# POSITIVE FLUID BALANCE PREDICTS MORTALITY IN INTENSIVE CARE UNIT PATIENTS

**By**

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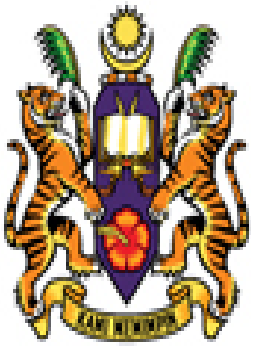


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| | |
|---|---|
| AKI | Acute Kidney Injury |
| ALI | Acute Lung Injury |
| APACHE | Acute Physiology Age and Chronic Health Evaluation |
| ARDS | Acute Respiratory Distress Syndrome |
| BA | Bronchial Asthma |
| CCIS | Critical Care Information System |
| CI | Confidence interval |
| CRF | Chronic renal failure |
| CVP | Central Venous Pressure |
| DM | Diabetes mellitus |
| ECF | Extracellular fluid |
| HIS | Hospital Information System |
| HSNZ | Hospital Sultanah Nur Zahirah |
| HUSM | Hospital Universiti Sains Malaysia |
| HPT | hypertension |
| ICU | Intensive Care Unit |
| ICF | Intracellular fluid |
| I/O | Input - Output |
| LOS | Length of stay |
| MI | Myocardial infarction. |
| PPV | Pulse Pressure Variation |
| OR | Odds ratio |
| PFB | Positive fluid balance more than 1 liter |
| RR | Relative risk |

| | |
|---|---|
| SAPS II | Simplified Acute Physiology Score II |
| SOFA | Sepsis Related Organ Failure Assessment |
| SVV | Stroke Volume Variation |
| TWBC | Total White Blood Cell |
| TBW | Total Body Water |

# ABSTRAK

Keseimbangan cecair badan yang positif adalah faktor yang telah diketahui yang boleh menyebabkan  kesan yang buruk pada pesakit-pesakit kritikal terutamanya pada pesakit yang mempunyai kegagalan buah pinggang yang akut. Sasaran kajian ini adalah untuk menilai kesan keseimbangan cecair badan yang positif di kalangan pesakit yang dimasukkan ke Unit Rawatan Rapi, Hospital Sultanah Nur Zahirah.

**Objektif**

Objektif utama kajian ini adalah untuk menentukan kaitan di antara keseimbangan cecair badan yang positif dan kematian di kalangan pesakit yang dirawat di unit rawatan rapi.

**Kaedah**

Kajian ini adalah kajian retrospektif. Semua pesakit yang memenuhi kriteria dan dimasukkan ke ward diantara 1hb April 2012 dan 31hb Disember 2012 dimasukkan ke dalam sampel kajian ini. Data kajian diambil daripada rekod perubatan. Analisis statistikal dijalankan untuk menentukan kaitan diantara keseimbangan cecair badan yang positif untuk menjangka peratusan kematian di unit rawatan rapi.

**Keputusan**

Sebanyak 200 orang pesakit dimasukkan ke dalam kajian ini dimana 40 orang didapati mati dan 160 orang hidup ketika discaj daripada unit rawatan rapi. Lebih daripada 90% daripada jumlah pesakit adalah berbangsa Melayu 53.4 ± 18.1 (mean ± SD). Penyebab utama kemasukan ke unit rawatan rapi adalah kegagalan sistem pernafasan (46%) dan "septic shock" berserta kegagalan system pernafasan (51%). Statistik analisis menunjukkan keseimbangan cecair badan yang positif, iaitu melebihi satu liter sehari mempunyai 4 kali ganda untuk risiko kematian berbanding dengan pesakit yang mempunyai keseimbangan cecair badan kurang daripada satu liter sehari. (RR=4.0, 95% CI 2.20, 7.36, P <0.01). Faktor lain yang menyumbang kepada kematian pula adalah kegagalan buah pinggang yang akut (P<0.01). Analisis 'ROC' menunjukkan purata cecair keseimbangan badan yang boleh membawa risiko kematian adalah purata cecair yang melebihi 987 ml sehari.

**Kesimpulan**

Purata keseimbangan cecair badan melebihi satu liter sehari adalah risiko kematian di kalangan pesakit yang menerima rawatan di unit rawatan rapi.

# ABSTRACT


**Background**

Positive fluid balance is known to be a factor to cause poor outcome in critically ill patients especially in patient with acute kidney injury. The goal of this study is to assess the outcome of positive fluid balance in general patients admitted to intensive care unit, Hospital Sultanah Nur Zahirah.

**Objectives**

The main objective is to determine the association of positive fluid balance in causing mortality of the critically patients who were managed in ICU.

**Methodology**

This is a retrospective cohort study. The patients who fulfilled the inclusion criteria and were admitted to ICU between April 1st, 2012 and December 31st, 2013 were included in this study. Data were abstracted from the medical record. Univariate analysis and multivariate analysis were carried out to determine the association and the risk ratio of PFB in predicting the death in ICU patients. ROC curve was plotted to assess the optimal cut-off point.

