas, adrenal glands). Starling's theory holds that the rate of escape depends on the permeability of the wall and

hydrostatic and oncotic pressures on either side of the wall[63].Half of the escaping albumin does so through the continuous capillaries, and there appears to be an active transport mechanism to facilitate this[16].

The mechanism of breakdown involves uptake into endocytotic vesicles, which fuse with lysosomes in endothelial cells[64]. They bind altered or denatured albumin, and it is likely that chemical modification of the circulating albumin is a signal for receptor-linked lysosomal degradation.

Albumin is pinocytosed in to cells at a rate that is related to atrial natriuretic peptide (ANP) concentrations[65].

The final breakdown products are free amino acids that add to the pools of amino acids within cells and in the plasma[1].

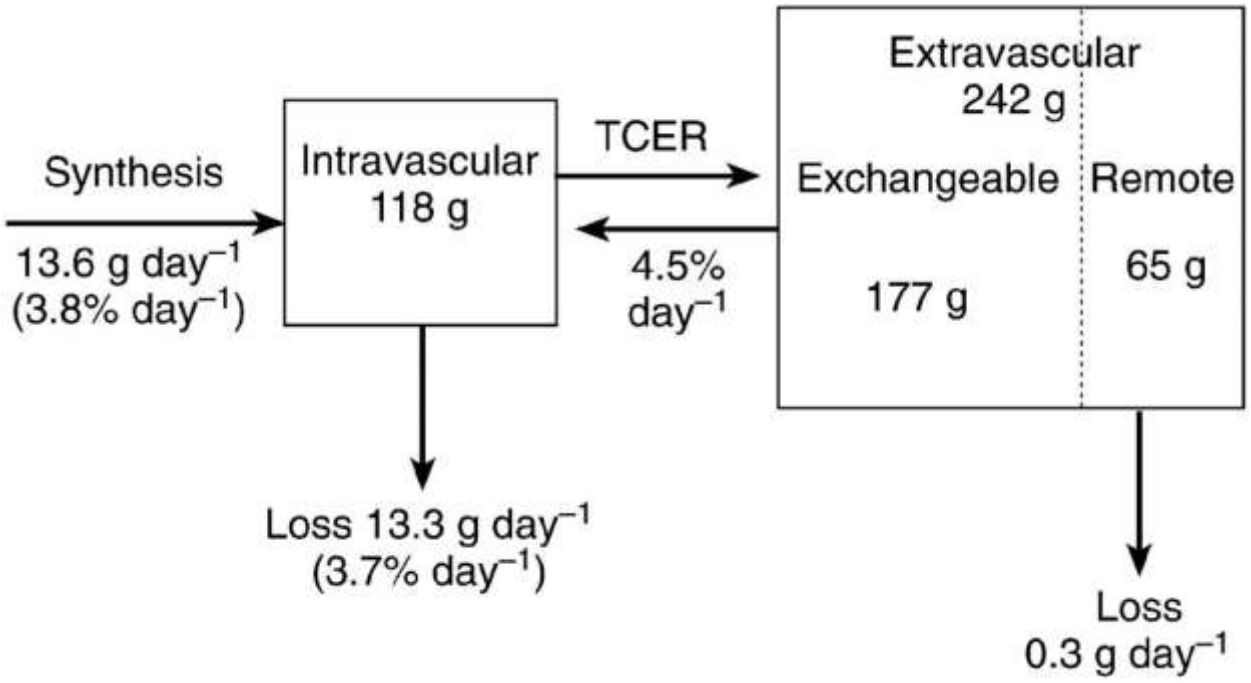


Fig No IV: Typical albumin distribution in a healthy 70 kg adult.

FUNCTIONS OF ALBUMIN

Albumin has extensively studied and well-established physiological functions in health[1].

Oncotic pressure

In healthy subjects, the role of albumin in the maintenance of normal Capillary Oncotic Pressure (COP) is well recognized, but there appears to be little correlation between albumin and COP in the critically ill[66].In health, albumin contributes up to 80% of the normal COP of about 25 mmHg[7,67,68]. This is because of its high molecular weight and concentration in plasma. Albumin is present at a higher concentration than other plasma

proteins, it still has the greatest osmotic significance. So, 60% of the oncotic pressure of albumin results in direct osmotic pressure. The remaining 40% is a result of its negative charge, providing an attractive force for the intravascular retention of positively charged solute particles[1].

It is the COP gradient across the capillary membrane rather than the absolute plasma value which is of greater importance in determining fluid shift into the interstitium[13].

The depressed level of albumin might not represent defective synthesis, but essentially the appropriate response to a change in the content of plasma colloids[28.69,70].

It is of interest that when excess albumin is infused, the accumulation of excess colloid is prevented not by changes in albumin synthesis, but by a marked increase in albumin degradation and albuminuria. The site of oncotic regulation of albumin synthesis is unknown, but it has been postulated to reside in the hepatic interstitial volume, since albumin synthesis bears an inverse relationship to the content in this volume[71].

Critically ill patients have a lowered serum COP[68]. A lowered COP is associated with increased morbidity and mortality in critically ill

patients[68,72,73]. A serum COP of 15 mmHg was associated with a survival rate of 50%.

Binding of substances to albumin

The structure of the albumin molecule is such that it can incorporate many different substances. It is a flexible molecule, and bound compounds can be buried within the structure. Some general trends have emerged from binding studies. Most strongly bound are medium-sized hydrophobic organic anions, including long-chain fatty acids, bilirubin and haematin. Less hydrophobic and smaller substances can be bound specifically but with lower affinity, such as ascorbate and tryptophan. The chirality of the compound may be important, L- tryptophan is bound more strongly than D-tryptophan. Monovalent cations do not bind but divalent cations do, namely calcium and magnesium[74].

It also binds covalently and irreversibly with Ag^{2+}, Hg^{2+}, D-glucose and D-galactose[75]. The glycosylation of albumin has effects upon its charge and can have significant effects upon its subsequent permeability characteristics.

Albumin has a strong negative charge, but there is little correlation between the charge of the compound and the degree of binding to

albumin[76]. Acidic drugs tend to bind to other plasma proteins such as α_1-acid glycoprotein whereas basic drugs tend to bind to albumin. There are exceptions, and drugs may bind to both[1].

Other endogenous compounds that bind to albumin include bile acids, eicosanoids, copper, zinc, folate, and aqua cobalamin. Albumin is also a secondary or tertiary carrier for some substances that have specific binding proteins, for example, steroids, including derivatives such as vitamin D and thyroxine. This can be clinically significant. Steroids have a low binding affinity for albumin but there is a large capacity owing to the high concentration of albumin[74].Thus a significant amount may be carried by albumin, and the lower binding affinity means that there is easy off-loading at target sites[1].

Displacement of drugs from their binding sites by other drugs or by endogenous substances occurs and may alter the distribution, pharmacological action, metabolism, and excretion of the displaced drug. There are a variety of binding sites on the albumin molecule[1].If a drug, or any other ligand, is bound to albumin then there is only a fraction (the amount depending upon the degree of binding) of the drug available for distribution to areas inaccessible to albumin thus, creating a circulating reservoir of the drug[8].

The rate of hepatic clearance would be proportional to the concentration of free drug determined by the laws of equilibrium. However, with many substance (e.g. bile acids, fatty acids, bilirubin and rose Bengal), binding to albumin enhanced their hepatic clearance, suggesting the presence of ligand-albumin receptors on the hepatocyte that favour dissociation of the ligand from albumin, probably because of a conformational change in the albumin molecule[77,78,79]. Ligands cannot only compete with other ligands for the same site, but can displace a ligand from a binding site. No specific albumin receptor, yet has been isolated from the liver plasma membrane[80,81].

There are many factors influencing drug–albumin interactions that become relevant in critically ill patients. Renal failure provides a good example of the mechanisms involved. The serum albumin concentration may be directly altered, due to increased loss of albumin through damaged glomeruli. Renal failure may influence drug binding to albumin[82]. Possible mechanisms involved include changes in pH[83]and the accumulation of compounds which compete with drugs for binding sites. Thus, there may be an increase in the free fraction of drugs in renal failure, resulting in an increased drug effect.

A thorough knowledge of the pharmacokinetic principles outlined above, and of possible drug interactions and displacement reactions, is vital for the management of critically ill patients[1].

Metabolic function

Albumin is also involved in the inactivation of a small group of compounds[16].Disulfiram is inactivated by binding with albumin. Members of the penem group of antibiotics bind irreversibly to albumin, through acetylation of an –Ɛ lysine group close to the surface of the molecule in the region of Sudlow site 1[74].Penicillin allergy has been linked to irreversible coupling of penicilloyl groups to these lysine groups[84].

Albumin is also involved in the metabolism of endogenous substances such as lipids and eicosanoids, because of the avidity with which these compounds bind to albumin. Albumin can stabilize some eicosanoids during metabolism, such as prostaglandin I_2 and thromboxane A_2, it can increase the release of arachidonate from macrophages; and it seems to favour lipo-oxygenase over cyclo-oxygenase activity[16].

Acid–base function

The presence of many charged residues on the albumin molecule and the relative abundance of albumin in plasma mean that it can act as an

effective plasma buffer[9]. At physiological pH, albumin has a net charge of negative[17]. It is responsible for about half of the normal anion gap. A reduction in plasma protein concentration causes metabolic alkalosis. A decrease in serum albumin of 1 g/dl may increase standard bicarbonate by 3.4 mmol/litre, produce a base excess of 3.7 mmol/Litre and reduce the anion gap by 3 mmol/Litre .[85]

Antioxidant function

Under physiological conditions, albumin may have significant antioxidant potential. It is involved in the scavenging of oxygen free radicals, which have been implicated in the pathogenesis of inflammatory diseases[1].

Albumin at concentrations less than physiological can inhibit markedly copper stimulated peroxidation and haemolysis of erythrocyte membranes. Albumin also inhibits generation of free hydroxyl radicals from systems containing copper ions and H2O2[86].This may be related to the abundance of sulfhydryl (-SH) groups on the albumin molecule. These are important scavengers of oxidizing agents, such as hypochlorous acid (HOCl) formed from the enzyme myeloperoxidase, which is released by activated neutrophils[87,88]. An important biological target that can be inactivated by HOCl is probably α_1-antiprotease, permitting uncontrolled elastase activity.

However, albumin also reacts with HOCl. The albumin is damaged by the HOCl, but this is again probably biologically insignificant in view of albumin's high concentration and rapid turnover[86].

Another aspect of the antioxidant action of albumin may be its ability to scavenging peroxy radicals, which may partly account for its reported ability to decrease lipooxygenase activity[86]. The implication of this is that hypoalbuminemic patients have a reduced potential for oxygen radical scavenging[89].

An early event in tissue damage is increased vascular permeability. One beneficial effect of increased vascular permeability will be to increase the extracellular fluid content of proteins such as albumin, transferrin and ceruloplasmin. Allowing more protein, such as albumin to cross a membrane barrier may help to prevent excessive damage by oxidants[86].

Maintaining microvascular integrity

It is possible that albumin has a role in limiting the leakage from capillary beds during stress-induced increases in capillary permeability[90].Endothelial cells seem to be able to control the permeability properties of the capillary membrane,

possibly by altering the nature and distribution of glycoproteins in the vessel wall. Albumin plays a part in this action, though the exact mechanism is not clear. It may involve the strong negative charge on the albumin molecule repelling other negatively charged molecules in the membrane or it may be a space-occupying function of the albumin molecule that reduces the size of channels[91].

It has been suggested that albumin may bind within the sub endothelium and interstitial matrix and alter permeability of these layers to the large molecules and other solutes[92,93].

Albumin is the most important source of sulfhydryl groups in the circulation. Nitric oxide (NO) binds to these sulfhydryl groups to form a stable S-nitroso thiol group and is thus protected from rapid degradation. The effects of albumin on the vasodilatory properties of NO have been studied in vitro[94,95]. Albumin slowed the onset and reduced the maximal intensity of the vasodilatory response to NO.

Anticoagulant effects

Albumin has effects on blood coagulation. It seems to exert a heparin-like action, perhaps related to a similarity in the structures of the two molecules. There is a negative correlation between albumin concentration

and the heparin requirement in patients undergoing haemodialysis[96]. These investigations have shown a heparin-like activity of albumin, through enhancement of the neutralization of factor Xa by antithrombin III. They suggest that the hypercoagulable state seen in the nephrotic syndrome may, in part, be explained by the accompanying hypoalbuminemia.

This may in part be mediated by albumin binding nitric oxide radicals as S-nitroso thiols, inhibiting their rapid inaction and allowing a more prolonged antiaggregatory platelet effect[13,97].

The liver manufactures albumin at a massive rate and decreases production in times of environmental, nutritional, toxic and trauma stress. Osmotic pressure is a basic evolutionary regulatory factor, and hormonal control over albumin production has been demonstrated. Albumin is important as a transport protein, as a measure of evolution and as a model to study secretion following synthesis without the intervening steps of glycosylation[8].

ALBUMIN AND CRITICAL ILLNESS

Critically ill patients have been defined as those that by dysfunction or failure of one or more organs/system depend on survival from advanced instruments of monitoring and therapy[98]. They may have an immediate requirement for any form of organ support, (intubation,

ventilation, inotropes) or is likely to suffer acute cardiac, respiratory, haematological, hepatological or neurological deterioration requiring such support[99].

The function of circulating albumin in critical illness is not fully understood. It may differ significantly from that in healthy subjects. A low serum albumin concentration in critical illness is associated with a poor outcome[100,101,102]. Critical illness alters the distribution of albumin between the intravascular and extravascular compartments. There are also changes in the rates of synthesis and degradation of the protein. The serum albumin concentration will decrease, often dramatically, from early during a critical illness. It will not increase again until the recovery phase of the illness. The kinetics of albumin given intravenous will differ greatly between critically ill patients and healthy subjects. The implication of this, given the important functions of albumin as in health, is that using exogenous albumin to increase the intravascular albumin concentration during critical illness is beneficial[1].

The altered distribution in critical illness is related to an increase in capillary leakage[103]. This occurs in sepsis and after major surgical stress[104,105]. It involves dysfunction of the endothelial barrier, resulting in capillary leakage and loss of protein, inflammatory cells, and large volumes

of fluid into the interstitial space. The effects of bacterial exotoxins on cell monolayers leading to a fivefold increase in permeability to albumin have been demonstrated which lead to cell retraction and the appearance of large intercellular gaps in cell culture monolayers[106].

The precise mediators of this capillary leakage are still being discovered and currently include:

- Endotoxin from Gram-negative bacteria[107,108];
- cytokines—TNF-α and IL-6[21,22];
- Arachidonic acid metabolites-leukotrienes and prostaglandins[109,110];
- Complement components C_{3a} and C_{5a}[110];
- Other vasoactive peptides—bradykinin, histamine[108];
- Chemokines macrophage inflammatory protein 1[111].

The acute phase response mediated by the cytokine from white cells (the interleukin), leads to a markedly increased synthesis of many other plasma proteins but not of albumin. Production and secretion of these acute phase proteins, the antiproteases and procoagulants such as C-reactive protein, fibrinogen, α_1 antitrypsin and complement C_3 are increased, whilst the plasma concentration of constitutive proteins such as albumin and transferrin are decreased, leading to the description of these proteins as

negative acute phase proteins[112]. There is an initial reduction in albumin production whilst acute phase protein synthesis increases, which is followed by a subsequent global increase in hepatic proteins synthesis including albumin[13].

The normal trans capillary escape rate for albumin increases by up to 300% in patients with septic shock, and by 100% after cardiac surgery[103].In septic patients, the trans capillary exchange rate may well improve with appropriate treatment. With increased flow of albumin across capillary membranes, there should be an increase in lymphatic return to the intravascular compartment[1].

It seems likely that lymphatic dysfunction plays a significant role in oedema formation in the critically ill. Free radicals have been shown to impair lymphatic function and this has been suggested as an important contributing factor towards the formation of oedema during inflammation[113]. Studies of albumin kinetics during major surgery have shown a reduction in the flow rate of lymph and the albumin concentration in lymph[87]. It is not known if this extends into the postoperative period. Measurement of total circulating and total exchangeable albumin pools shows a 30% reduction with major surgery[87], consistent with sequestration of albumin into non-

exchangeable sites, such as wounds, the intestine and extra-abdominal sites[114].

The rate of albumin synthesis may be significantly altered in the critically ill[115].In these patients the decreased albumin is compensated for by an increase in acute phase proteins[62]. In the acute-phase response to trauma, inflammation or sepsis, there is an increase in the gene transcription rate for the positive acute-phase proteins such as C-reactive protein, and decreases in the rate of transcription of albumin mRNA and the synthesis of albumin[20]. IL-6 and TNF- α both act to reduce gene transcription[21,22]. Induced inflammation in rats decreased the concentration of albumin mRNA and the rate of albumin synthesis, which reached a minimum by about 36 h and then began to rise again[116,117]. A sustained inflammatory response in critical illness may lead to prolonged inhibition of albumin synthesis.

