UNIVERSITY OF NAIROBI

ACUTE TRAUMATIC COAGULOPATHY IN MAJOR TRAUMA ORTHOPAEDIC PATIENTS AT KENYATTA NATIONAL HOSPITAL

BY

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A dissertation submitted for examination in partial fulfillment of the requirements for the Award of degree of Master of Medicine (M.med) in Orthopaedic surgery in University of Nairobi.

DECLARATION

I hereby declare that this dissertation is my original work and has not been presented as a dissertation at any other University. Where other people's work or my own work has been used, this has properly been acknowledged and referenced according to University of Nairobi's plagiarism policy.

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DEDICATION

I dedicate this dissertation to my dear wife, Lucy Mutua, for her unconditional love, patience and encouragement as well as to my daughter Tiffany and son Emmanuel. I also dedicate it to my parents for their support throughout my education.

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LIST OF ABBREVIATIONS

AcoTS	Acute Coagulopathy of Traumatic Shock
A & E	Accident & Emergency
AIS	Abbreviated Injury Score
ATC	Acute Traumatic Coagulopathy
BD	Base deficit
BGA	Blood Gas Analysis
DIC	Disseminated Intravascular coagulopathy
E.G	Example
ERC	Ethics and Research Committee
GCS	Glasgow Coma Score
ISS	Injury Severity Score
KNH	Kenyatta National Hospital
MPs	Microparticles
PS	Phosphatidyl serine
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
ROC	Receiver Operator Characteristics
ROTEM	Rotation Thromboelastometry
SPSS	Statistical Package for Social Science
TIC	Trauma Induced Coagulopathy
TT	Thrombin Time
UoN	University of Nairobi
WHO	World Health Organisation
GOK	Government of Kenya

DEFINITIONS

1. **ACUTE TRAUMATIC COAGULOPATHY**-An endogenous coagulation impairment early after trauma. It is also known as trauma induced coagulopathy (TIC) or Acute coagulopathy of Traumatic shock(ACOTS). A clinical imbalance between clotting, anticoagulation and fibrinolysis occurs. It usually occurs when there is trauma and tissue hypoperfusion (1).

2. **MAJOR TRAUMA**-Any injury having potential to cause prolonged disability or death. The trauma is graded using Abbreviated Injury Score (AIS) for the different body regions (Appendix 5.2). For research purpose, major musculoskeletal trauma is an Injury severity score (ISS) of >15. This is achieved by taking the sum of AIS of the 3 most injured body regions. In such, the extremities (upper and lower) including pelvis should be having the highest AIS score of the 3 most injured body organs. For the extremities and pelvis, an AIS of 4 and above is required for definition and grading of major musculoskeletal trauma(2,3).

3. **DISSEMINATED INTRAVASCULAR COAGULOPATHY (DIC)** - A disorder in which proteins which control blood coagulation become overactive. There are two types; Thrombotic (abnormal clotting in blood vessels), hyperfibrinolytic (excess, uncontrolled bleeding).

   ATC is a type of DIC with fibrinolytic phenotype(4,5).

4. **OUTCOME**- Final result of a process or activity. Part of this study was to determine outcomes in patients with Acute traumatic coagulopathy. Outcomes of interest in this study were Anaemia and need for blood transfusion, Acute renal failure and mortality.

ABSTRACT

Background: Mortality due to trauma is a major public health issue. It is among leading causes of death in persons aged between 25-44yrs. Within the first 48hrs of admission, uncontrolled haemorrhage and coagulopathy is responsible for 50% of all trauma related deaths. This early development is known as Acute Traumatic coagulopathy (ATC). It is associated with increased transfusion requirement, organs failure and high mortality rate. In Kenya, mechanisms of injuries include road traffic accidents (36.8%), falls (26.4%) and been assaulted by a person or object (20.1%). Orthopaedic related injuries were the most commonly encountered in a multisite surveillance study in four referral hospitals in Kenya . In musculoskeletal trauma patients, presence of coagulopathy at admission can be used as a predictor of complications such as sepsis, acute renal failure, multiple organs failure, need for blood transfusion and even death. In musculoskeletal trauma patients, a high Injury severity score (ISS) correlates with hypocoagulability. Previous studies have observed that ISS in musculoskeletal trauma patients can be used as a predictor of hypocoagulability complications. In many resources limited settings, coagulation profiles are not routinely done among patients with major trauma. Early identification of ATC in musculoskeletal injuries guides resuscitation protocol and prevent of ATC progression. The purpose of this study was to determine the incidence of acute coagulopathy among musculoskeletal trauma patients, and the predictive value of ISS in diagnosis of ATC. This study was also to determine the utility of injury scoring systems in predicting ATC associated outcomes among musculoskeletal trauma patients.

Broad Objective: To determine the incidence of acute coagulopathy among musculoskeletal trauma patients

Setting: The A & E department and orthopaedic wards at KNH

Study design: Prospective analytical study of convenient patient sampling

Patients and Methods: Convenient sample of 102 patients in three months. Ethical approval was obtained from KNH/ERC. Consent was obtained from each patient conveniently sampled according to the set criteria. Data collected included the patient's demographics, mechanism of injury, duration before presenting to the hospital, type and amount of fluids received, injury severity score, coagulation profile parameters (PT,PTT, INR), full blood count and renal function test. The coagulation profile was determined at first contact with the patient during admission.

In this study each patient was followed up for a duration of 14 days and monitored for occurrence of any ATC related outcome/complication. Patients were monitored by doing

physical examinations and drawing blood for laboratory investigations. The schedule for monitoring was day 0,7 and 14 post admission. Outcomes of interest in the study were presence of acute renal failure and anaemia and need for blood transfusion.

Data Collection and Analysis: Data was collected on a printed questionnaire, which was checked for completeness and free of error, thereafter it was entered into a Microsoft Excel spreadsheet. The data was later exported to Statistical Package for Social Sciences version 25 for analysis.

Demographic data and clinical data were analyzed and presented as frequencies and proportions for categorical data and as means with standard deviation for continous data. The prevalence of ATC among major trauma orthopaedic patients presenting to A&E was calculated as a proportion and presented as a percentage of the total number of major trauma patients. The predictive value of ISS in diagnosing ATC among major trauma orthopaedic patients was calculated with the use of an ROC curve. Independent t-tests as well as chi-square tests were used to test the associations between outcome of patients and ATC. All statistical tests were considered significant where $p < 0.05$.

Results: Majority (82.4%) of the 102 patients recruited were male and, the mean age was 32.6 (S.D=9.5). Acute traumatic coagulopathy was present in 61.8% of the patients. The mean Injury severity score at admission was 20.2 (SD=9). Patients with ATC has a relatively higher mean ISS at admission 23.3 (SD=10). Patients with coagulopathy developed acute renal failure (p=0.022). Patients with a high ISS were more predisposed to ATC associated outcomes or mortality (p=0.001). There was a statistical association between receiving fluids and ATC, with those receiving fluids being 3 times likely to develop ATC (OR 3.1 (1.4-7.1), P=0.007)

Conclusion: Acute Traumatic Coagulopathy is common in major musculoskeletal trauma patients. A greater proportion of males suffer major trauma leading to ATC. There is a significant association between Injury Severity Score and ATC in major musculoskeletal trauma patients. A rise in ISS in major musculoskeletal trauma patients can be used to predict occurrence of ATC related outcomes such as acute renal failure and anaemia plus need for blood transfusion.

The two main drivers for ATC are tissue trauma and systemic hypo perfusion. Medical interventions such as fluid administration may propagate and worsen an already established ATC

INTRODUCTION

In 2013, it is estimated that 900 million people sustained injuries which required some form of health care while 4.6 million people died as a result of injuries(6). Globally, trauma leads to around10% of all deaths (7). In Nairobi, Kenya, deaths resulting from injuries account for 10.6% of all recorded deaths. Most of these deaths occur in persons aged between 25-44yrs (48.1%). The leading causes of injury include blunt force (30.5%), road traffic accidents (25.9%) and firearm injuries at 15% (8). Sustained severe haemorrhage leads to over 50% of all early trauma related deaths after hospital admission (9). In Kenya, the most common mechanisms of injuries are road traffic accidents (36.8%), falls (26.4%) and been hit/struck by a person or object (20.1%). Orthopaedic related injuries were the most commonly encountered in a multisite surveillance study in four referral hospitals in Kenya (10). Major trauma is any injury having the potential to cause prolonged disability or death. It encompasses patients who have or at risk of most severe or critical types of injuries. It therefore requires a systems approach. The systems approach can lead to so life and limb saving(2). For research purpose, major trauma is based on injury severity score (ISS) of more than 15.

In trauma, immediate death can be due to exsanguinations. In patients who survive the exsanguinations, bleeding and hypo perfusion increase the risk of delayed mortality and organs failure (5). Trauma leads to an endogenous impairment of haemostasis. This occurs early after injury and is known as Acute Traumatic coagulopathy (ATC or Trauma Induced Coagulopahty (TIC). Its presence is associated with a higher mortality rate, increased transfusion requirement and organs failure(3).

In a study by Brohi and his team (11) they proposed that TIC which is identified by prolonged Partial Thromboplastin time (APTT), Prothrombin time (PT) and International normalized ration (INR) occurs in presence of shock and trauma and importantly tissue hypo perfusion. This is based on mechanism that enhanced early generation of activated coagulation factors, including thrombin.

Reduced thrombin clearance results in increased thrombin-thrombomodulin on adjacent endothelial cells. This results in activation of protein C. Protein C is a natural anti-coagulant present in circulation. Activated protein inhibits activated Factor V and Factor VIII and this

leads to decreased thrombin generation, decreased fibrinogen utilization and enhanced fibrinolysis. The team also importantly emphasized that micro vascular thrombosis does not occur in ATC. Platelets and fibrinogen are also relatively spared, thus differentiating ATC from DIC of thrombotic type which occurs in sepsis (5).

Acute traumatic coagulopathy is often multifactorial. It can be induced partly by early trauma patient treatment interventions leading to hypothermia, homeostasis derangements and haemodilution. The coagulopathy also has an endogenous cause. This occurs in combination of shock and tissue damage. It can occur independent of the iatrogenic causes (11). Injury severity has a positive association with development of Acute traumatic coagulopathy (11). This coagulopathy occurs in 28 to 34% of multiple injured patients (5). In multiple variables analysis, coagulopathy has been identified as an independent mortality predictor (3). The other factors are injury severity score and the severity of shock although the three variables are interdependent. Traditionally coagulation profile (activated partial thromboplastin time and prothrombin time) along with platelet count and fibrinogen concentrations have been used frequently in diagnosis of ATC (3). Coagulation profile is a reliable predictor of Acute traumatic coagulopathy related mortality. Increasing systemic hypo perfusion is associated with prolongation of PT and APTT (3). Coagulopathy after trauma is not only associated with mortality but also associated with other outcomes of trauma such as organ failure due to hypo perfusion and hypoxia, transfusion requirements and long hospital stay (5).

Patients with isolated musculoskeletal trauma have been noted to have ATC which is commensurate with the high ISS level (12). ISS in musculoskeletal trauma patients can be used as a predictor of hypocoagulability complications (13). In many resources limited settings, coagulation profiles are not routinely done among patients with major trauma. Early identification of ATC in a trauma patient would be essential in guiding the resuscitation protocol of patients and prevention of ATC progression and complications. The purpose of the study was to evaluate prevalence of ATC and the predictive value of ISS in diagnosis of ATC among musculoskeletal trauma patients presenting to KNH Accident and Emergency department. This study also sought to evaluate the utility of injury scoring systems in predicting ATC associated outcomes among musculoskeletal trauma patients.

1.1 STUDY QUESTION

What is the incidence of acute traumatic coagulopathy among major musculoskeletal trauma patients presenting to KNH Accident and Emergency department

1.2 STUDY JUSTIFICATION

Trauma is one of the leading causes of morbidity and mortality in Nairobi and Kenya at large. (3). In Kenya, the most common mechanisms of injuries are road traffic accidents (36.8%), falls (26.4%) and been hit/struck by a person or object (20.1%). Orthopaedic related injuries were the most commonly encountered in a multisite surveillance study in four referral hospitals in Kenya (10). In musculoskeletal trauma patients, presence of coagulopathy at admission can be used as a predictor of complications such as sepsis, acute renal failure, multiple organs failure, need for blood transfusion and even death (13).