**Results:**

A total of 200 patients were recruited for this study from which 40 patients were died and 160 patients were alive during discharge from ICU. More than 90% of the patients were Malays. The mean (SD) age group was 53.4 (18.1) years old. The main reasons for ICU admission were respiratory failure (46%) and septic shock with respiratory failure

(51%). Univariate analysis and multivariate analysis showed that those with positive fluid balance of > 1L per day had 4-fold risk of dying as compared to those with average fluid balance of <1L per day (RR=4.0, 95% CI 2.20, 7.36, P <0.01). The ROC curve showed the cut off point for average fluid balance that risk to mortality was 987 ml per day.

**Conclusion:**

The average positive fluid balance of ≥1L per day during ICU stay is a risk factor for mortality among the critically ill patients managed in ICU.

# CHAPTER 1: INTRODUCTION

## 1.1 Background

Critically ill Patients of all ages from various departments who needed intensive care and very close monitoring, and those who needed assisted ventilation are referred to Intensive Care Unit (ICU) for combine management. Whatever reasons for their admission to ICU, fluid therapy remain the mainstay and vital treatment for all cases. The main reasons for administering the fluid therapy are; for fluid resuscitation for those who are in shock and for fluid replacement for those who are not able to take orally such as comatose patients, patients on ventilator, those who has feeding intolerance, etc.

Fluid therapy is the routine treatment in intensive care unit. Intravenous fluids are widely administered to critically ill patients especially for resuscitation and also for maintenance. Appropriate fluid administration is vital for those in intensive care unit especially who are not able to start on enteral feeding.

In general intensive care unit, there are varieties of patient who came from multidisciplinary area which can be classified as operative and non-operative patient. The other classification was elective or non-elective admission to ICU. Most of these patients were hemodynamically unstable at the early part of presentation to ICU, thus they required fluid resuscitation.

Fluid resuscitation is needed to restore cardiac output and maintain adequate mean arterial pressure (MAP) for tissue perfusion. The aim is to prevent organ failure. For example, in patient with septic shock, aggressive initial fluid resuscitation improve clinical outcome by improving tissue perfusion (Smith and Perner, 2012). But, how much fluid that needs to be administered is not well recognized. In patients such as fluid overloaded patient, fluid resuscitation may cause further harm to the patients.

Furthermore, the management of fluid therapy in ICU is challenging especially when dealing with patients with acute kidney injury. Most of the care provider will seek a balance between the competing needs of adequate fluid resuscitation while avoiding a progressively positive fluid balance. If too much fluid balances, it may lead to tissue edema, thereby contributing to ongoing organ dysfunction which can further delay recovery of the critically ill patient (Prawle *et al.*2009). Positive fluid balance also impaired wound healing, may cause prolonged ventilation and nosocomial infection, particularly in critically ill patient in whom fluid challenges are frequent. However, if too little fluid is given, this may lead to poor tissue perfusion that also contributes to organ dysfunction e.g. acute renal failure. Appropriate management of intravenous fluid replacement is a key aspect of the outcome of the critically ill patient in intensive care unit.

There were recent studies demonstrated that a positive fluid balance in critical illness is strongly associated with worse outcome (Klein *et al.*, 2007; Shum and Lee.,2011). There was clear evidence suggesting that fluid overload may be detrimental in many conditions. The adverse effects of fluid overload may be most pronounced in situations such as underlying myocardial insufficiency, systemic sepsis, major surgery or trauma, which predispose to acute kidney injury.

Fluid balance should be considered as a potentially valuable biomarker of critical illness. We conducted a retrospective cohort study aimed to assess the relationship between positive fluid balance during intensive care in ICU and the mortality among the patients. This study was conducted in Hospital Sultanah Nur Zahirah, Kuala Terengganu. The hospital consists of 18 ICU beds with two intensivist incharged helped by anaesthetist and trained medical officer in anaesthesia and intensive care unit department. In this study, we defined the positive fluid balance for the average balance of fluid of more than 1 liter (Upadya *et al.*, 2005; Payen *et al.*, 2008a).In addition to that, we also investigated the association with some covariates such as SAPS II score and other characteristics (sepsis and acute kidney injury) which may also contribute to mortality among ICU patients.

## 1.2 Problem statements.

Problem statement 1:

Fluid overload / positive fluid balance predispose to organ dysfunction which may lead to mortality in critically ill patients.

Problem statement 2:

The optimal cut off point for fluid balance is not well documented.

## 1.3 Research justification

Previous studies reports suggested that accurate fluid balance monitoring results in a better outcome while a positive fluid outcome may predict higher mortality in critically ill patients. This study is crucial in providing more evidence of such relationships in Malaysian hospital setting. The knowledge gained from this study will provide information to support evidence-based practices on accurate fluid management of critically ill patients in ICU.