Stress whether surgical, trauma, infection, or radiation, has also been associated with hypoalbuminemia and protein synthesis and serum levels are altered. It was postulated that a messenger substance passed from the site of injury to the liver, and alterations in the synthesis of various proteins made in the liver followed[118,119,120].

In wounds or following surgical procedure, there is complicating factor: the actual loss of albumin in the wound area. This will result in a

further lowering of the serum albumin[121-128]. Other factors potentially common to all forms of stress such as altered hepatic circulation, impaired nutrition, and the production of interleukin 1, contribute to lowered albumin production during the acute stressful periods. Major surgical stress and infection is associated with a 3 to 5-fold increase in amino acid clearance by the liver. This increased peripheral release and central clearance probably is a major contributor to increased hepatic protein synthesis following trauma[129,130,131].

Catabolism of albumin may also be altered. Serum albumin does not appear to decrease in starvation. The body maintains the serum albumin at the expense of muscular protein. Decreased albumin in adults is a marker of associated disease not a feature of isolated protein-energy malnutrition[62].

Although increased catabolism of proteins is a feature of acute illness, albumin is relatively spared with muscle being the predominant site of protein breakdown. A reduction in intravascular mass secondary to haemorrhage or exudative losses (e.g., burns, or raw area following surgery) results in a rapid decrease in serum albumin especially if maintenance of the plasma volume using non-albumin containing fluids adds a dilutional component. Although there is a tendency for an increased return of albumin from the interstitium to compensate for any acute reduction, the overall

result of each of these conditions will be a decreased intravascular albumin mass[13].

During period of starvation and decreased energy supply the body thus appears to maintain serum albumin concentrations at the expense of other protein sources predominantly muscle. Although synthesis is decreased as reflected by decrease in pre-albumin, redistribution and a reduction in catabolism appear to compensate and prevent decrease in the serum albumin concentration until the very late pre-terminal phase[13].

The Fractional Degradation Rate (FDR) is mass-dependent. That is, as the serum albumin concentration decreases, so does the FDR. Studies have shown a significantly shorter plasma half-life in hypoalbuminemic patients on total parenteral nutrition (9 days), but with a catabolic rate similar to normal[132]. However, in situations of increased trans capillary albumin flux, an increase in the FDR has been observed[8]. It is possible that the vascular endothelium has an important role in the degradation of albumin. In animal experiments, the tissues most actively involved in albumin catabolism are those with fenestrated or discontinuous capillaries[61].It may be that a high rate of tissue exposure in situations of increased capillary permeability may increase catabolism[1].

If the distribution of the albumin between intravascular and interstitial compartments is altered, by either an increase in vascular permeability and hence increased protein flux or a decrease in lymphatic clearance and decreased protein return, then the concentration gradient between these components will tend to equilibrate and serum albumin concentrations will tend to diminish. Increased vascular permeability is probably the predominant mechanism by which redistribution occurs in the acute phase[13].

Each of these mechanisms causes change to serum albumin concentration at a different rate and to a different degree, dilution secondary to fluid infusion will cause the most rapid reduction in albumin concentrations, over minutes to hours, but the degree of change will be small, unless there is simultaneous albumin loss. Redistribution secondary to altered vascular permeability causes a less rapid reduction in serum albumin concentrations over hours to days, but the magnitude of change will be greater. A decrease in total body albumin, secondary to reduction in synthesis and increased catabolism or continuing renal or gut losses, has the potential to cause the greatest fall in concentrations, but takes weeks to months to do so[13].

Whilst albumin is the prime determinant of COP in the normal situation, this is often not so in the critically ill where the correlation between COP and serum albumin is poor. The relationship between COP and total protein is stronger. In these patients the reduction in COP mediated by the decrease in intravascular albumin concentration is compensated by the increase in the concentration of the acute phase proteins[13].

Decreased plasma albumin:

1. Decreased synthesis.

2. Increased catabolism [very slow]

3. Increased loss:

o Nephrotic syndrome

o Exudative loss in burns

o Haemorrhage

o Gut loss

4. Redistribution:

o Haemodilution

o Increased capillary permeability (Increased interstitial albumin)

o Decreased lymph clearance[62].

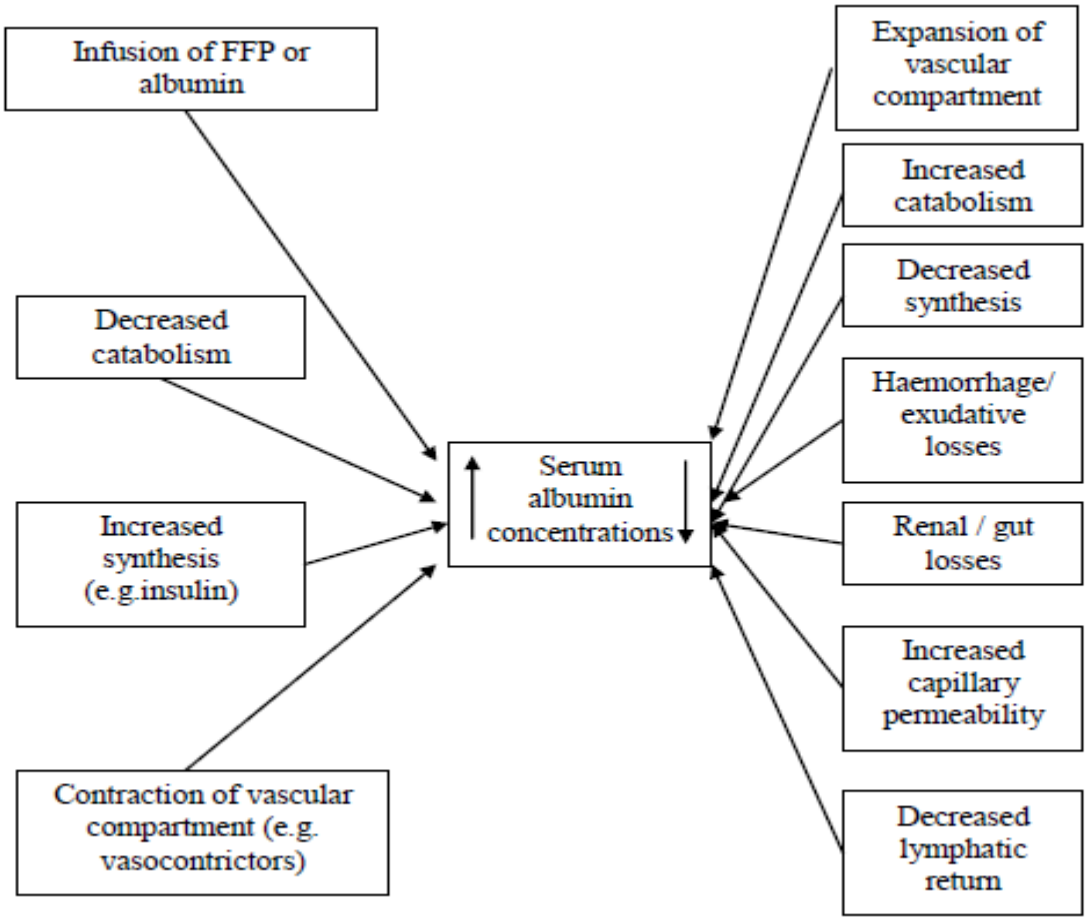


Fig No V: Factors affecting serum albumin in the critically ill.

Consequences of decreased plasma albumin

1. Decreased ligand binding

2. Decreased plasma colloid pressure: decreased colloid oncotic pressure, and edema formation.

Overall, the picture in the stress response is;

1. Initial decrease in albumin associated with increase in acute phase proteins.

2. Subsequent global increase in hepatic protein synthesis; including albumin[62].

Analysis of factors affecting serum albumin in patients during the five days following uncomplicated major aortic surgery indicated that some 18% of the decrease was due to hemorrhage, 6% due to increased catabolism and 77% due to re-distribution[13,133]. The mean reduction in albumin in this group was maximal at 24 hours when concentrations had decreased by 12 g/l. By day five the concentrations had returned to within 7 g/l of the preoperative value.

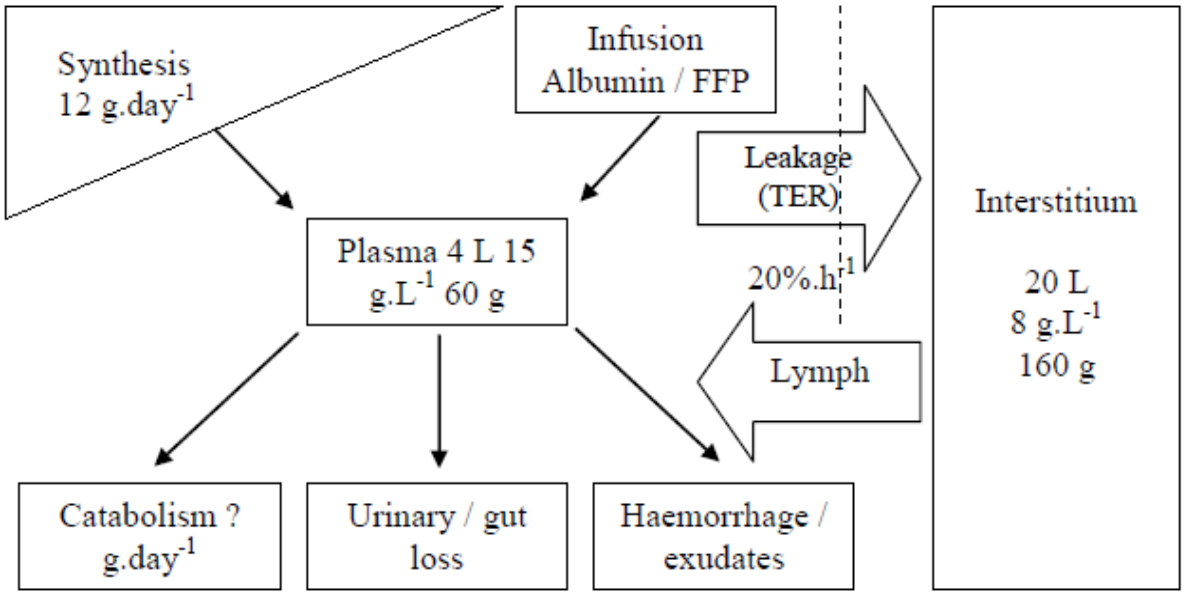


Fig No VI: Albumin pharmacokinetics in the critically ill. Typical values several days after initial insult and factors affecting values.

SERUM ALBUMIN AS PROGNOSTIC MARKER

It is important to identify patients at the time of admission who are likely to have poor outcome, so that such patients can be managed aggressively[2].

Serum albumin is routinely measured and reported in almost every hospital. The measurement is interpreted and acted upon in a wide range of circumstances[13]. It is a relatively low-cost test that should be used more frequently as a prognostic tool to detect malnutrition and risk of adverse surgical outcomes, particularly in populations in whom comorbid conditions are relatively frequent[134].

One study reported 10 strongest predictors of 30-day mortality and morbidity, from the set of 62 preoperative variables. For both outcomes albumin level was the best predictor, with American Society of Anesthesiology and hematocrit ranking second and third, respectively. Albumin level alone correctly discriminated between survivors and non-survivors 78% of the time[134].

Prolonged stay in hospital is costly[135]. It is desirable to identify responsible factors. If these factors can be identified management directed at modifying them may speed the process of rehabilitation[136].

Serum albumin appears to be a reliable prognostic indicator in various contexts. Reviews suggests that serum albumin could be an independent predictor of mortality in a wide range of clinical and research settings[1,4].

The reported frequency of hypoalbuminemia, defined as a serum albumin concentration of less than 34 g/L, was 21% at the time of admission in adult hospitalized patients[5,137]. After admission, worsening of existing hypoalbuminemia and development of de novo hypoalbuminemia are both frequently encountered[3,5].

It reports an estimated increase in the death from 24 to 56% for each 2.5 g/L reduction in serum albumin concentration over the range of studies reviewed[1].

The mortality rate increases from less than 1% for albumin levels of 46 g/L or higher to 28% for albumin levels below 21 g/L. The increase in mortality seems to be exponential as albumin level decreases from a level of approximately 40 g/L. Morbidity increase from approximately 10% to 65% as albumin values decline from 46 g/L to less than 21 g/L[134].

The odds ratio for albumin level in the all operations models indicate that a decrease of 10 g/L in albumin value was associated with more than a 2-fold increase in the odds of dying and almost a 2-fold increase in the odds of a complication[134].

Another study reported the odds of death were increased by 137% with each 10g/L decline in serum albumin, and the effect was statistically significant. Similarly, based on pooling within clinical indications, statistically significant increases in mortality odds of 102%, 116%, 180%, and 148% were observed for the hospitalization, cardiac surgery, noncardiac surgery, and renal dysfunction categories, respectively[5].

Large community based studies have shown a link between low serum albumin and an increase in morbidity and mortality. Albumin concentrations may be a marker for subclinical disease in elderly patients[1,138,139].

Albumin has also proven to be a sensitive and independent indicator for hospital outcome in the elderly[140,141,142] and one study supports the finding that admission serum albumin level is highly correlated with disposition. This study demonstrates that a serum albumin level ≥ 3.5g/dL is correlated with a shorter hospitalization and improved disposition. Age did not predict length of hospitalization, outcome or nutritional status. This suggests that the physiologic state, not age is the more important variable[142].

For the 133 subjects aged 70 and younger, albumin did not vary significant with age. The variance explained by age was a trivial 3%, and age seems to have little or no association with albumin up to the age of 70. However, for the 108 subjects over age 70, albumin decreased significantly with age, $P < 0.0001$. For this group, age explained 36% of the variance[143].

In noninstitutionalized, presumably healthy individuals old age is associated with a very small but statistically significant fall in serum albumin, about 4% per decade. This fall in albumin is not very noticeable until the age 70. Besides age, the small observed decline in serum albumin may be due to other causes. There may be a correlation between nutrition and albumin; medications may affect serum albumin[143].

The small observed age-related albumin decline could also be accounted for by the increased prevalence of undetected chronic disease in older subjects. The conclusion of this study was that while age

may have a statistically significant association with albumin, clinically the association is very small[143].

Albumin, as a continuous variable was significantly associated with mortality in one institutional population group, independent of age and sex. For every increase of 10.0 g/L of albumin the risk of mortality decreased. The covariates blood urea nitrogen, transferrin, history of stroke and age were confounders of the association between albumin and mortality[144].

Albumin remained a strong predictor of mortality after controlling for these variables. This association remained strong even after the deaths that occurred within the first 5 years of the study were eliminated. Ceruloplasmin, an acute phase response protein, was not correlated with albumin and was not associated with lower mortality[144].

In this study the albumin values among noninstitutionalized subjects decreased by 0.9 g/L per age decade. The results of this survey indicate that even after age matched controls, decreased albumin remained a predictor of mortality. The range in albumin was between 30.0 and 46.7 g/L, the upper limit being lower among younger populations in other studies, which show ranges of 30.0 to greater than 50 g/L[144].

In another study, it was reported that a decrease of 10 g/L in albumin level was associated with a higher risk of dying than a 10-year increment in age. Thus, a patient with an albumin level of 30 g/L at

admission is 1.22 times (1/odds ratio) more likely to be readmitted than a patient with in albumin level of 40 g/L. An 80-year-old patient is 1.04 times is likely to be readmitted than a 70-year-old. Serum albumin level was inversely related to length of stay. The older the patient, longer the stay. Albumin level was a significant predictor of this outcome for the whole group of patients and for half of the 10 predefined conditions namely cancer, chronic obstructive pulmonary disease, diabetes, congestive heart failure and cholecystectomy[137].

Patients with hypoalbuminemia on admission stayed in the hospital longer, had an increased risk of dying during hospitalization, and were more likely to be readmitted than patients with normal albumin levels[137].

The serum albumin level on admission helps to identify patients with a poor prognosis but whether an intervention designed to increase serum albumin levels directly in patients with a synthetic defect secondary to nutritional deficiency or treatable illness could change outcomes and reduce hospital costs is unclear[137].

In studies of hospitalized patients, hypoalbuminemia is associated with increased length of stay, higher complication rates and higher mortality[1,145,146]. In one study, a serum albumin concentration of less than 34 g/L was associated with a 30-day mortality rate of 24.6%. This increased to 62% if the serum albumin concentration was 20 g/L or less[147]. The authors

found SA levels to offer no predictive value in estimating basal hepatic synthetic activity[129].

The association between hypoalbuminemia and mortality was also shown to be independent of other nutritional indices such as body weight, dry weight, body fat percentage, weight loss, cachexia, midarm circumference, biceps and triceps skinfold thicknesses. Hypoalbuminemia remained a significant mortality predictor with the effects of CRP taken into account[5].

The prognostic value of serum albumin extends to critically ill patients[1,148,149]. The greatly increased capillary permeability and frequent massive fluid shifts results in patients on the intensive care unit developing the most severe degrees of hypoalbuminemia seen in hospital practice. This is the patient population in whom the most marked sequelae of low serum albumin may be expected to be seen[13].