In musculoskeletal trauma patients, an increase in Injury severity as evident by a high Injury Severity Score (ISS) correlates with hypocoagulability(12). ISS in orthopaedic patients can be used as a predictor of hypocoagulability complications (13). In many resources limited settings, coagulation profiles are not routinely done among patients with major trauma. Early identification of ATC in a trauma patient would be essential in guiding the resuscitation protocol of patients and prevention of ATC progression.

The purpose of the study was to determine the incidence of acute coagulopathy among musculoskeletal trauma patients. The study also sought to evaluate the predictive value of ISS in diagnosis of ATC among musculoskeletal trauma patients presenting to KNH Accident and Emergency department. This study also sought to evaluate the utility of injury scoring systems in predicting ATC associated outcomes among musculoskeletal trauma patients.

1.3 MAIN OBJECTIVE

To determine the incidence of acute traumatic coagulopathy among major musculoskeletal trauma patients presenting to KNH Accident and Emergency department

1.4 SECONDARY OBJECTIVES

i. To determine the predictive value of ISS in diagnosis of ATC among musculoskeletal trauma patients presenting to KNH Accident and Emergency department.

ii. To determine the early outcome of major musculoskeletal trauma patients diagnosed with ATC

iii. To determine the utility of injury scoring systems in predicting ATC associated outcomes among musculoskeletal trauma patients

iv. To determine the effect of pre-admission fluids administration (Type and amount) on ATC in musculoskeletal trauma patients

2.0 LITERATURE REVIEW

2.1 COAGULATION PATHYWAY

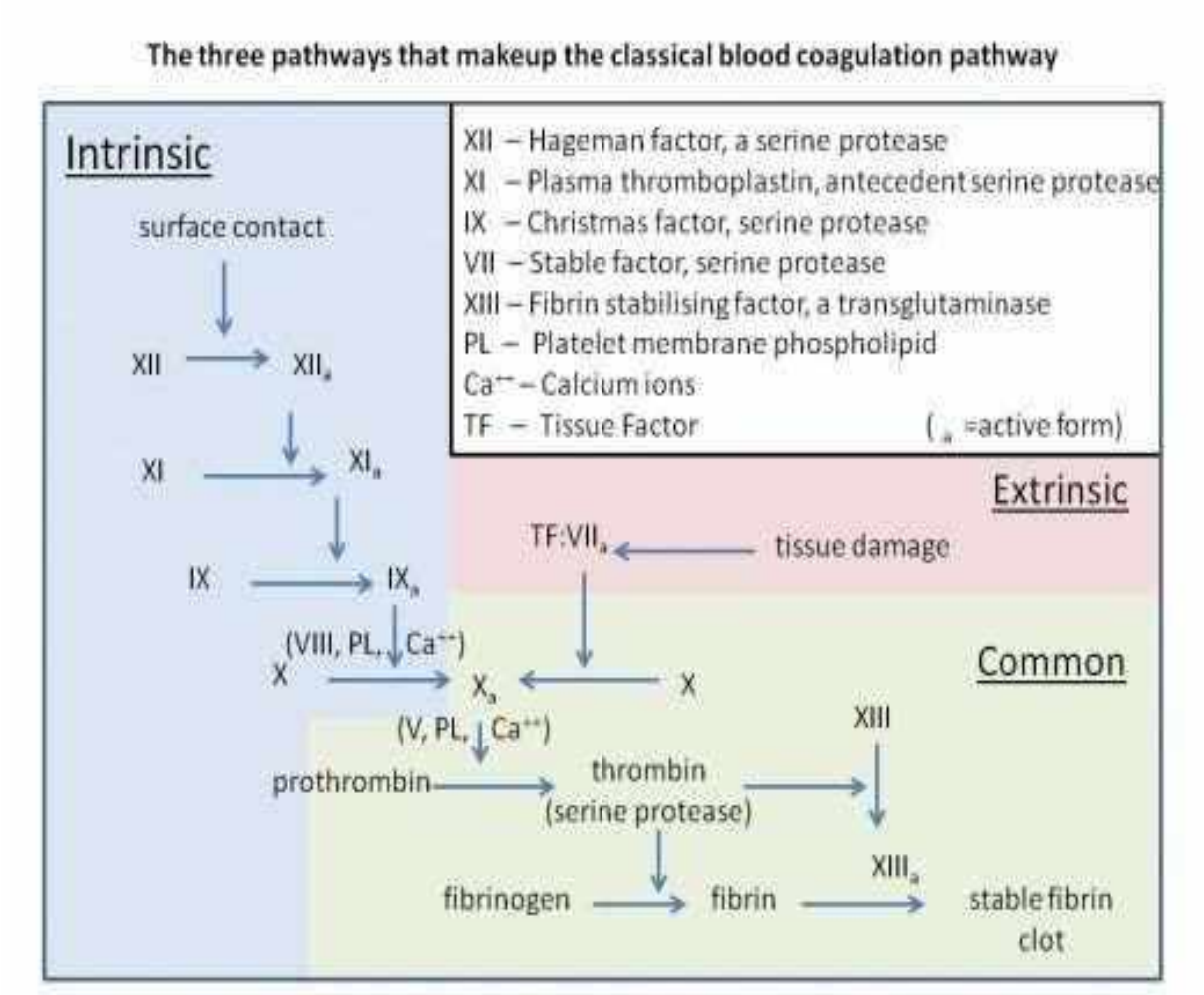
The coagulation pathway is a sequence of events which lead to haemostasis. Primary haemostasis involves platelets forming a plug where endothelial damage occurs. There are two pathways in secondary haemostasis, namely Intrinsic and Extrinsic. The two originate separately but later converge at a point. This leads to activation of fibrin and formation of a mesh that stabilizes the platelet plug (14).

There are thirteen coagulation factors named using roman numbers I-XIII. They circulate in the blood stream as zymogens. They are activated into serine proteases ultimately activating fibrinogen. Exposure to endothelial collagen activates intrinsic pathway. When external damage to endothelial cells occurs, tissue factor is released and this activates extrinsic pathway (14).

In both pathways, when a zymogene factor is activated into a serine protease, it activates the factor in the next step till the two pathways join forming the common pathway. Intrinsic pathway activity is measured using partial thromboplastin time assay. Prothrombin time assay is used to measure extrinsic pathway activity(14). Both measurements measure the time it takes for both pathways to take effect.

Common pathway begins when factor X is activated to Xa from both pathways with factor VIII as a cofactor. The factor Xa then activates factor II (prothrombin) to IIa (thrombin) with factor Va as a cofactor. Fibrinogen is activated to fibrin by thrombin (Figure 1)(14)

Figure 1:



Summary of coagulation cascade. (14) *Surface contact=collagen*

2.2 DEFINITION OF ATC

Acute traumatic coagulopathy occurs early after an injury. It is a haemostasis impairment. It commonly leads to a 4-fold increase in mortality, more transfusion needs and organs failure(3). Currently, a clinical definition of ATC has not been established. Due to lack of a defined clinical definition there has been variation in ATC prevalence reporting (3). Coagulopathy due to trauma can be viewed as a loss, dilution or dysfunction of coagulation proteases. Loss occurs due to bleeding or consumption of coagulation proteases.

Administration of intravenous fluids and also massive transfusion leads to dilution. Low core body temperature (hypothermia) and low blood PH (acidosis) leads to proteases dysfunction (15).-

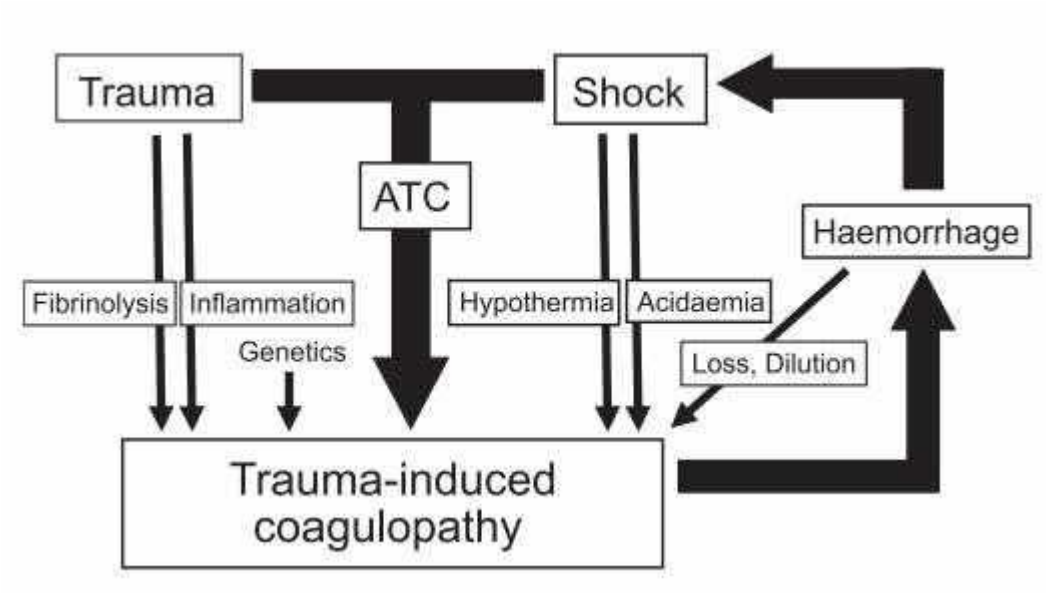
Acute traumatic coagulopathy has two components:

1) Endogenous ATC-Due to trauma 2) Iatrogenic induced ATC-Due to resuscitation methods leading to low body core temperature {hypothermia),Low blood ph (metabolic acidosis) and dilutional coagulopathy (16).

2.3 INSTIGATORS OF ACUTE TRAUMATIC COAGULOPATHY

Acute traumatic coagulopathy appears to have an endogenous component .This occurs in trauma when shock and tissue damage coexist. It can develop in the absence of exogenous factors. Exogenous factors can propagate the already established ATC in a particular patient. They include dilution, hypothermia, acidemia -associated coagulation dysfunction. None of the propagators appear to be the primary cause and shock plus tissue damage are regarded as the primary initiator of ATC (6).

Figure 2: Multifactorial factors of acute traumatic coagulopathy (17)



Dilution

In an international multicentre study in London and Germany on trauma patients by Brohi et al, (11) some patients received less than 500ml pre-hospital fluid and others more than 2200ml either crystalloids or colloids. In patients who received less than 500ml of intravenous fluids, 10% developed coagulopathy. In those who received more than 3litres of fluid, around 50% had developed coagulopathy. This study suggested that there is another mechanism for Acute traumatic coagulopathy apart from dilution.

Use of intravenous fluids (crystalloids and colloids)can lead to decreased levels of soluble haemostatic factors. This can lead to dilutional coagulopathy. Although use of fresh frozen plasma leads to dilution of corpuscular elements in blood, it maintains nearly normal levels of soluble clotting factors (18)**.**

Massive haemorrhage and hemodilution during resuscitation can lead to fibrinolytic and antifibrinolytic activities. Plasmin is inactivated by Alpha $(\alpha)_2$ antiplasmin. Plasmin is responsible for fibrin breakdown. Activated factor VIII also crosslinks Alpha 2 antiplasmin to fibrin chains. This increases fibrin resistance to fibrinolysis. Hemodilution leads to decreased level of α-$_2$ antiplasmin and FVIII in circulation. This leads to reduced fibrin crosslinks. There is also prolonged half life of plasmin leading to fibrinolysis (18).

A meta-analysis review by Giordano et.al established that when hematocrit is above 30%, blood flow occurs in a manner that red blood cells are at the centre of the blood vessel and platelets at the periphery so that they adhere incase of any damage. A decrease in hematocrit to below 25% due to dilution leads to impairment of the platelets skimming therefore decreased rate and capability of formation of platelet aggregate when endothelial injury occurs. Dilutional coagulopathy has been reported to start after administration of 1litre of fluid. The coagulopathy is directly proportional to amount of fluid administered. Crystalloids were reported to reduce factor VII activity while colloids were reported to lead to platelet and fibrinogen dysfunction. They concluded that hemodilution can lead to overall impairment in clot formation and stability (19).

Trauma patient should be accurately assessed and monitored to identify early when massive transfusion protocol should be activated. Current ATLS protocol advocates for low

volume resuscitation with fluids up to 1 litre and permissive hypotension using vasopressors for bleeding trauma patients (20).

Hypothermia

Loss of heat from the body can occur before a patient arrives in a health facility or while in the health facility. Some of the factors leading to heat loss include massive bleeding, exposure to the environmental agents due to prolonged rescue procedures, fluid administration at environmental temperature or below, exposure of the patient during clinical assessment without adequate thermal protection, use of muscle relaxants or sedatives.