# CHAPTER 2: LITERATURE REVIEW

This chapter discusses about the fluid management of ICU patients from what could be established from available literatures. These include from electronic databases such as OvidMedline, Pubmed, Ebscohost and science direct; books and scholars researches obtained from internet.

## 2.1 An overview of patients in intensive care unit

An intensive care unit is a specific area in the hospital, specially staffed and equipped unit, where patients with life-threatening illnesses or disorders are monitored and treated (Elliot et al., 2007). It is dedicated to the observation, care and treatment of patients with life threatening illnesses, injuries or complications from which recovery is generally possible. The patients in intensive care unit can be classified either surgical or medical patients. The common causes of ICU admission from surgical discipline are perioperative stabilization, post-operative weaning, hypovolemic shock and septic shock. The common causes of medical admission are septicaemic shock and acute respiratory failure requiring ventilator support. The patients with acute respiratory failure who were admitted to ICU require noninvasive or invasive mechanical ventilation.

The first intensive care unit (ICU) in Malaysia was established in 1968. Since then, intensive care has developed rapidly and ICUs are now available in all tertiary care hospitals and selected secondary care hospitals in the Ministry of Health. There are wide varieties of critically ill patients managed in ICU which can be categorized as

operative and non- operative patients. SAPS II score is a scoring system which provides an estimation of ICU mortality. The other scores used for prediction of in-hospital mortality were APACHE score and SOFA score.

## 2.2 Simplified Acute Physiology Score (SAPS) II

The Simplified Acute Physiology Score (SAPS) was based on data derived from Europe.(Le Gall *et al.*, 1984) It was then revised to new score named SAPS II. The SAPS II, based on a large international sample of patients, provides an estimate of the risk of death without having to specify a primary diagnosis (Le Gall et al., 1993). The SAPS II includes 17 variables: 12 physiology variables, age, type of admission (scheduled surgical, unscheduled surgical, or medical), and three underlying disease variables (acquired immunodeficiency syndrome, metastatic cancer, and hematologic malignancy). The 12 physiology variables are heart rate, systolic blood pressure, body temperature, PaO2/FiO2 ratio, urinary output in ml/kg/h, serum urea, TWBC, serum potassium, serum sodium, serum bicarbonate, bilirubin level and glascow coma scale. The worst values within 24 hours were taken to calculate the score. The score then will be converted to percentage by certain formula derived to estimate the probability of hospital mortality. In Malaysia, SAPS II scoring system is used in the general ICUs of 14 major states hospital and became one of the criteria in the Malaysian Registry of Intensive Care annual report.

## 2.3 Physiology of Body Fluid

Fluid management strategies need to be guided by an understanding of the pathophysiologic mechanisms underlying fluid imbalance. Understanding the pathophysiology of the body fluid is very important in managing fluid especially in critically ill patients managed in intensive care unit.

Most of the patients admitted to ICU require boluses of fluid. Physiologically, intravenous fluid administration serves two purposes, to replete or maintain intravascular fluid volume and to maintain or replete free water, electrolyte, blood component and protein concentration derangement. Ultimately, the purpose of fluid volume administration is to maintain cardiac preload and cardiac output, oxygen delivery and tissue perfusion for cellular homeostasis.

Total Body Water (TBW) is distributed freely throughout the body except for a very few areas in which movement of water is limited (e.g. parts of renal tubules and collecting ducts) Bongard and Sue, 2002). In normal persons, 50-60% of total body weight is made up of water. TBW commonly divided into the extracellular fluid (ECF) space and intracellular fluid (ICF) space. ECF can be further divided into intravascular fluid and interstitial fluid. ECF comprises one-third of total body water and the other two-third is in the ICF. In an average adult male weight 75kg, the total amount of water in the body is 45 litres (sixty percent of body weight); 30 litres are in the cells (ICF), 12 litres are between the cells (interstitial), and three litres are in the blood vessels (intravascular). The exchange between the ICF and ECF compartments occurs through a semipermeable cell membrane, which allows water and small molecules to pass

through.(Scales and Pilsworth, 2008) Total body water as a percentage of total body weight decreases progressively with increasing age. By the age of 60 years, total body water (TBW) has decreased to only 50% of total body weight in males mostly due to an increase in adipose tissue. In critical illness patient, it does not only result from abnormalities in the amount and distribution of water but can also cause strikingly abnormal disorders of water and solutes.(Bongard and Sue, 2002)

Water diffuses freely between the intracellular space and extracellular space in response to solute concentration gradients. Therefore the concentration of solute everywhere in the body is made equal by water movement and the amount of water in different compartments of the body depends on the quantity of solute present in that compartment (Bongard and Sue, 2002). The distribution of water between these two compartments is complex in normal subject and more so during disease state in which oedema (increase in interstitial volume) or accumulation of fluid in normally nearly dry space (peritoneal cavity, pleural space) is present. The volume of intravascular compartment directly determines the adequacy of the circulation; this in turn determines the adequacy of delivery oxygen, nutrients and other substances needed for organ system function.