A low serum albumin concentration correlates with increased length of stay in the intensive care unit and with complication rates, such as ventilator dependency and the development of new infection[1,102]. It indicates a significant 28% increase in odds for prolonged ICU stay per 10 g/L decrement in serum albumin. It also indicates a significant hypoalbuminemia related increase of 71% in odds of prolonged hospital stay. Hypoalbuminemia significantly increased resource utilization by 66% per 10g/L serum albumin decline[5].

The daily trend of serum albumin can be a useful tool in predicting the weaning capability of patients needing mechanical ventilation[1,150].

Although pulmonary function tests are important in determining mechanical ventilation dependency, other components of the clinical situation need to be considered when attempting to wean a patient from mechanical ventilation[150,151]. Thus, metabolic and nutritional status, as well as the severity of illness, should be taken into account[150,152,153,154]. Serum albumin concentration is one of the parameters used to follow the metabolic and nutritional status of patients[150,155].

Although the circulating albumin concentration was significantly lower, and the APACHE II score was significantly higher in ICU non-survivors than in ICU survivors, albumin concentration on ICU admission was not a predictor of the length of time spent receiving mechanical ventilation[150].

The serum albumin concentration on the day of ICU admission did not predict the duration of mechanical ventilation. However, the serum albumin profile during mechanical ventilation was a determinant of weaning success. This effect of albumin was independent of the severity of illness (APACHE II), fluid balance, or the cause of respiratory failure[150].

Weaning from prolonged mechanical ventilation associated with increase in serum albumin concentration and decrease in body weight, and the odds of being weaned are 5 times greater if the change

in albumin is > 0.2 and there is weight loss of at least 4 lbs; the odds of weaning are 12 times greater if an albumin level > 3.2 g/dL is reached[156].

Measurements of serum albumin are of little prognostic value in the critically ill patient when considered in isolation. In one intensive care study the mean albumin on admission was 25 g/L, but the difference between the albumin levels of survivors and non-survivors was only 3g/L.[3,13]

Following up of serum albumin levels in the critically ill may be more helpful. After a major insult SA inevitably decreases and then tends to increase slowly as the patient recovers. In those who fail to recover, it remains low. This trend of lower values of SA in non-survivors as compared with survivors is well recognized[13].

Serum Albumin estimated with in first 24 hrs of admission was also found to be a strong predictor of mortality. SA has also been reported to be of good prognostic value in the past. Albumin has a long half-life of approximately 20 days and because of this fact it is unlikely to change with development of acute respiratory failure in patients with COPD. On the other hand, SA is known to reflect the underlying nutritional status and to be affected by the severity of chronic illness. These factors are of obvious significance in deciding the outcome of these patients[2].

Non-survivors of critical illness have lower serum albumin concentrations than survivors[149,157]. A study was able to demonstrate that its predictive role is not as much dependent on its individual value as it is on the

profile of changes in concentration. It was observed in the study that albumin concentration was lower in ICU non-survivors than in ICU survivors[150].

In one study, non-survivors had lower serum albumin concentrations on admission to the ICU, and their albumin concentrations decreased more rapidly in the first 24 to 48 h[1,3].

Not only was the initial albumin concentration different between ICU survivors and non-survivors but the profile of their albumin concentration was different while in the ICU. Although there was an initial decrease in albumin concentration in both groups in the first few ICU days, a continuous decrease was noted in the last 5 days in the non-survivor group. This difference in the profile of serum albumin concentration was also observed in patients being weaned from mechanical ventilation. When patients were successfully weaned, their median albumin concentration was higher than in those patients who continued to be supported by mechanical ventilation[150].

However, one other study reports that the albumin concentration on admission was not a sensitive indicator of outcome, but the value at 24 to 48 h was as accurate as the APACHE II score in predicting mortality[1].

The survivors had lower APACHE II score and higher admission albumin than non-survivors. Between survivors and non-survivors, there was a statistically significant difference in the serum albumin concentrations on admission and in the initial 72 hours after readmission. In both groups the serum albumin levels fell after ICU admission. This decrease in serum

albumin levels was most marked in the initial 24 hours and was similar in both survivors and non-survivors, (2.6 g/L for survivors and 2.5 g/L for non-survivors, p = 0.9)[158].

The results showed that serum albumin levels decreased after ICU admission in both survivors and non-survivors. This was most marked in the first twenty-four hours, and this initial fall in serum albumin levels was similar in the two groups. Theoretically, more severely ill patients will have more capillary leakage and therefore require more fluid resuscitation and develop more profound hypoalbuminemia[158].

Although there was significant difference in the mean serum albumin concentrations between survivors and non-survivors, both at and after ICU admission, the mean difference was small and there was a wide overlap of value between the two group. This study showed that in critically ill patients serum albumin concentrations markedly decrease after ICU admission, both for survivors and non-survivors and for both medical and surgical patients. There is an association between serum albumin concentration and hospital mortality[158].

A multivariate analysis showed that the hospital mortality rate was greater for female patients compared with male patients despite similar severity of illness and numbers of organ system derangements at the start of mechanical ventilation[161,162]. Another study, in 1231 patients with ARF and ARDS, also demonstrated that sex was not independently associated with

mortality[161,163]. The study also found a hospital mortality of 28% in patients with COPD receiving mechanical ventilation due to an acute exacerbation of their disease[161].The major risk factors for hospital mortality are the development and severity of non-respiratory organ system dysfunction and acute illness, while severity of the underlying respiratory function substantially influences mortality following hospital discharge[161,164,165].

Investigators have shown that non-pulmonary organ failure markedly decreases survival in ARDS[167-170].The reason for the initiation of mechanical ventilation influences the outcome of ventilated patients. After adjusting for other variables, the only factors independently associated with decreased survival were coma, ARDS, and sepsis[161].

Authors reported that both acute lung injury and sepsis leading to the initiation of mechanical ventilation were independently associated with an increased hospital mortality rate[161,171]. Another study found that the presence of ARDS was independently associated with hospital mortality[161,162]. While development of non-pulmonary organ failures increased the risk of mortality in this study, development of pulmonary failure that resulted in a ratio of PaO2/FIO2 less than 100 carried an even higher risk[161].

One study has also shown significant difference between serum albumin concentrations of non-survivors and survivors of prolonged critical illness. Patients who were in the ICU for 7 days or more and survived had higher mean serum albumin concentrations than non-survivors, and could

recover to a higher mean serum albumin concentration than non-survivors[1,3]. Using a survival model, the study was able to demonstrate that an increase of 5 g/L (0.5 g/dL) in serum albumin concentration multiplied the relative success probability by 1.27.150 Significantly, there was no difference between the COPs of the two groups[1].

A substantial proportion of spinal cord injured patients are reported to be malnourished. Low serum albumin viewed as a nutritional indicator correlates well with delayed completion of stabilization and reduced mobility outcome. The study infers that the increased length of stay in hospital was caused either by unrecognized sepsis or by the debilitating effects of the anemia and or hypoalbuminemia[136].

Regulation of albumin synthesis has been shown to be sensitive to the patient's nutritional status[173,174]. However, the use of serum albumin concentration has not proved to be a sensitive index of the efficacy of a nutritional support regimen, because changes in size of fluid compartments, the extracellular space, can mask changes in rates of protein synthesis and degradation[173,175]. During nutritional depletion, ECF often increases in relation to total body water[173,176]. This relative expansion of the ECF, combined with a decrease in albumin synthesis, leads to significant decreases in serum albumin levels[173,177].

However, it is now accepted that serum albumin is not a reliable marker of nutritional status in critically ill patients[1,138].

Reduced protein synthesis is associated with advanced liver disease or malnutrition [129,173,178]whereas altered compartmentation or increased catabolism of plasma proteins has been suggested to account for hypoproteinemia following burn and traumatic injury as well as infection[129].

Burnt patients are a specific group for whom albumin may have a beneficial role. In the first 24 h there is a marked increase in capillary permeability and trans capillary fluid shifts. It is argued that colloid infusion is unjustified in this situation, as it is inefficient in reducing fluid shift and may contribute to delayed pulmonary edema[1,179].

Like any therapy, albumin has its side-effects. Injudicious use can lead to fluid overload, as plasma volume increases linearly with the dose of albumin. It may cause myocardial depression, perhaps related to the binding of calcium ions[1,180].

Albumin has well-established and important functions in health. Its kinetic and dynamic properties are significantly altered in the critically ill. There is no significant correlation between serum albumin concentration and COP in these patients. Drug binding by albumin is important in critically ill patients, but the increased free fraction of drugs in patients with hypoalbuminemia does not necessitate treating the decreased serum albumin concentration[1].

Low albumin concentrations could, however, be due to other factors, such as hepatocellular dysfunction or stressful stimuli such as sepsis or

surgery. In acute disease, injury, surgery, or sepsis, the metabolic response adapts to produce large amounts of acute-phase proteins. Since albumin is not an acute-phase protein, its synthesis may diminish. This response is thought to be mediated by the release of cytokines such as tumor necrosis factors and interleukin-1.[5,150,155] The decreased synthesis of albumin is probably related to a reduction in the number of cells that synthesize it[181].Diminished albumin synthesis in these acute states is compounded by increased vascular permeability, which would induce a greater shift of albumin from the vascular to the interstitial space[5,155].Finally, in prolonged stress, albumin degradation could be partially responsible for its decreased concentration. This process is possible since in prolonged stress, albumin may contribute to the amino acid pool. Albumin, therefore, may be a good predictor of weaning because it is a reliable indicator of the physiologic response to stress. The inability to increase the serum albumin concentration probably means that the acute inflammatory response is not adequately controlled, making weaning more difficult[150].

A study found hypoalbuminemia to be a powerful, reproducible, dose-dependent, independent risk factor for poor outcome in the acutely ill. This association was striking both for its consistency and pervasiveness. Unfavorable sequelae associated with lower serum albumin were evident in hospitalized patients generally and in populations undergoing cardiac and noncardiac surgery or suffering from renal dysfunction. The

hypoalbuminemia effect manifested itself across the full spectrum of clinical outcomes: mortality, morbidity, length of both ICU and hospital stay, and increased resource utilization[5].

The data of this study indicates that two important potential confounding variables malnutrition and inflammation cannot fully explain the hypoalbuminemia effect. The authors found that the significant association between hypoalbuminemia and poor outcome persisted after adjustment for body mass index and other measures of nutritional status[5]. The authors found the effects of hypoalbuminemia on outcome to be independent of CRP, as well as other markers of inflammation. Such observations india that inflammation, at least as manifested by altered levels of currently identified inflammatory markers, may contribute to reduced serum albumin levels but nevertheless cannot fully account for the association between hypoalbuminemia and poor outcome[5].

MATERIALS & METHODS

METHODOLOGY

The present study was carried out at R.L. JALAPPA. Hospital and Medical Research Centre, Kolar over a period of nineteen months during APRIL 2016 to October 2017 among the patients admitted in MICU who needed ventilatory support for at least 5 days or more.

Study Design

Nineteen months Cross Sectional Study.

Source of data

Patients who were admitted in MICU at R.L. JALAPPA. Hospital and Medical Research Centre, Kolar and requiring mechanical ventilatory support for 5 days or more over a period of Nineteen months from April 2016 to October 2017 were included in the study.

Sample size

A total of 64 patients were included in the study.

Selection Criteria

INCLUSION CRITERIA:

Critically ill patients suffering from medical illnesses requiring admission and ventilatory care for 5 days or more.

EXCLUSION CRITERIA:

1. Chronic liver disease
2. Acute and chronic kidney disease with proteinuria
3. Malnutrition
4. Protein losing enteropathy

Method of collection of data

The selected patient's informed consent was taken from the relative of the patient explaining the nature of the study. Prospectively collected data of patients, who were admitted to MICU of R.L. JALAPPA. Hospital and Medical Research Centre, Kolar and were put on invasive mechanical ventilation. The study included patients with all etiologies who were intubated and were put on mechanical ventilation. The decision for mechanical ventilation was taken by the treating physician. Study period extended for Nineteen Months.

Clinical and demographic profile at the time of admission to MICU including age, sex, smoking status, history of previous hospital admissions, associated chronic illnesses like hypertension, diabetes mellitus, chronic obstructive pulmonary disease were recorded. A careful and detailed history

was recorded, and thorough clinical examination was conducted. All the points mentioned in the proforma were recorded. Additional information if any was recorded. Total blood counts, renal functions, liver functions and serum albumin (SA) done at the time of admission were also recorded. Chest X-ray and arterial blood gas analysis were obtained. Days on ventilator, days of ICU stay, and days of hospital stay were recorded for all the patients.

Duration of mechanical ventilation was defined as the time elapsed from

the initiation of ventilatory support to the onset of weaning. The onset of weaning was the time that the physician in charge considered the patient likely to resume and sustain spontaneous breathing. Weaning was performed by either a reduction in the level of ventilator support or a trial of spontaneous breathing. Mechanical ventilation was delivered through an orotracheal tube.

The patients were followed up till their discharge from the hospital. They qualified for the study if they were on mechanical ventilator for 5 days or more. They were excluded from the study if they were weaned from mechanical ventilation before 5 days or died within 5 days of being put on mechanical ventilator.

For patients who were included in the study, serum albumin estimation was done on the day when they were put on mechanical ventilator and subsequently on day three, day five and day 10 of their hospital stay.

Serum albumin was assayed using an automated Bromo cresol purple (BCP) specific dye binding method. This method is more sensitive measure of low albumin concentrations than the older Bromo cresol green (BCG) method. The BCG method tended to overestimate serum albumin concentrations due to a reaction with other serum proteins, including positive acute phase proteins which are increased in critical illness. Calibrations were performed according to manufacturer's guidelines.

The outcome of the patient was recorded either as discharge of the patient from the hospital (survivor group) or patient's death in hospital (non-survivor group).

STATISTICAL ANALYSIS

Data will be entered into Microsoft excel data sheet and will be analyzed using SPSS 22 version software. Categorical data will be represented in the form of Frequencies and proportions. Chi-square will be used as test of significance. Continuous data will be represented as mean and standard deviation. Independent t test will be used as test of significance to identify the mean difference between two groups. p value <0.05 will be considered as statistically significant

RESULTS

RESULTS

Table 1: - Distribution of subjects according to age group and outcome

AGE group	OUTCOME		Total
	DIS	DTH	
<30yrs	10	9	19
	24.4%	39.1%	29.7%
31-40yrs	8	2	10
	19.5%	8.7%	15.6%
41-50yrs	8	1	9
	19.5%	4.3%	14.1%
51-60yrs	7	2	9
	17.1%	8.7%	14.1%
61-70yrs	5	6	11
	12.2%	26.1%	17.2%
>70yrs	3	3	6
	7.3%	13.0%	9.4%
Total	41	23	64
	100.0%	100.0%	100.0%

P value 0.186, there was no statistically significant difference found between age group and outcome

Figure 1:- Graph showing Distribution of subjects according to age group and outcome

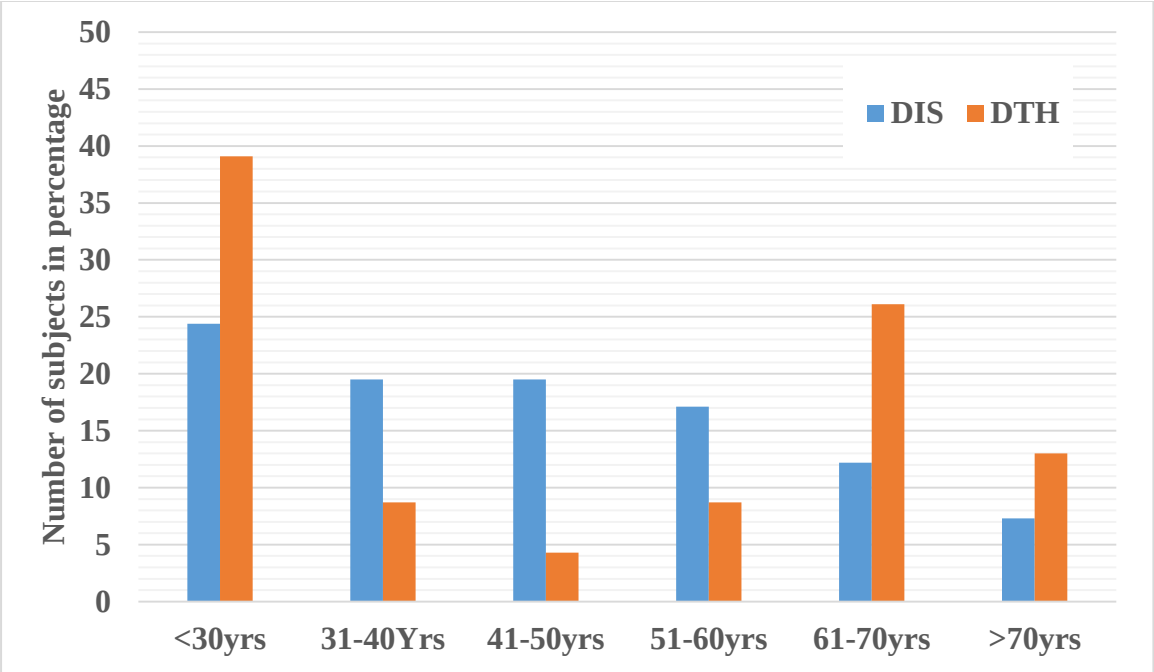


Table 2:- Distribution of subjects according to sex and outcome

SEX	OUTCOME		Total	P Value
	DIS	DTH		
Female	8	8	16	0.232
	19.5%	34.8%	25.0%	
Male	33	15	48	
	80.5%	65.2%	75.0%	
Total	41	23	64	
	100.0%	100.0%	100.0%	