A low percentage of trauma patients (<9%) have moderate or severe hypothermia. Temperature level has little effect on coagulation proteases. For significant effect on coagulation proteases function, with resultant bleeding, the core body temperature should be less than 33 degrees (11).

Hypothermia impairs the coagulation cascade by different mechanisms. It primarily inhibits the thrombin generation phase of coagulation. It also inhibits fibrinogen synthesis (21). Hypothermia also alters platelet function by reducing their adhesion, activation and aggregation capacity (19).

Acidemia

Metabolic acidosis in trauma may occur through two mechanisms: tissue damage leading to haemorrhage and hypo perfusion therefore decreased tissues oxygen supply with resultant anaerobic metabolism and lactic acid production. The second mechanism is by fluid resuscitation leading to hyper chloremic acidosis (19).

A ph of 7.2 has very little clinical significance on function of coagulation proteases. Animal studies done have shown that a ph of 7.1 and below leads to 20% increase in PT and Partial Thromboplastin time. Acidosis leads to an irreversible effect on coagulation function despite correction of the acidosis (11).

Acidosis inhibits propagation phase of thrombin generation. It also accelerates fibrinogen degradation leading to enhanced bleeding. Neutralization of ph alone does not reverse the coagulation derangement (21).

In a study by Gissel et al on the effect of acidic environment on coagulation dynamics, it was reported that there is a decrease in procoagulant activity at a ph of 7.0 and below. Viscoelastic analysis in the study showed a 25% increase in clot time and a 25% decrease in maximum clot firmness at a ph of 7.0 and below (22).

In a study by Martin et al. On effect of acidosis on coagulation, it was reported that there is a strong correlation between ph and impairment of coagulation. A ph of 7.4 and below lead to a weak clot strength. A ph of 6.8 and below increased clot formation time by 168% as compared with ph of 7.4. Acidosis retards polymerization activities required in clot formation and strength. Coagulation impairment due to low ph can be reversed by addition of a buffer(23).

Hypo perfusion

Shock and tissue hypo perfusion are strong independent risk factors for poor outcome in trauma. Different studies have portrayed that patients with a normal base deficit have normal partial thromboplastin or Prothrombin time. This is irrespective of injury severity or rate of thrombin generation. Increasing systemic hypo perfusion and increase in base deficit has been shown to cause a relative prolongation of clotting time. High injury severity score increases the incidence of hypocoagulabitity in shocked patients. Different researchers have proposed that one of the key drivers of ATC are shock and systemic hypo perfusion (11).
In a rat experimental study by Frith et al, (6) on effect of trauma compared to haemoarrhage on coagulation function, those who were subjected to trauma had no change in coagulation profile, while those subjected to both trauma and haemorrhage had a slight prolongation in PT and Partial thromboplastin time. Only those who were subjected to trauma and haemorrhagic shock had marked ATC.

In the experimental rat model by Frith et al, (6) there was control of exogenous causes of coagulopathy. This include hypothermia and haemodilution. Despite control of exogenous causes, coagulopathy occurred in the rats and had clinical features consistent of ATC.
In a study by Jansen et al. On effect of hypoperfusion to coagulation activity in severely injured patients, it was reported that hypo perfusion is associated with a dose dependent reduction in coagulation factors II,VII,IX, X and XI. In that study, base deficit analyses was used to assess the degree perfusion(24).

2.4 PATHOPHYSIOLOGY OF ACUTE TRAUMATIC COAGULOPATHY

Most of the bleeding after trauma is due to bleeding from arteries and veins. This can be controlled by compression, embolization or repair of the blood vessel(25). Acute traumatic coagulopathy does not occur due to a dysfunction in coagulation proteases. It mainly occurs as a result of anticoagulation and fibrinolytic pathyways activation. Activation of protein C to active form by Thrombin-Thrombomodulin complex is the main pathway leading to anticoagulation and fibrinolytic pathways activation (4).

Coagulation activation in trauma

Massive tissue injury in severe blunt trauma accelerates thrombin generation. Several procoagulants are seen in circulation shortly after trauma leading to thrombin generation (26). Cells surrounding endothelium of blood vessels e.g. muscles express a transmembrane protein. This transmembrane protein is known as tissue factor. The protein has receptors for factor VII/VIIa. The endothelial cells form a barrier between TF and Factor VII in circulation. Endothelial breakage leads to activation of Factor VII and the coagulation cascade.TF is also expressed in small amounts in the brain and heart (27). The extrinsic pathway coagulation cascade is primarily instigated by tissue factor. In healthy individuals, very low levels of Tissue factor have been detected in circulation(26). Tissue factor is expressed when endothelial cell wall is breached and this leads to activation of extrinsic coagulation pathway with thrombin generation (11). The generated thrombin cleaves fibrinogen to form fibrin.

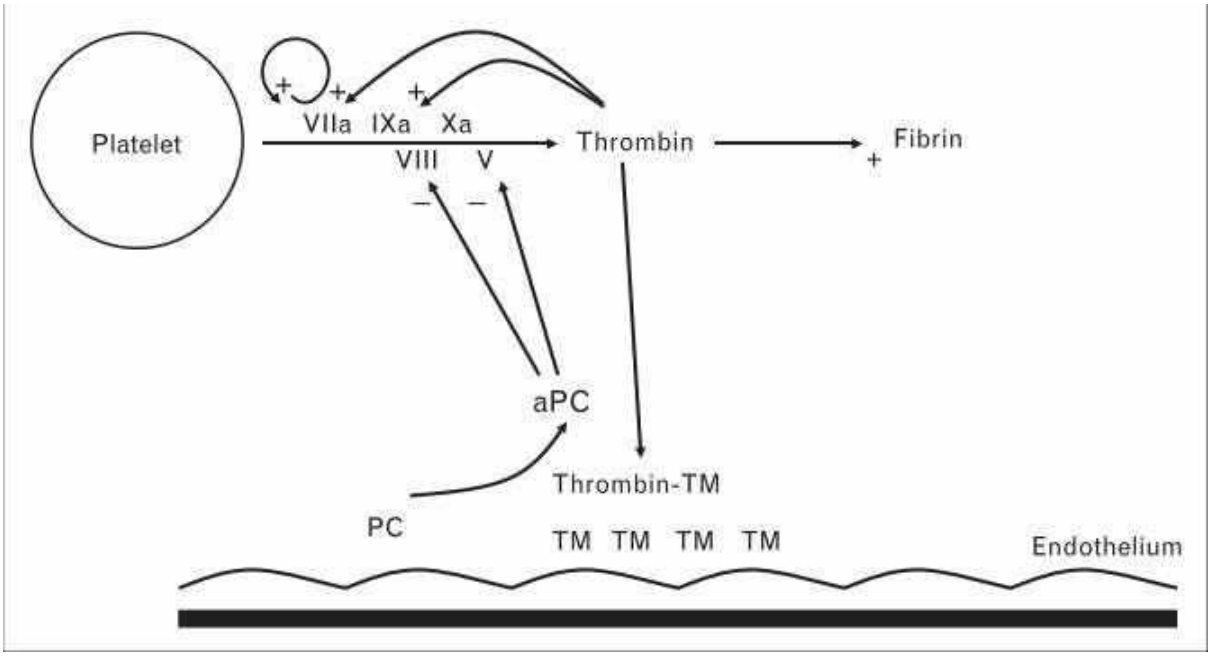
A review by Kushimoto et al. stated that in physiological conditions, when tissue injury occurs, there is generation of thrombin. This leads to clot formation through the extrinsic coagulation pathway. Excess thrombin generation is regulated by anthithrombin. It is also regulated by formation of thrombin-Thrombomodulin complex (9). Thrombomodulin is an integral membrane protein. It is usually found on endothelial cells surface. It inhibits coagulation activity by binding to thrombin and converting it from a pro coagulant to an anticoagulant complex (Thrombin-Thrombomodulin complex).

Systemic anticoagulation through protein C activation

Thrombomodulin is produced by endothelial cells in the presence of tissue hypoperfusion. Thrombomodulin form a complex with thrombin. Formation of the complex deviates thrombin from its pro-coagulation activity of cleaving fibrinogen to fibrin. The Thrombomodulin-Thrombin complex leads to activation of protein C. Activated protein C inhibits the activity of cofactors Va and VIIIa. This leads to inhibition of extrinsic coagulation pathway (28). Inhibition of the two cofactors leads to inhibition of procoagulation pathway. With increase in hypo perfusion as evidenced by increase in serum base deficit, there is an increase in thrombomodulin levels, a decrease in protein C and an increase in activated protein C levels. The net effect is prevention of clot formation in the injured blood vessels with a resultant flow of blood in fluid state leading to haemorrhage. With normal base deficit, there is usually no change in thrombomodulin and protein C levels despite the injury severity (13). Therefore, for ATC to occur , there has to be a combination of trauma and tissue hypo perfusion.

In a study done by Brohi et al. as tissue hypo perfusion increased, evidenced by an increase in base deficit, there was an increase in both Prothrombin time and partial Thromboplastin time. In the absence of hypo perfusion, coagulopathy did not occur despite the amount of thrombin generated (29). Hypo perfusion leads to anaerobic metabolism resulting in metabolic acidosis due to decreased tissues oxygen supply therefore generation of lactic acid. In the same study, it was noted that a decrease in ph was associated with an increase in quantity of soluble thrombomodulin, a decrease in protein C levels and an increase in activated protein C levels.

Figure 3: Protein C pathway of hypocoagulability



Thrombomodulin from endothelial cells forms a complex with thrombin. This deviates thrombin from cleaving fibrinogen. The complex activates protein C. Protein C inhibits cofactors V and VIII. This blocks the procoagulant cascade (29)

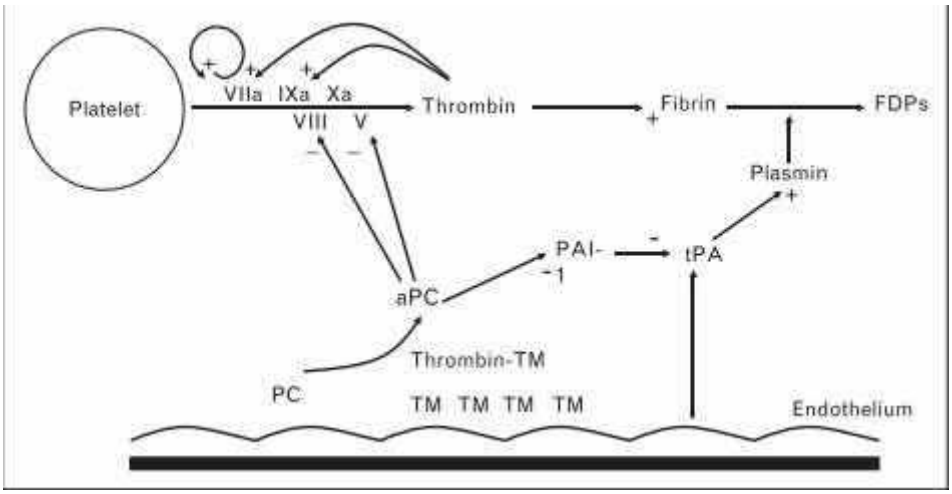
Hyperfibrinolysis

Trauma leads to an increase in fibrinogen breakdown and this is evidenced by a rise in Ddimer levels in circulation following injury. The breakdown occurs when tissue plasminogen activator (tPA) is released from the endothelium after an injury and ischaemia occurs. The tissue plasminogen activator cleaves inactive plasminogen to active plasmin that lyses firbin. This helps in preventing clot formation or extension into the normal, non-injured, blood vessels (14).

In normal circulation, plasminogen activator inhibitor-1 (PAI-1) inhibits excess fibrinolysis by inhibiting the activity of tPA. This ensures that the haemostasis fibrin clot is not cleaved leading to bleeding. In shock, when protein C activation occurs, the protein leads to a decrease in the tissue plasminogen inhibitor-1 (PAI-1). A decrease in PAI-1 level results in enhanced activity of Tissue plasminogen activator leading to hyperfibrinolysis and thus continued bleeding (13).

Acute coagulopathy of trauma occurs in presence of hypoperfusion. It leads to generalized hypocoagulability and fibrinogen breakdown. Brohi et al. in his study made strong evidence based conclusion that in the pathophysiology of ATC, thrombin-thrombomodulin complex is should be present/formed so as to activate Protein C (13).

