GLYCATED HAEMOGLOBIN (HBA1C) AS A PREDICTOR OF OUTCOME IN TRAUMA PATIENTS IN THE SURGICAL INTENSIVE CARE UNIT

Dissertation submitted in partial fulfillment of the requirement of The Tamil Nadu Dr. M.G.R. Medical University for the M.D. Branch X (Anaesthesiology) Examination to be held in April 2011

CERTIFICATE

This is to certify that "Glycated Haemoglobin (HbA1C) as a predictor of outcome in trauma patients in the surgical intensive care unit" is a bonafide work of Dr. Karen Ruby Lionel in partial fulfillment of the requirements for the M.D. Anaesthesiology examination (Branch X) of The Tamil Nadu Dr. M.G.R Medical University to be held in April 2011.

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Introduction

The prevalence of diabetes in adult population in India has now reached alarming proportions with about 15 percent of those aged above 20 years in urban settings being diabetic.(1) Using similar diagnostic criteria (known diabetes and/or fasting and post-glucose load hyperglycaemia) the age-adjusted diabetes prevalence among adults in urban Chennai increased from 8.3% in 1988-89, to 11.6% (1994-95), 13.5% (2000) and 14.3% in 2003-04. Increase in diabetes prevalence has also been reported from rural Tamil Nadu.(2) Most diabetics remain unrecognized as a result of inadequate access to healthcare and screening programs and because they are not symptomatic until they have advanced stages of disease. A substantial proportion of those without overt diabetes has one or both of the pre-diabetic states: Impaired fasting glucose and impaired glucose tolerance with risk of progression to diabetes.(3) With the emerging epidemic of diabetes in India, it is imperative to know if the pre-admission diabetic status influences ICU outcomes, and if so further research would be warranted into management paradigms that will optimize outcomes.

HbA_1C expressed as a percentage of adult hemoglobin that is glycated, is the most widely used measure of chronic glycaemia. HbA_1C assay that was introduced in the late 1970's has become the

benchmark in assessing chronic glycaemia in research and the management of diabetes. Maintaining HbA_1C within normal limits has been shown to reduce long term complications.(4)

HBA_1C reflects the average plasma glucose levels over the previous 120 days which corresponds with the lifespan of an RBC. Standardized methods for estimating HBA_1C is now readily available in most tertiary care facilities. Large studies have validated the correlation between mean plasma glucose levels in diabetics with HBA_1C and have shown that HBA_1C can be used to prognosticate outcomes in diabetics. (5)

Patients in intensive care units frequently develop elevated blood sugars as a response to stress. Stressed Induced Hyperglycaemia (SIH) refers to a complex metabolic response to stress through raised catecholamines and stress hormones resulting in elevated blood sugar levels.(6) Intensive care experts recognize that this hyperglycaemia is associated with higher mortality. Patients requiring prolonged intensive care are at high risk for multiple organ failure and death. (7)

Differentiating SIH from diabetic hyperglycaemia is challenging in the ICU setting in view of the universally elevated blood sugars.(8) HBA_1C provides intensive care physicians a means to detect those with

diabetes and those at risk of developing diabetes in ICU settings and also helps to differentiate SIH from diabetics.

Recently there is a divided opinion on how tight the glycaemic control in critically ill patients should be.(9-16) Several important issues contribute to the complexity of the understanding and preclude consensus on tight glycaemic control.(8) Initially it was believed that increased blood sugars are a coping response of the human body to acute stress and should not be controlled.(12) Subsequently it was postulated and supported by several coronary care and acute medical care setting studies that controlling blood sugars improved outcomes.(17) Furthermore, glycaemic excursions have different effects in diabetic and non-diabetic individuals. A growing body of evidence that includes both SIH and diabetic hyperglycaemia suggests that these are different phenomena with different prognosis and needs to be approached differently.(18, 19).

The 2010 American Diabetes Association guidelines incorporate HbA_1C in the diagnosis of diabetes with values above 6.5% being diabetes and those between 5.7 and 6.4% as at risk of diabetes.(8) Risk stratification based on HbA_1C will provide greater clarity into whether diabetics and those at risk of diabetes have poorer outcomes in critical care settings. We have not found other studies that examine the relationship between elevated HbA_1C and ICU outcomes in trauma

patients. This study prognosticates the ICU stay among trauma patients on basis of their admission HbA_1C.

Aims & Objectives

Aim:

To evaluate if initial glycated hemoglobin (HbA1C) level in trauma patients predicts the outcome of patients admitted to Surgical Intensive Care Unit (SICU).

Objectives:

1) Estimate the prevalence of abnormal HbA_1C levels in trauma patients irrespective of their admission glycaemic status.

2) To explore the relationship between the initial HbA_1C and the outcome of SICU admission among trauma patients.

3) Estimate the correlation between the initial HbA_1C level and the

   a) duration of SICU stay

   b) length of ventilated days

   c) and incidence of hospital acquired infections (HAI) among trauma patients admitted to SICU

Hypothesis:

Trauma patients with HbA_1C levels above 6.0% will have a greater incidence of HAI, increased number of ventilated days, increased duration of stay in SICU and poorer outcomes in terms of mortality.

Literature Review

Hyperglycaemia in hospitalized patients: (3)

Three types of patients are described in literature with hyperglycaemia:

a) Hospital-related hyperglycaemia (Stress Induced Hyperglycaemia): hyperglycaemia occurring during the hospitalization that reverts to normal after hospital discharge.

b) Unrecognized diabetes: hyperglycaemia occurring during hospitalization and subsequently confirmed as diabetes after hospitalization but unrecognized as diabetes during the episode.

c) Medical history of diabetes: diabetes previously diagnosed and recognized by the treating physician.

Hyperglycaemia in the hospital may result from stress and the body's response to it; decompensation of type 1, type 2, or other forms of diabetes; and/or may be iatrogenic due to withholding of anti-hyperglycaemia medications or administration of hyperglycaemia-provoking agents such as glucocorticoids or vasopressors. (3)

Hospital related hyperglycaemia:

In the mid-1800s, Reyboso observed glycosuria, a condition induced by ether anesthesia, in which glucose is discharged in the urine, and in 1877 Claude Bernard described hyperglycemia during hemorrhagic shock.(7) Today, it is well known that any type of acute illness or injury results in insulin resistance, glucose intolerance, and hyperglycemia, a constellation termed “diabetes of injury”. (7) Illness or trauma increases hepatic glucose production with ongoing gluconeogenesis despite hyperglycemia and abundantly released insulin. Hepatic insulin resistance is further characterized by elevated circulating levels of Insulin like Growth Factor binding protein–1 (IGFBP-1). Glucose uptake in critically ill patients is increased but takes place mainly in the tissues that are not dependent on insulin for glucose uptake, such as, among others, the nervous system and the blood cells. Hyperglycaemia associated with critical illness is likely a consequence of many factors, including increased cortisol, catecholamines, glucagon, growth hormone, gluconeogenesis, and glycogenolysis.(6) Pro-inflammatory cytokines affect glucose homeostasis indirectly, by stimulating counter-regulatory hormone secretion, and directly, by altering insulin receptor signaling. (7) Insulin resistance may also be a contributing factor, since it has been demonstrated in more than 80

percent of critically ill patients.(6, 20) Various studies have shown that patients in the intensive care unit (ICU) commonly develop hyperglycaemia. (9, 13, 21) Hyperglycaemia was previously considered an adaptive response essential for survival and was not routinely controlled in intensive care units. (21, 22) However, more recent evidence indicating that uncontrolled hyperglycaemia is associated with poor outcomes has prompted efforts to routinely correct and prevent hyperglycaemia in critically ill patients. Patients who are hyperglycaemic following trauma have an admission preoperative glucose which is predictive of morbidity mortality rate, length of hospital stay, length of ICU stay, and incidence of nosocomial infection. (9, 12, 13, 16, 23-25)

Hyperglycaemia is also associated with poorer neurologic outcomes and increased intracranial pressure in patients with traumatic brain injury.(26) In a retrospective cohort study of 77 patients with severe traumatic brain injury, hyperglycaemia (blood glucose ≥170 mg/dl) at the time of ICU admission was an independent predictor of a poor Glasgow coma score five days later.(26, 27) Whether SIH per se causes harm or, instead, is a marker of severity of counter-regulatory hormone release, inflammatory response, and degree of illness is unknown.

Occult diabetes mellitus diagnosed based on an HbA_1C level in trauma patients was found to be as high as 22%.(28) The presence of diabetes not diagnosed prior to hospitalization necessitates differentiating diabetes from SIH. In the ICU setting this is challenging. Recent literature suggests that SIH and diabetic hyperglycaemia are not the same; SIH, compared with diabetic hyperglycaemia, seems to have a higher risk for adverse outcomes in hospitalized patients, including an increased risk of in-hospital mortality and longer duration of stay. (29-31) Identifying pre diabetes in patients who are critically ill using conventional blood sugar estimation is inappropriate as stress response causes an increase in the blood sugars. Pre diabetics are those patients who have either impaired glucose tolerance or have an impaired fasting glucose. Impaired glucose tolerance is defined by the ADA as a fasting plasma glucose of <126mg/dl or a two hour post prandial plasma glucose between 140 to 200mg/dl. Impaired fasting glucose is defined as a fasting glucose between 110mg/dl and 126mg/dl and a two hour post prandial glucose of >140mg/dl. HbA_1C, a marker of glycaemic control for the preceding 3 months, is now endorsed by the American Diabetes Association for diabetic screening.(8) HbA_1C is currently the only tool available for differentiation once the patients are critically ill and may be appropriate for risk stratification. The A1C–Derived Average Glucose Study data demonstrate that hemoglobin A1C levels of 6.0% and 7.0% equal

average glucose levels of 126 and 154 mg/dl, respectively.(32) The 2010 American Diabetic Association standards for medical management of diabetes incorporate HbA_1C as diagnostic modality alongside FPG and IGT. HbA_1C less than 5.7 is considered normal, between 5.7 and 6.4 at risk for diabetes and those with HbA_1C 6.5 or more is diagnostic of diabetes.(8) Further studies of A1C in critically ill patients could potentially validate these numbers for risk-stratification purposes.(33)

Glycaemic control in critically ill:

While the management of hyperglycaemia in the hospital has logically been considered secondary in importance to the condition that prompted admission, a body of literature now supports targeted glucose control in the hospital setting for potential improved clinical outcomes.(14) There is substantial observational evidence linking hyperglycaemia in hospitalized patients (with or without diabetes) to poor outcomes.(12, 13, 34, 35)

A few early randomized controlled trials and observational cohort studies suggested that intensive treatment of hyperglycaemia improved hospital outcomes.(11, 15, 36) Van den Berg et al, reported a 42% relative reduction in intensive care unit (ICU) mortality in critically ill surgical patients treated to a target blood glucose of 80 –110 mg/dl.(11)

Interventions for glycaemic control, however, have had inconsistent results. Recent trials in critically ill patients have failed to show a significant improvement in mortality with intensive glycaemic control (10, 37) or have even shown increased mortality risk.(13) Moreover, these recent RCTs have highlighted the risk of severe hypoglycaemia resulting from such efforts. (10, 13, 37, 38)

NICE-SUGAR, a large multicenter, multinational RCT, tested the effect of tight glycaemic control (target 81–108 mg/dl) as opposed to conventional glycaemic control (target 144–180 mg/dl) on outcomes among 6,104 critically ill participants, the majority of who required mechanical ventilation.(13) Ninety-day mortality was significantly higher in the intensive versus the conventional group (78 excess deaths; 27.5 vs. 24.9%, P 0.02) in both surgical and medical patients. Severe hypoglycaemia was also more common in the intensively treated group (6.8 vs. 0.5%; P < 0.001). The precise reason for the increased mortality in the tightly controlled group is unknown. It must be noted however that the control group in NICE-SUGAR had reasonably good blood glucose management, maintained at a mean glucose of 144 mg/dl and might explain partially the good outcomes in the control arm and does not detract from the notion that glycaemic control in the ICU is important. The conclusions of the NICE study suggest that it a highly stringent target of < 110 mg/dl actually may be dangerous.