There was no statistically significant difference found between sex and outcome

Figure 2:- Graph showing Distribution of subjects according to sex and outcome

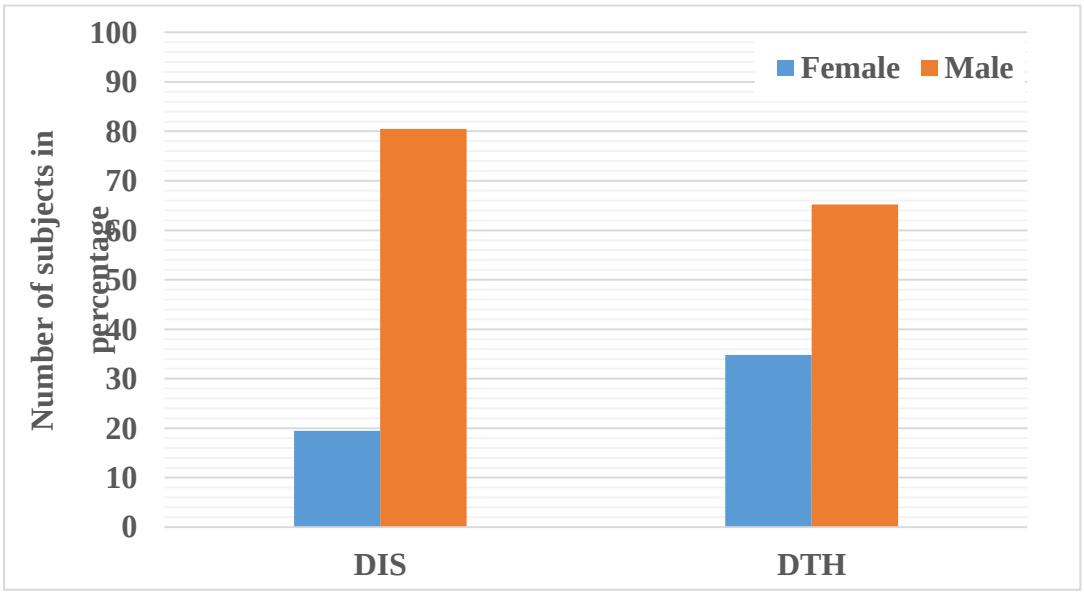


Table 3:- Serum albumin level on day one between outcome

Serum albumin (gm/dl)	OUTCOME		Total	P Value
	DIS	DTH		
<3.5	24	18	42	0.170
	58.5%	78.3%	65.6%	
≥3.5	17	5	22	
	41.5%	21.7%	34.4%	
Total	41	23	64	
	100.0%	100.0%	100.0%	

There was no statistically significant difference found between serum albumin level on day 1 and outcome

Figure 3: - Graph showing Serum albumin level on day one between outcomes

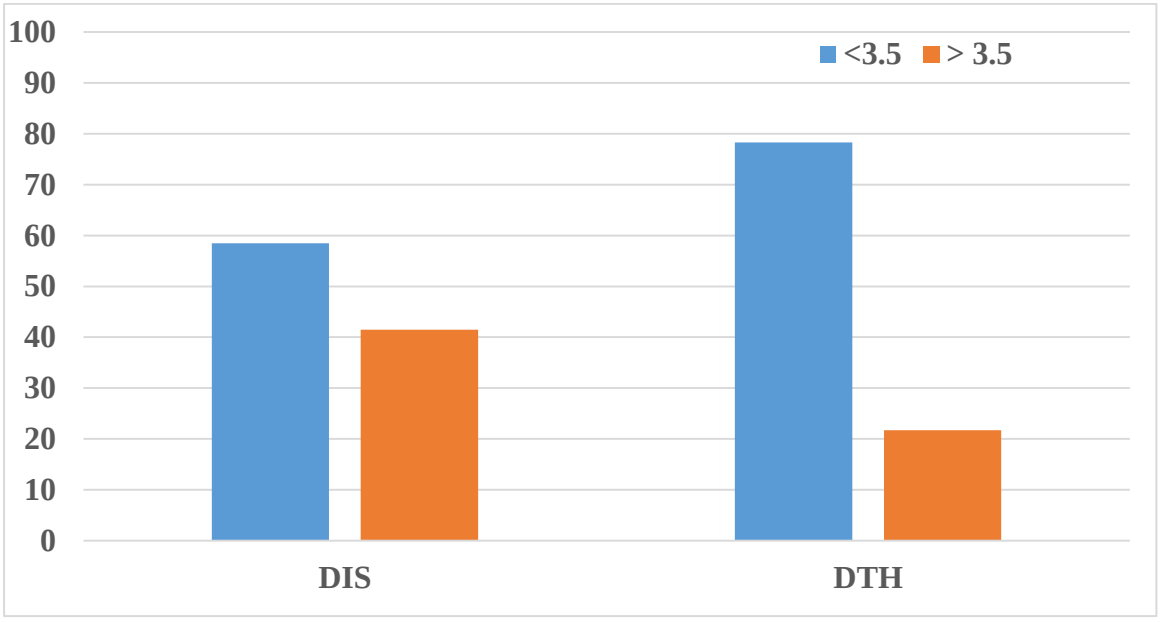


Table 4:- Serum albumin level on day 3 between two outcome

Serum albumin (gm/dl)	OUTCOME		Total	P Value
	DIS	DTH		
<3.5	31	23	54	0.001
	75.6%	100.0%	84.4%	
≥3.5	10	0	10	
	24.4%	.0%	15.6%	
Total	41	23	64	
	100.0%	100.0%	100.0%	

There was a statistically significant difference found between serum albumin level on day 3 and outcome

Figure 4:- Graph showing Serum albumin level on day 3 between outcomes

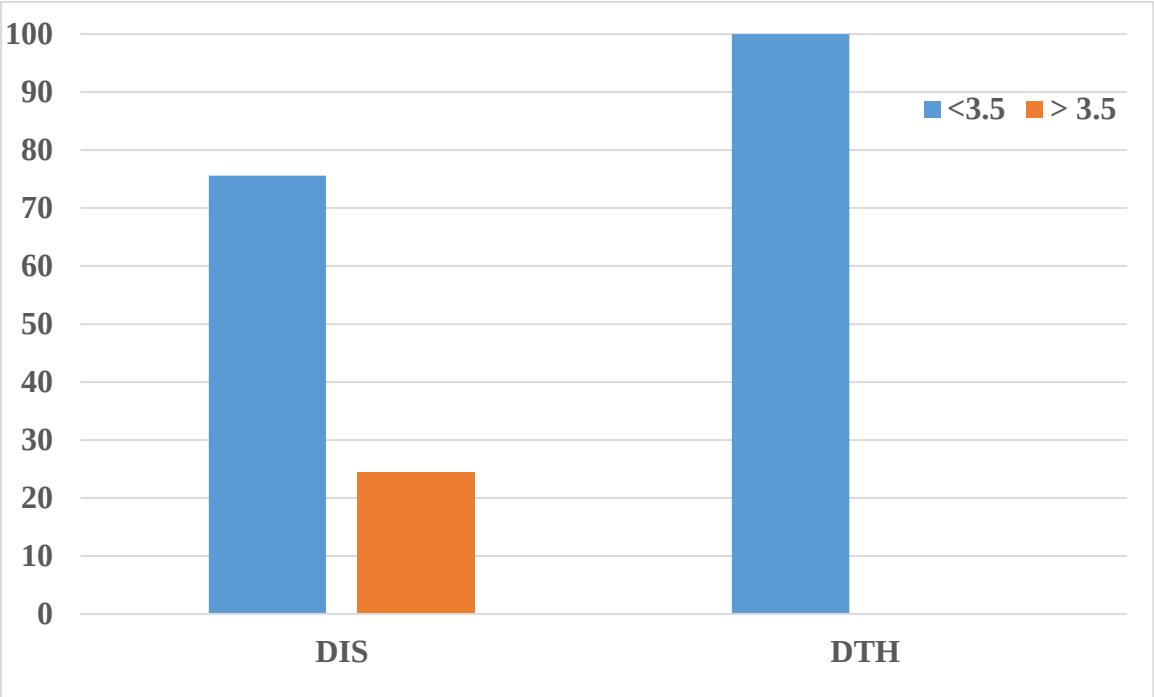


Table 5: - Serum albumin level on day 5 between two outcome

Serum albumin (gm/dl)	OUTCOME		Total	P Value
	DIS	DTH		
<3.5	35	23	58	0.08
	85.4%	100.0%	90.6%	
≥3.5	6	0	6	
	14.6%	.0%	9.4%	
Total	41	23	64	
	100.0%	100.0%	100.0%	

There was no statistically significant difference found between serum albumin level on day 5 and outcome

Figure 5: - Graph showing Serum albumin level on day 5 between outcomes

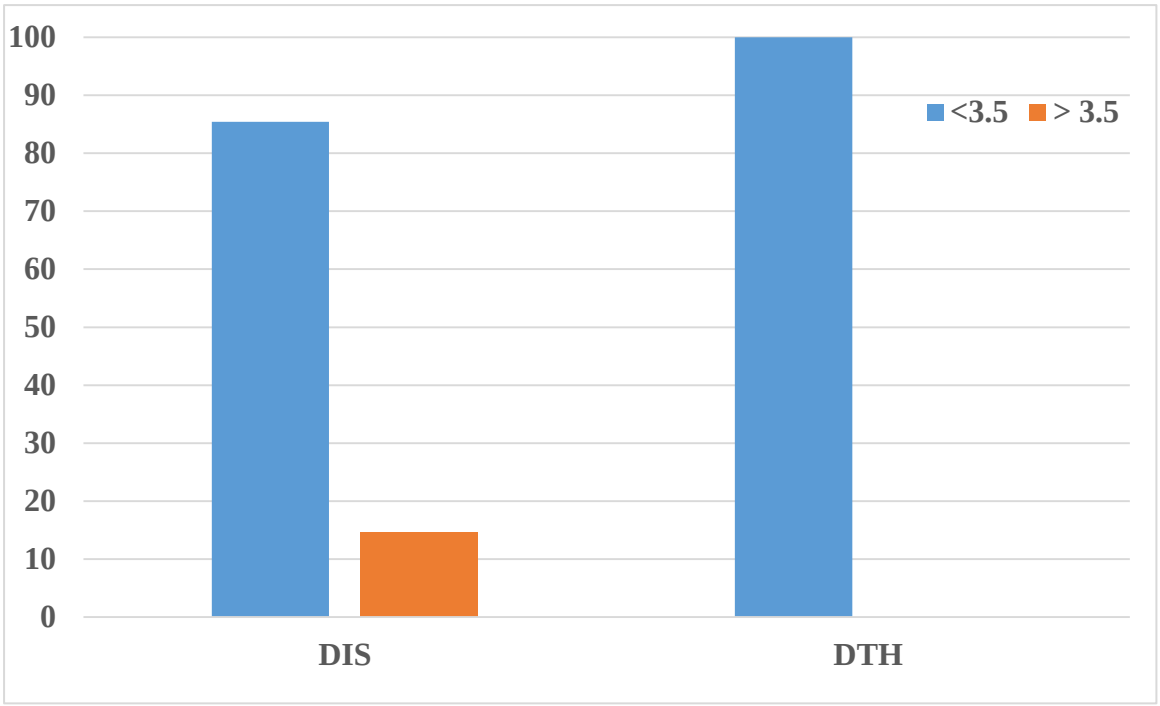


Table 6: - Serum albumin level on day 10 between two out come

Serum albumin (gm/dl)	OUTCOME		Total	P Value
	DIS	DTH		
<3.5	39	23	62	0.532
	95.1%	100.0%	96.9%	
≥3.5	2	0	2	
	4.9%	.0%	3.1%	
Total	41	23	64	
	100.0%	100.0%	100.0%	

There was no statistically significant difference found between serum albumin level on day 10 and outcome

Figure 6: - Graph showing Serum albumin level on day 10 between outcomes

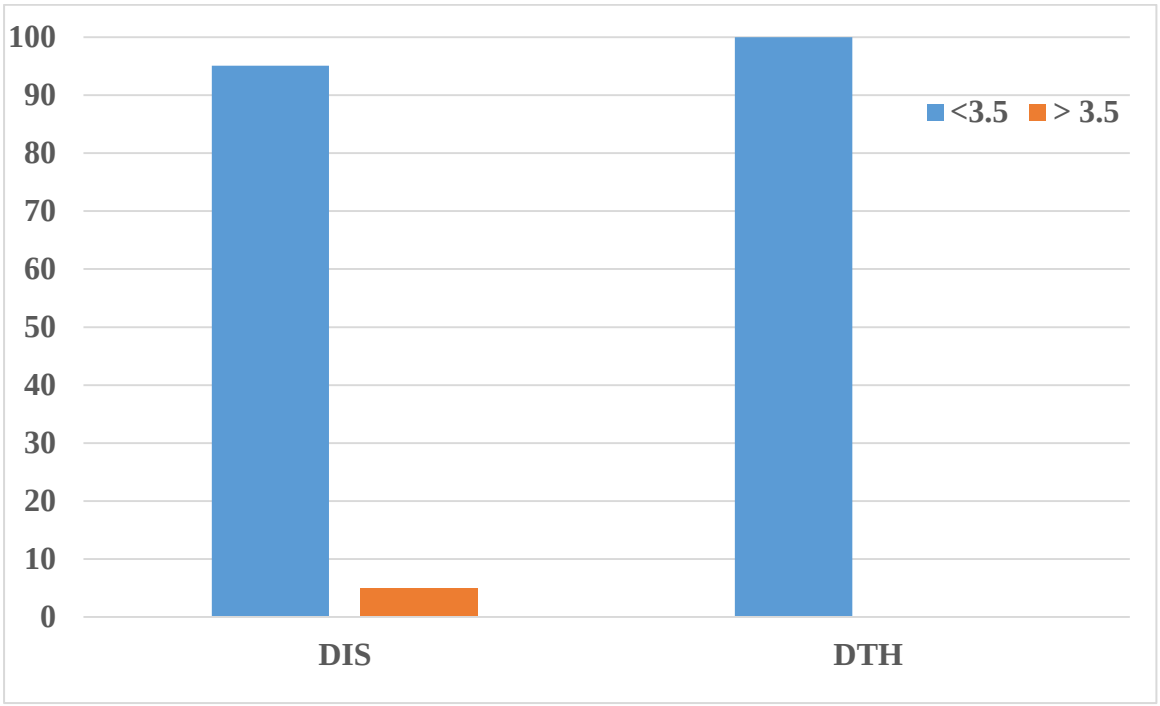


Table 7:- Comparison of mean serum albumin level on different days between two outcome

	OUTCOME	Mean	Std. Deviation	P value
DAY 1	DIS	3.409756	0.412	.053
	DTH	3.213043	0.362	
DAY 3	DIS	3.041463	0.496	.001
	DTH	2.730435	0.205	
DAY 5	DIS	2.802439	0.543	.004
	DTH	2.473913	0.333	
DAY 10	DIS	2.504878	0.531	.197
	DTH	2.330435	0.499	

There was statistically significant difference found between mean serum albumin and two outcome on day 3 and day 5. There was no statistically significant difference found between mean serum albumin and two out come on day 1 and day 10.