Figure 4: Hyperfibrinolysis



Injury and hypoperfusion results in release of Tissue plasminogen activator (tPA) from the endothelium. tPA leads to fibrinogen breakdown. When activated protein C (aPC) is present in excess levels, it blocks the activity of plasminogen activator inhibitor-1 (PAI-1. Low levels of PAI-1 results in an increase tPA activity and fibrinogen breakdown (29)

2.5 DISSEMINATED INTRAVASCULAR COAGULOPATHY

Disseminated intravascular coagulopathy is a disorder in which proteins controlling blood clotting become overactive(4).

There are two phenotypes of DIC, thrombotic and fibrinolytic type. Thrombotic phenotype occurs in presence of sepsis and is characterized by suppression of fibrinolysis leading to thrombosis in small blood vessels and failure of some organs. Coagulopathy due to trauma is a type of DIC with fibrinolytic phenotype. Tissue plasminogen activator (t-PA) leads to fibrinogen breakdown. Massive bleeding in early phase of trauma occurs due to the fibrinolytic phenotype of DIC. Fibrinolytic phenotype can occur in acute phase of trauma and transition to a thrombotic type if no intervention is done(4).

The fibrinolytic type of DIC is also characterized by insufficient anticoagulation thrombomodulin/protein C, tissue factor pathway inhibitors, antithrombin /glycosaminoglycans systems. International society of Haemostasis and thrombosis has recently published an official communication regarding DIC of fibrinolytic type and ATC. Based on current available evidenced based studies trying to differentiate between the two, the society concluded that ATC is a disease entity similar to or same as DIC with fibrinolytic phenotype(30).

Current review articles and studies have concluded that both ATC and DIC with fibrinolytic phenotype have lead to consumption coagulopathy due to consumption of coagulation factors as the body tries to maintain homeostasis when bleeding occurs (5).

2.6 HOW TO DIAGNOSE ACUTE TRAUMATIC COAGULOPATHY

There are different previous studies which have been done and the researchers were able to identify presence of ATC in trauma patients. Most of the studies used prothrombin time and partial prothrombin time values in diagnosing ATC (31–33) The two laboratory tests are used to evaluate coagulation disorders. PT measures integrity of the extrinsic coagulation system as well as factors common to both systems. APTT measure the activity of intrinsic system and common pathway(14). In a study by Mac Leod et al, more patients had a more deranged PT value compared to PTT. In the same study by Mac Leod, PT appeared to be a better predictor of mortality compared to APTT. In the studies, blood samples for PT and PTT analysis were taken immediately the patients arrived at the health institution or immediately after initiation of resuscitation (31).

In a study by Brohi et al, PT had a better correlation with a decrease in protein C compared to APTT(28). In the same study, a PT of more than 18 seconds, a PTT of more than 60 seconds and a thrombin time of more than 15 seconds were used to diagnose coagulopathy. The values were based on British National blood transfusion services and American college of pathologists' guidelines (34).

In a prospective cohort study by Brohi et al, it was established that as tissue hypo perfusion increased (measured by base deficit), there was also an increase in PT and PTT (29).

In a prospective cohort study by Mujunu et al, of 182 patients with major trauma, initial coagulation profiles, PT and PTT were determined. Elevated PT was noted in 67(37%) the

patients. A total of 99 (54%) had coagulopathy but not all had elevated PTT. After doing Logistic regression he concluded that PT can be used as a reliably predict on mortality (35). In a study by B.Childs et al, acute coagulopathy was defined as one or more of the following : Platelet count <100,000, PT >14, PTT>35, INR>1.2 (13).

There are recent studies in diagnosing ATC though not readily available everywhere especially in a low resource setting. Rugeri et al, in their study concluded that RoTEM(Rotation Thromboelastometry) can be used to diagnose ATC and also give a guide on blood transfusion in trauma patients (36).

2.7 TRAUMA SCORING

The purpose of trauma scoring systems is done for appropriate triage, classification of trauma patients and predict outcome. It is also done for family counseling, quality assurance and research(For study of outcomes).The scoring systems can be physiologic e.g. Revised Trauma Score (RTS) or Anatomic e.g. Injury Severity Score (ISS) and Abbreviated Injury Score (AIS) (2).

Injury severity scale is based on anatomic criteria and it defines injury severity for comparative purposes. The variables are based on nine anatomic regions including head, face, neck, thorax, abdomen and pelvic contents, spine, upper extremity, lower extremity and external. It is calculated using Abbreviated injury scale (AIS) grades (Appendix 8.4). To calculate ISS, identify the top three most severely injured regions. Then square the grades of the top three injured regions. A sum of the squares of the three regions is then taken. Scores range from 1-75. Any region with a score of 6 leads to automatic score of 75.
An ISS of more than 15 is associated with 10% mortality (2).

2.8 INJURY SEVERITY SCALE IN ACUTE TRAUMATIC COAGULOPATHY

Different researchers on doing different studies have concluded that there is a direct proportional relationship between Injury severity and Acute traumatic coagulopathy. Acute traumatic coagulopathy is evidenced by an increase in PT and PTT. A study by Mujunu et al, of 182 patients with ATC found that the mean ISS was 32 (SD 14 CI 30-34) among major trauma patients. He also established that there was a high ISS in patients who were diagnosed with ATC compared to those without ATC (P=0.001). In his study, blood sample for

PT/APTT analysis was drawn from a suitable vein within 10 minutes of patient's arrival to A/E (35).

Frith et al, in his study demonstrated that ATC associated with coexistence of both tissue damage as evidenced by increase in ISS and systemic hypo perfusion as evidenced by a rise in base deficit (BD). He also concluded that clinically, ATC should be anticipated in patients with significant trauma and abnormal base deficit (3).

In a study by Cap et al, of 1867 patients admitted with trauma it was established that the median ISS was 20. The results established that 33.1% of those with an ISS of more than 15 had increased PT. The percentage of patients with coagulopathy increased to 61.7% for patients who had an ISS greater than 45. There was a higher risk of mortality in patients with a high injury score plus coagulopathy compared to those without (32).

2.9 MUSCULOSKELETAL INJURIES IN KENYA

In the last 15 years, there has been an increase in injury related death worldwide. The increase had been occurring mainly in Low and Middle income countries (LMIC) . Kenya is one of the countries in the LMIC group. Factors contributing to high injury mortalities in those countries include rapid urbanization, poor road networks, under developed trauma care systems and low enforcement of road safety laws (10).

In the last15 years, the number of registered motorcycles in Kenya has drastically increased.. This has been due to the government policy on exemption of tax on imported motorcycles. The increase in motorcycles has led to a proportional increase in road traffic crashes, injuries and deaths relating to motorcycle users (38). A study done in Kirinyaga county in Kenya by C.Ndwiga et al, reported that broken bones were among the most common form of injuries recorded from motorcycle crashes (40).

In a prospective multisite surveillance study by I. Botchey et al, on epidemiology and outcomes of injuries in Kenya, it was established that the most common mechanisms of injuries were road traffic accidents (36.8%), falls (26.4%) and been assaulted by a person or struck with an object (20.1%). In the same study, it was established that body injuries commonly injured were lower extremity (35.1%), upper extremity (33.4%) and head (26.0%) (10).

Upper and lower extremity injuries are part musculoskeletal injuries and constitute the biggest percentage of orthopaedic trauma cases.

In a study by C. Wilberforce et al, on Incidence of road traffic accidents and pattern of Injuries among commercial motorcyclist in Naivasha Town, Kenya, it was established that musculoskeletal injuries constituted the highest form of reported injuries(55.3%) (39). Based on the available data from the different studies done in the country, is evident that orthopaedic trauma related injuries constitute the biggest percentage of all trauma cases presenting in different hospitals across the country.

3.1 COAGULOPATHY IN PATIENTS WITH ORTHOPAEDIC TRAUMA

Different researchers have done studies on coagulation changes in patients with orthopaedic trauma.

In a study of 48 patients by A. Subramanian on coagulation studies in patients with isolated Orthopaedic trauma, it was reported that there was an existing hypocoagulopathy in 20 (41%) of the patients at the time of presenting to the hospital. In those patients there was an increase in PT, PTT and fibrinogen levels. In the same study, it was also reported that in increase in injury severity as shown by high ISS score correlated with hypocoagulopathy (12).

In a study by B.Childs et al, on presenting coagulopathy as a predictor of complications and death in musculoskeletal trauma patients, it was reported that an elevated PT and INR, increased age and ISS were associated with an increased rate of multiple organ failure, sepsis and death. In the study, it was concluded that coagulopathy at admission is a predictor of complications, sepsis and death. It was also concluded that an increase in ISS was predictor of complications (13).

In the study by B.Childs, some of the outcomes of interest were Acute renal failure, Pneumonia, Sepsis, Deep venous thrombosis, Multiple organs failure, Acute respiratory distress syndrome (ARDS) and anaemia. Acute renal failure was defined as 50% increase of creatinine from baseline level. Anaemia was defined as a decrease in red blood cell and haemoglobin below the normal reference range for a particular age and gender.

3.2 OUTCOME OF ACUTE TRAUMATIC COAGULOPATHY

Presence of acute traumatic coagulopathy in patients on arrival to the ER before has some degree of poor prognosis/outcome indication. Knowledge on identification, treatment and prevention of ATC is essential so as to decrease the rate of poor outcomes. Some of the established outcomes of patients presenting to ER with ATC include, high transfusion requirements, prolonged duration of hospital stay, end organ failure e.g. renal failure and also an increased mortality rate.

In a study by Mujunu et al, ATC patients had a longer hospital stay compared to those without ATC. They also had a higher transfusion requirement and high incidence of acute renal injury. In the same study, there was also an increase in mortality rate among the ATC group. On doing logistic regression, he concluded that in absence of other mortality causes, ATC can be used to independently predict for mortality(35).

A retrospective review study by Brohi et al, made the conclusion that coagulopathy in patient arriving to ER with ATC can be used to independently predict on possibility of death occurring. Multivariate analysis included injury severity and tissue hypoperfusion, although there still exists some interdependence between these variables. Admission coagulopathy was also associated with longer hospital stay and a high possibility of developing end organs failure (28).

3.0 STUDY PATIENTS AND METHOD

3.1 STUDY DESIGN

Prospective analytical study with convenient patient sampling.

3.2 STUDY SETTING

The study was conducted in the A/E department, orthopaedic wards and ICU of Kenyatta National Hospital (KNH).

3.3 STUDY DURATION

November 2020 to April 2021

3.4 STUDY POPULATION

All musculoskeletal trauma patients aged 18 yrs and above presenting to the A/E department with major trauma and met the inclusion criteria were considered for the study. An informed consent was obtained from each patient upon coming into first contact with them at the A/E department. For recruited patients, blood sample for coagulation profile was taken on presenting to the hospital. Injury severity score was also graded and recorded. Abbreviated injury score was used in calculating the injury severity score. Recruited patients were followed up for duration of two weeks and recording of outcome variables done. Each recruited patient was reviewed on day 0, 7 and 14 post admission and evaluated for the outcomes of interest. Outcomes of interest in this study were presence of acute renal failure, anaemia and need for blood transfusion.

Each patient's demographic characteristics were captured in the study questionnaire. The study variables included Injury severity score, PT, PTT, Patient's core body temperature, amount and types of fluid administered to the patient before contact with researcher, hours before presentation to the hospital.

3.5 INCLUSION CRITERIA

1. All patients aged 18yrs and above presenting with major musculoskeletal (axial, appendicular) injuries (ISS>15)

2. Patients who gave an informed consent/ Guardian for those with head injury

3.6 EXCLUSION CRITERIA

1. Patients who had history of use of anticoagulant drugs
2. Patients with known co-morbidities such as liver disease or renal failure which may impair the normal coagulation cascade
3. Patients with history of coagulopathies e.g. hemophilia
4. Patients referred from other facilities and lacked proper documentation on interventions/treatment given

3.7 SAMPLING

Patients were recruited into the study by the principal researcher and two well trained assistants (Two A&E based medical officers) by convenient sampling, and each was assessed on the admission day at A/E during primary and secondary survey or after initiation of resuscitation or treatment process at A/E. The timing of recruitment depended on when the principal researcher or his assistant came into contact with the patient. Each patient also underwent trauma grading at initial contact using AIS and respective ISS recorded. Trauma grading of each patient was done by at least two people, the principal researcher plus one of the trained assistants or both assistants together. Where possible, this was done with either two people being physically present at the patient's site. The two research assistants underwent proper training on how to do clinical trauma grading using AIS. This was done in reference to the AIS protocols. At all times, the trauma grading was done in reference to the attached Abbreviated Injury Score chart (Appendix 8.4).