In managing patients in intensive care unit, the term hypovolemia and hypervolemia is commonly used. Hypovolaemia or sometimes referred to ‘fluid loss’ or ‘volume depleted’ condition, generally refers to decreased intravascular volume and not decreased extracellular volume. This disorder can be results from bleeding, increasing vascular permeability (e.g. sepsis), polyuria state, insensible loss (e.g. evaporation) and insufficient function of the normal mechanism of intravascular volume maintenance. On the other hand, the term hypervolaemia generally refers to increased extracellular

volume with or without increased intravascular volume. Thus patient with oedema or ascites have hypervolaemia.

Hypovolaemia is evidenced by multiple clinical variables including heart rate, blood pressure, urinary output, arterial oxygenation and pH (Hemmings and Egan, 2013). Even though hypovolaemia defined as diminished in intravascular volume, hypovolaemia can presence in normal or increased extracellular volume. For example, patients with pulmonary oedema and ascites but they are having depletion of intravascular volume. The assessment of adequacy of intravascular volume in the presence of normal or increased extracellular volume is often difficult, especially in critically ill patients. (Bongard and Sue, 2002). Thus fluid balance management is a challenge part of the process of care in critically ill patients.

Hypovolaemia with normal extracellular volume occurs as a result of any disorder that alters the balance between intravascular and extravascular fluid compartments. Intravascular oncotic pressure and intact vascular integrity largely maintain intravascular volume, while hydrostatic pressure tends to push fluid out of the circulation. Sepsis, ARDS, shock, and other critical illnesses alter this balance by increasing permeability of the vasculature. The result is an increase in the interstitial fluid compartment (e.g. pleural effusions and ascites). Although decreased vascular oncotic pressure and increased hydrostatic pressure should also shift fluid balance in this direction, these rarely develop rapidly enough to allow total ECF volume to remain constant. Patients with shock or severe sepsis, aggressive initial fluid resuscitation has been shown to improve overall prognosis. However, in critically ill patients, cumulative

fluid accumulation result from fluid administration is recognized as a potential contributing factor to increased morbidity and mortality. (Bouchard and Mehta, 2010)

Hypervolaemia or excessive fluid in the body always refer to increase ECF volume and associated with peripheral oedema, ascites, pleural effusion or other fluid collection. The intravascular volume may be low, normal or high. Increased ECF volume by itself is usually not an emergency situation in ICU patients, but it depends on how much and where the excess fluid accumulates. If associated with decreased effective intravascular volume or increased intravascular volume (congestive heart failure with pulmonary oedema), rapid intervention may be required.

Increased ECF volume may be localized to certain compartments (e.g. pleural effusion or ascites) or generalized (e.g. anasarca). Generalized oedema is often a major feature of increased ECF volume. Oedema usually occurs at dependent areas of the body, such as the lower back and sacral areas among the critically ill patients. Oedema always indicates increased ECF volume except when there is a localized mechanism of fluid transudation or exudation. However the presence of oedema may or may not signify that the intravascular volume is increased. If low, evidence of inadequate circulation may be found, including tachycardia, peripheral cyanosis and altered mental status. The critically ill patient with decreased intravascular volume and increased extracellular volume may have an acute increase in permeability of the vascular system with leakage of fluid into the interstitial space (e.g. sepsis). In most patients, some worsening of (oedema) must be accepted for a time until intravascular volume is replete. However by giving fluid thus improving of renal perfusion, there may be appropriate natriuresis with mobilization of oedema fluid. At this point, the care provider has to accept the polyuria

state and observe for the clinical measures to avoid excessive loss of urine that again will lead to hypovolaemia.

Intravascular volume is essential to maintain cardiac filling volume. Preload is measured directly as end-diastolic volume or indirectly as end-diastolic pressure. Preload determines cardiac function, measured as cardiac output or ejection fraction. Cardiac output is a key determinant of tissue and organ perfusion. Diminished organ perfusion is associated with decreased oxygen and nutrient delivery and also decreased removal of metabolic by products (Papadakos and Szalados, 2005).

Maintaining harmony in the body fluids is essential for human beings. A fluid loss will cause hemodynamic instability and a fluid gain will cause an overload of fluid which may contribute to further deterioration of the patient especially in critically ill patien (Mooney, 2007). Fluid balance is represented as interval and cumulative intake/output (I/O). Positive fluid balances occur when I>O and typically represent third space fluid sequestration, persistent vasodilatation or compromised elimination (renal failure) (Papadakos and Szalados, 2005). Disturbances in the fluid balance can lead to serious complications for the patient (Mooney, 2007).