Figure 7: - Graph showing Comparison of mean serum albumin level on different days between two outcomes

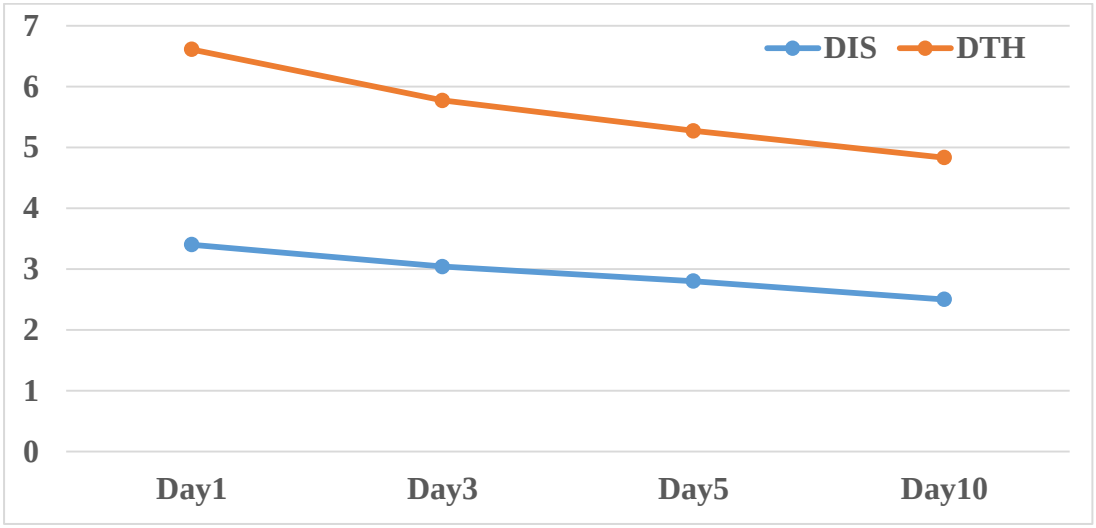


Table 8:- Distribution of subjects according to Number of days on Ventilation and two outcome

Number of days	OUTCOME		Total	P value
	DIS	DTH		
5-7day	17	8	25	0.282
	41.5%	34.8%	39.1%	
8-10days	15	5	20	
	36.6%	21.7%	31.3%	
11-13days	8	8	16	
	19.5%	34.8%	25.0%	
>13days	1	2	3	
	2.4%	8.7%	4.7%	
Total	41	23	64	
	100.0%	100.0%	100.0%	

Mean number of days of hospital stay was 8.34 $\pm$ 2.5days in DIS outcome subjects and 9.48 $\pm$ 2.9days in DTH outcome. There was no statistically significant difference found between Number of days on Ventilation and two out come

Figure 8: - Graph showing Distribution of subjects according to Number of days on Ventilation and two outcome

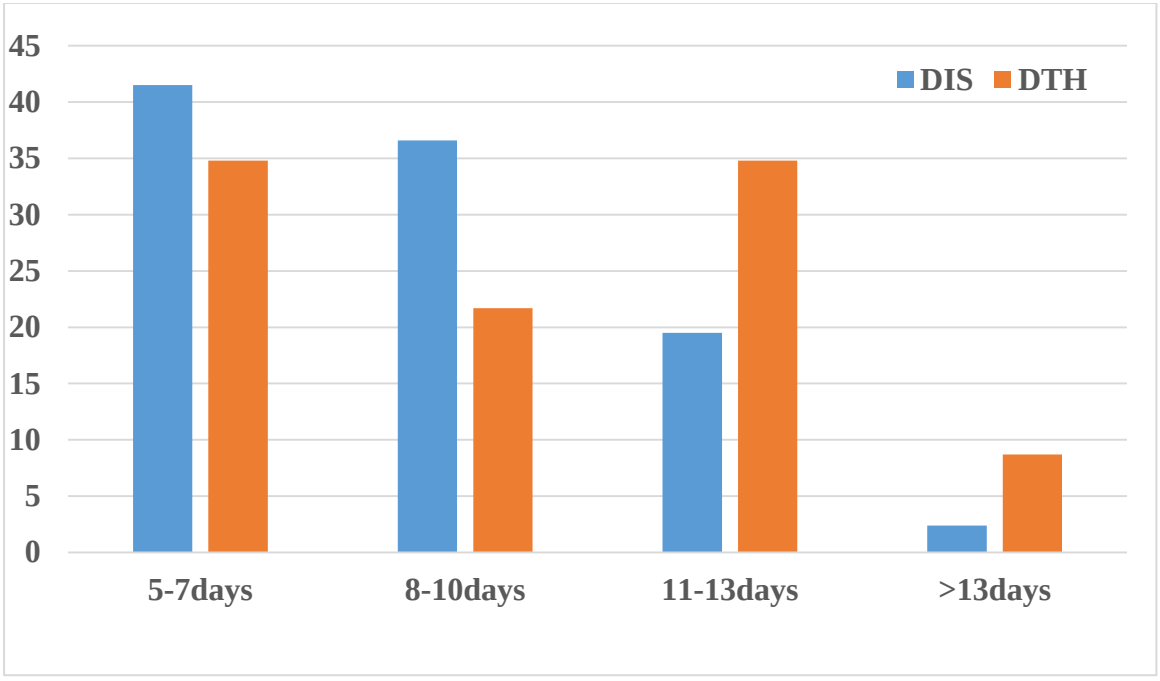


Table 9:- Distribution of subjects according to Number of days of ICU stay and two outcome

Number of days	OUTCOME		Total	P value
	DIS	DTH		
5-7day	2	0	2	0.001
	4.9%	.0%	3.1%	
8-10days	16	0	16	
	39.0%	.0%	25.0%	
11-13days	13	9	22	
	31.7%	39.1%	34.4%	
>13days	10	14	24	
	24.4%	60.9%	37.5%	
Total	41	23	64	
	100.0%	100.0%	100.0%	

Mean number of days of hospital stay was 11.83 ± 3.5days in DIS outcome subjects and 14.39 ± 2.8days in DTH outcome. There was no statistically significant difference found between Number of days of ICU stay and two out come

Figure 9:- Graph showing Distribution of subjects according to Number of ICU stay and two outcome

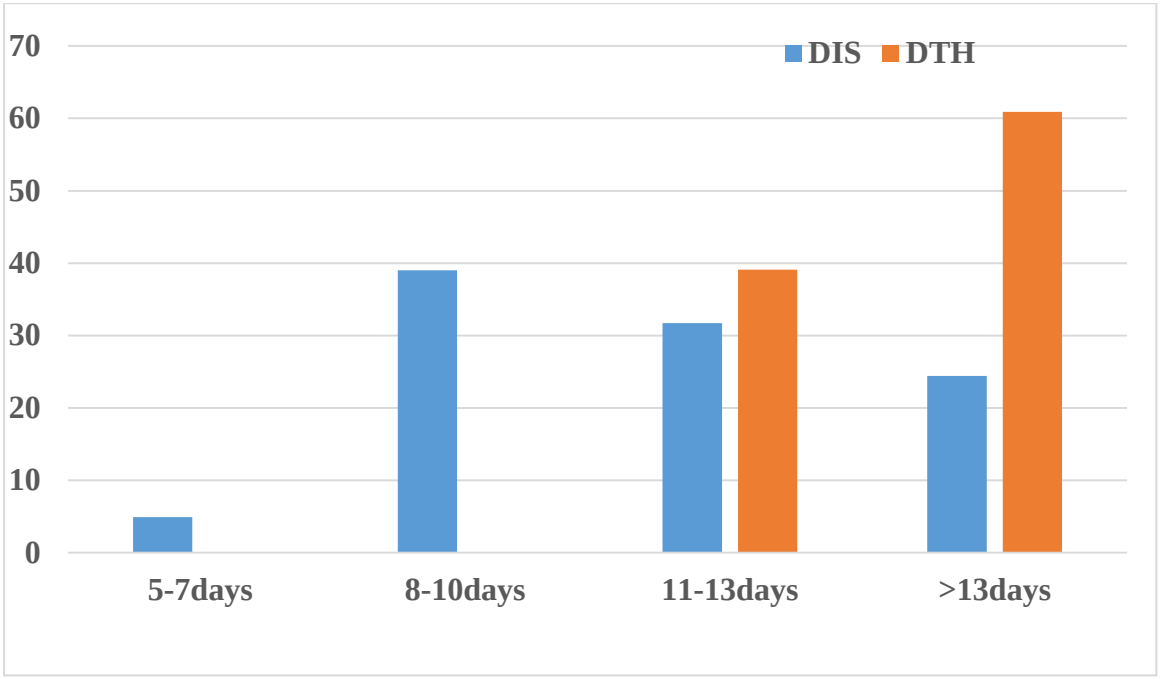
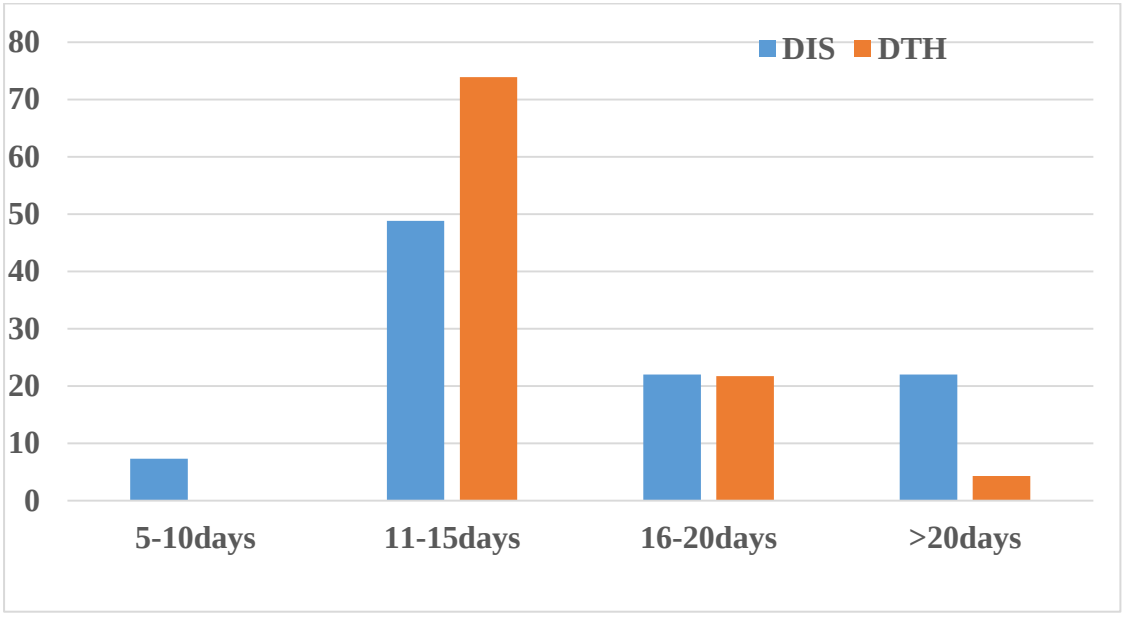


Table 10:- Distribution of subjects according to Number of days of hospital stay and two outcome

Number of days	OUTCOME		Total	P value
	DIS	DTH		
5-10days	3	0	3	0.102
	7.3%	.0%	4.7%	
11-15days	20	17	37	
	48.8%	73.9%	57.8%	
16-20days	9	5	14	
	22.0%	21.7%	21.9%	
>20days	9	1	10	
	22.0%	4.3%	15.6%	
Total	41	23	64	
	100.0%	100.0%	100.0%	

Mean number of days of hospital stay was 16.66 ± 4.4days in DIS outcome subjects and 14.83 ± 3.3days in DTH outcome. There was no statistically significant difference found between Number of days of hospital stay and two outcome

Figure 10: - Graph showing Distribution of subjects according to Number of days of hospital stay and two outcome



DISCUSSION

DISCUSSION

The present study was conducted on 64 patients who were critically ill and required mechanical ventilation for five days or more. Serial serum albumin concentrations were measured as a prognostic marker to predict their outcome as either death in the hospital or discharge from the hospital.

Our study also compared the duration of mechanical ventilation, the length of ICU stays, and length of hospital stay between survivors and non-survivors.

AGE

In our study, the mean age of the patients was 45.89 years (± 20.04 years). The mean age of survivors was 42.92 years and that of non-survivors was 51.9 years. There was no significant difference ($p = 0.011$) between the 2 groups.

One study reported the mean age of patients to be put on mechanical ventilator to be 59.2 years (± 17.3 years).[161]

Another study reports the age of non-survivors as 58 years (± 3.8 years) which is significantly more ($P < 0.05$) than survivors as 49 years. (± 4.1 years). [172]

SEX

Our study included 48 males (75%) and 16 females (25%). Amongst survivors (41), 33 (80.5%) were males and 8 (19.5%) were females. In non-survivors (23), 15 (65.2 %) were males and 8 (34.8 %) were females. The study shows that males are more likely to suffer from a critical illness than females.

In one study, this was found to be 59.3% males and 38.7% females.[161] Another study reported it to be 57% males and 43% females.[172]

DIVISION OF PATIENTS BASED ON OUTCOME AT THE END OF THE STUDY

Our study included 64 patients. Out of these, 41 patients (64.06%) were discharged from the hospital (survivors) and 23 patients (35.93%) expired in the hospital (non-survivors). One similar study has reported 70% survivors and 30% non-survivors.[3] One another study reported 54% survivors and 46% non-survivors.[172]

SERUM ALBUMIN LEVELS AS PROGNOSTIC MARKER

In our study, mean serum albumin level on day of admission (Day 1) for the study group was 3.3 g/dl (± 0.4 g/dl). In survivors, it was 3.4 g/dl (± 0.4

g/dl) and in non-survivors it was 3.1 g/dl (± 0.19 g/dl). It was significantly lower in non-survivors. In the survivor group, 43.9% patients have normal serum albumin levels on admission as compared to just 10.5% in the non-survivor group, suggesting hypoalbuminemia at admission indicates a poorer prognosis in terms of increased mortality. More non-survivors were hypoalbuminemic at admission than survivors suggesting that a low serum albumin at admission indicates a poor prognosis. One study reports survivors had higher admission albumin (2.57 g/dl vs 2.10 g/dl, $p<0.005$) than non survivors.[158] Another study reports similar findings with survivors having higher mean albumin concentration (18.3 ± 4.6 $g.L^{-1}$) compared to non survivors (15.7 ± 5.1 $g.L^{-1}$) ($p < 0.05$).[172] In one study, the mean serum albumin levels on day one were reported to be 3.2 g/dl (± 0.7 g/dl) which is comparable to our study.[182]

In our study, the mean level of serum albumin on day three in study group was 2.92g/dl (± 0.4g/dl). In survivors it was 3.03 g/dl (± 0.51 g/dl) and in non-survivors it was 2.73g/dl (± 0.22 g/dl). It was significantly lower ($p = 0.001$) in non- survivors. All non-survivors were hypoalbuminemic at day three indicating that they have a poorer prognosis as compared to survivors where 43.9% patients had hypoalbuminemia. One study reports day three levels as 2.9 g/dl (± 0.6 g/dl) [182] .

Similarly, there was no statistically significant difference found between serum albumin level on day 5, and outcome (p=0.08). The mean for the study group was 2.6g/dl (± 0.5 g/dl). All the non-survivors were still hypoalbuminemic as compared to survivors.

The mean level of serum albumin on Day 10 in study group was 2.4 g/dl (± 0.5 g/dl). In survivors it was 2.64 g/dl (± 0.51 g/dl) and in non-survivors it was 2.08 g/dl (± 0.37 g/dl). There was no statistically significant difference found between serum albumin level on day 10 and outcome (p=0.532)

Our study shows that between survivors and non-survivors, there was a statistically significant difference in the serum albumin concentrations on Day three, Day five. In both groups, the serum albumin level fell after admission. This decrease in serum albumin was most marked in between Day three and Day five for both survivors and non-survivors.

However, a study reports most marked falls in first 24 hours in both groups.[3] This could be possibly explained by the fact that in the study, both survivors and non-survivors had had very aggressive fluid resuscitation after ICU admission, therefore both groups had a marked drop in their albumin concentration in first 24 hours.

Our study also shows that in spite of having hypoalbuminemia at admission, 23 patients survived, suggesting that there are other factors

associated with the prognosis of the patients in terms of mortality, since patients with hypoalbuminemia at admission survived.

Our study also shows that the serum albumin levels decreased more rapidly in non-survivors. The total decline in serum albumin in the survivors from admission to day 10 is 0.86 g/dl. In non-survivors it is 1.09 g/dl over a period of 10 days. This is similar to one study which reports that serum albumin levels decreased more steeply in non-survivors.[3] This suggests that patients who have a rapid decline in the serum albumin level have a poor prognosis in terms of increased mortality.

Our study indicates that the strongest predictor of outcome of the patient is serum albumin on day three. Outcome of the patient is poorly correlated with serum albumin level on day one. One study reports day five albumin levels to be the strongest predictor of mortality.[182] This difference is noted because of the method of analysis of data and the use of different kind of statistical test to predict the outcome.

DURATION OF MECHANICAL VENTILATION

In our study group, the mean duration of mechanical ventilation was 8.7 days (± 2.86 days). In the survivors, this duration was 8.34 days (± 2.5days) as compared to non-survivors in which it was 9.48 day (± 2.9 days). There was no statistically significant difference found between number of days on ventilation and outcome. One study reports this duration for all

reason for the initiation of mechanical ventilation to be 5.9 days (± 7.2 days).[161]

Another study reports this duration to be 10.5 ± 1.0 days.[150] This study also reports that albumin concentration on ICU admission was not a predictor of the length of time spent receiving mechanical ventilation. However, the profile of changes in serum concentration have a predictive value.

DURATION OF ICU STAY

In our study, the patients spent an average of 12.75 days (± 3.59 days) in Intensive Care Unit. This duration was 11.83 days (± 3.4 days) in survivors and 14.39 days (± 2.8 days) for non-survivors. There was no statistically significant difference found between Number of days of ICU stay and two outcome (0.001).

One study reports length of ICU stay for mechanically ventilated patients to be 11.2 days (± 13.7 days).[161] This difference is noted presumably because of a larger sample size, i.e. 5183 patients in the study versus 64 patients in our study.