Only those satisfying the inclusion criteria and gave informed consent (from patient or next of kin) were recruited. The data sheet was filled accordingly.

For eligible patients, 5ml of blood was drawn from a suitable vein during primary survey of the patient. This was done by the principal researcher or his assistant. During taking of the blood sample, a vein in the upper or lower limbs was identified. After getting a suitable vein, the skin was prepared using an alcohol swab. A gauge 18, 10cc needle was used to draw a blood sample from the vein with the help of a tourniquet. The collected sample was placed in a blue capped blood sample bottle which contains Sodium citrate 19. The bottle containing

the blood sample was well labelled and patient's details filled correctly. A laboratory request form was filled for each respective blood sample clearly indicating the test (coagulation profile) to be done for that particular sample. The coagulation profile assay entailed PT, APTT and INR.

After blood sample was drawn, it was placed in sample carrier bag and immediately taken to the respective laboratory in the hospital for analysis. This was done within fifteen minutes of drawing the blood sample. For this particular study, PT derangement was used to diagnose ATC. This was in reference to other studies which concluded that PT was a more reliable test in diagnosing ATC in comparison with PTT and INR. Coagulation analysis was done using Thrombolyzer XRM machine.

Sample collection and analysis in the laboratory was done anytime the patient came and after been recruited into the study by the principal researcher or his assistants. The hospital has a 24hours functioning laboratory. Information on amount of pre-admission fluids received (type and quantity) was obtained from the health personnel accompanying the patient or from the referral letter from the previous facility visited by the patient.

During patient follow up for outcomes of interest in this study, renal function test and full blood count samples were taken from each of the recruited participant on day 7 and day 14. The samples were then taken to the laboratory for analysis. Renal function test was done using Biolis 50i Superior machine. Acute renal failure was defined as 50% increase of creatinine from baseline level. Anaemia was defined as a decrease in haemoglobin level below the expected level for age and gender of each participant. Full blood count was done using Sysmex Haematology analyzer. In this study, since patient with pre existing conditions which could impair the renal function and haemoglobin level were excluded, it was assumed that there was no other causes of acute renal failure or low haemoglobin.

3.8 PATIENT IDENTIFICATION

Demographic details of the patient were recorded. The principal researcher developed a structured data collection sheet (Appendix 8.3). This sheet was administered to each patient or their next of kin after primary and secondary survey and when the patient was already resuscitated and stabilized. Information acquired during the follow up days of the study was also recorded in the data collection sheet.

3.9 PATIENT FOLLOW UP

Recruited patients were followed up and reviewed on day 0, 7 and 14 while in the ward. The selected clinical outcome variables (acute renal failure, anaemia and blood transfusion) were determined and recorded during this period. Maximum follow up time was 14 days.

4.0 SAMPLE SIZE

Cochran formula was used to estimate the sample size;

$$n_0 = \frac{Z^2 pq}{e^2}$$

n_o- Sample size

Z- Desired confidence level (95%) p-Estimated proportion of an attribute present in the population(0.5) q- 1-p e- Target margin of error which will be 5%(0.05) to increase precision

$$n_o = \frac{(1.96)^2 \times 0.5 \times 0.5}{(0.05)^2}$$

Hence n_o =384

However, given that KNH admits around 40 patients with major orthopaedic trauma per month, we modifified the sample size using Fischer's formula by using the finite population correction factor (FPC) as:

$$n = \frac{n_0}{1 + \frac{(n_0 - 1)}{N}}$$

n- Sample for finite population

N- Total population, data from KNH registry between May and July 2019 showed a total of 120 orthopaedic major trauma patients presented to the A&E department (average of 40patients per month).Considering a three months duration of data collection, a total of 120 patients make up the total population. n_0 retains its earlier definition and its 384 as calculated above.

Therefore,

$$N = \frac{384}{1 + \frac{(384-1)}{120}} \qquad n=91.61 \sim 92$$

With the assumption of an attrition rate of 10%, the expected sample size was calculated to be **102.** The author utilized purposive/convenient sampling based on the defined inclusion criteria until the appropriate sample of 102 was reached.

4.1 DATA COLLECTION TOOLS AND ANALYSIS

Data was collected on a printed data collection tool, which was checked for completeness and free of error, thereafter it was entered into a Microsoft Excel spreadsheet. The data was later exported to Statistical Package for Social Sciences version 25 for analysis.

Demographic data and clinical data were analyzed and presented as frequencies and proportions for categorical data and as means with standard deviation for continous data. The prevalence of ATC among major trauma orthopaedic patients presenting to A&E was calculated as a proportion and presented as a percentage of the total number of major trauma patients. The predictive value of ISS in diagnosing ATC among major trauma orthopaedic

patients was calculated with the use of an ROC curve. Independent t-tests as well as chi-square tests were used to test the associations between outcome of patients and ATC. All statistical tests were considered significant where $p < 0.05$.

4.2 ETHICAL APPROVAL AND CONSENT

During this research, all applicable regulations concerning use of human volunteers were followed. Ethical approval was sought from the Department of Orthopaedic Surgery, University of Nairobi as well as Kenyatta National Hospital, Ethics and Research Committee (KNH/UON-ERC).

Data collection commenced after ethical approval was granted by KNH/UON ERC (Appendix 5.7). Authority to undertake the study was also sought from KNH administration and we were issued with a study registration certificate (Appendix 5.8). A written informed consent was obtained from each of the participants recruited to the study (Appendix 5.1 and 5.2). In situations where the participant was not able to give an informed consent, the same was sought from the participant's next of kin. The consent sought enabled the investigator to take the patient's bio-data details as well as history related to the presenting illness. The investigator clarified to the participants the objective of the study. Recruitment into the study was purely on voluntary basis. It was clarified to the participants that one had freedom to withdraw from the study at anytime without giving any explanation. Withdrawal of participation would not affect the participant's treatment or management in any way whatsoever.

Utmost confidentiality was applied to all information obtained. Each participant was allocated a specific serial number. This number was linked to each participants bio-database. This was only accessible to the principal investigator. Patients' names were not used.

4.0 RESULTS

Demographic patterns of study participants

A total of 102 participants were recruited into the study. Eighty four (82.4%) were male while 18(17.6%) were female. The male to female ratio was 5:1. Mean patients age was 32.6 (SD=9.5) years. The range was between 20 and 64yrs. There was no statistical difference in mean age between patients with ATC and those without. This is summarized in table 1 and 2 below.

Table 1: Demographic characteristics of the study participants

	Frequency (n=102)	**Percent (%)**
Age categories in years		
20-29	47	46.1
30-39	32	31.4
40-49	16	15.7
50-59	5	4.9
60+	2	2.0
Total	**102**	
Sex		
Male	84	82.4
Female	18	17.6
Total	**102**	

Table 2: Age analysis in ATC

		n	%	Mean Age	S.D	p-value
ATC Diagnosis	Normal	39	38.2	32.3	11	0.803
	ATC	63	61.8	32.8	9	

Incidence of Acute Traumatic coagulopathy

Out of the 102 study participants, 63 (61.8%) were diagnosed to have Acute traumatic coagulopathy (Table 3). Prothrombin time was used to diagnose coagulopathy. The mean prothrombin time of the study participants was 16.8 (SD=3.5).

Table 3: Coagulation status

	Mean	Standard Deviation	Minimum	Maximum	Median	Percentile 25	Percentile 75
AGE (Yrs)	33	9	20	64	30	26	38
ISS-INJURY SEVERITY SCORE	20	9	9	75	19	13	23
PT-PROTHROMBIN TIME	16.8	3.5	12.0	29.0	16.9	14.0	18.9
DURATION BEFORE PRESENTING TO KNH (HRS)	6	11	1	96	3	2	6

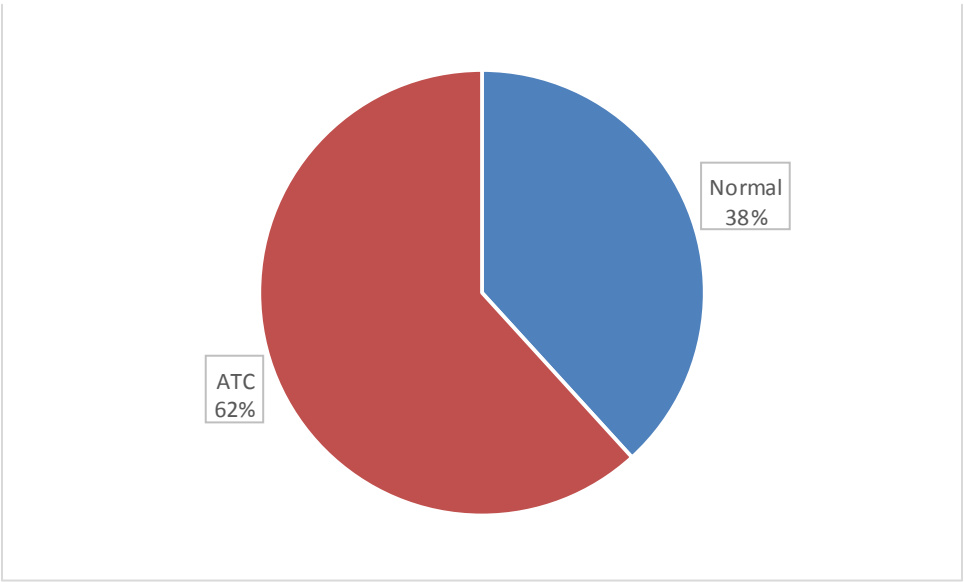


Figure 5: ATC analysis

There was no statistical difference in the mean age of coagulopathic patients (32.8, SD=9 years), compared to those without coagulopathy (32.3, SD=11 years) (p=0.803). There was no age related coagulation senescence.

INJURY SEVERITY SCORE IN STUDY PARTICIPANTS

The mean ISS score of the study participants at admission was 20 (S.D= 9). Patients diagnosed with acute traumatic coagulopathy had a relatively higher mean ISS of 23 (S.D= 10) compared to the total study population. The ISS range of the study participants was between 9 and 75. The average ISS of the participants who did not develop ATC was 15 (SD= 6). This is represented in table 5 below.

Table 5: Injury severity score

	INJURY SEVERITY SCORE						
	ALL PARTICIPANTS		WITHOUT ATC		ATC		
	Mean	S.D	Mean	Standard Deviation	Mean	Standard Deviation	p-value
INJURY SEVERITY SCORE	20.2	9.3	15	6	23.3	9.9	<0.0001

There was a statistical association between ISS and ATC, p<0.0001.

ACUTE TRAUMATIC COAGULOPATHY OUTCOMES

Seventy seven (75.5%) of the 102 participants in our study developed anaemia between day 0 and day 14 of the follow up period. Fifty (64.9%) of those who developed anaemia had acute traumatic coagulopathy. Majority of the patients who developed anaemia had to undergo transfusion of packed red blood cells during their stay in the wards or before they were taken to theatre for surgical intervention of the injuries they had sustained. The anaemia may be attributed to excess bleeding following trauma with development of ATC.

Eight (7.8%) of the 102 participants in our study developed acute renal failure during the follow up period. The eight who developed ARF also had acute traumatic coagulopathy.

None of the non-ATC patients developed ARF during the follow up period.

There were 5 (4.9%) patients who died out of the 102 study participants during the follow up period. The deaths were only reported in patients who developed ATC. Three of the deaths occurred on day 0 of admission and the other two occurred before the 7th day of admission. This is represented in table 6 and figure 5 below.