Griesdale et al, in a meta-analysis of 26 trials (N = 13,567), which included the NICE-SUGAR data report that the pooled relative risk (RR) of death with intensive insulin therapy was 0.93 as compared with conventional therapy (95% CI 0.83–1.04). Patients in surgical ICUs appeared to benefit from intensive insulin therapy (RR 0.63 [95% CI 0.44–0.91]), while those in other critical care settings did not (medical ICU: 1.0 [0.78 –1.28].(12)

In its consensus statement on standards for medical care of diabetes 2010, the American Diabetes Association states, “It is very clear that the management of hyperglycaemia in the hospital presents unique challenges. Accordingly, reasonable glucose targets in the hospital setting are modestly higher than may be routinely advised in patients with diabetes in the outpatient setting.” “Based on the weight of the available evidence, for the majority of critically ill patients in the ICU setting, insulin infusion should be used to control hyperglycaemia, with a starting threshold of >180 mg/dl. Once intravenous insulin is started, the glucose level should be maintained between 140 and 180 mg/dl. Greater benefit may be realized at the lower end of this range.” (8)

There is evidence to suggest that in-hospital hyperglycaemia is associated with adverse outcomes**.** A meta-analysis of 14 studies has shown that hyperglycaemia (blood glucose >140 mg/dL) with or without a prior diagnosis of diabetes increased both in-hospital mortality and

congestive heart failure (CHF) in patients admitted for acute myocardial infarction. (39) Similar data were reported in a prospective study of 336 patients. Hyperglycaemia (fasting blood glucose >126 mg/dL, random blood glucose >200 mg/dL in general medical and surgical units was associated with an 18-fold increase in in-hospital mortality, a longer length of stay , more subsequent nursing home care, and a greater risk of infection. (30)

Diabetes and Surgery:

The incidence of peri-operative morbidity and mortality among diabetic patients is higher when compared to non-diabetics (40) but better monitoring and control of peri-operative blood glucose have shown to be beneficial. (41)

Glycated Haemoglobin: (42)

Glycated Haemoglobin (HbA_1C) is a term used to describe a series of stable minor Haemoglobin components formed slowly from Haemoglobin and glucose. The rate of formation of HbA_1C is directly proportional to the glucose concentration. (43, 44) Since erythrocytes, with a life-span of 120 days, are freely permeable to glucose, the level of HbA1c in a blood sample provides a glycaemic history of the previous 2-3 months. Laboratory measurement of HbA_1C became available in the late 1970s.(4)

HbA1c is formed non-enzymatically by haemoglobin's exposure to plasma glucose. This simple reaction proceeds in two stages (Fig 1).

1. Glucose combines with the amino group of the valine residue at the N-terminus of 18 goblin chains to form an aldimine compound (Schiff base). This reaction is reversible, and dissociation back to Haemoglobin and glucose can occur readily.

2. Internal rearrangement of the aldimine intermediate by the amadori reaction yields a stable ketoamine derivative, which is irreversible.

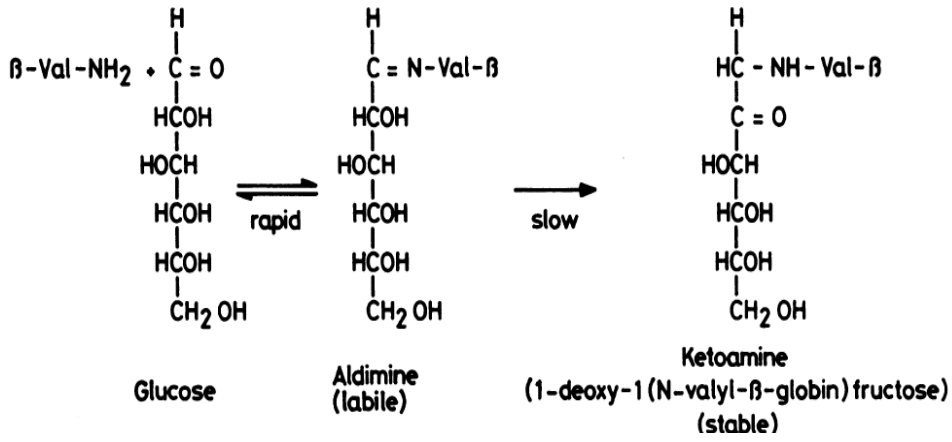

Figure 1 - HBA_1C formation

Glycosylation begins during erythropoiesis and continues slowly throughout the lifespan of the circulating Haemoglobin.

As each erythrocyte circulates for 120 days, there is opportunity for late maillard reactions or non-enzymatic browning to occur (the products of

these reactions are referred to as Advanced Glycation End products [AGE]) and the extent of these changes appear to correlate with the level of HbA1c. In connective tissues and vascular endothelium, AGEs may be important mediators of diabetes pathology as well as the normal aging process. AGE accumulate in diabetes as a result of hyperglycaemia, leading to glycosylation of collagen. This process results in abnormal collagen, which is highly inflexible and prone to breakdown, particularly over pressure areas. Research has shown that several biochemical pathways associated with hyperglycaemia, including glucose auto-oxidation, polyol pathway, prostanial synthesis, and protein glycation can increase the production of free radicals. (44) Free radicals generated by the auto-oxidation reactions of sugar and sugar attached to protein are possible sources of oxidation stress and damage to protein in patients with diabetes. Glyco-oxidation products accumulate in collagen at an accelerated rate in patients with diabetes.(45) This oxidative stress leads to complications in diabetes, such as tissue damage and cell death, which are reversed by antioxidants. Renal and hepatic diseases, haemolytic anemia and haemoglobinopathies shorten red cell survival and therefore the period of exposure to glucose, leading to a decrease in HbA_1C.(8)

High Performance Liquid Chromatography (HPLC) methods often used as “reference method” for the standardisation of routine tests provide

good precision and long-term stability but they are rather unspecific. Different values for HbA_1C can be obtained when the same blood samples are measured, depending on the chromatographic system, *e.g.* the kind of resin, lot-to-lot variation of resins, column size, buffer composition and elution times. (42)

In the first step Haemoglobin is cleaved into peptides by the proteolytic enzyme endoproteinase Glu-C. Thereafter the resulting glycated and non-glycated N-terminal hexapeptides of the β-chains are separated from the crude peptide mixture and quantified by HPLC and electrospray mass spectrometry or by HPLC followed by capillary electrophoresis with UV detection. The percentage of HbA1c is determined as a ratio of the glycated to non-glycated β -N-terminal hexapeptides of Haemoglobin. (42)

Hennesse et *al* investigated the interaction of blood glucose concentration and wound collagen glycosylation, collagen content, and proteolytic activity during wound healing in diabetic rats. They showed that long term hyperglycaemia leads to the formation of AGE, which contributes to many of the complications of diabetes. The amount of AGE is proportional to the duration of diabetes. AGE leads to abnormal cross linking causing increased phagocytosis of the affected proteins and protein catabolism. This increased catabolism of structurally

abnormal proteins in uncontrolled diabetic patients leads to impairment of wound healing. *(46)*

One percent increase in glycated Haemoglobin has been shown to be associated with 18% increase in the risk for coronary heart disease or stroke and a 28% increase in the risk for peripheral vascular disease. (47) These data highlight the utility of the glycated Haemoglobin level as a measure of risk for cardiovascular events in type 2 diabetes.

Khaw *et al* correlated the level of HbA_1C to the incidence of cardiovascular events. They demonstrated a 21% increase in cardiovascular events for every 1% increase in HbA_1C level above 5%. They also concluded that HbA_1C level of 6.59% in a non-diabetic predicts a higher cardiovascular risk than an HbA_1C level of 5.5% in a well-controlled diabetic. (48) These two studies (47, 48) have clearly proved that the glycated Haemoglobin level is an independent risk factor for cardiovascular events, regardless of diabetes status.

Latham et al analyzed 300 diabetic patients undergoing cardiac surgery and compared wound infection in patients with HbA_1C greater and less than 8%. They concluded that elevated HbA_1C was not associated with statistically significant increase risk of infection. However, the poorly controlled diabetics had significantly higher levels of blood glucose in the post-operative period. (49)

Dronge *et al* did a retrospective observational study on the relationship of long-term glycaemic control and post-operative infection in 490 diabetics. Oral treatment was the main form of diabetic therapy (59.0%). The HbA_{1c} levels ranged from 4.6% to 15.5% (median - 7.3%). The incidence of infection in patients with HbA_1C <7% was 12% while it was 20% in those with HbA_1C > 7%.(50) They concluded that good pre-operative glycaemic control (HbA_1C below 7%) reduces post-operative infections following a variety of surgical procedures.

Prospective studies indicate that people within the HbA_1C range of 5.5–6.0% have a 5-year cumulative incidence of diabetes that ranges from 12 to 25% (17, 49, 51), which is appreciably (three- to eightfold) higher than incidence in the population as a whole (52). HbA_1C range of 5.7 to 6.4% can be used to identify individuals with high risk for future diabetes and these patients are called as pre diabetics. Individuals with an HbA_1C of 5.7–6.4% should be informed of their increased risk for diabetes as well as cardiovascular disease and counseled about effective strategies, such as weight loss and physical activity, to lower their risks. As with glucose measurements, the continuum of risk is curvilinear, so that as HbA_1C rises, the risk of diabetes rises disproportionately. As recommended by the American Diabetic Association interventions should be most intensive and follow-up should be particularly vigilant for those with HbA_1C levels above

6.0%, who should be considered to be at very high risk. An HbA1c level of >6.5% is diagnostic of diabetes mellitus. Epidemiologic datasets show a relationship between A1C and the risk of retinopathy similar to that which has been shown for corresponding Fasting Plasma Glucose (FPG) and 2-h Post Prandial Glucose (PPG) thresholds. The HbA_1C has several advantages to the FPG, including greater convenience, since fasting is not required; evidence to suggest greater pre-analytical stability; and less day-to-day perturbations during periods of stress and illness.