One another study reports a significant 28% increase in odds for prolonged ICU stay per 10g/L decrement in serum albumin.[5]

DURATION OF HOSPITAL STAY

In our study group, patients spent a mean of 12.75 days (± 4.23 days) in hospital. Survivors spent 16.66 days (± 4.4 days) in hospital whereas non-survivors spent 14.83 days (± 3.3 days) in hospital. There was no statistically significant difference found between Number of days of hospital stay and two outcomes (0.001). One cohort study reports a significant hypoalbuminemia related increase of 71% in odds of prolonged hospital stay.[5] However, the broad inclusion criteria adopted in the study and a larger sample size of 2,91,443 patients have made a significant difference in the observations.

One study reports an average of 22.5 days (± 23.7 days) as length of stay in hospital for mechanically ventilated patients.[161] This difference is observed because of a larger sample size of 5183 patients included in the study.

CONCLUSION

CONCLUSION

In our study of 64 critically ill patients of different etiologies, requiring mechanical ventilation

a. The mean age of survivors was 42.92 years and that of non-survivors was 51.9 years. There was statistically no significant difference ($p = 0.011$) between the 2 Age groups.
b. The study had 64% survivors and 36% non-survivors.
c. Patients who had normal serum albumin level at admission are more likely to survive as compared to patients who had hypoalbuminemia which is shown by the results that 43.9 % survivors had normal serum albumin levels at admission as compared to just 10.5 % of non-survivors.
d. The mean serum albumin on day three, day five was significantly higher in survivors as compared to non-survivors suggesting serial serum albumin levels is a good prognostic indicator of the outcome of the patients.
e. There was fall in mean serum albumin levels in both groups, but it was steeper in non-survivors. This indicates that patients who had a steep decline in serum albumin level had a poor prognosis in terms of increased mortality.

f. Serial serum albumin levels also suggest that there are other factors associated with prognosis of the patients since 21 (51%) patients who had hypoalbuminemia at admission survived the critical illness.

g. The strongest predictor of outcome of the patient is serum albumin on day three.

h. Mean number of days on ventilation was 8.34 ± 2.5 days in survivor subjects and 9.48 ±2.9 days in non-survivors. There was no statistically significant difference found between Number of days on ventilation and the outcome.

i. Mean number of days of ICU stay was 11.83 ± 3.5days in survivor subjects and 14.39 ± 2.8days in non-survivors. There was no statistically significant difference found between Number of days of ICU stay and the outcome.

j. Mean number of days of hospital stay was 16.66 ± 4.4 days in survivor subjects and 14.83 ± 3.3 days in non-survivors. There was no statistically significant difference found between Number of days of hospital stay and the outcome.

k. In the present study, Low serum albumin level appears to be one of the major factors adversely affecting the outcome of critically ill patients on ventilator support.

SUMMARY

SUMMARY

Present study was conducted at R.L. JALAPPA. hospital, and Medical Research Centre, Kolar over a period of 19 months from April 2016 to October 2017 to evaluate the role of serial serum albumin estimation as a prognostic marker in critically ill patients who were on mechanical ventilator for 5 days or more.

The study included 64 critically ill patients of different etiologies who required mechanical ventilation for 5 days or more. Demographic characteristics were noted. Detailed history was noted, and clinical examination was done. Serum albumin was estimated on day 1, day 3, day 5 and day 10. Number of days of mechanical ventilation, duration of ICU stay, and duration of hospital stay was also noted.

The results showed that serial measurement of serum albumin can accurately predict the outcome of the patient in the form of discharge from hospital or death in the hospital. The survivors also had a significantly higher mean serum albumin levels at all days as compared to non-survivors. Patients who had a rapid decline in serum albumin level on day 3 had poorer prognosis in terms of increased mortality. There was no significant variation in duration of mechanical ventilation between survivors and non-survivors. From the present study, Low serum albumin appears to be one of the major

factors adversely affecting the outcome of critically ill patients requiring mechanical ventilation.

Serum albumin is routinely measured in all critically ill patients. It is a cheap and easily available test done in all laboratories. Its value as an important prognostic marker has been well established. The serial estimation of serum albumin provides the treating doctor an insight into the prognosis of the patient so that they can be managed aggressively.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Nicholson JP, Wolmarans MR, Park GR. The role of albumin in critical illness. Br J Anaesth 2000; 85: 599-610.
2. Khilnani GC, Banga A, Sharma SK. Predictors of mortality of patients with acute respiratory failure secondary to chronic obstructive pulmonary disease admitted to an intensive care unit. A one-year study. BMC Pulm Med 2004; 4: 12 doi: 10.11 86/1471-2466-4-12.
3. McCluskey A, Thomas AN, Bowles BJM, Kishen R. The prognostic value of serial measurements of serum albumin in patients admitted to an intensive care unit. Anesthesia 1996; 51: 724–7.
4. Goldwasser P, Feldman J. Association of serum albumin and mortality risk. J Clin Epidemiol 1997; 50: 693–703.
5. Vincent JL, dubois MJ, Navickis RJ, Wilkes MM. Hypoalbuminemia in Acute Illness: Is There a Rationale for Intervention? A Meta-Analysis of cohort studies & controlled trials. Ann Surg. 2003; 237(3): 319-34.
6. Peters TJ. Historical perspective. In: All About Albumin. Biochemistry, Genetics and Medical Applications. San Diego: Academic Press, 1996: 1– 8.
7. Gosling P. Albumin and the critically ill. Care Crit Ill 1995; 11: 57–61.

8. Rothschild MA, Oratz M, Schreiber SS. Serum albumin. Hepatology 1988; 8: 385–401.

9. Doweiko JP, Nompleggi DJ. Role of albumin in human physiology and pathophysiology. J Parent Enteral Nutr 1991; 15: 207–11.

10. He XM, Carter DC. Atomic structure and chemistry of human serum albumin. Nature 1992; 358: 209–15.

11. Peters TJ. The albumin molecule: its structure and chemical properties. In: All About Albumin. Biochemistry, Genetics and Medical Applications. San Diego: Academic Press; 1996.

12. Carter DC, Ho JX. Structure of serum albumin. Adv Protein Chem 1994; 45: 153–203

13. Margarson MP, Soni N. Serum Albumin: touchstone or totem? Anesthesia. 1998; 53: 789-803.

14. Lundsgaard-Hansen P. Physiology and pathophysiology of colloid osmotic pressure and albumin metabolism. Curr Stud Hematol Blood Transfusion 1986; 53: 1–17

15. Miller LL, Bly CG, Watson ML, Bale WF. The dominant role of the liver in plasma protein synthesis. A direct study of the isolated perfused rat liver with the aid of lysine- -C14. J Exp Med 1951; 94: 431–53.

16. Peters TJ. Metabolism: albumin in the body. In: All About Albumin. Biochemistry, Genetics and Medical Applications. San Diego: Academic Press, 1996: 188–250.

17. Oratz M, Rothschild MA, Schreiber SS. Effect of dextran infusions on protein synthesis by hepatic microsomes. Am J Physiol 1970; 218: 1108– 12.

18. Yamauchi A, Fukuhara Y, Yamamoto S, Yano F, Takenaka M, Imai E, et al. Oncotic pressure regulates gene transcriptions of albumin and apolipoprotein B in cultured rat hepatoma cells. Am J Physiol 1992; 263: C397–404.

19. Lloyd CE, Kalinyak JE, Hutson SM, Jefferson LS. Stimulation of albumin gene transcription by insulin in primary cultures of rat hepatocytes. Am J Physiol 1987; 252: C205–14.

20. Moshage HJ, Janssen J, Franssen JH, Hafkenscheid JCM, Yap SH. Study of the molecular mechanism of decreased liver synthesis of albumin in inflammation. J Clin Invest 1987; 79: 1635–41.

21. Brenner DA, Buck M, Feitelberg SP, Chojkier M. Tumor necrosis factor- α inhibits albumin gene expression in a murine model of cachexia. J Clin Invest 1990; 85: 248–55.

22. Castell JV, Gomez-Lechon MJ, David M, Fabra R, Trullenque R, Heinrich PC. Acute-phase response of human hepatocytes: regulation

of acute-phase protein synthesis by interleukin-6. Hepatology 1990; 12: 1179–86.

23. Perlmutter DH, Dinarello CA, Punsal PI, Colten HR. Cachectin/tumor necrosis factor regulates hepatic acute-phase gene expression. J Clin Invest 1986; 78: 1349–54.

24. De Feo P, Gaisano MG, Haymond MW. Differential effects of insulin deficiency on albumin and fibrinogen synthesis in humans. J Clin Invest 1991; 88: 833–40.

25. Hutson SM, Stinson-Fisher C, Shiman R, Jefferson LS. Regulation of albumin synthesis by hormones and amino acids in primary cultures of rat hepatocytes. Am J Physiol 1987; 252: E291–8.

26. Johnson TR, Rudin SD, Blossey BK, Ilan J. Newly synthesized RNA: simultaneous measurement in intact cells of transcription rates and RNA stability of insulin-like growth-factor 1, actin, and albumin in growth hormone-stimulated hepatocytes. Proc Natl Acad Sci USA 1991; 88: 5287–91.

27. Rothschild MA, Bauman A, Yalow RS. The effect of large doses of desiccated thyroid on the distribution and metabolism of albumin-I in euthyroid subjects. J Clin Invest 1957; 36: 422-8.

28. Rothschild MA, Schreiber SS, Oratz M. The effects of adrenocortical hormones on albumin metabolism studied with albumin I131 J Clin Invest 1958; 37: 1229-35.

29. Grossman J, Yalow AA, Weston RE. Albumin degradation and synthesis as influenced by hydrocortisone, corticotrophin and infection. Metabolism. J Clin Invest 1960; 9: 528-50.

30. Sterling K. The effect of Cushing's syndrome upon serum albumin metabolism. J Clin Invest 1960; 39: 1900-08.

31. Lewallen CG, Rall JE, Berman M. Studies of iodolbumin metabolism 2. The effects of thyroid hormone. J Clin Invest 1959; 38: 88-101.

32. Tata JR, Widnell CC. Ribonucleic acid synthesis during the early action of thyroid hormones. Biochem J 1966; 98: 604-20.

33. Jump DB, Narayan P, Towle H, et al Rapid effects of triiodothyronine on hepatic gene expressi. J Biol Chem 1984; 259: 2789-98.

34. Gallo G, Fugass E, voci A et al. Triiodothyroinine stimulated RNA synthesis in primary cultures of adult rat hepatocytes. Biochem Biophys Acta 1985; 847: 140-146.

35. Enwonwu CO, Munro HN. Changes in liver polyribosome pattern following administration of hydrocortisone and actinomycin D. Biochim Biophys Acta 1971; 238: 264-76.

36. Cain GD, mayer G, Jones EA. Augmentation of albumin but not fibrinogen synthesis by corticosteroids in patients with hepatocellular disease. J Clin Invest 1970; 49: 2198-2203.

37. Jefferson DM. Reid LM, Giambrone MA. Et al Effect of dexamethasone on albumin and collagen gene expression in primary cultures of adult rat hepatocytes. Hepatology 1985; 5: 14-20.

38. Welner FR, Czaja MJ, Glambrone MA, et al. Transcriptional and posttranscriptional effects of Dexamethasone on an in vivo model of fibrogenesi. Hepatology 1985; 5:1013.

39. Plant PW, Deeley Rg, Grieninger G. Selective block of albumin gene expresso in chick embryo hepatocytes cultured without hormones and its partial reversal by insulin. J boil Chem 1983; 258:1535-60.

40. Wagle SR. The influence of growth hormone, cortisol and insulin on the incorporation of amino acids into protein. Arch Biochem biophys 1963:102:373-8.

41. Rothschild MA, Oratz M, Mongelli J. et al. effects of a short term fast on albumin synthesis studied in vivo in the perfused liver and on amino acid incorporation by hepatic microsomes. J Clin Invest 1968; 47: 2591-99.

42. Staehelin T, Verney E, Sidransky H. The influence of nutritional change on polyribosomes of the liver. Biochim Biophys Acta 1967; 145: 105-119.

43. Baliga BS, Pronczuk AW, Munro HN. Regulation of polysome aggregation in a cell-free system through amino acid supply. J Molec Biol 1968; 34: 199-218.

44. Sidransky H, Sarma DSR, Rongiorno M, et al Effect of dietary tryptophan on hepatic polyribosomes and protein synthesis in fasted mice. J Biol Chem 1968; 243: 1123-32.

45. Rothschild MA, Oratz M, Mongelli J, et al Amino acid regulation of albumin synthesis. J Nutr 1969; 98: 395-403.

46. Waterlow JC, Observations on the mechanism of adoption to low protein intakes. Lancet 1968; 2:1091-1097.

47. Cohen S, Hansen JDL, Metabolism of albumin and γ-globulin in kwashiorkor. Clin Sci 1962; 23: 351-9.

48. Hoffenberg R, Black E, Brock JF. Albumin and γ-globulin tracer studies in protein depletion states. J Clin Invest 1966; 45:143-52.

49. Kirsch R, Firth L, Black E et al Regulation of albumin synthesis and catabolism by alteration of dietary protein. Nature 1968; 217: 578-9.

50. Clifford AJ. Riumallo JA, Baliga BS, et al Liver nucleotide metabolism in relation to amino acid supply. Biochim Biophys Acta 1972; 277: 43-458.

51. Grummet I, Smith VA, Grummet F. Amino acid starvation affects the initiation frequency of nucleolar RNA polymerase. Cell 1976; 7: 439-45.

52. Yap SH, Hafkenscheid JMC, Effect of starvation on the synthesis rate of albumin in vivo and its relation to the concentrations of amino

acids in the peripheral blood, the portal circulation and in the livery cytosolic fraction.

53. Rigotti P, Peters JC, Tranberg KG, et al. Effects of amino acid infusion on liver regeneration after partial hepatectomy in the rat J. Parent Enteral Nutr 1986; 10: 17-20.

54. Rothschild MA, Oratz M, Schreiber SS. Alcohol, amino acids, and albumin synthesis. Gastroenterology 1974*;* 67: 1200–13

55. Sakuma K, OH Yama T, Sogawa K, Fujii Kuriyama Y, Matsumura Y. Low protein–high energy diet induces repressed transcription of albumin mRNA in rat liver. J Nutr 1987; 117: 1141–8.

56. Princen JMG, Mal-Basks GRB, Yap SH. Restoration effects of glucose refeeding on reduced synthesis of albumin and total protein on disaggregated polyribosomes in liver of starved rats: evidence of post-transcriptional control mechanism. Ann Nutr Metab 1983; 27: 182–93

57. Smallwood RA, Jones EA, Craigie A, et al. The delivery of newly synthesized albumin and fibrinogen to the plasma of dogs. Clin Sci. 1968; 35:35-43.

58. Birke G. Regulation of protein metabolism in burns. In: Rothschild MA, Walmann T, eds. Plasma protein metabolism Regulation of synthesis, distribution and degradation. New York Academic Press, 1970;415-25.

59. Davies JWL, Albumin turnover in burns and trauma. In: bianchi R, Mariani G, Mc Farlane AS, eds. Plasma protein turnover. New York: Mac Millan, 1976;403-22.

60. Worm AM, Parving HH, Plasma and interstitial fluid volume in extensive skin disease J Invest Dermatol 1981;76:108-9.

61. Yedgar S, Carew TE, Pittman RC, Beltz WF, Steinberg D. Tissue sites of catabolism of albumin in rabbits. Am J Physiol 1983; 244: E101–7

62. Neligen Pat. What's all this fuss about Albumin? Available from URL:http://www.4um.com/tutorial/currents/albumin.htm.

63. Ganong WF. Dynamics of blood and lymph flow. In: Review of Medical Physiology, 17th edn. Connecticut: Appleton and Lange; 1995.

64. Schnitzer JE, Bravo J. High affinity binding, endocytosis and degradation of conformationally modified albumins. Potential role of gp30 and gp18 as novel scavenger receptors. J Biol Chem 1993; 268: 7562–70.

65. Tucker VL, Simanonok KE, Renkin EM. Fissure-specific effects of physiological ANP infusion on blood-tissue albumin transport. American Journal of Physiology 1992; 263: R945-53.

66. Grootendorst AF, Wilgenberg MGM, de Laat PHJM, van der Hoven B. Albumin abuse in intensive care medicine. Intensive Care Med 1988; 14: 554-7.

67. Traylor RJ, Pearl RG. Crystalloid versus colloid versus colloid: all colloids are not created equal. Anesth Analg 1996; 83: 209–12.

68. Weil MH, Henning RJ, Puri VK. Colloid oncotic pressure: clinical significance. Crit Care Med 1979; 7: 113–6.

69. Rothschild MA, Oratz M, Evans CD, et al. Role of hepatic interstitial albumin in regulating albumin synthesis. Am J Physiol 196; 210: 57-62.

70. Rothschild MA, Oratz M, Franklin Ec, et al. The effect of hypergammaglobulinemia on albumin metabolism in hyperimmunized rabbits studied with albumin I131. J Clin Invest 1962; 41: 1564-71.

71. Rothschild MA, Oratz M, Evans CD, et al. Alterations in albumin metabolism after serum and albumin infusions. J Clin Invest 1964; 43: 1874-80.

72. Morisette M, Weil MH, Shubin H. Reduction in colloid osmotic pressure associated with fatal progression of cardiopulmonary failure. Crit Care Med 1975; 3: 115.