Table 6: ATC outcomes

Anaemia	**ATC**	**Non-ATC**	**p-value**
Yes	50 (79.4)	27 (69.2)	0.248
No	13 (20.6)	12 (30.8)	
Acute renal failure			
Yes	8 (12.7)	0 (0.0)	0.022
No	55 (87.3)	39 (100.0)	
Mortality			
Yes	5 (7.9)	0 (0.0)	0.154
No	58 (92.1)	39 (100.0)	

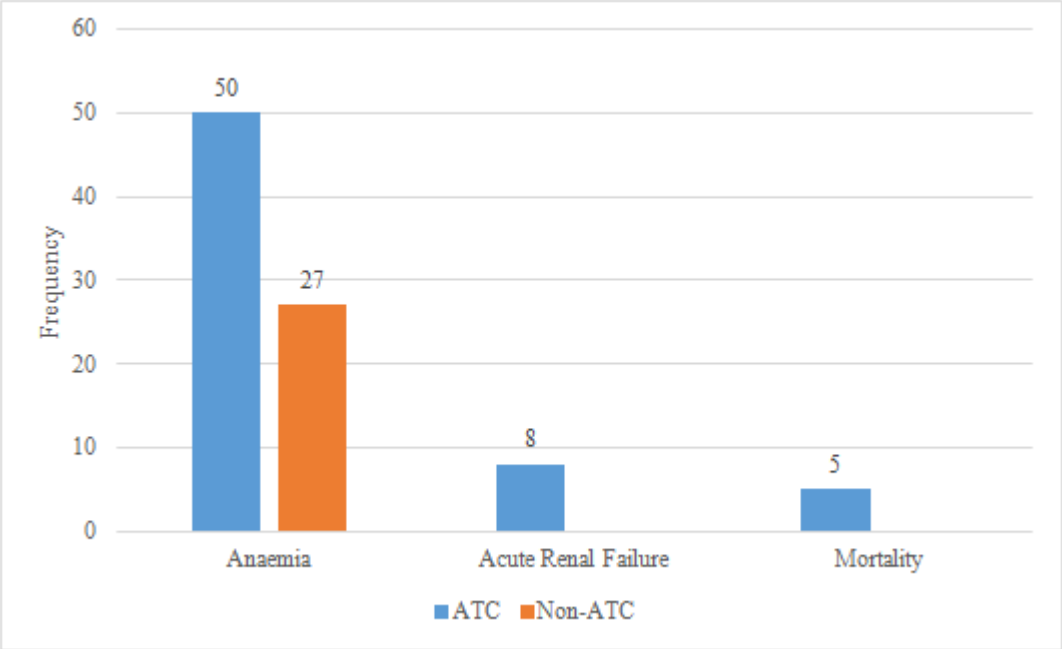


Figure 6: Acute traumatic Coagulopathy Outcomes

Fisher's exact test was used to determine if there was association between the occurrence of ATC and anaemia, acute renal failure and mortality. There was statistically significant association between ATC and acute renal failure (p=0.022), but no significant association with anaemia (p=0.248), and with mortality (p=0.154). Each of the associations were analyzed independently.

MEAN ISS FOR PATIENT OUTCOME

The mean ISS of all patients in the study who developed anaemia was 20(SD=9). The mean ISS for non-ATC patients who developed anaemia was 16(SD=6.0). The ATC patients who developed anaemia had a relatively higher mean ISS score of 22.3 (SD= 7.6).
There was a statistical difference in the mean ISS between the two groups (p=0.001).

The mean ISS of all patients and the ATC patients who developed Acute renal failure was 21.6 (SD=6.3). There was no comparison mean for non-ATC patients since none of them developed the Acute renal failure. Acute renal failure was defined as 50% increase of creatinine from baseline level with reference to the machine used for analysis.
The mean ISS for the ATC patients who died was 41.4 (SD=23.7). There were no deaths reported in the Non-ATC patients. There were significant statistical differences in the mean

ISS for patients' outcome between the ATC and non-ATC patients. This is represented in table 7 below.

Table 5: Mean ISS for Patients' outcome

	n	Mean (SD)
Anaemia		
Yes	77	20.4 (7.5)
No	25	19.7 (13.7)
Acute Renal Failure		
Yes	8	21.6 (6.3)
No	94	20.1 (9.6)
Mortality		
Yes	5	41.4 (23.7)
No	97	19.1 (6.6)

PRE ADMISSION FLUIDS

On coming into contact with the principal researcher or his research assistant, 54 (52.9%) of all patients in the study had received intravenous fluids. Out of the fifty four patients who received fluids, 40 (74.1%) had ATC while the remaining 14 (25.9%) were non-ATC patients. 40 (63%) of ATC patients had received fluids before admission. Each patient had received a particular type of fluid.

Two (3.7%) of the patient who received fluids were given hemacel, 11 (20.4%) received ringers lactate while 4 (75.9%) received normal saline. This is represented in table 6 below.

Table 6: Type and quantity of fluid administered

Type of fluid, *n (%)*	**ATC**	**Non-ATC**	**Total**
Hemacel	***2 (100.0)***	***0 (0.0)***	***2***
500 ml	1 (100.0)	0 (0.0)	
1 litre	1 (100.0)	0 (0.0)	
Normal saline	***30 (73.2)***	***11 (26.8)***	***41***
500 ml	15 (65.2)	8 (34.8)	
1 litre	10 (83.3)	2 (16.7)	
1.5 litre	4 (100.0)	0 (0.0)	
3 litres	1 (50.0)	1 (50.0)	
Ringer's lactate	***8 (72.7)***	***3 (27.3)***	***11***
500 ml	3 (60.0)	2 (40.0)	
1 litre	5 (83.3)	1 (16.7)	
Nil	***23 (47.9)***	***25 (51.2)***	***48***
Total	**63**	**39**	**102**

An analysis was done to determine if there was an association between receiving fluids and ATC. It was established that there was a statistical association between receiving fluids and ATC, with those receiving fluids being 3 times likely to develop ATC (Odds Ratio 3.1 (1.4-7.1), P=0.007). This is represented in table 7 below.

Table 7: Association between receiving of fluids and ATC

Received fluids, *n (%)*	**ATC**	**Non-ATC**	**Odd Ratio (95% CI)**	**p-value**
Yes	40 (74.1)	14 (25.9)	3.1 (1.4-7.1)	**0.007**
No	23 (47.9)	25 (52.1)		

Further research is needed to substantiate whether the high number of patients with ATC was due to fluids administration or injury severity

4.1 STUDY LIMITATIONS

1.Undiagnosed inter current illnesses that may have affected the outcome

2.Different laboratory personnel handling the patients' blood samples could have influenced the patients' results

3. Other ATC instigators such as hypothermia and acidosis were not included in the study

4.2 STUDY DELIMITATIONS

1.Medical history of each patient was taken so as to try and establish presence of undiagnosed concurrent illnesses which might have had an impact in the study

2.In this study, we used the same make of machines in assessing haemoglobin level, renal function test and coagulation status. This was to ensure the results of each patient were comparable and reproducible

5.0 DISCUSSION

Mortality due to trauma has remained a major public health issue. It is one of the leading causes of death in persons aged between 25-44yrs. Within the first 48hrs of admission, uncontrolled haemorrhage and coagulopathy is responsible for 50% of all trauma related deaths. Trauma leads to an endogenous impairment of haemostasis. This occurs early after injury and is known as Acute Traumatic coagulopathy (ATC). Its presence is associated with a high mortality rate, anaemia and increased transfusion requirement and organs failure (3).

The purpose of this study was to determine the incidence of Acute traumatic coagulopathy among musculoskeletal trauma patients at Kenyatta National Hospital. The study was conducted in A/E department and orthopaedic wards in KNH.

Majority of the patients in the study were male, 82.4%. This implies that males are more commonly involved in trauma. This can be either because they are the ones who are more involved in activities fending for their families or because they are more aggressive in nature. The mean age of the study participants was 33yrs with a majority 46.1% of the patients aged between 20 to 29 years. This is comparable to local and international studies (28,31,35,37). The huge proportion (93.2%) of patients in working age group (19-49 years) shows the potential economic consequences of trauma.

The incidence of ATC was 61.8%. This was much higher in comparison with other studies done locally and outside Kenya ranging from 24 to 54% (29,31,35,37). This could be due to the fact that the study design included only patients with major orthopaedic trauma while some of the other studies included all trauma patients (major and minor). In this study, we used abnormal PT as a marker of coagulation status. This was in reference to other studies which also used abnormal PT as a marker of coagulopathy (31,37).

Predictive value of injury severity score in diagnosis of ATC

Most of the injuries in the study were due to road traffic accidents. Majority of the patients in the study had polytrauma since eligibility criteria was an ISS of 15 and above. For a patient to

be eligible for trauma scoring in the study, injuries to the extremities, including pelvis had to have the highest score when calculating the ISS .
In this study, patients with coagulopathy had a high mean (23.3, SD=9.9) ISS score compared to those without coagulopathy (15, SD=6) (p value <0.0001). This high ISS in coagulopathy patients has also been observed in other studies (31,37,41). This could be attributed to the trauma and resultant hypoperfusion or due to other instigators such as hemodilution or acidosis secondary to tissue hypoperfusion.

The high injury severity score may be responsible for the high rate of coagulopathy at admission. As the level of tissue trauma increased (rising ISS), the incidence of coagulopathy increased.

In this study, blood gas analysis was not done.

Outcomes in patients diagnoses with ATC

The outcomes of interest in this study were acute renal failure, anaemia and need for blood transfusion and mortality. Patients in this study were followed up for a duration of 14 days and evaluated through physical examinations and samples taken for laboratory analysis for the outcomes. In this study, only patients with coagulopathy developed acute renal failure. This was 8 (12.3%) of the patients with coagulopathy. Fisher's exact test was used to determine if there was an association between the occurrence of acute renal failure and ATC. There was statistically significant association between ATC and acute renal failure (p=0.022). This association has also been established in previous studies(32,42).

In this study, there was no statistical association between ATC and occurrence of anaemia (p=0.248). This was in contrast to previous studies which had demonstrated an increased risk of developing anaemia and need for transfusion in patients with ATC (31,37). More studies need to be done to evaluate and explain this finding. Patient who developed anaemia in this study were transfused packed red blood cells. They were also started on hematenic drugs to help in raising the haemoglobin level.

In this study, there was no statistical association between ATC and mortality (p=0.154). This was in contrast to previous studies which had demonstrated and increased risk of mortality in

coagulopathic patients(31–33,37). This was also despite the fact that the deaths were only reported in ATC patients. Other factors such as head injury and sepsis could have contributed to the deaths. More studies need to be done to evaluate and explain this finding.

Utility of ISS in predicting ATC associated outcomes

In this study, as the ISS increased, there was a proportional increase in the incidence of ATC and ATC related outcomes. Patients with coagulopathy and developed anaemia had a high mean ISS (22.3, SD 7.6) than the non-ATC patients who developed anaemia (16.7, SD 6.0). There was a statistical difference in the mean ISS between the two groups (p value < 0.001.

In our study, only patients with ATC developed acute renal failure. The mean ISS for the patients who developed acute renal failure was 21.6 (SD=6.3). Patients who had mortality also has a significantly higher injury severity score. In our study, the mean ISS score for mortality was 41.4(SD=23.7).

Other studies have observed that as the ISS increases, there was also a proportional increase in coagulopathy incidences and coagulopathy associated outcomes (3,31,32,37).

Effect of pre admission fluid administration on Acute traumatic coagulopathy

In our study, a high percentage 74.1% of the patients who received intravenous fluids developed ATC. This was irrespective of the type of fluid infused. Patients who received fluids were 3 times more likely to develop ATC (O.R 3 (1.4-7.1) P value = 0.007). A high injury severity score correlated to occurrence of ATC. This had no association with the volume and type of fluid administered. Fluid administration in a patient who already had high ISS could have contributed in the propagation of ATC due to effect of dilution of coagulation factors. Dilution could have contributed to a further decrease in the coagulation factors which had already been consumed during the ATC development.

Other studies have observed that acute traumatic coagulopathy can occur in a patient with a high ISS irrespective of whether fluids are administered and that fluids administration could only be propagating the coagulopathy by enhancing dilution of coagulation factors (3,32).

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Acute traumatic coagulopathy is common in major musculoskeletal trauma patients. A greater proportion of males suffer major trauma leading to acute traumatic coagulopathy. This is either they are more involved in fending for their families or because of their aggressive nature. Trauma is more common in people of economically productive age bracket.

There is a significant association between level of ISS and occurrence of ATC in musculoskeletal trauma patients. A rise in injury severity score in trauma patients can be used as a predictor of presence of acute traumatic coagulopathy. A rise in injury severity score in major orthopaedic trauma patients can also be used to predict the occurrence of ATC related outcomes such as anaemia and need for blood transfusion, acute renal failure and mortality.

ATC develops in response to combination of tissue damage and systemic hypoperfusion. These two drivers are sufficient for development of coagulopathy. Medical interventions may augment this coagulopathy by hemodilution with large fluid volumes. However, presence of acute coagulopathy without significant fluid administration or resuscitation methods may be attributed to injury itself due to tissue damage and systemic hypoperfusion.

6.2 Recommendations

In order to improve the care of major trauma orthopaedic patients and also predict or avoid acute traumatic coagulopathy outcomes, this study recommends the following:

1. Coagulation screening should be included among the tests for severely injured musculoskeletal trauma patients
2. Patients with high ISS should be closely monitored owing to high likelihood of ATC
3. Intravenous fluids and blood transfusion should be given judiciously to minimize hemodilution
4. . Patients with an established coagulopathy are liable to poor outcomes and should be recognized as early as possible and managed directly and aggressively

5. In this study, there was no a determined statistical association between presence of ATC and development of anaemia or mortality. This was in contrast to previous studies. More studies need to be done to evaluate and explain this finding.