STUDY	No. of patients	Outcome studied	HbA1C cut off level	result
Hennesse et *al (1990)*	-	Wound healing in diabetic rats	-	Uncontrolled diabetes impaired wound healing
Khaw et al (2004)	Men – 4662 Women - 5570	Risk of cardiovascular disease in relation to HbA1C level	-	Risk of cardiovascular disease increases with an increase in HbA1C level
Latham et al (2001)	300	Wound healing in Diabetic patients undergoing cardiac surgery	8%	No statistical significant difference between the two groups
Dronge *et al (2006)*	480	Postoperative infection in diabetic patients	7%	8% more infection in patients with a HbA1C >7%

Table 1 - Studies on HBA1C

Diabetes and Hospital Acquired Infection (HAI):

A diabetic patient is at greater risk during the post-operative period to systemic and surgical site infection and they are also prone to metabolic decompensation, such as fluctuating blood glucose levels and keto-acidosis. The association between hyperglycaemia and the susceptibility to Hospital Acquired Infection is multi-factorial.

i) Hyperglycaemia has been shown to impair the normal functions of the neutrophils, which include adherence, chemotaxis, phagocytosis and intracellular bactericidal activity. The degree of neutrophil impairment correlates with the degree of hyperglycaemia. The glucose level threshold for neutrophil dysfunction is 200 mg/dL (range - 130-275 mg/dL). (53)

ii) Hyperglycaemia alters vascular permeability and the normal redox reactions which creates a state of pseudo-hypoxia and impaired tissue defenses. Elevated tissue levels of glucose and the formation of edema due to the increased vascular permeability, promotes bacterial growth. (53)

iii) Micro and macro-vascular manifestations of diabetes may disrupt supply of nutrients, oxygen, leukocytes and antibiotics to the operated

site leading to impaired wound healing. Oxygen is necessary for macrophage mobility and growth of granulation tissue. (53)

iv) In patients with diabetic neuropathy, disruption of the skin may go undetected which can form a portal for entry of the bacteria. (53)

v) Glucose is a pro-inflammatory mediator that has been shown to stimulate cytokine production and inhibit endothelial nitric oxide levels. Insulin enhances the ability of cytotoxic lymphocytes to attack target cells. Therefore, insulin deficiency makes the diabetic patients more susceptible to infection.

vi) The bone marrow-derived endothelial progenitor cell is vital in vasculogenesis and wound healing, but their numbers are decreased in diabetes due to impaired activity of endothelial derived nitric oxide synthetase. Poor healing of diabetic wounds is characterized by impaired angiogenesis and vasculogenesis. Control of blood sugar level also retards the progression of vascular complications.

Latham *et al* studied the association of glucose control with surgical site infections among patients undergoing cardio-thoracic surgery. In a prospective cohort and case-control study, to assess the importance of diabetes, diabetes control, hyperglycaemia, and previously undiagnosed diabetes in the development of surgical-site infections. They found that presence of diabetes and post-operative

hyperglycaemia was independently associated with development of surgical site infection. (49)

Carson, *et al* did a retrospective cohort study to determine the impact of diabetes mellitus on short-term mortality and morbidity in patients undergoing coronary artery bypass surgery. They found that the 30-day mortality was 3.7% in patients with diabetes and 2.7% in those without. Morbidity, infections and the composite outcomes occurred more commonly in diabetic patients and were associated with a risk about 35% higher in diabetics than in non-diabetics. They concluded that diabetes is an important risk factor for mortality and morbidity among those undergoing coronary artery bypass surgery. (40)

Bhatia *et al* did a prospective study to evaluate the risk factors for postoperative wound infection in 615 patients undergoing coronary artery bypass graft surgery, of whom 269 (43%) were diabetic. 116 (18.86%) patients developed infection of the surgical sites involving sternum (75%), leg (21.3%) and forearm (3.44%). Sternal site, obesity, diabetes mellitus and female gender were associated with significantly higher infection rates. Diabetes, especially uncontrolled, was a significant risk factor for the development of surgical site infection. (54)

Golden *et al* studied the peri-operative glycaemic control and the risk of infections complications in 411 diabetics, who underwent coronary

artery surgery. Peri-operative glycaemic control was assessed by the average of six capillary glucose measurements taken during the 36 hour following surgery. The major outcomes studied were infections of the leg and the chest wounds, pneumonia and urinary tract infection. They found that patients with higher mean capillary glucose readings were at increased risk of developing infections compared with those with the low post-operative glucose levels. They concluded that in diabetics who undergo coronary artery surgery, hyperglycaemia is an independent predictor of short-term infections in the post-operative period, and the physician should consider a glucose concentration target of <200 mg.dL-1 to reduce the risk of infection. (53)

Nosocomial Infections: (55, 56)

A nosocomial infection is a localized or systemic condition 1) that results from adverse reaction to the presence of an infectious agent 2) that was not present or incubating at the time of admission to the hospital. (55, 56)For most bacterial nosocomial infections, this means that the infection usually becomes evident 48 hours or more after admission

URINARY TRACT INFECTION:

Symptomatic urinary tract Infection should meet one of the following criteria:

Criterion 1: Patient has at least one of the following signs or symptoms with no other recognized cause: fever (>38° C), urgency, frequency, dysuria, or supra-pubic tenderness and patient has a positive urine culture, that is, 10^5 microorganisms per cm^3 or urine with no more than two species of microorganisms.

Criterion 2: Patient has at least two of the following signs or symptoms with no other recognized cause: fever (>38° C), urgency, frequency, dysuria, or supra-pubic tenderness and at least one of the following:

a. positive dipstick for leukocyte esterase and/or nitrate
b. Pyuria (urine specimen with 10 wbc/mm^3 or 3 wbc/high power field of unspun urine)
c. organisms seen on Gram stain of unspun urine
d. at least two urine cultures with repeated isolation of the same uropathogen (gram-negative bacteria or S. saprophyticus) with 10^2 colonies/ml in non-voided specimens
e. 10^5 colonies/ml of a single uropathogen (gram-negative bacteria or S. saprophyticus) in a patient being treated with an effective antimicrobial agent for a urinary tract infection
f. physician diagnosis of a urinary tract infection
g. physician institutes appropriate therapy for a urinary tract infection.

An asymptomatic bacteruria must meet at least one of the following criteria:

Criterion 1: Patient has had an indwelling urinary catheter within 7 days before the culture

And patient has a positive urine culture, that is, 10^5 microorganisms per cm^3 of urine with no more than two species of microorganisms and patient has no fever (>38° C), urgency, frequency, dysuria, or supra-pubic tenderness.

Criterion 2: Patient has not had an indwelling urinary catheter within 7 days before the first positive culture and patient has had a least two positive urine cultures, that is, 10^5 microorganisms per cm^3 of urine with repeated isolation of the same microorganism and no more than two species of microorganisms and patient has no fever (>38° C), urgency, frequency, dysuria, or supra-pubic tenderness.

SURGICAL SITE INFECTION (Superficial incision)

DEFINITION: A superficial SSI must meet the following criterion: Infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision and patient has at least one of the following:

a. purulent draining from the superficial incision

b. organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision

c. at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon, unless incision is culture-negative

SURGICAL SITE INFECTION (Deep incision)

DEFINITION: A deep incision SSI must meet the following criterion: Infection occurs within 30 days after the operative procedure if no implant is left in place or within one year if implant is in place and the infection appears to be related to the operative procedure and involves deep soft tissues (e.g., fascial and muscle layers) of the incision and patient has at least one of the following:

a. purulent drainage from the deep incision but not from the organ/space component of the surgical site

b. a deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38° C), or localized pain or tenderness, unless incision is culture-negative

c. an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histo-pathologic or radiologic examination

BLOODSTREAM INFECTION

Laboratory-confirmed bloodstream infection must meet at least one of the following Criteria:

Criterion 1: Patient has a recognized pathogen cultured from one or more blood cultures and organism cultured from blood is not related to an infection at another site.

Criterion 2: Patient has at least one of the following signs or symptoms: fever (>38° C), chills, or hypotension and at least one of the following:

a. common skin contaminant (e.g., diphtheroids, Bacillus sp., Propionibacterium sp., coagulase-negative staphylococci, or micrococci) is cultured from two or more blood cultures drawn on separate occasions

b. common skin contaminant (e.g., diphtheroids, Bacillus sp., Propionibacterium sp., coagulase-negative staphylococci, or micrococci) is cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy

c. Positive antigen test on blood (e.g., H. influenzae, S. pneumoniae, N. meningitidis, or group B Streptococcus) and signs and symptoms and positive laboratory results are not related to an infection at another site.

Ventilator Associated Pneumonia

Ventilator-associated bacterial pneumonia (VAP) is a major threat to the recovery of patients receiving mechanical ventilation, and is one of the most important intensive care unit (ICU)-acquired infections in mechanically ventilated patients. The European Prevalence of Infection in Intensive Care (EPIC) study found that VAP was the most common Hospital Acquired Infection accounting for up to 45% of all infections in the ICU. The Clinical Pulmonary Infection Score (CPIS), a diagnostic algorithm for the diagnosis of VAP that relies on easily available clinical, radiographic, and microbiological criteria. A CPIS of 6 or more is diagnostic of a VAP.

CPIS Points	**0**	**1**	**2**
Tracheal secretions	Rare	Abundant	Abundant + purulent
Chest X-ray infiltrates	No infiltrate	Diffused	Localized
Temperature, °C	⩾36.5 and ⩽38.4	⩾38.5 and ⩽38.9	⩾39 or ⩽36
Leukocytes count, per mm^3	⩾4,000 and ⩽11,000	< 4,000 or > 11,000	< 4,000 or > 11,000 & band forms ⩾500
PA_{O2}/FI_{O2}, mm Hg	> 240 or ARDS		⩽240 and no evidence of ARDS
Microbiology	Negative		Positive

Table 2 CPIS SCORING SYSTEM

APACHE II SCORE(57)

APACHE II – Acute Physiology and Chronic Health Evaluation System is a severity of disease classification which was first validated and used by Knaus W A et al and published in the Critical Care Medicine Journal in 1985.(57) APACHE II uses a point score based upon initial values of 12 routine physiologic measurements, age, and previous health status to provide a general measure of severity of disease. (Appendix 1)The physiological measurements include the temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, arterial pH, serum sodium levels, serum potassium level, serum creatinine (with or without acute renal failure), haematocrit, the total count and the Glasgow Coma Score. (Appendix 1). The score ranges from 0 to 71 with a worsening outcome as the score rises. When APACHE II scores are combined with an accurate description of disease, it can be used to prognosticate acutely ill patients and will also guide investigators to compare new modes of treatment. Another use of the APACHE II score is that it can be used to evaluate the use of hospital resources and compare between intensive care units as to the efficacy of care. APACHE II has been used universally in many clinical trials since it provides a consistency between different groups. An objective scoring system such as the APACHE II score, allows audits of different units or

the same unit with historical controls, and comparisons of different treatment modalities in those with similar severity of illnesses. In the current environment of escalating medical costs the APACHE II scores may allow us to restrict intensive care to those most at need, and provide a gauge of illness for deciding how aggressive management should be. The popularity in the use of the APACHE II score is that it is simple to use and there is available software to simplify analysis.

INJURY SEVERITY SCORE (58, 59)

It is a scoring system that is used to simplify complex and variable patient data to a single number. In this process some amount of accuracy and information is lost. Abbreviated Injury Score – Is an anatomical scoring that was first introduced in 1969 with multiple revisions since, the latest on being in 1998.(59) Injuries are graded on a scale from 1 to 6 as shown in the following table 3.

INJURY	AIS Score
1	minor
2	Moderate
3	Serious
4	Severe
5	Critical
6	Un-survivable

Table 3 - Injury Severity Score

The injury severity score is an anatomical scoring system that uses the AIS in its calculation. The body is divided into six regions and the respective AIS are calculated. The 3 most severely injured body regions have their score squared and added together to produce the ISS score. The ISS score ranges from a minimum score of 0 to a maximum of 75. If an injury is assigned an AIS of 6 (un-survivable injury), the ISS score is automatically assigned to 75.The ISS score relates well with the mortality, morbidity and the hospital stay. The draw backs in the ISS are that a small error in the AIS scoring increases the corresponding error in the calculated ISS and different injury patterns can yield the same ISS score and injuries to different body regions are not weighted.