73. Tonnesen AS, Gabel JC, McLeavey CA. Relation between lowered colloid osmotic pressure, respiratory failure, and death. Crit Care Med 1977; 5: 239–40.

74. Peters TJ. Ligand binding by albumin. In: All About Albumin. Biochemistry, Genetics and Medical Applications. San Diego: Academic Press, 1996: 76–132.

75. Kragh-Hansen U. Structure and ligand binding properties of human serum albumin. Danish Medical Bulletin 1990; 37: 57-83.

76. Koch-Weser J, Sellers EM. Binding of drugs to serum albumin. N Engl J Med 1976; 294: 311–6.

77. Forker EL, Lux on Ba, Snell M, et al. Effect of albumin binding on the hepatic transport of rose Bengal: surface mediated dissociation of limited capacity. J Pharmacol Exp Ther 1982; 223: 342-7.

78. Weisiger R, Gollan J, Ockner R. Receptors for albumin on the liver cell may mediate uptake of fatty acids and other albumin found substances. Science 1981; 211: 1048-51.

79. Forker EL, Lux on BA, Albumin helps mediate removal of taurocholate by rat liver. J Clin Invest 1981; 67: 1517-22.

80. Weisiger Ra. Dissociation from albumin: a potentially rate limiting step in the clearance of substances by the liver. Proc Natl Acad Sci USA 1985; 82: 1563-7.

81. Berk PD. Potter BJ, Stremmel W. Role of plasma membrane ligand-binding proteins in the hepatocellular uptake of albumin bound organic anions. Hepatology 1987; 7: 165-76.

82. Andreasen F. Protein binding of drugs in plasma from patients with acute renal failure. Acta Pharmacol Toxicol 1973; 32: 417–29.

83. Crooks MJ, Brown KF. The binding of sulphonylureas to serum albumin. J Pharm Pharmacol 1974; 26: 304–11.

84. Lafaye P, Lapresle C. Fixation of penicilloyl groups to albumin and appearance of anti-penicilloyl antibodies in penicillin-treated patients. J Clin Invest 1988; 82: 7–12.

85. McAuliffe JJ, Lind LJ, Leith DE, Fencl V. Hypoproteinemic alkalosis. Am J Med 1986; 81: 86–90.

86. Halliwell Barry. Albumin – An Important extracellular antioxidant? Biochem Pharmacol 1988; 37(4): 569-71.

87. Hoye RC, Bennett SH, Geelhoed GW, Gorschboth C. Fluid volume and albumin kinetics occurring with major surgery. J Am Med Assoc 1972; 222: 1255–61.

88. Tullis JL. Albumin 1. Background and use. J Am Med Assoc 1977; 237: 355–9.

89. Wasil M, Halliwell B, Hutchinson DCS, Baum H. The antioxidant action of human extracellular fluids. Biochem J 1987; 243: 219–23.

90. Demling RH. Effect of plasma and interstitial protein content on tissue oedema formation. Curr Stud Hematol Blood Transfusion 1986; **53**: 36– 52.

91. Zoellner H, Hofler M, Beckmann R, Hufnagl P, Vanyek E, Bielek E, et al. Serum albumin is a specific inhibitor of apoptosis in human endothelial cells. J Cell Sci 1996; 109: 2571–80.

92. Ramirez-Vick J, Vargas FF. Albumin modulation of paracellular permeability of pig vena caval endothelium shows specificity for pig albumin. American Journal of Physiology 1993; 264: H1382-7.

93. Qiao R, Siflinger-Birnboim A, Lum H, Tirupati C, Malik AB. Albumin and Ricinus communis agglutinin decrease endothelial permeability via interactions with matrix. American Journal of Physiology 1993; 265: C439-46.

94. Kaufmann MA, Castelli I, Pargger H, Drop LJ. Nitric oxide dose–response study in the isolated perfused rat kidney after inhibition of endothelium-derived relaxing factor synthesis: the role of albumin. J Pharmacol Exp Ther 1995; 273: 855–62.

95. Kearney JF, Simon DI, Stamler JS, Jaraki O, Scharfstein J, Vita JA, et al. NO forms an adduct with serum albumin that has endothelium-derived relaxing factor-like properties. J Clin Invest 1993; 91: 1582–9.

96. Jorgensen KA, Stoffersen E. Heparin like activity of albumin. Thromb Res 1979; 16: 569–74.

97. Simon DI, Stamler JS, Jaraki O Et al. Anti-platelet properties of protein S-nitrosothoils derived from nitric oxide and endothelium-

derived relaxing factor. Arteriosclerosis and thrombosis 1993; 13: 791-99.

98. Waydhays C. Equipment review. Intra Hospital transport of critically ill patients. Crit Care Med. 1999; 5: 83-9.

99. Sussex critical care network interhospital transfer of Adult Critically ill patients. Available from URL: http://www.succexcritcare.nhs. uk/profclinical/audit /documetns/transfers.pdf.

100. Apelgren KN, Rombeau JL, Twomey PL, Miller RA. Comparison of nutritional indices and outcomes in critically ill patients. Crit Care Med 1982; 10: 305–7.

101. Bradley JA, Cunningham KJ, Jackson VJ, Hamilton DNH, Ledingham IM. Serum protein levels in critically ill surgical patients. Intensive Care Med 1981; **7**: 291–5.

102. Murray MJ, Marsh HM, Wochos DN, Moxness KE, Offord KP, Callaway W. Nutritional assessment of intensive-care unit patients. Mayo Clin Proc 1988; 63: 1106–15.

103. Fleck A, Hawker F, Wallace PI, Raines G, Trotter J, Ledingham IM, et al. Increased vascular permeability: a major cause of hypoalbuminemia in disease and injury. Lancet 1985; **i**: 781–4.

104. Hu M, Louie S, Cross CE, Motchnik P, Halliwell B. Antioxidant protection against hypochlorous acid in human plasma. J Lab Clin Med 1993; 121: 885–92.

105. Sun X, Iles M, Weissman C. Physiological variables and fluid resuscitation in the postoperative intensive care unit patient. Crit Care Med 1993; 21: 555–61.

106. Suttorp N, Hessz T, Seeger W Et al. Bacterial exotoxins and endothelial permeability for water and albumin in vitro. American Journal of Physiology 1988; 255: C368-76.

107. Berman RS, Frew JD, Martin W. Endotoxin-induced arterial endothelial barrier dysfunction assessed by an in vitro model. Br J Pharmacol 1993; 110:1282–4.

108. Parrillo JE. Pathogenesis of human septic shock. Ann Intern Med 1990; 113:227–42.

109. Bone RC. The pathogenesis of sepsis. Ann Intern Med 1991; 115: 457–69.

110. Glauser MP, Heumann D, Baumgartner JD, Cohen J. Pathogenesis and potential strategies for prevention and treatment of septic shock: an update. Clin Infect Dis 1994; 18: S205–16.

111. Staniford TJ, Kunkel SL, Lukacs NW, Greenburger MJ, Danforth JM, Kunkel RG, et al. Macrophage inflammatory protein-1a mediates lung leukocyte recruitment, lung capillary leak, and early mortality in murine endotoxemia. J Immunol 1995; 155: 1515–24.

112. Myers MA. Aspects of the acute phase response. PhD thesis University of Londong, 1987.

113. Zawieja DC. Lymphatic microcirculation, Microcirculation 1996; 3: 241-3.

114. Mouridsen HT. Turnover of human serum albumin before and after operations. Clin Sci 1967; 33: 345–54.

115. Fleck A, Raines G, Hawker F, Ledingham IM. Synthesis of albumin by patients in septic shock [abstract]. Arch Emergency Med 1984; 1: 177.

116. Liao WS, Jefferson LS, Taylor JM. Changes in plasma albumin concentration, synthesis rate and mRNA level during acute inflammation. Am J Physiol 1986; 251: C928–34.

117. Schreiber G, Howlett G, Nagashima M, Millership A, Martin H, Urban J, et al. The acute phase response of plasma protein synthesis during experimental inflammation. J Biol Chem 1982; 257: 10271–7.

118. Kukral JC, Zeineth R, Dobryszyckn W, et al. I Turnover rates of fibrinogen I burned patients labeled with I310 Slmethionine. Clin Sci 1969; 36: 221-30.

119. Moshage HJ. Janssen JAM, Franssen JH, et al Study of the molecular mechanism of decreased liver synthesis of albumin in inflammation J Clin Invent 1987; 79: 1635-41.

120. Gordon AH. The effects of trauma and partial hepatectomy on the rates of synthesis of plasma proteins by the liver. In: Rothschild MA, Waldmann TA, eds. Plasma protein metabolism. Regulation of

synthesis, distribution, and degradation. New York: Academic Press, 1970;351-68.

121. OW, Balegno HF, Chandler AM. Induction of plasma protein synthesis in response to trauma. Am J Physiol 1966; 211: 151-56.

122. Ragnotti G, Cajone F, Zazera AB. Structural and functional changes in polysomes from ischemic livers. Exp Molec Pathol 1970; 13: 295-06.

123. Davies JWL, Ricketts CR, Bull JP. Studies of plasma protein metabolism II. Pooled γ-globulin in burned and injured patients. Clin Sci 1963; 24: 371-82.

124. Clarke HGM, Freeman T, Phillips WP. Serum protein changes after injury. Clin Sci 1971; 40: 334-44.

125. Davies JWL, Ricketts CR, Bull JP. Studies of plasma protein metabolism. I. Albumin in burned and injured patients. Clin Sci 1962; 23: 411-23.

126. Birke G, Lilijedahl SO, Plantin LO, et al. Studies on burns. IX The distribution and losses through the wound of 131I albumin measured by whole-body counting. Acta Chir Scand 1967; 134: 27-36.

127. Perlmutter DH, Dinarello CA, Pusal PI, et al. Cachectin/tumor necrosis factor regulates hepatic acute-phase gene expression. J Clin Invest 1986; 78: 1349-54.

128. Ramadori G, Sipe JD, Dinarello CA, et al. Pre-translational modulation of acute phase hepatic protein synthesis by murine recombinant interleukin-1 (II-1) and purified human II-1 J Exp. Med 1985;162:930-42.

129. Dahn MS, Jacohs LA, Smith S, Lange MP, Mitchell RA, Kirkpatrick JR. The significance of Hypoalbuminemia Following injury and injection. Am Surg. 1985 Jun; 51(6):340-3.

130. Clowes GHA, Heideman M, Lindberg D. Effects of parenteral alimentation on amino acid metabolism in septic patients. Surgery1980; 88: 531-45.

131. Rosenblatt S, Clowes GHA, George BC et al. Exchange of amino acid by muscle and liver in sepsis. Arch Surg 1983; 118: 167-75.

132. Spiess A, Mikalunas V, Carlson S, Zimmer M, Craig RM. Albumin kinetics in hypoalbuminaemic patients receiving total parenteral nutrition. J Parent Enteral Nutr 1996; 20: 424–8.

133. Smeets HJ, Kievet J, Dulfer FT, Hermans J, Moolenaar AJ, Analysis of postoperative hypoalbuminaeumia: a clinical study. International Surgery 1994; 79: 152-7.

134. Gibbs J, Cull W, Henderson W, Daley J, Hur K, Khuri SF, Preoperative serum albumin level as a predictor of operative mortality and morbidity. Arch Surg 1999; 134: 36-42.

135. Reilly JJ, Hull SF, Albert N. Waller A, Bringardener S. Economic impact of malnutrition: a model system for hospitalized patients. J Parent Ent Nutr 1987; 12:317-6.

136. Burr RG, Cuft-Peace L, Nuseibeh I. Hemoglobin and albumin as predictors of length of stay of spinal injured patients in a rehabilitation centre. Paraplegia 1993; 31: 473-8.

137. Herrmenn FR, Safron C, Levkoff SE, Minaker KL. Serum Albumin Level on Admission as a predictor of Death, Length of stay and Readmission. Arch Intern Med. 1992; 152(1):125-30.

138. Klonoff-Cohen H, Barrett-Connor EL, Edelstein SL. Albumin levels as a predictor of mortality in the elderly. J Clin Epidemiol 1992; 45: 207–12 Klonoff-Cohen H, Barrett-Connor EL, Edelstein SL. Albumin levels as a predictor of mortality in the elderly. J Clin Epidemiol 1992; 45: 207–12.

139. Phillips A, Shaper AG, Whincup PH. Association between serum albumin and mortality from cardiovascular disease, cancer, and other causes. Lancet 1989; 2: 1434–6.

140. Agarwal N, Acevedo F, Leighton LS. Et al Predictive ability of various nutritional variables for mortality in elderly people. Am J Clin Nutr 1988; 48: 1173-8.

141. Sullivan DH, Patch GA, Walls RC. Impact of nutrition status on morbidity and mortality in a select population of geriatric rehabilitation patients. Am J Clin Nutr 1990; 51: 749-758.

142. McEllistrum MC, Collins JC, Powers JS. Admission Serum Albumin Level as a Predictor of outcome Among Geriatric patients. South Med. J. 1993; 86:1360-1.

143. Cooper JK, Gardner C. Effects of Aging on Serum Albumin. J. Am Geriatr Soc. 1989; 37: 1039-42.

144. Sahyoun NR, Jacques PF, Dallal G, Russell RM. Use of Albumin as a predictor of mortality in community dwelling and institutionalized elderly population. J. Clin Epidemiol 1996; 49(9): 981-8.

145. Finestone HM, Greene-Finestone LS, Wilson ES, Teasell RW. Prolonged length of stay and reduced functional improvement rate in malnourished stroke rehabilitation patients. Arch Phys Med Rehabil 1996; 77: 340–5.

146. Spiegel DM, Breyer JA. Serum albumin: a predictor of long-term outcome in peritoneal dialysis patients. Am J Kidney Dis 1994; 23: 283–5.

147. Reinhardt GF, Myscofski JW, Wilkens DB, Dobrin PB, Mangan JE, Stannard RT. Incidence and mortality of hypoalbuminemic patients in hospitalised veterans. J Parent Enter Nutr 1980; 4: 357–9.

148. Ching N, Grossi CE, Angers J, Zurawinsky HS, Jham G, Mills CB, et al. The outcome of surgical treatment as related to the response of the serum albumin level to nutritional support. Surg Gynecol Obstet 1980; 151: 199–202.

149. Golub R, Sorrento JJ, Cantu RJ, Nierman DM, Moideen A, Stein HD. Efficacy of albumin supplementation in the surgical intensive care unit: a prospective, randomised study. Crit Care Med 1994; 22: 613–9.

150. Sapijaszko MJA, Brant R, Sandham D, Berthiaume Y. Non-respiratory predictor of mechanical ventilation dependency in intensive care unit patients. Crit Care Med 1996; 24: 601–7.

151. Sporn PH, Morganorth ML. Discontinuation of mechanical ventilation. Clin Chest Med 1988; 9: 113-26.

152. Benotti PN, Bistrian B. Metabolic and nutritional aspects of weaning from mechanical ventilation. Crit Care Med. 1989; 17: 181-5.

153. Pingleton SK. Nutritional support in the mechanically ventilated patient. Clin Chest Med 1988; 9: 101-12.

154. Bassili HR, Dietel M. Effect of nutritional support on weaning patients off mechanical ventilators. JPEN 1981; 5: 161-3.

155. Doweiko JP, Nompleggi DJ. The role of albumin in human physiology and pathophysiology. Part III: Albumin and diseases states. JEPN 1991; 15: 476-83.

156. Schienhorn DJ. Increase in Serum albumin and decrease in body weight correlate with weaning from prolonged mechanical ventilation. Am Rev Respir dis 1992;145: A522.

157. Schnitzer JE, Carley WW, Palade GE. Specific albumin binding to microvascular endothelium in culture. Am J Physiol 1988; 254: H425–37.

158. Yap FM, Joynt GM, Buckley TA, Wong ELY. Association of serum albumin concentration and mortality Risk in Critically ill patients. Anaesth Intensive Care 2002, 30(2) :202-7.

159. Pollack AJ, Strong RM, Gribbon R, Shah H. Lack of predictive value of the APACHE II score in hypoalbuminemic patients. J Parent Enteral Nutr 1991; 15: 313–5.

160. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalised adults. Chest 1991; 100: 1619–36.

161. Esteban A, Anzueto A, Frutos F, Alia I, Brochard L, Stewart TE, Benito S, Epstein SK, Apezteguia C, Nightingale P, Arroliga AC, Tobin MJ, Mechanical Ventilation International Study Group: Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. JAMA 2002, 287:345-355.

162. Kollef MH, O'Brien JD, Silver P. The impact of gender on outcome form mechanical ventilation. Chest 1997; 111: 434-41.

163. Luhr OW, Antonsen K, Karlson M, et al and the ARF study Group. Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark and Iceland. Am J Respir Crit Care Med. 1999; 159:1849-61.

164. Seneff MG, Wagner DP, Wagner RP et al. Hospital to 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. JAMA 1995; 274: 1852-7.

165. Nevins ML, Epstein SK. Predictors of outcome for patients with COPD requiring invasive mechanical ventilation, Chest, 2001;119:1840-9.