6.3 Disclaimer

I, Dr. Kelvin Yulu Maweu, have not received any financial benefit or incentive from any party or individual that may benefit from this study.

7.0 REFERENCES

1. Kornblith LZ, Moore HB, Cohen MJ. Trauma-induced coagulopathy: The past, present, and future. Vol. 17, Journal of Thrombosis and Haemostasis; 2019. p. 852–62.
2. Martin RF. Trauma 2017. Surg Clin North Am. 2017;97(5):xiii–xiv.
3. Frith D, Goslings JC, Gaarder C, Maegele M, Cohen MJ, Allard S, et al. Definition and drivers of acute traumatic coagulopathy: Clinical and experimental investigations. J Thromb Haemost. 2010;8(9):1919–25.
4. Hayakawa M. Pathophysiology of trauma-induced coagulopathy: Disseminated intravascular coagulation with the fibrinolytic phenotype. J Intensive Care. 2017;5(1):1–7.
5. Johansson PI, Sørensen A, Perner A, Welling K, Wanscher M, Larsen CF, et al. Disseminated intravascular coagulation or acute coagulopathy of trauma shock early after trauma? An observational study. Crit Care. 2011;15(6):R272.
6. Haagsma JA, Graetz N, Bolliger I, Naghavi M, Higashi H, Mullany EC, et al. The global burden of injury: Incidence, mortality, disability-adjusted life years and time trends from the global burden of disease study 2013. Inj Prev. 2016; Feb 22(1):3-18
7. Heron M. National Vital Statistics Reports Deaths: leading causes for 2013. National vital statistics reports: from the Centers for Disease Control and Prevention, National Center for Health Statistics, National Vital Statistics System. 2016;Feb 16;65(2):1-95
8. Gathecha GK, Githinji WM, Maina AK. Demographic profile and pattern of fatal injuries in Nairobi, Kenya, January-June 2014. BMC Public Health. 2017; Jan;34(17):12-16
9. Holcomb JB, Fox EE, Wade CE. The prospective observational multicenter major trauma transfusion (PROMMTT) study. Journal of Trauma and Acute Care Surgery. 2013;Feb;148(2):127-136
10. Botchey IM, Hung YW, Bachani AM, Paruk F, Mehmood A, Saidi H, et al. Epidemiology and outcomes of injuries in Kenya: A multisite surveillance study. Surg (United States). 2017;162(6):S45–53.
11. Brohi K, Jasmin S, Miscah H, et al. Acute coagulopathy of trauma: Hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. J Trauma - Inj Infect Crit Care. 2008;

12. Subramanian A, Gandhi J, Saraf N, Sharma V, Farooque K, Rangarajan K. Coagulation studies in patients with orthopedic trauma. J Emerg Trauma Shock. 2010;3(1):4.
13. Childs BR, Verhotz DR, Moore TA, Vallier HA. Presentation coagulopathy and persistent acidosis predict complications in orthopaedic trauma patients. J Orthop Trauma. 2017;31(12):617–23.
14. Chaudhry R, Babiker HM. Physiology, Coagulation Pathways.2018;Jan;5(3):23-28.
15. Schreiber MA. Coagulopathy in the trauma patient. Current Opinion in Critical Care. 2005;Dec;11(6):590-597.
16. Kushimoto S, Kudo D, Kawazoe Y. Acute traumatic coagulopathy and trauma-induced coagulopathy: An overview. J Intensive Care. 2017;5(1):1–7.
17. Davenport R, Khan S. Management of major trauma haemorrhage: Treatment priorities and controversies. Br J Haematol. 2011;155(5):537–48.
18. Bolliger D, Görlinger K, Tanaka KA. Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. Anesthesiology. 2010;113(5):1205–19.
19. Giordano S, Spiezia L, Campello E, Simioni P. The current understanding of traumainduced coagulopathy (TIC): a focused review on pathophysiology. Intern Emerg Med.
2017;12(7):981–91.
20. Schöchl H, Voelckel W, Schlimp CJ. Management of traumatic haemorrhage--the European perspective. Anaesthesia. 2015;70:102–7.
21. Kashuk JL, Moore EE. Editorial comment. J Trauma - Inj Infect Crit Care. 2009;67(1):208–9.
22. Gissel M, Brummel-Ziedins KE, Butenas S, Pusateri AE, Mann KG, Orfeo T. Effects of an acidic environment on coagulation dynamics. J Thromb Haemost. 2016;14(10):2001–10.
23. Engström M, Schött U, Romner B, Reinstrup P. Acidosis impairs the coagulation: A thromboelastographic study. J Trauma - Inj Infect Crit Care. 2006;61(3):624–8.
24. Jansen JO, Scarpelini S, Pinto R, Tien HC, Callum J, Rizoli SB. Hypoperfusion in severely injured trauma patients is associated with reduced coagulation factor activity. J Trauma - Inj Infect Crit Care. 2011;71(5):13–8.

25. Chang R, Cardenas JC, Wade CE, Holcomb JB. Advances in the understanding of trauma-induced coagulopathy. Blood. 2016;128(8):1043–9.
26. Iii APO, Mackman N. Microparticles in hemostasis. 2012;108(10):1284–97.
27. MacKman N. The role of tissue factor and factor VIIa in hemostasis. Anesth Analg. 2009;108(5):1447–52.
28. Brohi K, Cohen MJ, Davenport RA. Acute coagulopathy of trauma: Mechanism, identification and effect. Curr Opin Crit Care. 2007;13(6):680–5.
29. Brohi K, Cohen MJ, Ganter MT, Matthay MA, MacKersie RC, Pittet JF. Acute traumatic coagulopathy: Initiated by hypoperfusion: Modulated through the protein C pathway? Ann Surg. 2007;5(7)1.
30. Gall LS. Trauma-Induced Coagulopathy : an Investigation of Fibrinolysis and the Effect of Tranexamic Acid. 2018;1(9):1-124.
31. MacLeod JBA, Lynn M, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. J Trauma. 2003;11(5)4.
32. Cap A, Hunt B. Acute traumatic coagulopathy. Curr Opin Crit Care. 2014;20(6):638–45.
33. Maegele M, Schöchl H, Cohen MJ. An update on the coagulopathy of trauma. Shock. 2014;5(3)6.
34. Brohi K, Cohen MJ, Davenport RA. Acute coagulopathy of trauma: Mechanism, identification and effect. Current Opinion in Critical Care. 2007;4(2)1.
35. Mujuni E, Wangoda R, Ongom P, Galukande M. Acute traumatic coagulopathy among major trauma patients in an urban tertiary hospital in sub Saharan Africa. BMC Emerg Med 2012;12(1):1.
36. Rugeri L, Levrat A, David JS, Delecroix E, Floccard B, Gros A, et al. Diagnosis of early coagulation abnormalities in trauma patients by rotation thrombelastography. J Thromb Haemost. 2007;13(4):2.
37. Ojuka D, Mwendwa J, Odhiambo P. Incidence and Early Outcome of Coagulopathy among Major Trauma Patients. Ann African Surg. 2018;15(1).
38. World Health Organization. Motorcycle-related road traffic crashes in Kenya Facts & figures. violence_Injury_ Prev. 2011;(2010).
39. Wilberforce Odiwuor C, Nyamusi E, Odero W, Cholo Wilberforce Odiwuor C.

Incidence of Road Traffic Crashes and Pattern of Injuries among Commercial Motorcyclists in Naivasha Town. Int J Appl Res.. 2015;1(11):541–9.

40. Ndwiga SM, Mbakaya C, Kiiyukia C. Factors associated with road traffic accidents involving motorcyclists in Mwea Town, Kirinyaga County, Kenya. Afr J Health Sci. 2019;32(1):59–73.

41. Davenport RA, Brohi K. Cause of trauma-induced coagulopathy. Current Opinion in Anaesthesiology. 2016;20(1):12-16.

42. Maegele M, Lefering R, Yucel N, Tjardes T, Rixen D, Paffrath T, et al. Early coagulopathy in multiple injury: An analysis from the German Trauma Registry on 8724 patients. Injury. 2007;May;41(1):21-25.

8.0 APPENDIX

A. CONSENT FORM RESEARCH TOPIC

ACUTE TRAUMATIC COAGULOPATHY IN MAJOR TRAUMA ORTHOPAEDIC PATIENTS AT KENYATTA NATIONAL HOSPITAL

ENGLISH VERSION

This form is to ask for Consent from patients and/or their kin who present to KNH with major orthopaedic trauma and would be assessed for presence of hypocoagulopathy. Injury severity score will also be done to the patients and they will also be followed up for hypocoagulopathy outcomes.

Principal investigator: DR. KELVIN YULU MAWEU

Institution: School of Medicine, Department of Orthopaedic surgery- University of Nairobi

Supervisors: DR. VINCENT MUTISO and DR. EDWARD GAKUYA

This informed consent has three parts:

- Information sheet (to share information about the research with you)
- Certificate of Consent (for signatures if you agree to take part)
- Statement by the researcher

Part I: Information sheet

My name is Dr. Kelvin Yulu Maweu, an Orthopaedics Surgery post graduate student at the University of Nairobi, School of Medicine. I am carrying out a study entitled **"ACUTE TRAUMATIC COAGULOPATHY IN MAJOR TRAUMA ORTHOPAEDIC PATIENTS AT KENYATTA NATIONAL HOSPITAL"**

The purpose of this study is to determine effect of major injury to a patient's blood coagulation activity. The study aims to establish how severity of the injury affects a patient's coagulation activity. It will also help to establish how a patient's injury severity can be used

to predict traumatic coagulopathy associated complications/Outcomes. The study will also help in determing how fluid resuscitation in trauma affects one's coagulation activity.

I am inviting you to willingly take part in this study

1. Benefits of the Study

The results of the study may inform the incidence of hypocoagulopathy in orthopaedic trauma patients. It will shed light to information on the severity of injury which can be used to determine the presence of hypocoagulopathy in orthopaedic trauma patients. The study will also shed light on use of injury scoring system in determining hypocoagulopathy related complications. The study will also shed light on whether the amount and type of intravenous fluids a patient receives post injury may be contributing to coagulopathy. This information will be essential especially in health facilities which handle orthopaedic trauma patients and do not have laboratory facilities to do coagulation profile studies.

2. Costs and Potential Harm

If you decline to participate in the study be assured that your decision will not jeopardize the required care for the patient. Furthermore, this study poses no harm to the patient and there will be no extra cost incurred for participating in the study. There will be no financial grant to the participants.

3. Your Obligation

If you agree to participate in this study, the following will happen.

You will be examined by the principal researcher or his trained assistant. The aim of the examination is to establish the type and degree of injury you have. A scoring system will be used to grade your degree of injury. After that blood samples will be taken from one of your blood vessels. This blood will be taken to the lab for analysis of your blood clotting activity. There will also be samples taken to the laboratory for analysis of the level of activity of your kidneys and also the amount of red blood cells and haemoglobin in your body. We will then do a follow up on your progress when in the ward and we will also do repeat blood samples

on the seventh and fourteenth day after you are admitted. Your treatment for the injury you have will continue as planned and will not be affected by your participation in the research.

4. Confidentiality

All the information gathered will be taken in confidence and no one will see it except my assistant, my supervisors and I, all who are duty-bound to ensure confidentiality.

The patient's name or identity will not appear in any research document. The information about the patient will be identified by a unique research number and only the researchers can relate the number to you/your patient as a person. Other than for (2) above, your information will only be used for this study and will not be shared with anyone else unless authorized by the Kenyatta National Hospital/University of Nairobi - Ethics and Research Committee (KNH/UoN-ERC).

5. Study Credibility and Legitimacy

My two supervisors approved this study. It was appraised and approved by the Chairman of the Department of Orthopaedic Surgery, School of Medicine at the University of Nairobi. It was then submitted to KNH/UoN-ERC, which reviewed and approved it to be done for a duration of four months. KNH/UoN-ERC is the regulatory body in the hospital whose work is to make sure research process is safe for the participants and that you are protected from harm.

6. Whom to Contact?

You can ask questions or seek clarifications about the study any time you wish to. If need be, you may also talk to anyone you are comfortable with about the research before deciding.