Patients & Methods

Settings:

The study was done in the Surgical Intensive Care Unit (SICU) of Christian Medical College Hospital, Vellore which is a 2000 bedded tertiary care hospital serving about 90,000 inpatients and 1.5 million outpatients annually. Tight glycaemic control in SICU patients is done to maintain the blood sugar level between 80 to 120 mg/ dl.

Control of sugars in the SICU is done following a sliding scale. When sugars are abnormal the following algorithm is used. The algorithm is explained in appendix 2.

Algorithm	Category of patients
I	Non Diabetic
II	Diabetics, Hypertensives and Patients on TPN
III	Uncontrolled Diabetics on Total Parenteral Nutrition
IV	Uncontrolled diabetics

Table 4 - Insulin algorithm

Insulin is given as an infusion with the help of a syringe pump which contains 20 units of short acting insulin in 20 ml of normal saline. Insulin infusion is started when there are more than two blood sugars values of greater than 120mg/dl. Blood sugars are checked every four

hours on a routine basis and in some cases every one hour till appropriate control of sugars is achieved.

Inclusion criteria:

1. Age more than 16 years

2. All trauma patients who came to the operation theatre and required post-operative SICU care or those who required pre – operative stabilization in the SICU

Exclusion criteria:

1. Age less than 16 years

2. If consent was not given by the patients' relatives/guardians

The study recruited consecutive patients who met the inclusion criteria from January to October 2010 after informed consent was obtained from their legally acceptable guardian. The protocol received approval from the Institutional Review Board of Christian Medical College, Vellore and was funded by the fluid research fund of the Christian Medical College.

An initial blood sugar level was checked by the nurses using Accucheck hand held point of care glucometers. The HbA1C sample was collected from all trauma patients admitted to SICU within 24 hours of admission to the hospital. The blood sample was sent to the

department of biochemistry for analysis using high performance liquid chromatography method. High-performance liquid chromatography (HPLC) is a form of liquid chromatography to separate compounds that are dissolved in solution. The charge difference between haemoglobin A0 and HbA1c has been widely utilized to separate these two fractions, by the ion-exchange high-performance liquid chromatography system. The ion exchange high pressure liquid chromatography (HPLC) also allows the detection of the most common haemoglobin variants. HPLC instruments consist of a reservoir of mobile phase, a pump, an injector, a separation column, and a detector. Compounds are separated by injecting a plug of the sample mixture onto the column. The different components in the mixture pass through the column at different rates due to differences in their partitioning behaviour between the mobile liquid phase and the stationary phase.

At admission, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, Injury Severity Score and demographic information were collected using the case report form appended in Appendix 3. Patient's relatives were questioned for further information about the patient such as other comorbidities including hypertension, obesity, chronic obstructive airway diseases and coronary heart disease. Details of the circumstances leading to the injury were also

sought. A description of each injury in addition to the injury severity score was obtained to grade the grievousness of the injury.

The patients were followed up from the time of admission to the SICU till discharge from the SICU for the incidence of hospital acquired infections (HAI), the number of ventilated days, number of days of central venous access, the duration and outcome of stay in the SICU and mortality. The treating physician in SICU who was blinded to the HBA_1C levels in the subject assessed outcomes and potential effect modifiers such as APACHE II and Injury Severity Score. The National Nosocomial Infections Surveillance System (NNIS) criteria from the Centers of Disease Control were used for the diagnosis of HAI. Death and "Discharge Against Medical Advice" (DAMA) were considered poor outcomes. When the study was designed, HBA_1C of 6.0 or greater was considered high and those less than 6.0 were categorized as normal. Supplementary analysis has been included to reflect recent ADA recommendations of 2010.(8)

Sample size:

A one sided test to detect with 80% power and an alpha error of 5% a 30% prevalence of poor outcomes in trauma patients with diabetes as compared to 10% poor outcomes in non-diabetic trauma patients will require 58 subjects in each arm. Expecting one third of patients to have HBA_1C greater than 6%, we chose a ratio of 1:3 elevated HBA_1C to

normal HBA_1C. The study sought to recruit 40 subjects with elevated HBA_1C and 120 subjects with normal HBA_1C within a consecutive cohort of 160 subjects. The study was censored at 120 subjects in order to meet the deadline for submission of thesis.

Statistical methods:

The primary analysis used a binary logistic regression to estimate risk for poor outcomes between those with high and low HBA_1C groups (>=6 or <6) adjusted for APACHE II score, injury severity score, admission blood sugars and age. Risk estimates were provided with exact p values and a 95% CI of the odds ratio. Univariate analysis used appropriate tests of significance (independent samples T test for normally distributed continuous variables and Pearson's χ^2 or Fishers exact test for categorical variables). Secondary analysis included estimates of association between diabetic status, APACHE II scores, comorbidities and the incidence of HAI, number of ventilated days and number of SICU days. Exploratory analysis of these relationships at different levels of admission blood sugars were also carried out in a hypothesis generation exercise. Statistical analysis was done with STATA 11 (StataCorp, Texas USA).

Results

One hundred and twenty trauma patients requiring admission to SICU between January and October 2010 were recruited. Male patients 108/120 (90%) dominated SICU admissions for trauma. The age at admission ranged from 16 to 75 with a mean of 36 years (SD 15yrs). The mean APACHE II was 9.8 (SD 6.9) and the mean Injury Severity scores was 17.2 (SD 7.1). The mean HbA_1C was 5.8% (SD 1.0). The mean admission blood sugar was 180.3 mg/dl (SD 102.1). Admission RBS was not available in seven of the patients. The right skewed distribution of admission RBS is shown in figure 2

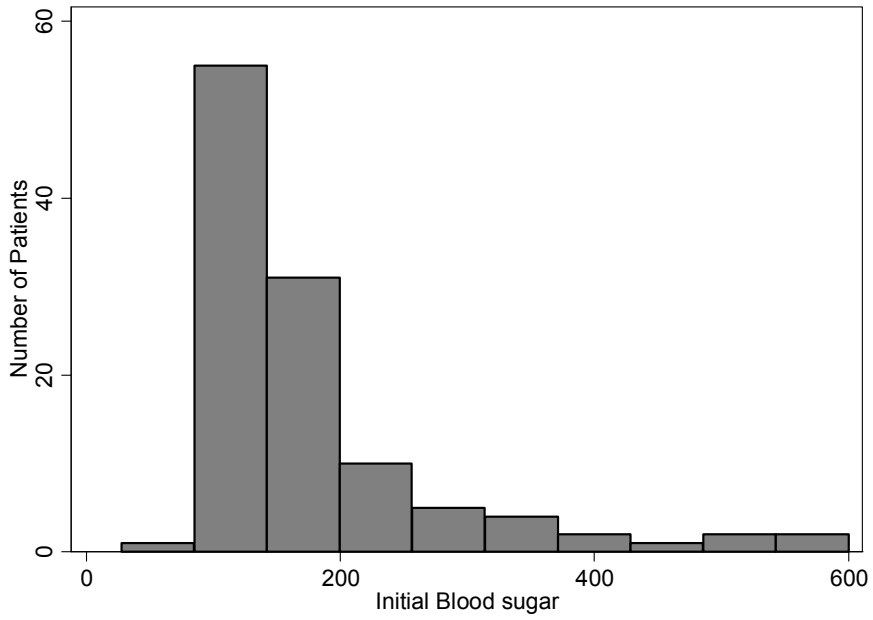

Figure 2 - Distribution of admission RBS

Twenty-six of the 113 patients (23%) with a Random Blood Sugar (RBS) measurement at admission had hyperglycaemia of greater than 200 mg/dL. Eleven of the patients had a pre-trauma diagnosis of diabetes. These and other key baseline parameters are presented in table 5 below.

		HbA_1C	
		Low (<6) n = 91	High (>=6) n = 29
Gender	Female	7 (58%)	5 (42%)
	Male	84 (78%)	24 (22%)
RBS*	200 or more	13	13
	Less than 200	71	16
History of Diabetes	Yes	2 (18%)	9 (82%)
	No	89 (82%)	20 (18%)
AGE (years)	Mean	34.3	42.7
APACHE II	Mean	9.2	11.7
Inj. Sev. Score	Mean	17.8	15.5

Table 5- Baseline data

* Admission RBS was available for 113 participants

Younger patients (<35 years) had a significantly better outcome to ICU stay as compared to the older people (1.6% poor outcomes vs. 27 poor outcomes; p< 0.0001). Figure 3 demonstrates the poor outcomes with increasing age and HbA_1C levels. Most adverse outcomes occurred in those above 35 years and most of those who had higher HBA_1C levels were in the older age groups.

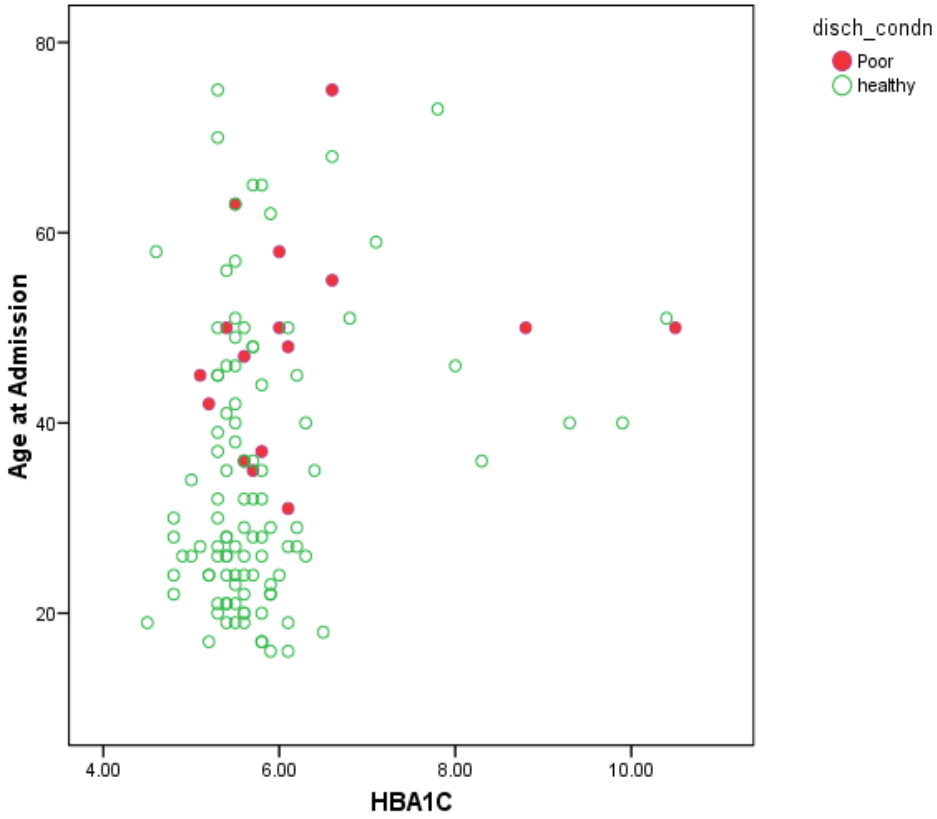

Figure 3 - Scatter plot of Age at event and HBA_1C

One hundred and seventeen admissions (97.5%) were a result of blunt trauma and the rest due to penetrating injuries. The common causes of blunt trauma were road traffic injuries (98/117) or fall from heights especially into unprotected wells (8/117).