166. Zilberberg MD, Epstein SK. Acute lung injury in the medical ICU. Am J Respir Crit Care Med. 1998; 157: 1159-64.

167. Roupie E, Lepage E, Wysocki M, et al for the SRLF Collaborative Group on Mechanical Ventilation. Prevalence, etiologies and outcome of the acute respiratory distress syndrome among hypoxemic ventilated patients. Intensive Care Med. 1999; 25-920-9.

168. Valta P, Uusaro A, Nunes S, et al. Acute respiratory distress syndrome. Crit Care Med. 1999; 27: 3267-74.

169. Navarrete-Navarro P, Ruiz-Ballen M, Rivera Fernandz R, et al. Acute respiratory distress syndrome in trauma patients. Intensive Care Med. 2000; 26: 1624-9.

170. Ferring M, Vincent JL. Is outcome from ARDS related to the severity of respiratory failure? Eur Respir 1997; 10: 1297-1300.

171. Epstein SK, Vuong V. Lack of influence of gender on outcome of mechanically ventilated medical ICU patients. Chest 1999; 116: 732-9.

172. Blunt MC, Nicholson JP, Park GR. Serum albumin and colloid osmotic pressure in survivors and non-survivors of prolonged critical illness. Anesthesia 1998; 53: 755–61.

173. Starker PM, gump FE, Askanagi J, Elcogn H, Kinney JM. Serum albumin levels as an index of nutritional support. Surgery; 91(2): 194-199.

174. Skillman JJ, Rosenoer VM, Smith PC, Fang MS. Improved albumin synthesis in postoperative patients by amino acid infusion. N Engl J Med 1976; 295: 1037-40.

175. Keys AB, Brozek J, Henschel A, Mickelson O, Taylor HL. Biology of human starvation. Vol. 1. Minneapolis: University of Minnersota Press; 1950.

176. Barac-Nicto M, Spurr GB, Lotero H, Maksud MG, Dalner WH. Body composition during nutritional repletion of severely undernourished man. Am J Clin Nurr 1979; 32: 981-91.

177. Levenson SH, Crosley LV, Seifter E. Starvation. In Ballinger WF. Manual of surgical nutrition. Philadelphia: WB Saunders Co; 1975.

178. Powanda MC. Plasma proteins and wound healing. Surg Gynecol Obstet 1981; 153: 749-55.

179. .Manelli JC. [Is albumin administration useful in critical care for burnt patients?]. Ann Fr Anesth Reanim 1996; 15: 507–13.

180. Doweiko JP, Nompleggi DJ. Use of albumin as a volume expander. J Parent Enteral Nutr 1991; 15: 484–7.

181. Michaelson J. The significance of cell death in apoptosis. The molecular basis of cell death. In Current communications in Cell ad Molecular Biology, Tomei LD, Cope FO (Eds). New York, Cold Spring Harbour Laboratory Press, 1991, pp 31-46.

182. Banga A, Guleria R, Khilnani GC, Khanna S. Serum albumin as A Prognostic Marker in Critically ill patient. JAPI 2003; 51:1223-4.

183. Burl R. Don, George Kasen. Poor nutritional status and inflammation: serum albumin: relationship to inflammation and nutrition. Semi in dial 2004; 17:432-437.

184. Lim SH, Lee JS, Chae SH, Ahn BS, Chang DJ, Shin CS. Prealbumin is Not Sensitive Indicator of Nutrition and Prognosis in Critical Ill Patients. Yonsei Med J. 2005 Feb;46(1):21-26.

185. Alan Shenkin. Serum Prealbumin: Is It a Marker of Nutritional Status or of Risk of Malnutrition? Clinical Chemistry Dec 2006, 52 (12) 2177-2179.

186. Giuseppe Caso, Joshua Feiner, Izolda Mileva, Leslie J Bryan.Response of albumin synthesis to oral nutrients in young and elderly subjects. Am J Clin Nutr 2007; 85:446 –51.

187. Amy v. trow, dvm; elizabeth a. rozanski, dvm. evaluation of use of human albumin in critically ill dogs: 73 cases. Journal of the American veterinary medical association, august 15, 2008, vol. 233, no. 4, pages 607-612.

188. Falcao Haroldo, Japiassu Andre Miguel. Albumin in critically ill patients: controversies and recommendations. Rev. bras. ter. intensiva. 2011 Mar; 23(1): 87-95.

189. Fulks M, Stout RL, Dolan VF. Albumin and all-cause mortality risk in insurance applicants. J Insur Med.2010;42(1):11-17.

190. Delaney, Anthony P. MD. The role of albumin as a resuscitation fluid for patients with sepsis: A systematic review and meta-analysis. Critical Care Medicine: Feb 2011;39(2):386-391.

191. Gupta, Leena, James. Hypoalbuminemia as a prognostic marker in sepsis, severe sepsis and septic shock. Crit Care Med.2012;40(12):1-328.

192. Aguayo-Becerra Olivia Alejandra, Torres-Garibay Carlos, M et al. Serum albumin level as a risk factor for mortality in burn patients. Clinics. 2013; 68(7): 940-945.

193. Viasus, Diego.et al. Prognostic value of serum albumin levels in hospitalized adults with community-acquired pneumonia. J of Inf.2014; 66(5):415-423.

194. Jean-Louis Vincent, James A Russell, Matthias Jacob. Albumin administration in the acutely ill: what is new and where next? Critical Care. 2014; 18:231-35.

195. Bhadade R R, Desouza R.et al. Microalbuminuria: A biomarker of sepsis and efficacy of treatment in patients admitted to a medical intensive care unit of a tertiary referral Centre. J Postgrad Med 2014; 60:145-50.

196. Pietro Caironi, Gianni Tognoni, et.al. Albumin replacement in patients with severe sepsis or septic shock. N Eng J Med.2014; 370:1412-21.

197. Chen CW, Chen YY, Lu CL. Severe hypoalbuminemia is a strong independent risk factor for acute respiratory failure in COPD: A nationwide cohort study. Int J of chr obs pul dis.2015;10(1):1147-54.

198. Pal A, Jain A, Parashar MK. Serum Serial Albumin as a Prognostic Marker in Critically Ill Patients. Int J Sci Stud 2017;5(2):156-159.

199. Santosh Gosavi, Prashanth Shinde. Serum Albumin: A Prognostic marker in critically ill patients. Int J of Sci Res 2017;5(5).

ANNEXURE

ANNEXURE – I

PROFORMA

Name:	Address:
Father's/Husband's Name:	Age:
Sex:	Religion:
Occupation:	D.O.A.:
Education:	D.O.D.:
Marital Status:	I.P. No.:
Unit:	Ward:

Final Diagnosis:

PRESENTING COMPLAINTS

\

HISTORY OF PRESENT ILLNESS

- Duration
- Onset
- Progress
- Severity
- Aggravating Factors
- Relieving Factors
- Any other

PAST HISTORY

- Any previous similar complaints in the past
- History of Major Illnesses, like
  - Diabetes Mellitus
  - Hypertension
  - Jaundice
  - Chronic Obstructive Pulmonary Diseases
- Any previous Hospitalization
- Any major operations and/or accidents
- History of blood transfusion
- Any other

PERSONAL HISTORY

- Diet
- Appetite
- Sleep
- Micturition / Bowels

- Habits: Smoking Quantity Duration

  Alcohol Quantity Duration

  Drugs Quantity Duration

- Mode of Life: Sedentary / Executive / Moderately active / very active

FAMILY HISTORY

History of hereditary familial diseases like

- Diabetes Mellitus
- Hypertension
- Chronic Obstructive Pulmonary Disease

GENERAL PHYSICAL EXAMINATION

Height (in cm.) :

Weight (in kg.) :

Built : Obese / Average / Thin

Nourishment : Good / Moderate / Poor

Subcutaneous Fat :

Mental State : Conscious / Altered / Drowsy / Emotional

B. Anemia: Present / Absent

C. Cyanosis: Present / Absent

D. Clubbing: Present / Absent

E. Jaundice: Present / Absent

F. Lymphadenopathy: Present / Absent

G. Edema: Present / Absent

VITAL SIGNS

- Pulse
- Respiratory Rate
- B.P.
- Temperature

SYSTEMIC EXAMINATION

A) Respiratory system

B) Cardiovascular system

C) Abdominal system

D) Central Nervous system

INVESTIGATIONS

CBC

- Hb%
- TC
- DC
- ESR
- PS

BLOOD SUGAR

MINI RENAL PROFILE

LIVER FUNCTION TESTS

SERUM TOTAL PROTEINS

SERUM ALBUMIN (Day 1)

(Day 3)

(Day 5)

(Day 10)

BLOOD GAS ANALYSIS (if done)

CHEST X-RAY (if done)

OTHER INVESTIGATIONS

HISTORY OF ALBUMIN INFUSION (PRESENT/ABSENT)

TOTAL NO. OF DAYS ON VENTILATION:

TOTAL NO. OF DAYS OF MICU STAY:

TOTAL NO. OF DAYS OF HOSPITAL STAY:

FINAL OUTCOME OF THE PATIENT (DISCHARGED/DEATH)

ANNEXURE II

CONSENT FORM

"SERIAL SERUM ALBUMIN AS PROGNOSTIC MARKER IN CRITICALLY ILL PATIENTS ADMITTED IN MICU AT R.L. JALAPPA HOSPITAL, TAMAKA, KOLAR."

Purpose of Study:

Patients who are admitted in ICU are at an increased risk of mortality due to the severity of their illness. Hypoalbuminemia has been associated with increased hospital mortality and morbidity. By evaluating the role of serial SA concentrations as prognostic marker, we will be able to predict poor outcome patients and manage them aggressively. There will be 64 critically ill patients participating in the study during the period of 18 months. This study will be under the supervision of Dr. K. V. Thanuj Reddy and under the guidance of Dr. V. LAKSHMAIAH, Professor Dept. of Medicine, SRI DEVARAJ URS MEDICAL COLLEGE, TAMAKA, KOLAR.

Procedure and Treatment:

Patients admitted in MICU of R.L. JALAPPA HOSPITAL, who require ventilatory support for 5 days or more are eligible for inclusion in the study group.

Baseline SA concentration estimation will be done for all patients who are admitted in MICU and are put on mechanical ventilation. Serial SA concentration estimation will again be repeated on days 3, 5, and 10 if the patient is still on mechanical ventilation for 5 days or more. For SA concentration estimation, venipuncture will be done. Other investigations as necessary may also be done.

The outcome of the patient will be recorded either as discharge of the patient from the hospital or patient's death in the hospital.

Risks:

There are certain risks and discomforts that you may experience as a result of participating in this study. These may include hematoma and/or infection at the site of venipuncture, which will be adequately treated.

Benefits:

On the basis of new information, the patient's outcome could be better predicted. There will be no extra benefits to the patient otherwise.

Financial Incentive for participation:

You will not receive any payment for participating in this study.

Alternatives:

If you decide not to participate in the study, you will receive the standard treatment for patients with this condition.

Authorization to publish results:

Results of this study may be published for scientific purposes and/or presented to scientific groups; however, you will not be identified.

Sponsors Policy:

There are no sponsors for this study.

Institutional Policy:

There will neither be any compensation to or for the patient and his/her relatives nor would there be any monetary benefits for the damage incurred.

ANNEXURE III

KEY TO MASTER CHART

DIS	-	Discharged from hospital (survivor)
DTH	-	Death in hospital (non-survivor)
F	-	Female
IPD No.	-	In patient number
M	-	Male
MICU	-	Medical Intensive Care Unit
Sl No.	-	Serial number
Sr. albumin	-	Serum albumin levels in g/dL

SL.NO	IP.NO	AGE	SEX	S.A DAY 1	S.A DAY 3	S.A DAY 5	S.A DAY 10	DAY OF VENTILATION	DAYS OF MICU STAY	DAYS OF HOSPITAL STAY	OUTCOME
1	401863	67	M	4	3.9	3.8	3.6	5	7	10	DIS
2	397493	55	M	4.1	3.9	3.5	3.9	6	10	15	DIS
3	322434	45	M	4	3.9	3.5	3.2	6	9	15	DIS
4	325844	30	M	2.8	2.7	2.1	1.8	10	10	10	DIS
5	372462	35	M	3.1	2.9	3	3	8	12	12	DIS
6	382296	59	M	3.4	2.6	2.1	2.4	10	15	21	DIS
7	453816	25	M	3.5	3	2.8	1.8	11	14	16	DIS
8	373369	55	M	3.6	2.3	2.1	1.8	11	11	11	DIS
9	433938	35	M	3.1	2.9	2.3	2.1	6	8	15	DIS
10	384660	80	M	3	2.5	2.1	1.8	8	12	15	DIS
11	318691	18	F	3.1	2.6	2.7	2.6	10	15	20	DIS
12	317459	22	M	3.5	3.4	2.9	2.7	7	10	20	DIS
13	469243	32	M	3	2.6	2.1	2.2	6	12	18	DIS
14	379349	54	M	3.1	2.5	2.1	2.1	8	11	15	DIS
15	407719	70	M	3.6	3.1	2.8	2.7	6	10	12	DIS
16	478946	28	M	3.2	2.5	3	2.8	5	6	10	DIS
17	386245	68	M	3.1	2.7	2.5	2.6	10	12	15	DIS
18	456536	40	M	3.4	3	3.1	2.7	11	12	24	DIS
19	318691	20	F	2.7	2.4	2.2	2.4	6	8	12	DIS
20	325880	23	F	3.2	2.5	2.3	2.5	6	8	12	DIS
21	387110	30	F	3.5	2.9	2.5	2.4	10	15	20	DIS
22	402578	58	M	3.6	3.1	2.7	2.4	8	10	15	DIS
23	456712	40	M	3.3	2.7	2.6	2.3	7	9	20	DIS
24	325880	42	F	4.1	3.9	2.9	2.5	17	22	25	DIS
25	352486	80	F	4	3.7	3.6	3.1	12	18	25	DIS
26	285397	40	M	4	3.6	3	2	11	16	22	DIS
27	325812	65	F	3.1	3	2.7	2.8	8	12	20	DIS
28	351467	30	F	3.4	3.1	2.9	2.8	5	8	13	DIS
29	352499	18	M	4	3.8	3.5	3.3	6	10	13	DIS
30	359492	20	F	3.1	3	2.8	2.5	9	13	21	DIS
31	359279	20	M	3.9	3.7	3.4	2.9	6	10	14	DIS
32	366130	28	M	4	3	2.8	2.9	9	10	14	DIS
33	350533	26	M	3.1	3.1	3.4	2.5	6	13	21	DIS

34	349146	30	M	3.2	3.8	3.2	3.1	8	13	16	DIS
35	338580	34	M	3	3.7	3.4	2.8	8	22	25	DIS
36	345686	36	M	4.1	2.5	2.8	3.3	9	12	16	DIS
37	344831	44	M	3.6	2.4	3.4	3.1	6	15	24	DIS
38	340413	52	F	4	2.9	3.2	2.1	6	15	21	DIS
39	116275	64	M	4	3.1	3	2.9	12	9	13	DIS
40	342023	72	F	2.7	2.7	3	3.1	12	9	13	DIS
41	349626	70	M	3.9	2.9	3.6	2.8	11	12	16	DIS
42	395574	42	M	3	2.5	2.1	1.7	7	15	15	DTH
43	365191	70	M	3.5	2.9	2.1	1.9	11	11	11	DTH
44	397493	58	M	3.2	2.9	2.3	2.1	12	12	12	DTH
45	403139	24	F	3.1	2.5	1.9	2.1	7	11	11	DTH
46	363091	42	F	3.2	2.7	2.2	1.9	11	11	11	DTH
47	420556	70	M	3.1	2.6	1.8	1.3	7	12	12	DTH
48	427445	21	M	3	2.4	1.8	1.3	11	20	20	DTH
49	426349	68	M	3.2	2.6	2	1.6	15	20	20	DTH
50	462306	60	M	3	3.1	3	2.6	9	15	15	DTH
51	371334	58	F	2.7	2.6	2.4	2.1	6	18	18	DTH
52	418942	80	M	3.1	2.8	2.3	2	6	13	14	DTH
53	465566	62	M	3.3	2.9	2.6	2.4	13	14	14	DTH
54	455668	46	M	3.1	2.9	2.5	2.3	8	15	15	DTH
55	364745	42	F	2.9	2.6	2.3	2	12	14	14	DTH
56	444125	81	M	3.5	3.3	2.9	2.7	8	16	16	DTH
57	444134	30	M	3	2.6	2.3	2.2	6	20	25	DTH
58	482119	45	M	3.2	2.8	2.4	2.1	9	12	12	DTH
59	476280	62	M	3	2.8	2.5	2.1	12	14	14	DTH
60	486103	38	M	3.3	2.8	2.5	2.3	15	15	15	DTH
61	488542	28	M	3.3	2.6	2.3	2.7	6	15	15	DTH
62	490318	34	M	3.2	2.4	2.9	2.2	9	12	16	DTH
63	415436	44	F	3	2.9	2.8	2.3	12	14	14	DTH
64	294266	72	M	2.7	2.8	2.5	2.1	6	12	12	DTH