The physiologic rationale for fluid resuscitation in critically ill patients is to augment the circulating blood volume in order to increase cardiac stroke volume by the means of the Frank–Starling effect (Ertmer *et al.*, 2013). Accordingly, it is anticipated that the increase in cardiac output improves the end-organ perfusion and thus prevents or ameliorates acute organ dysfunction. This physiologic rationale has been challenged by the finding that fluid resuscitation beyond normovolaemia triggers an endogenous

cascade to eliminate excessive intravascular volume and to prevent hypervolemic cardiac decompensation (Lobo *et al.*, 2006).This cascade involves the release of natriuretic peptides and the suppression of the renin–angiotensin–aldosterone system and results in increased diuresis, vasodilation, and increased endothelial permeability. Furthermore, the release of natriuretic peptides may also trigger the degradation of the endothelial glycocalyx which has been reported with intravascular hypervolemia.(Ertmer *et al.*, 2013)

## 2.4 Fluid monitoring in intensive care unit

Monitoring of the fluid balance is the assessment, recording and calculation of the fluid intake and the fluid output (Reid *et al.*, 2004).Fluid intake is the amount of fluid that comes into the body orally or by intravenous infusion. Fluid output is the amount of fluid that leaves the body by means of urine, sweat, respiration and stools (Scales and Pilsworth, 2008). In the normal state, fluid intake may vary between 1 500 and 2 500 ml/day, and urine output should be at least 0.5 ml/kg bodyweight/hour, depending on the intake.

Scales and Pilsworth emphasise the importance of fluid balance charts. These charts allow the recording of all measurable ingested and excreted fluids. The heading “intake” must include all medication and fluids taken orally, medication and fluids given intravenously, and all fluids administered via any other tube. The heading “output” must include all urine, drainage, vomit, measurable stools (colostomy bag) and nasogastric tube secretions. However I/O balances represented on intensive care unit (ICU) chart do not include insensible losses. Insensible losses are normally approximately 1-1.5L/day

in adults but can be much greater in pathologic conditions such as loss of epithelial integrity, fever, unhumidified respiratory gases and diarrhea (Papadakos and Szalados, 2005). It is important to recognise the insensible loss of fluid especially via respiration, fever and perspiration .It may not always be possible to measure the fluid balance exactly, for instance in the case of large, unmeasurable amounts of diarrhea. I/O balances on ICU chart, generally also fail to account for the differences in crystalloid, colloid or blood component volume infused; this is important because the relative contributions of these different fluids to volume expansion varies significantly (Papadakos and Szalados, 2005). It is noted by Vincent et al. that accurate fluid balance monitoring results in a better outcome for the patient, while a positive fluid balance may predict higher mortality in critically ill patients. (Vincent *et al.*, 2005).

## 2.5 Factors which influence the mortality of ICU patients

Change in ICU management has evolved significantly over time. Reduction in mortality among ICU patients has fallen dramatically since 1980. Such reduction can be attributed to changes in the delivery of critical care, establishment of clinical networks, an implementation of ventilator care bundles and ongoing researches done among intensive care unit patients. There are few factors than known to have association with mortality in ICU. The three most common factors are severe sepsis, acute kidney injury and ARDS(Geok et al., 2013). The other factors that known to contribute higher mortality rate among ICU patients are hospital acquired pneumonia, cerebrovascular disease and infection/gangrene of limb (including necrotizing fasciitis and osteomyelitis)

Severe sepsis within 24 hours of ICU admission carries in-hospital mortality of 43.1%. (Geok *et al.*, 2013) In the Sepsis Occurrence in Acutely Ill Patients (SOAP) study, the in-ICU mortality was 27% in patients with sepsis on ICU admission (Vincent *et al.*, 2006).

Reported mortality in ICU patients with AKI varies considerably between studies depending on definition of AKI, patient population (e.g., sepsis, trauma) and severity of AKI. Patients with maximum RIFLE class R, class I and class F had hospital mortality rates of 8.8%, 11.4% and 26.3%, respectively (Hoste EA, 2006). Payen et al reported that patients with acute renal failure had higher mortality rates than patients without acute renal failure among patients enrolled in the SOAP study (60-day mortality 35.7% versus 16.4%; $P < 0.01$)(Payen *et al.*, 2008a).

The scoring systems used in the intensive care unit also influence the survival of the ICU patients. The scoring systems predict the mortality of the patients. APACHE II, SAPS II and SOFA scoring systems are the most widely used in intensive care unit. The greater score estimate higher chances for mortality among the ICU patients. The SAPS II, based on a large international sample of patients, able to provides an estimation of the risk of death without having to specify a primary diagnosis (Le Gall et al., 1993).
The other factor that may contribute to mortality is ARDS (Towfigh et al., 2009). Study done by Ranes et al showed VAP is associated with a high rate of hospital and long-term mortality (Ranes et al., 2006). Study done by Feng et al suggests that age and duration of mechanical ventilation are strongly associated with mortality (Feng et al., 2009). Presence of comorbidities also can contribute to the factor that causes mortality in ICU (Johnston et al., 2002).

Recently, fluid balance was found to be a biomarker for prediction of survival. Several studies had shown that positive fluid balance predict mortality in critically ill patients (Bagshaw et al., 2008; Shum and Lee, 2011). Positive fluid balance was also known to be associated with increased mortality by other cohort study (Russell *et al.*, 2000; Vincent and De Backer, 2005; Abraham and Singer, 2007). This can be explained by the underlying pathophysiology that leads to organ failure.