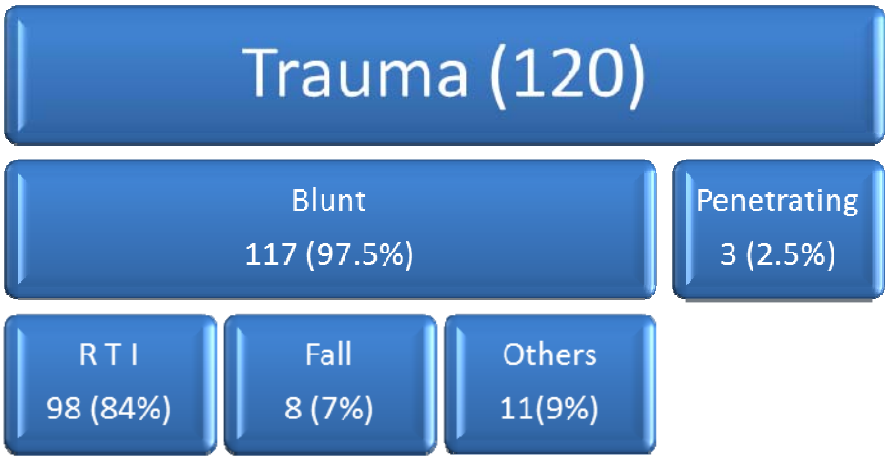

Figure 4 – Description of Injuries

The duration of ICU stay ranged between 1 and 39 days with a mean of 9.5 days (SD 7.6). Ninety-nine of the 120 participants (83%) required ventilation and the mean duration of ventilation was 7.6 days (SD 6.4). 65 participants (54%) developed hospital acquired infections as defined in the NNIS criteria.

Of those ventilated, 39 (39.4%) developed Ventilator Associated Pneumonia (VAP). Thirty one participants developed surgical site infection, 15 urinary tract infection and 18 catheter related blood stream infection.

Classification of infection	N =120
HAI	65 (54%)
VAP	39 (39.4%)
SSI	31 (25.8%)
CRBSI	18 (15%)
UTI	15 (12.5%)

Table 6 - Incidence of infections

Distribution of HbA_1C in the study group:

Figure 5 below shows the distribution of HBA_1C in the study population.

Most values are clustered around 5 and 6 with the mean of 5.8%

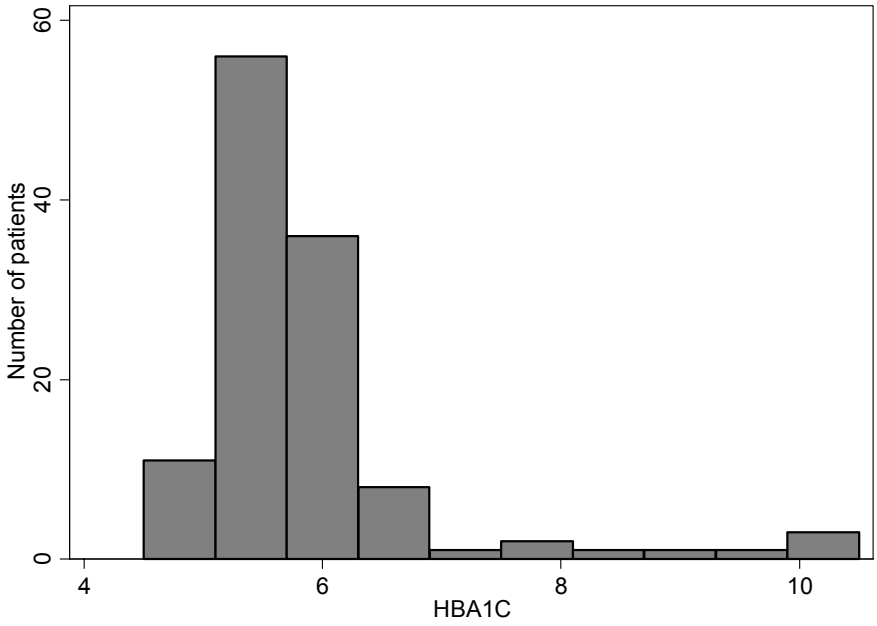

Figure 5 - Distribution of HbA_1C

Twenty nine (24%) of the120 patients had an HbA_1C >= 6. Thirteen of 84 patients (15%) with low HBA_1C had admission blood glucose levels above 200 mg/dL while 13 of 29 patients (45%) with high HBA_1C had admission sugars above 200 mg/dL. The relationship between admission RBS and HbA_1C is shown in figure 6 below.

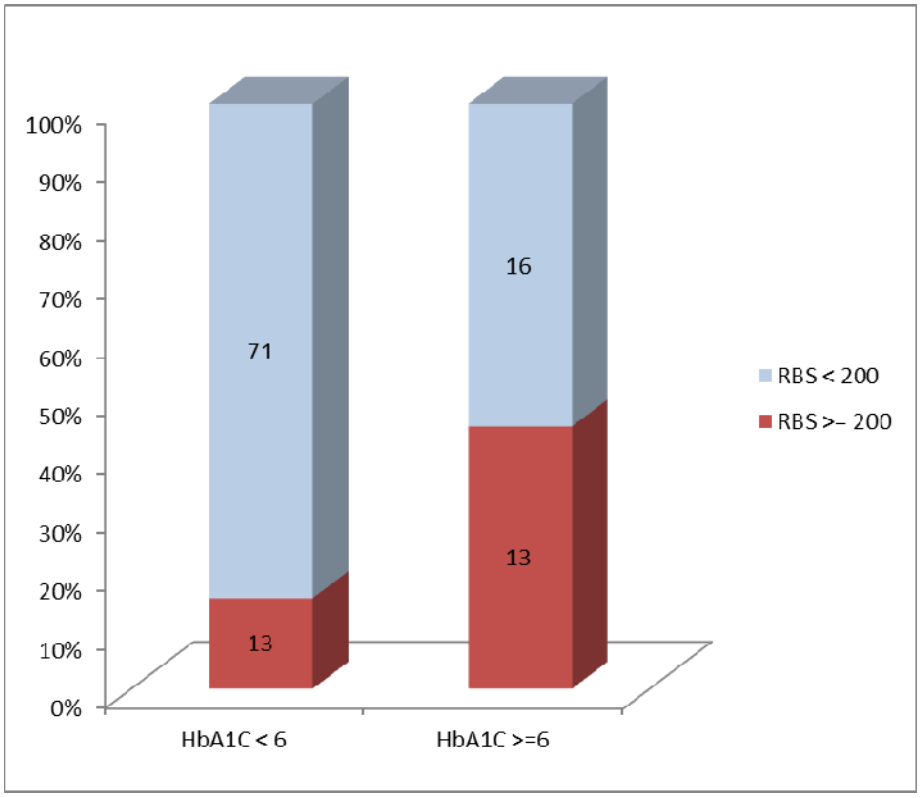

Figure 6 - Comparison of HBA_1C and admission RBS

SUBANALYSIS:

Classifying by the 2010 ADA criteria, 67(56%) had HbA_1C <5.7, 39 (32%) an HbA_1C between 5.7 and 6.4 and 14(12%) an HbA_1C 6.5 and above. According ADA 2010 standards of clinical management of diabetes these represent people who do not have diabetes, those at risk and those with diabetes respectively. The pie diagram in figure 7 shows the relative proportions of HbA_1C across ADA 2010 categories.

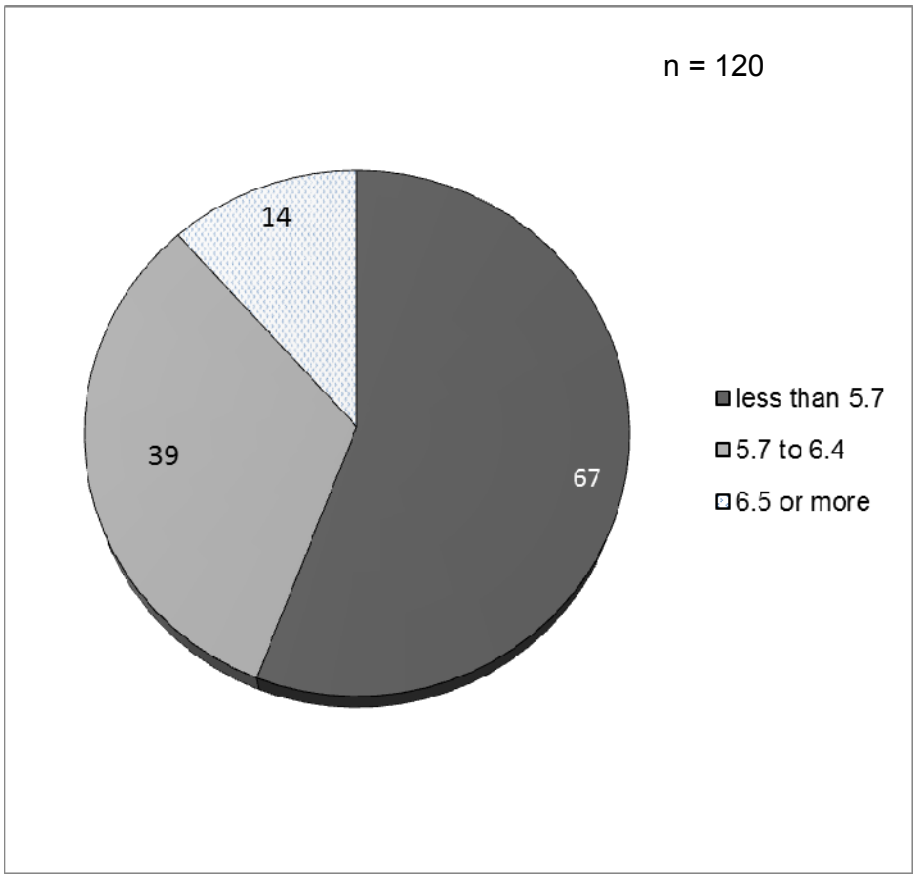

Figure 7 - Distribution of patients by HBA_1C Categories

Six of 17 patients (35%) who met the 2010 ADA criteria for diagnosis of diabetes (The 17 included those with $HbA_1C \geq 6.5$ or were on treatment for diabetes) were previously undiagnosed to be diabetic. Of the eleven patients who had a pre-trauma diagnosis of diabetes, 2 had an HbA_1C of < 6%, one person had an HbA_1C level between 6 & 6.5% and 8 had more than 6.5%. The figure 8 shows the distribution of diabetics across their current HbA_1C levels.