## 2.6 Management of fluid in critically ill patients

The objectives of fluid management in ICU are to maintain adequate blood pressure, tissue oxygenation and intravascular volume. The management strategies need to be guided by an understanding of the pathophysiologic underlying fluid imbalance. Both hypovolaemic and hypervolaemic produced devastating effects to the patient. The correct amount and timing for fluid administration must always according to any of the available parameters to assess fluid-responsiveness, not only blood pressure and heart rate but more accurate parameters such as sonographic inferior vena cava diameter index, cardiac output measurement and pulse pressure variation. These are the essential points in order to optimize fluid resuscitation by avoiding deleterious effects in critically ill patients.

Fluid management in intensive care unit has evolved significantly over time. There are many studies done recently focused on excessive fluid therapy in critically ill patients and outcome of the patients. Efforts have focused on improving patient outcome by optimizing fluid administration. Concepts for goal-directed fluid therapy and new

modalities for the assessment of fluid status as well as for the prediction of responsiveness to different interventions is continue to emerge.(Bartels et al., 2013)

Most critically ill patients will require fluid resuscitation at some juncture during their stay in the intensive care unit (ICU). Surgical patients also typically require fluids therapy perioperative. An array of additional clinical situation may prompt fluid administration; for instance, in burn victims, hypoproteinaemic patients, cirrhotic patients with ascites undergoing therapeutic paracentesis, and so on. Assessment of the adequacy of fluid resuscitation integrates multiple clinical variables, including heart rate, blood pressure, urinary output, arterial oxygenation and pH.

Fluid balance management is most crucial element in management of critically ill patients. It is very important to maintain the balance as any excessive and depleted in fluid may cause harm to the patient in intensive care unit. In the hypovolaemic patient, reduced circulating blood volume and venous return will altered tissue perfusion and may initiate a cascade of pathophysiologic processes culminating in multiple organ failure eventually death. Therefore, rapid fluid resuscitation accompanied by aggressive efforts at maintaining hemostasis is required to save lives. The objectives of fluid management are to maintain adequate blood pressure, tissue oxygenation and intravascular fluid volume hence to avoid organ failure. Conservative strategies of fluid management mandate a switch towards neutral balance and then negative balance once hemodynamic stabilization is achieved.

There are many types of fluid available in intensive care unit and classified as colloid and crystalloid. The benefits of each type of fluid have been widely debated for many years and controversy continues as to whether crystalloid or colloids are preferred for

intravascular volume replacement. However, both fluids are capable of correcting hypovolaemia (Ali Al-Khafaji and Webb, 2004) All patients require a predictable volume of maintenance fluid, which is usually given as combination of nutritional fluid and crystalloid. Colloid fluids are reserved for supplementation of the intravascular volume. However, choice of fluid is in states of increased lung capillary permeability is less important (Vincent, 2000). In contrast to sepsis patient, choice of fluid is very important. In our study, we do not differentiate between colloid and crystalloid administration. We considered 'fluid' as combination of all types of fluid given to the patients while in ICU.

Recently there are few studies demonstrated the effect of crystalloid especially normal saline solution. Chowdhury et al. investigated the effects of isotonic saline or balanced crystalloids on renal blood flow in healthy volunteers. The authors found that balanced crystalloid infusion does not alter renal blood flow and cortical tissue perfusion, whereas saline even reduced these variables of kidney perfusion (Chowdhury *et al.*, 2012). The underlying pathophysiology may involve hyperchloraemia which is a known mediator of renal afferent arteriolar vasoconstriction and, thus, reduced glomerular perfusion (Wilcox, 1983;Aksu *et al.*, 2012; Yunos *et al.*, 2012). Fluid resuscitation therefore does not guarantee increased organ perfusion. Moreover, an increase in organ perfusion per se has not yet been proven beneficial. (Ertmer *et al.*, 2013) An increase in organ perfusion and microvascular blood flow in early sepsis may foster the invasion of bacteria, toxins and oxygen radicals into the hypoperfused tissue and thus cause severe ischemia–reperfusion injury (Russell, 1998; Hilton and Bellomo, 2012).

For decades, attempts at answering the question 'how much fluid do I give?'. In the early 2000s, several landmark papers suggested that there might be a more rational way to manage hemodynamics particularly focused on the amount and timing of fluid administration. By manipulating hemodynamics to achieve specific targets for mean arterial pressure, urine output, and central venous oxygen saturation in septic patients, Rivers and colleagues showed that mortality could be improved by expanding one's hemodynamic goals beyond simply maintaining adequate blood pressure (Rivers *et al.*, 2001).

The clinical value of goal-directed fluid administration has also been demonstrated in other clinical settings and long-term beneficial effects in patients undergoing high-risk procedures have been suggested (Rhodes *et al.*, 2010) . Study done by Lobo et al. suggesting that a fluid restrictive strategy in conjunction with goal-directed therapy might be beneficial after major surgery. They demonstrated, limiting the total amounts of crystalloid infused was associated with decreased complications after major surgery in two groups that were randomized to a low rate or a high rate of crystalloid maintenance (Lobo *et al.*, 2011).However, not all data are supportive. In an earlier study by Gattinoni and colleagues, no difference in mortality in the ICU and at 6 months was detected in 762 critically ill patients randomized to three different hemodynamic goals (normal cardiac index, cardiac index >4.5 l/minute/$m^2$, or normal mixed venous oxygen saturation ≥70%) (Gattinoni *et al.*, 1995).

A recent trial studying the effects of goal-directed intraoperative fluid therapy using esophageal Doppler monitoring also failed to show a beneficial effect and actually found adverse effects in the intervention group. However, this study did not show a

difference in the amount of fluid (colloid or crystalloid) administered to both groups (Challand *et al.*, 2012).

Overall, it appears that hemodynamic management protocols that focus on either preload or stroke volume optimization, as opposed to maintenance of blood pressure can improve outcomes. In a meta-analysis of 5,056 surgical patients randomized to tissue-perfusion-based hemodynamic protocols in 32 studies, mortality was reduced (pooled odds ratio = 0.67, 95% confidence interval = 0.55 to 0.82) (Gurgel and do Nascimento, 2011).

Besides of dynamics measurement of intravascular volume (e.g. intra-arterial blood pressure, heart rate, urine output), the static measurements to assess intravascular volume widely used in the present decades. The static measurement used to assess fluid responsiveness are central venous pressure (CVP), sonographic inferior vena cava (IVC) diameter, pulmonary artery occlusion pressure, transoesophageal echocardiography, stroke volume variation (SVV), pulse pressure variation (PPV), oesophageal doppler catheter and near infrared spectroscopy (Hemmings and Egan, 2013). Common variants available in clinical practice to assess fluid responsiveness include systolic pressure variation, SVV, PPV and the sonographic IVC diameter. Systolic pressure variation, SVV and PPV can be determined via arterial blood pressure tracings. SVV can also be obtained from minimally invasive methods, such as esophageal doppler measurements, and non-invasive cardiac output monitoring using bioreactance technology - but other methods, such as low-frequency oscillations in the plethysmographic waveform (Pleth Variability Index) are also predictive of arterial blood pressure changes induced by mechanical ventilation, and have also been used to

successfully predict fluid responsiveness.(Natalini *et al.*, 2006). To determine whether or not these new monitoring technologies will also lead to improved patient outcomes will require appropriately powered clinical trials in the future.

Hemodynamic indices attempt to predict the hemodynamic response to volume administration (that is, change in cardiac output after a standardized fluid bolus) and are based on the interaction between intrathoracic pressure changes and left ventricular end-diastolic volume and cardiac output. (Marik *et al.*, 2009) These new modalities seem to better answer the question 'what will happen to oxygen delivery if I administer fluids?) (Marik *et al.*2009).

The response of hemodynamic indices should be monitored during a fluid challenge. The basis of the fluid challenge is to achieve a known increase in intravascular volume by rapid infusion of a bolus of fluid (e.g. 200 ml of colloid).The change in CVP or PAWP after a 200 ml of increment in intravascular volume depends on the starting circulating volume. CVP or PAWP is used as it is widely used in critical care practice. However, both are not physiological because end-diastolic filling depends on physiological factors other than filling pressures(Ali Al-Khafaji and Webb, 2004). The other indices that easily be used is sonographic IVC diameter measurement which now commonly used in our clinical practice.

Using fluids to correct hypovolaemia is a dynamic process that requires ongoing evaluation of clinical and hemodynamic indices. Thus, the use of the hemodynamic indices provides a successful method of adjusting fluid volume to the patient’s need,

without increase the risk of the patient to get excessive fluid in the body which further contributes complications in critically ill patients.

## 2.7 The effects and outcome of positive fluid balance in critically ill patients

The aim of this study is to see the association of fluid balance and outcome of the patients managed in intensive care unit. Excessive fluid balance is recognized to be a factor which may decrease the speed of recovery in critically ill patients. Several studies had been done to show association between fluid balance and mortality or morbidity in critically ill patients.

There are varieties of patient in intensive care unit. They can be categorized based on referring unit or based on disease severity. Most of the patient in intensive care unit had acute kidney injury (AKI) before they were admitted to ICU or at some point during their ICU stay. Recent data imply that, after acute resuscitation, additional fluid therapy may cause harm in patients with acute kidney injury and/or oliguria. In large European multicenter study, a positive fluid balance was an important factor associated with increased 60-day mortality (Payen *et al.*, 2008a).

The renal system is essential for the homeostasis of fluids and electrolytes, the regulation of the acid-base balance, the regulation of blood pressure and the production of hormones. Renal fluid regulation is a process of filtration, re-absorption and secretion.