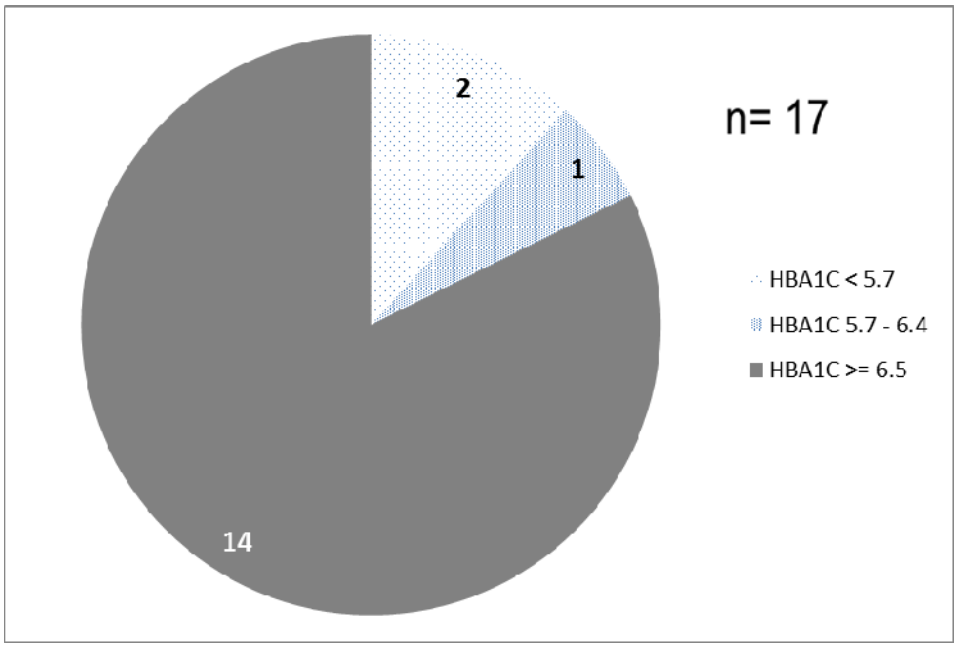

Figure 8 - Distribution of HBA_1C amongst diabetics

Five out of the 11 patients who had a pre-admission diagnosis of diabetes and 2 of the 6 newly diagnosed diabetics had HbA_1C greater than 7% which is considered the sub-optimal glycaemic control.

HbA_1C and ICU outcomes:

In the unadjusted analysis, those with HBA_1C >= 6 had 3.14 times greater risk of poor outcome at the end of hospital stay as compared to those with HBA_1C <6 (95% CI 1.29 to 7.61; P = 0.02).

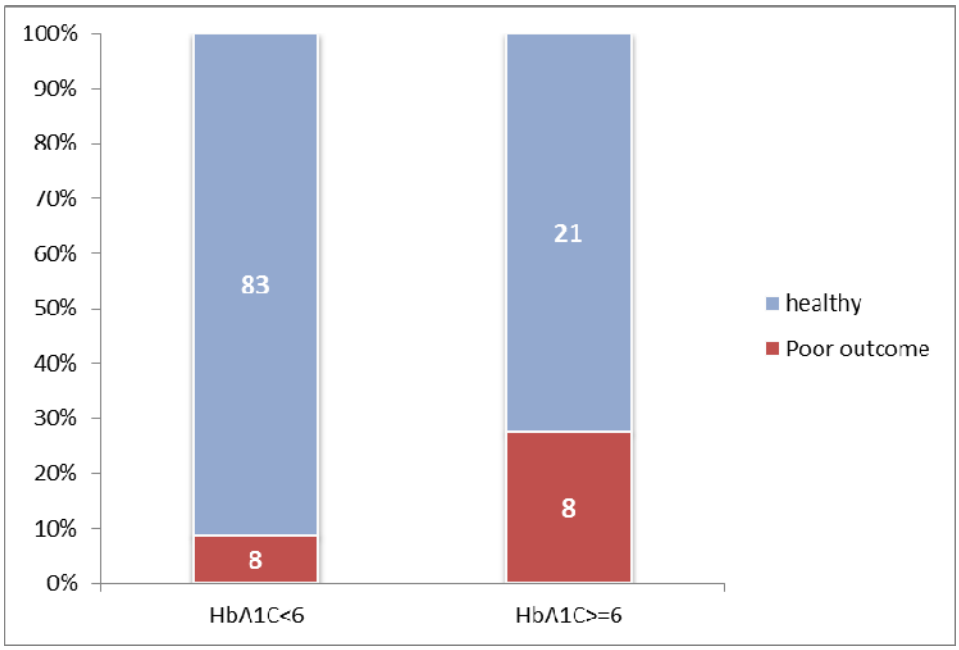

Figure 9 - HBA_1C and ICU outcomes

When we classified HBA_1C by ADA 2010 guidelines, we noticed a trend of increasing risk for poor outcomes across the normal, at risk group and diabetics as shown in figure 10.

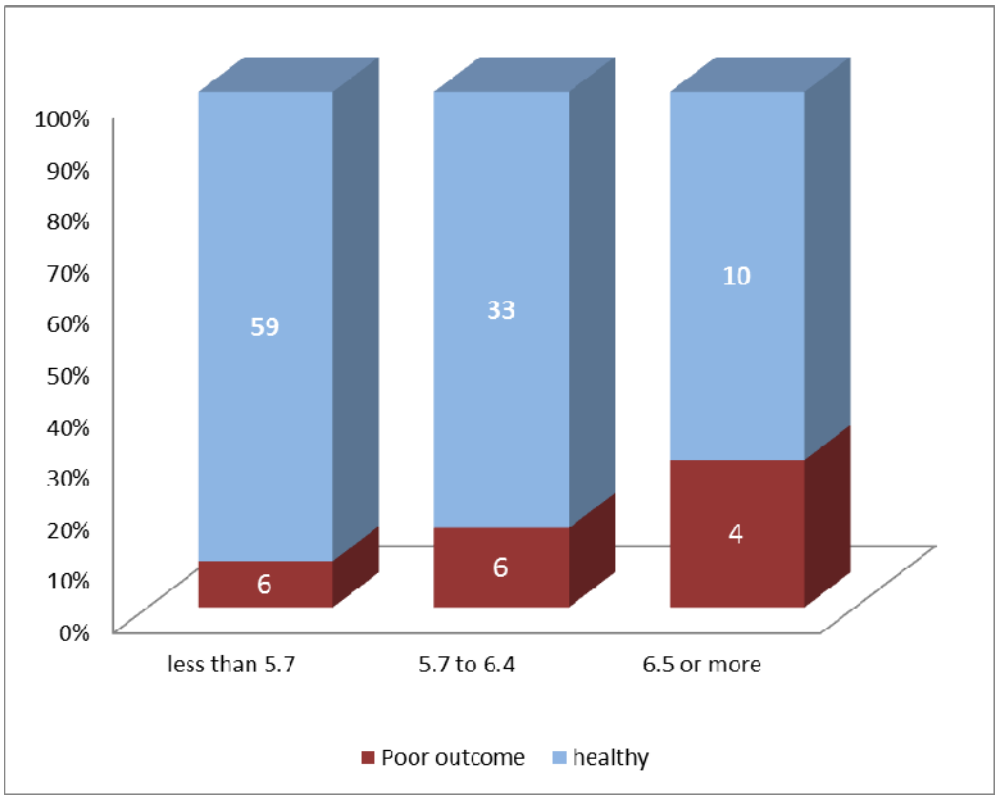

Figure 10 - HBA_1C (ADA 2010) and outcomes

We observed a trend of increasing risk of poor outcomes with increasing HBA_1C and that in non-diabetics, higher admission RBS implied higher risk of poor outcome, however the trend reverses in the diabetic group as illustrated in the graph in figure 11.

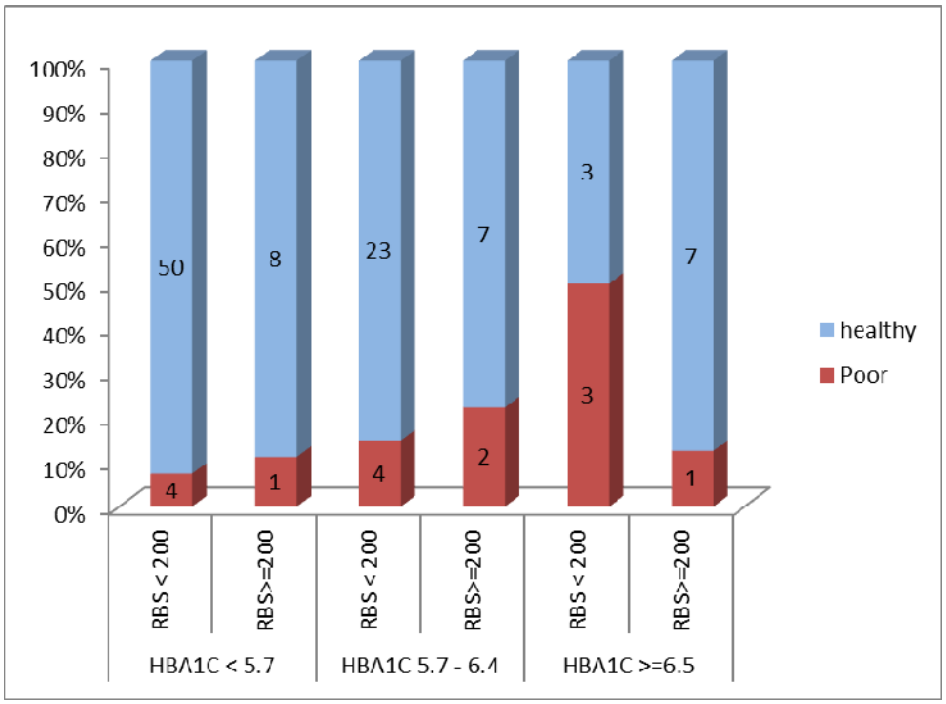

Figure 11 - Outcome across HBA_1C categories stratified by admission RBS

Those with HbA_1C >= 6 also showed a prolongation of ICU stay (1.5 days p-0.38), increased number of ventilated days (2.1 days; p0.16), ventilator associated pneumonia (RR 1.23; p-0.5) and higher risk for bloodstream infections (RR 1.16; p-0.37). This is depicted in the graphs in figure 12 and 13. Sixty five (54%) of the participants developed Hospital Acquired Infections. Twelve of 17 diabetics (70%) and 53 of 103 (52%) non-diabetics developed HAI. ICU stay and ventilated days were greater for those with higher HBA_1C however the difference was not statistically significant.

	HBA_1C < 6 (n=91)	HBA_1C >= 6 (n=29)	P Value
H A I	49 (54%)	16 (55%)	0.901
VAP	28 (31%)	11 (38%)	0.473
Ventilated days [Mean]	7.12	9.21	0.161
ICU stay (days) [Mean]	10.3	11.8	0.387
Poor outcome	8 (9%)	8(28%)	0.010

Table 7- HBA_1C and key outcomes measures

The mean duration of ICU admission, number of ventilated days and incidence of HAI and VAP are tabulated in table 8 using the ADA 2010 cut-offs.

HBA_1C	< 5.7 (n=67)	5.7– 6.4 (n=39)	>= 6.5 (n=14)	P value
Hospital Acquired Infection	36 (54%)	20(51%)	9 (64%)	0.70
VAP	27 (30%)	14(36%)	5 (36%)	0.78
Ventilated days [Mean (SD)]	7.3 (6.0)	7.4 (7.2)	10 (6.2)	0.43
ICU stay (days) [Mean (SD)]	10 (6.9)	11.1 (9.1)	12.9 (8.7)	0.55
Poor outcome	6 (9%)	6(15%)	4(29%)	0.13

Table 8 - HBA_1C by ADA 2010 criteria and key outcome measures

The increasing risk of HAI and VAP with increasing HBA_1C levels is depicted in the graph (figure 12) below.

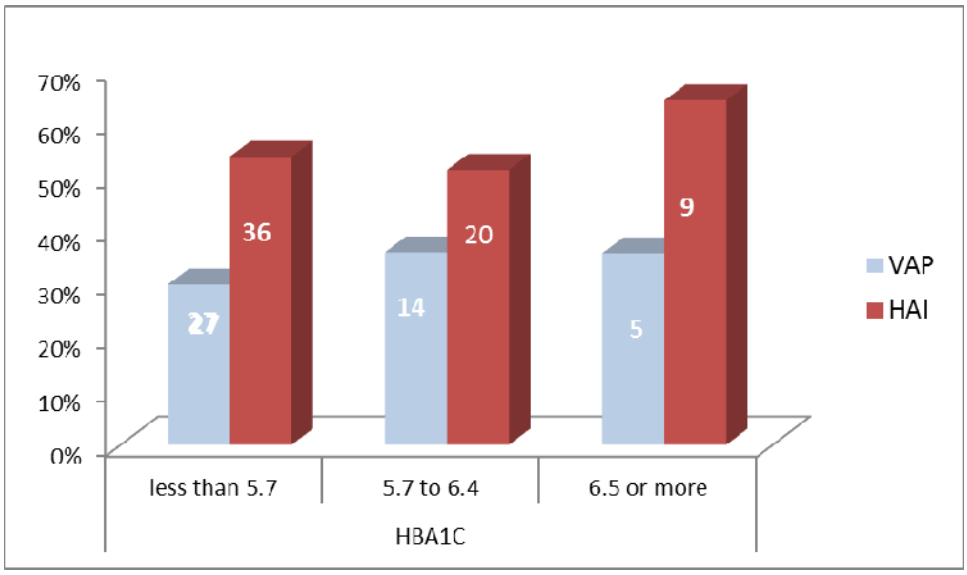

Figure 12 - Incidence of VAP / HAI across HBA_1C levels

Similarly number of ventilated days and ICU days increased with HBA_1C levels as illustrated in figure 13 below.

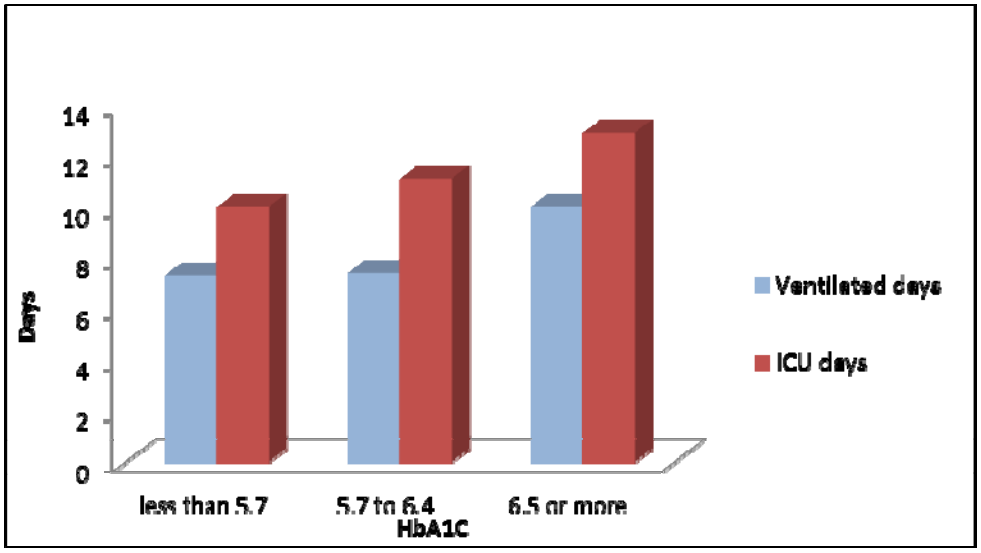

Figure 13 - Mean ventilated days / ICU stay across HBA_1C levels

The predictors of poor outcome to ICU stay were age, APACHE II HBA_1C and history of diabetes. The univariate analysis of the predictors is presented in table 9.

Parameter	Good outcome	Poor outcome	P value
Number (N)	*104*	*16*	
Age (Mean)	34.5	48.25	0.001
APACHE II (Mean)	9	15.1	0.02
Injury Severity (Mean)	17.3	16.9	0.87
Initial RBS >=200	22(22%)	4(27%)	0.744
HBA_1C >=6%	21(20%)	8(50%)	0.01
Diabetes *N* (%)	12(11.5%)	5(31.3%)	0.035
V A P *N* (%)	28(26.9%)	11(69%)	0.001
Blood stream *N* (%)	15(14.4%)	3(18.8%)	0.652
UTI N (%)	14(13.5%)	1(6.3%)	0.417
SSI N (%)	25 (24.1%)	6(37.5%)	0.252

Table 9 - Predictors of poor outcomes

In order to predict the risk of developing a poor outcome in those with HBA_1C >=6 a logistic model was developed which adjusted for APACHE II score, Injury severity score, baseline random blood sugar

and age at admission. In this model, those with HBA_1C >=6 had a 4.57 times greater risk of poor outcome than those with HBA_1C <6 (95% CI 1.1 to 18.9). Age and APACHE II scores were the other important predictors of ICU stay. The parameters used in the model are shown in table 10.

	Odds Ratio	P value	(95% CI)	
Age	1.06	0.01	(1.02	1.11)
HBA1C ≥ 6%	4.57	0.04	(1.11	18.88)
Admission RBS	0.99	0.14	(0.99	1.00)
APACHE II	1.08	0.08	(0.99	1.17)
Injury Severity	1.04	0.39	(0.95	1.14)

Table 10 - Adjusted OR for predictors of poor outcomes

Discussion

Blood sugar control in intensive care settings has seen paradigm shifts over the years. While several large studies have conclusively demonstrated the association between hyperglycaemia and adverse ICU outcomes, (7, 12, 17) it is only in the recent past that literature has been forthcoming in the context of trauma related admissions. (60) There is however, considerable debate on whether the relationship is causal or confounded and how tight the control of blood sugar needs to be. Stress hyperglycaemia is defined as a transient plasma glucose level above 200 mg/dL.(8) It is postulated that increased levels of cortisol, glucagon, and epinephrine as a consequence of derangement of a finely tuned neuroendocrine homeostasis is responsible for the elevated blood sugars.(7, 12) The magnitude of stress response is proportional to the magnitude of tissue trauma (7).

Kopelman et al found the prevalence of abnormal HBA_1C in trauma patients to be 22%. (21) In our study we found that 24.2% of our patients had a similarly abnormal HBA_1C of >= 6%. Those with higher HBA_1C had higher incidence of adverse outcomes to ICU stay as shown in table 7. This study suggests that HBA_1C might be a more useful predictor of ICU outcomes than admission blood sugars in

trauma patients with an adjusted OR of 4.5 as compared to 0.99 for admission RBS (table 10).

This cohort of trauma patients were predominantly male (90%) and this possibly reflects the risk of trauma in the community and health seeking characteristics of the populations. Other studies have also had higher proportion of patients being male.(60) The mean APACHE II scores of 9.8 and the mean ISS of 17 suggests that the severity of injuries in this cohort were less severe than those in western cohorts which usually result from higher velocity blunt trauma. (60)

Despite the lower mean age in this cohort, we found 9% of the patients had a pre-trauma diagnosis of diabetes. In addition, using HBA_1C and the ADA 2010 criteria, we identified six additional diabetic individuals indicating that 14.1% of this cohort were diabetic. A further 38 individuals (32%) had an HbA1C between 5.7 and 6.4 classified by ADA as at risk for diabetes mellitus. The high prevalence of diabetes is consistent with recent observations from community based cohorts that estimate the prevalence of diabetes in those above 20 years of age to be as high as 15%.(1)

Age at admission is a strong predictor of ICU outcomes with all but one poor outcomes occurring in those more than 35 years. APACHE II scores unsurprisingly predicted the outcomes well. Like a few recent studies we also noticed that the ISS when adjusting for other risk

factors such as age, obesity, APACHE II and HbA_1C was a poor predictor of ICU outcome.(12, 60) This poor discrimination may be a consequence of the lack of spread of ISS values with most of our patients having lower Injury severity scores. The mean admission RBS value of 180 mg/dl is higher than those observed in cohorts of trauma patients in other studies. (9, 60) HbA_1C was an independent predictor of ICU outcome after adjusting for age, admission blood sugar, APACHE II and Injury Severity Score (table 10). Higher HBA_1C was also associated with increase in mean duration of ICU stay and mean number of ventilated days, and the incidence of HAIs though these relationships were not statistically significant which might be due to an inadequate sample size for secondary outcomes (table 7 & 8).

In an interesting ambispective cohort study, (19) Brian B. Graham et al, analyse two large patient datasets from the University HealthSystem Consortium and Mayo Clinic APACHEIII database and conclude that Diabetes may not be an independent risk factor and suggest that it might be a protective factor in medical ICU settings. In contrast this study shows an unambiguous trend on increased mortality for those with diabetes in trauma related ICU care.

In our study the admission RBS of ≥ 200 mg/dL is associated with adverse outcomes though not significant statistically. Higher admission RBS while a risk factor amongst those without diabetes(RR 1.25)

appears to be protective for those with diabetes (RR 0.47) and suggests a qualitative interaction between diabetic status and admission RBS in terms of ICU outcome though the association was not statistically significant. It is postulated the stress induced hyperglycaemia is a greater risk factor amongst non-diabetics as compared to diabetics. (18, 19, 61) It must be noted that this study only documented initial blood sugars at admission and did not measure fluctuations of sugar or the effects of the insulin therapy and therefore may be incomplete in representing the complex and still poorly understood relationship between hyperglycaemia, HBA_1C and ICU outcome.

Conclusions

This cohort study of trauma patients admitted to Surgical ICU examined the relationship between HBA_1C and the outcomes of ICU stay.

1. The prevalence of $HBA_1C \geq 6\%$ in this study was 24.2% and these individuals would be either diabetic or at risk of developing diabetes.
2. Six out of 17 diabetic patients (35%) did not know that they were diabetic at admission. 5.5% (6/109) of this cohort has occult diabetes mellitus.
3. There was a 3.14 times greater risk of poor outcomes in those with $HBA_1C \geq 6\%$ or above as compared to those with $HBA_1C < 6\%$. This association strengthened on adjusting for admission blood sugars, APACHE II, ISS to an odds ratio of 4.6.
4. Those with elevated HBA_1C (>=6%) had, on average, 2.1 days more of ventilation and 1.5 days longer ICU admission.
5. Sixty five (54%) of the participants developed Hospital Acquired Infections with similar proportions in those with normal and elevated HBA_1C.
6. That 14.2% of the adults were diabetic and that 35% of these diabetic individuals were undiagnosed before admission combined with the increased risk of poor outcomes among those

with higher HBA_1C suggests screening for diabetes may be useful in managing patients in ICU settings.

Limitations

The small sample size, while adequate to assess the primary outcome was insufficient to address secondary objectives like HAI and number of ventilated days. We did not measure how well the sugars were controlled or quantify the duration of hyperglycemia or the number of hypoglycaemic episodes which could confound the association. The quantum of blood transfusion in those who did not have their HBA_1C sample drawn prior to transfusion was not documented. This might have falsely lowered the values as diabetics are not permitted to donate blood.