Despite significant improvement in managing patient with AKI in intensive care unit, the prognosis of AKI remains poor. The Management of AKI in the ICU patient is very heterogeneous, with little consensus about therapeutic measures such as fluid administration. Few studies have examined the impact of fluid balance on clinical outcomes in critically ill adults with acute kidney injury. Payen and coworkers, in a secondary analysis of the SOAP (Sepsis Occurrence in Acutely Ill Patients) study, now present evidence that there is an independent association between mortality and positive fluid balance in a cohort of critically ill patients with acute kidney injury. However there are several factors may contribute to the high mortality rate of AKI, including the underlying disease (de Mendonca *et al.*, 2000; Schroeder *et al.*, 2004), the circumstances leading to the development of AKI , the presence of anemia , and the severity of illness(Dharan *et al.*, 2005). In addition, therapeutic measures such as mechanical ventilation and the use of vasopressors have been demonstrated to be related to intensive care unit (ICU) mortality in patients with AKI (Uchino *et al.*, 2005).

The management of AKI in the ICU patient is very heterogeneous, with little consensus about therapeutic measures such as fluid administration, vasopressors, diuretics, and timing of renal replacement therapy (RRT). In a cohort study done in septic patients with AKI, Van Biesen and colleagues showed that additional fluid therapy (despite apparent optimal haemodynamics, restoration of intravascular volume and a high rate of diuretic use) not only failed to improve kidney function but also led to unnecessary fluid accumulation and impaired gas exchange.(Van Biesen *et al.*, 2005; Bagshaw *et al.*, 2008).

Other than acute kidney injury, sepsis is common among the ICU patients. Sepsis is characterized by inflammation-induced endothelial dysfunction leading to vascular leakage and vasodilatation. Ultimately, these will results absolute hypovolaemia, organ hypoperfusion and finally septic shock.

Severe sepsis and septic shock are major cause of death in intensive care patients (Weycker *et al.*, 2003; Dombrovskiy *et al.*, 2007). Most deaths from septic shock can be attributed to either cardiovascular or multiorgan failure (Ruokonen *et al.*, 1991). The causes of organ dysfunction and failure are unclear, but inadequate tissue perfusion, systemic inflammation, and direct metabolic changes at the cellular level are all likely to contribute (Russell *et al.*, 2000; Vincent and De Backer, 2005; Abraham and Singer, 2007).

Fluid resuscitation is a major component of cardiovascular support in early sepsis. Fluid resuscitation means to administer IV fluid until able to achieve good organ perfusion. If failed fluid resuscitation, inotrope/vasopressor drugs is administered to optimize cardiac preload and organ perfusion (Boyd *et al.*, 2011). Although the need for fluid resuscitation in sepsis is well established, the goals and components of this treatment are still a matter of debate (Alsous *et al.*, 2000). In other word, patients with septic shock require fluid, but the optimum amount is unknown. Care providers making this as an issue. How much fluid should be given? It is currently unknown whether a strategy using higher or lower fluid volume is better. The Surviving Sepsis Campaign (SSC) recommends goal-directed optimization in the first 6 hours followed by fluid challenges in case of persistent hypoperfusion. The former is based on one relatively small, single-center, randomized clinical trial (RCT) (Upadya *et al.*, 2005) and the latter on expert

opinion. Even though these approaches may be physiologically rational, the recommendations illustrate the low level of evidence for fluid volume in septic shock.

Several recent studies have shown that a positive fluid balance in critical illness is strongly associated with a higher severity of organ dysfunction and with worse outcome (Schuller *et al.*, 1991; Sakka *et al.*, 2002; Sakr *et al.*, 2005; Vincent *et al.*, 2006; Wiedemann *et al.*, 2006; Arlati *et al.*, 2007; Klein *et al.*, 2007). Positive fluid balance was also known to be associated with increased mortality by other cohort study (Russell *et al.*, 2000;Vincent and De Backer, 2005; Abraham and Singer, 2007). It is unclear whether this is the primary consequence of fluid therapy *perse*, or reflects the severity of illness. So, in this study, we categorized the patient with the severity of illness by using SAPS II scoring system.

Boyd, Forbes et al demonstrated a more positive fluid balance both early in resuscitation and cumulatively over 4 days is associated with an increased risk of mortality in septic shock. Central venous pressure may be used to gauge fluid balance <12 hours but becomes an unreliable marker of fluid balance thereafter. A normal CVP does not exclude hypovolaemia and the CVP is particularly unreliable in pulmonary vascular disease, right ventricular disease, patients with tense ascites, isolated left ventricular failure and valvular heart disease. Optimal survival in the VASST study occurred with a positive fluid balance of approximately 3 L at 12 hrs (Boyd, Forbes et al. 2011).

However in the other study, which had been done to septic animals, fluid resuscitation results in positive fluid balance in both septic and control animals will leads to circulatory stabilization of septic animals, but not a decrease in the anaerobic share of