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Appendix

APPENDIX 1: APACHE II SCORE

Apache II was scoring system developed by Knaus W A to classify the severity of disease among patients admitted in critical care settings. The following twelve physiological measurements along with age and previous health status are used to provide a general measure of severity of disease:

Temperature ^{0}C	Score
≤ 29.9 °C	4
30 - 31.9 °C	3
32 - 33.9 °C	2
34 - 35.9 °C	1
36 - 38.4 °C	0
38.5 - 38.9 °C	1
39 - 40.9 °C	3
≥ 41°C	4

Mean Arterial Pressure	Score
≤ 49 mm Hg	4
50 - 69 mm Hg	2
70 - 109 mm Hg	0
110 -129 mm Hg	2
130 - 159 mm Hg	3
≥ 160 mm Hg	4

Heart Rate (bpm)	Score
≤ 39	4
40 – 54	3
55 – 69	2
70 – 109	0
110 – 139	2
140 – 179	3
≥ 180	4

Respiratory Rate (/min)	Score
≤ 5	4
6 – 9	2
10 –11	1
12 – 24	0
25 – 34	1
35 – 49	3
≥ 50	4

If $FiO_2 \geq 0.5$	
$(A\text{-}a)O_2$ mm Hg	Score
< 200	0
200 – 349	2
350 – 449	3
≥ 50	4

If $FiO_2 < 0.5$:	
(PaO_2) mm Hg	Score
< 55	4
55 – 60	3
61 – 70	1
≥ 70	0

If ABG is not available	
HCO_3 mmol/L	Score
≥ 52	4
41 – 51.9	3
32 – 40.9	1
22 – 31.9	0
18 – 21.9	2
15 – 17.9	3
≤15	4

Arterial PH	Score
≥ 7.7	4
7.6 – 7.69	3
7.5 – 7.59	1
7.33 – 7.49	0
7.25 – 7.32	2
7.15 – 7.24	3
≤ 7.15	4

Serum Na^+ (mmol/L)	Score
≥ 180	4
160 – 179	3
155 – 159	2
150 – 154	1
130 – 149	0
120 – 129	2
111 - 119	3
≤ 110	4

Serum K^+ (mmol/L)	Score
≥ 7	4
6 – 6.9	3
5.5 – 5.9	1
3.5 – 5.4	0
3 – 3.4	1
2.5 – 2.9	2
≤2.5	4

Patient with ARF	
Se Creatinine mg/dL	Score
≤ 0.6	4
0.6 – 1.4	0
1.5 – 1.9	4
2.0 – 3.4	6
≥ 3.5	8

Patient without ARF	
Se Creatinine mg/dL	Score
≤ 0.6	2
0.6 – 1.4	0
1.5 – 1.9	2
2.0 – 3.4	3
≥ 3.5	4

Haematocrit (%)	Score
≤ 20	4
20 – 29.9	2
30 – 45.9	0
46 – 49.9	1
50 – 59.9	2
≥ 60	4

WBC (x10^3 /mm^3)	Score
≤ 1	4
1 – 2.9	2
3 – 14.9	0
15 – 19.9	1
20 – 39.9	2
≥ 40	4

GCS	Score	GCS	Score
15	0	8	7
14	1	7	8
13	2	6	9
12	3	5	10
11	4	4	11
10	5	3	12
9	6		13

Age	Score
≤ 44	0
45 – 54	2
55 – 64	3
65 – 74	5
≥ 75	6

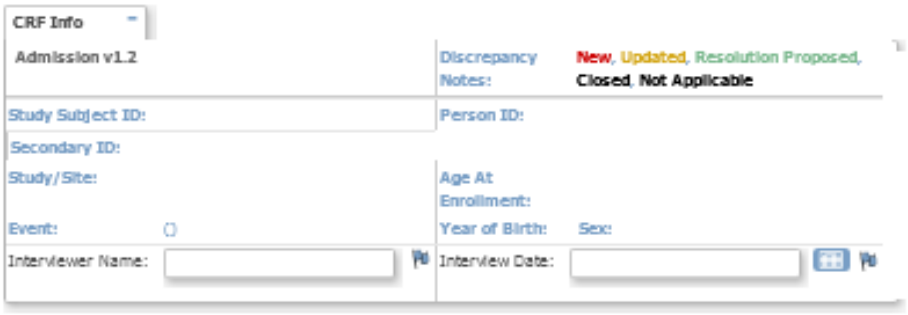
Chronic Organ Insufficiency in patients admitted for	SCORE
Postoperative – Emergency	5
postoperative – Elective	2
Non operative	5

CHRONIC ORGAN INSUFFICIENCY / IMMUNOCOMPROMISED STATE				
Liver insufficiency	**Cardiovascular**	**Respiratory**	**Renal**	**Immuno depression**
Biopsy proven cirrhosis Documented portal hypertension, Episodes of past upper GI bleeding attributed to portal hypertension Prior episodes of hepatic failure / encephalopathy / coma.	NYHA Class IV	Chronic restrictive, obstructive or vascular disease resulting in severe exercice restriction. Documented chronic hypoxia, hypercapnia, secondary polycythemia , severe pulmonary hypertension (> 40 mmHg), or respirator dependency.	Receiving chronic dialysis	The patient has received therapy that suppresses resistance to infection

	Insulin infusion rate (unit / ml / hour)			
Plasma glucose levels (mg %)	Algorithm 1 Non DM	Algorithm 2 DM,HTN, TPN	Algorithm 3	Algorithm 4
< 50	Hypoglycaemia protocol			
50 - 80	0	0	0	0
81 - 100	0.2	0.5	1	1.5
101 - 120	0.5	1	2	3
121 - 140	1	1.5	3	5
141 - 180	1.5	2	4	7
181 - 200	2	3	5	9
201 - 230	2	4	6	12
231 - 270	3	5	8	16
271 - 290	3	6	10	20
291 - 320	4	7	12	24
321 - 360	4	8	14	28
>360	6	12	16	28

Appendix 2 – Glucose control protocol – SICU, CMC Vellore

View Section Data Entry for Admission v1.2



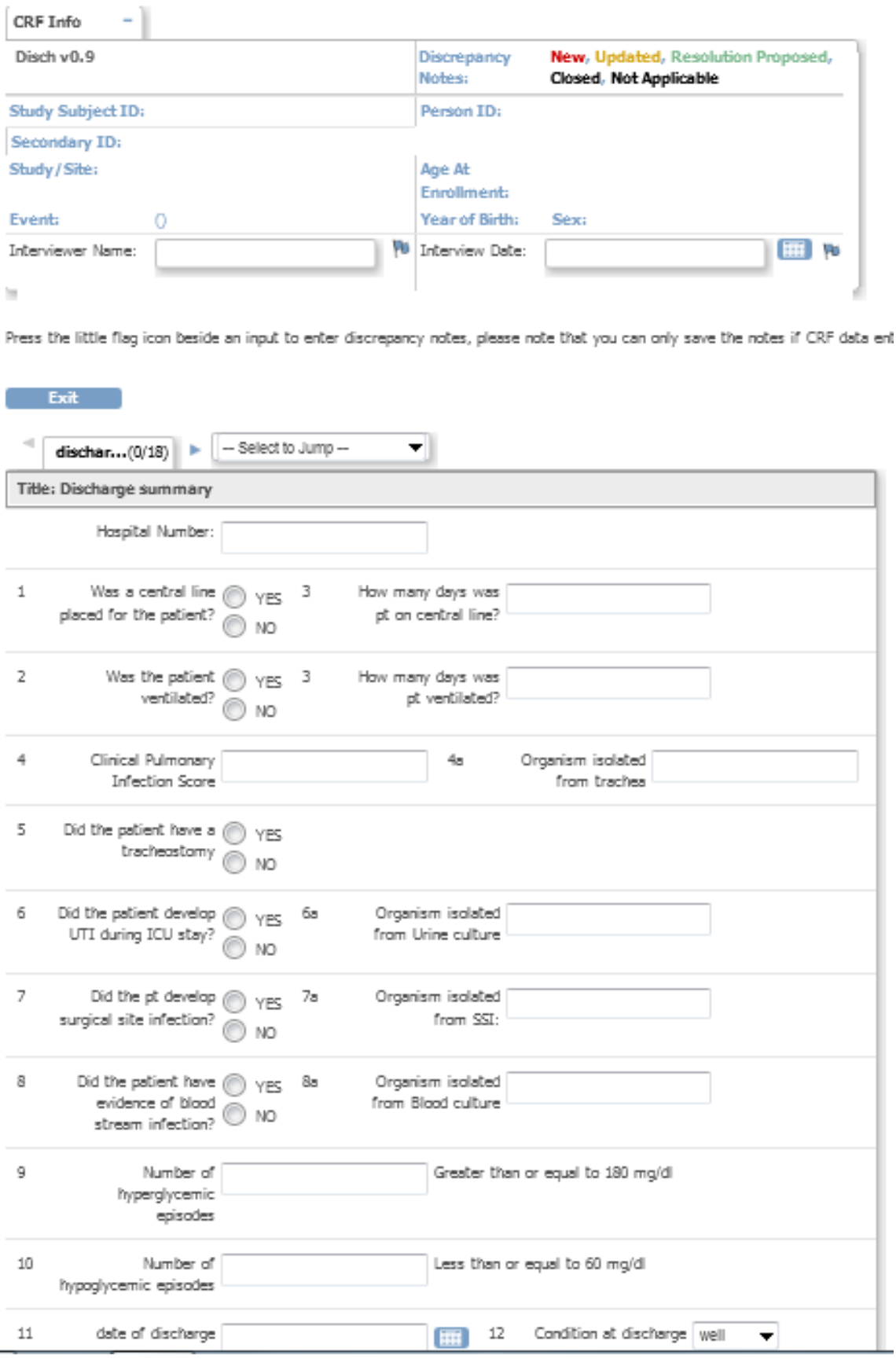
Press the little flag icon beside an input to enter discrepancy notes, please note that you can only save the notes if CRF data entry has already started.

Exit

admissi...(0/23) – Select to Jump –

Title: Admission Notes

1	Name:						
2	Describe briefly the injury / cause:						
3	Is the patient a known diabetic?	YES / NO	Prior history of diabetes	4	Does anyone in the immediate family have diabetes?	YES / NO	(Parents / siblings)
5	Date of injury			6	Date of admission to casualty		
7	Date of admission to SICU						
8	Blood Sugar:		(mg/dl) First blood sugar done after arrival				
9	Admission HbA1C		(%)	10	Was sample collected prior to transfusion?	YES / NO	
11	Any Cardiac co-morbidity?	YES / NO	12	Any h/o COPD?	YES / NO	13	Any h/o Hypertension? YES / NO 14 Is the patient obese? YES / NO
15	List other significant co-morbidities:						
16	AIS for Head & Neck	None	17	AIS for Face	None		
18	AIS for Chest	None	19	AIS for Abdomen	None		
20	AIS for extremity	None	21	AIS for external	None		
22	Injury Severity Score						
23	APACHE II Score						


CRF Info
Disch v0.9
Discrepancy Notes:
New, Updated, Resolution Proposed, Closed, Not Applicable
Study Subject ID:
Person ID:
Secondary ID:
Study / Site:
Age At Enrollment:
Event:
Year of Birth:
Sex:
Interviewer Name:
Interview Date:
Press the little flag icon beside an input to enter discrepancy notes, please note that you can only save the notes if CRF data ent
Exit
dischar...(0/18)
-- Select to Jump --
Title: Discharge summary
Hospital Number:
1 Was a central line placed for the patient? YES NO
3 How many days was pt on central line?
2 Was the patient ventilated? YES NO
3 How many days was pt ventilated?
4 Clinical Pulmonary Infection Score
4a Organism isolated from trachea
5 Did the patient have a tracheostomy YES NO
6 Did the patient develop UTI during ICU stay? YES NO
6a Organism isolated from Urine culture
7 Did the pt develop surgical site infection? YES NO
7a Organism isolated from SSI:
8 Did the patient have evidence of blood stream infection? YES NO
8a Organism isolated from Blood culture
9 Number of hyperglycemic episodes
Greater than or equal to 180 mg/dl
10 Number of hypoglycemic episodes
Less than or equal to 60 mg/dl
11 date of discharge
12 Condition at discharge
well