If you have any query about the research you want addressed by another person other than the researchers, please feel free to contact the following who will address your concerns:

a) Secretary, KNH/UoN-ERC
P.O. Box 20723 -00202

KNH, Nairobi
Tel: +254-020-2726300-9 ext. 44355

Email: KNHplan@Ken.Healthnet.org or uonknh_erc@uonbi.ac.ke

Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

Facebook: https://www.facebook.com/uonknh.erc

b) Research Supervisors from University of Nairobi

- DR. VINCENT MUOKI MUTISO

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c) Principal Researcher:

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Mobile phone: 0728019378 (reachable any time)

Email: kmaweu82@gmail.com

B. CONSENT CERTIFICATE

Consent Certificate (confidential once signed) Research Track Number _____

…….....…..freely give consent to take part in the study conducted by Dr. Kelvin Yulu Maweu, the nature of which has been explained to me by him/his research assistant. I have been informed and have understood that my participation is voluntary and understand that I am free to withdraw from it any time I wish and this will not in any way alter the care given to me/my patient. The results of the study may or may not benefit me/my patient directly but may benefit similar future patients. Furthermore, it will help Medical professionals to better understand "**ACUTE TRAUMATIC COAGULOPATHY IN MAJOR TRAUMA ORTHOPAEDIC PATIENTS AT KENYATTA NATIONAL HOSPITAL**

SIGNED CONSENT……

(Patient/Kin)

Date.....

DD/MM/YY

SIGNED ASSENT ….....

Thumb print of participant if Unable to sign due to illiteracy

Date……

DD/MM/YY

Statement by a witness if participant is illiterate

I have witnessed the accurate reading of the consent form to the participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Name of witness……

Signature of witness…….

Date….....

Part III: Statement by the researcher

I have clearly read out the information sheet to the participant, and to the best of my ability made sure that the participant understood the following:

- All information gathered will be treated with confidentiality.
- Refusal to participate or withdrawal from the study will not compromise the quality of care and treatment given to the patient.

The results of this study might be published in a reputable journal to enhance the knowledge of the "**ACUTE TRAUMATIC COAGULOPATHY IN MAJOR TRAUMA ORTHOPAEDIC PATIENTS AT KENYATTA NATIONAL HOSPITAL"**

In addition, I confirm that the participant was given opportunity to seek clarification about his concerns in the study, and all the queries clarified to the best of my ability.

I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this Informed Consent Form has been provided to the participant and duly signed by the participant.

Name of researcher taking consent……

Signature of researcher taking the consent……
Date……

…

FOMU LA IDHINI

MADA YA UTAFITI: UPUNGUFU WA DAMU KUGANDA KATIKA WAGONJWA WALIOUMIA MIFUPA SANA KATIKA HOSPITALI YA KENYATTA

TAFSIRI YA KIWAHILI

Fomu hii ni ya kuomba idhini kutoka kwa wagonjwa na/au jamaa zao ambao wanafika Hospitali ya kitaifa ya Kenyatta na majeraha ya mifupa. Maudhui ya utafiti huu ni kuchunguza jinsi majeraha yanavyo sababisha upungufu wa damu kuganda katika wagonjwa hao. Pia tungependa kuchunguza jinsi kiwango cha majeraha kinaweza kutumika kutabiri upungufu wa damu kuganda katika wagonjwa hao.

Mtafiti mkuu: DKT. KELVIN YULU MAWEU

Wahadhiri wasimamizi: DKT. VINCENT MUTISO na DKT. EDWARD GAKUYA

Wote wa kitengo cha upasuaji wa mifupa katika Chuo Kikuu cha Nairobi na hospitali kuu ya Kenyatta.

Makubaliano haya yana sehemu tatu:

- Maelezo kuhusu utafiti huu.
- Cheti cha Kibali (kitakacho tiwa sahihi na wahusika wanaokubali kujumuishwa utafitini)
- Ithibati ya mtafiti

Sehemu ya kwanza: Maelezo

1. Utangulizi

Jina langu ni Dkt. Kelvin Yulu Maweu, mwanafunzi wa kuhitimu katika mafunzo ya upasuaji wa mifupa katika Chuo Kikuu cha Shule ya Dawa ya Nairobi. Langu ni kufanya utafiti kuwa na haki ya "**UPUNGUFU WA DAMU KUGANDA KATIKA WAGONJWA**

WALIOUMIA MIFUPA SANA KATIKA HOSPITALI YA KENYATTA

Kiini cha utafiti huu ni kuchunguza jinsi maumivu ya mifupa yanavyo fanya ubadilifu wa hali ya damu kuganda mwilini. Pia tutachunguza ni kiwango gani cha maumivu kinachofanya ubadilifu huo wa damu kuganda na jinsi kiwango hicho kinaweza kutumika kutabiri matokeo ya upungufu wa damu kuganda mwa mtu aliyeumia. Pia tungependa kuchunguza jinsi aina na kiwango cha maji mgonjwa anawekwa anapoumia huchangia katika kusababisha upungufu wa damu kuganda mwilini.

Nitakuuliza maswali machache na kufanya baadhi ya uchunguzi juu ya majeraha yako..
Ninakualika kwa hiari kushiriki katika utafiti huu

2. Faida ya Utafiti huu

Matokeo ya utafiti huo yanaweza kutugulisha asilimia gani ya wangonjwa walioumia mifupa hupatwa na hali ya kutoganda damu mwilini na kusababisha upunjujaji wa damu kupitia kiasi. Matokeo pia yanaweza kutujulisha ni kiwangi gani cha maumivu ambacho husababisha hali hii ya upungufu wa damu kuganda, pia ni kiwango gani cha maumivu kinachoweza kumsaidia mhudumu wa afya kutabiri madhara ya upunjaji wa damu kwa mgonjwa aliyeumia. Matokeo hayo pia yanaweza kutujulisha jinsi aina na kiwango cha maji ya utabibu ambayo mgonjwa aliyeumia huongezwa yanavyochangia katika upungufu wa damu kuganda na upunjaji wa damu mwilini mwa mgonjwa.

Kuna hospitali kadhaa nchini ambazo huudumia wagonjwa walioumia mifupa lakini hazina mahabara ambazo ziko na uwezo wa kufanya utafiti wa kiwango cha damu kuganda mwilini. Matokeo ya utafiti huu yanaweza kutumika na wahudumu wa afya katika hospitali hizo kutabiri upungufu wa damu kuganda na pia kutabiri matokeo ya upungufu huo katika wagonjwa walioumia.

3. Gharama na Madhara za Utafiti

Natoa hakikisho kwamba hata kama hutaki kushiriki kwenye utafiti huu, wewe au mgonjwa wako hutakashifiwa na utapata matibabu yanayostahili. Utafiti huu haupanii kuleta madhara aina yoyote kwa muathiriwa. Hautatozwa fedha za ziada kwa minajili ya utafiti huu wala hakuna fedha mhusika atapewa.

4. Jukumu Lako Katika Utafiti

Ukikubali kushiriki katika utafiti huu, yatakayo fanyika ni:

Utakaguliwa na mtafiti mkuu au msaidizi wake. Kiini cha ukaguzi ni kuweza kujua aina na kiasi ya majeraha uliyopata. Majeraha hayo yatajumuishwa na kufanyiwa kiwango kwa kutumia jinsi ya kisayansi ya kujumuisha majeraha. Muhudumu atatoa damu kiasi kutoka kwa mshipa mmoja wako. Damu hiyo itapelekwa kwenye maabara ya hospitali na kufanyiwa kipimo kuhusu hali yako ya kuganda kwa damu. Pia kuna kiasi cha damu kitakacho pelekwa kwa maabara kupima hali ya afya ya figo zako na pia kiwango cha damu kwenye mwili wako. Tutakuwa tukifuatilia hali yako utakapokuwa kwenye hospitali na tutafanya vipimo vingine vya damu siku ya saba na siku ya kumi na nne utakapokuwa kwenye hospitali.
Matibabu ya majeraha uliyopata yataendelea kama kawaida na inavyostahili.

5. Faragha ya Habari za Mhusika

Habari zote zitakazo kusanywa kwa ajili ya utafiti zitabanwa na watafiti na hazitatolewa ovyo. Jina au kitambulisho cha mgonjwa haitanakiliwa popote ila tu atapewa nambari maalum ya utafiti. Watafiti watatumia mbinu fiche itakayo kutambulisha kwao. Licha yaliyokaririwa (2), habari za mgonjwa zitatumiwa tu kwa ajili ya utafiti huu na hazitatolewa kwa yeyote pasipo na idhini ya Kamati ya Maadili ya Utafiti wa Hospitali Kuu ya Kenyatta na ile ya Chuo Kikuu Cha Nairobi (kwa ufupi KNH/UoN-ERC).

6. Uhalali wa Utafiti huu

Utafiti huu umekubaliwa na wahadhiri wasimamizi wangu, ukapigwa msasa na Mwenyekiti wa kitengo cha upasuaji wa mifupa wa chuo kikuu cha Nairobi ambaye aliuwasilisha kwa Kamati ya Maadili ya Utafiti wa Hospitali Kuu ya Kenyatta na ile ya Chuo Kikuu Cha Nairobi (KNH/UoN-ERC) ambayo iliidhinisha uweze kufanywa kwa muda wa miezi sita. Kamati hii ndio ihakikishayo usalama wa wanaohusishwa kwa utafiti na kwamba hawadhuriwi kwa vyovyote vile.

7. Jukwa la Malalamishi na Habari Zaidi

Waweza kutuuliza maswali yoyote wakati wowote au umuulize yeyote utakaye kuhusu mchakato wa utafiti huu kabla au hata baada ya kukubali kuhusishwa.

Iwapo una swali lolote kuhusu utafiti huu ambao waona heri lishughulikiwe na mtu mwingine isipokuwa watafiti, waweza kuwasiliana na wafuatao ambao wako tayari kuushughulikia ipasavyo:

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- DR. EDWARD GAKUYA

Idara ya upasuaji wa mifupa, shule ya tiba, Chuo Kikuu cha Nairobi
S.L.P. Box 19676-00202, KNH, Nairobi
Tel: 0202726300
Seli: 0721932799; Barua pepe: kibaka62@gmail.com

b) Mtafiti Mkuu (mimi)

DKT. MAWEU KELVIN YULU

Kitengo cha Upasuaji wa mifupa, Chuo kikuu cha Nairobi

S.L.P. 19676-00202

KNH, Nairobi

Rununu: 0728019378 (wazi usiku na mchana)

Barua pepe: kmaweu82@gmail.com

Sehemu ya Pili: Cheti cha Kibali (siri baada ya kutiwa sahihi) **Nambari *Maalum*_____**

Mimi …….....…. ninakubali kwa hiari kuhusishwa kwa utafiti unaoendelezwa na Dkt. Muriithi Crispus Mwangi kuambatana na maelezo yeye mwenyewe/ msaidizi wake amenipa. Ninaelewa kwamba nimehusishwa kwa hiari na kwamba niko huru kujiondoa wakati wowote nitakao hata bila sababu, na hii haitaathiri kwa namna yoyote matibabu ipasayo. Aidha naelewa kwamba matokeo ya utafiti huu huenda usi nifaidi binafsi lakini huenda ukawa wa manufaa siku zijazo kwa waathiriwa wa moto kama nilivyo. Kuna uwezekano utafiti huu utaongeza maarifa kwa taaluma ya utabibu kuhusu "**UPUNGUFU WA DAMU KUGANDA KATIKA WAGONJWA WALIOUMIA MIFUPA SANA KATIKA HOSPITALI YA KENYATTA"**

SAHIHI (KIBALI HALISI) ……

(Mgonjwa/jamaa)

Tarehe.....

Siku/mwezi/mwaka

KIBALI MAALUM …….....……

Tarehe ……

Siku/mwezi/mwaka

Chapa cha kidole gumba cha kushoto kwa wasio na elimu ya kusoma na kuandika

Taarifa ya shahidi ya makubaliano na mhusika asiyejua kusoma

Nimeshuhudia mgonjwa akisomewa kwa njia inayoeleweka kwa rahisi, naye akapewa fursa nzuri ya kuulaza maswali. Nina dhibitisha mhusika alipeana kibali kwa hiari yake mwenyewe.

Jina la shahidi.....……

Sahihi la shahidi.....…….

Tarehe.....……

Siku/mwezi/mwaka

Sehemu ya tatu: Taarifa ya Mtafiti

Nimesomea mhusika na kadiri ya uwezo wangu kumuelewesha yafuatayo:

- Habari zozote zitokazo kwake zitawekwa siri.
- Kukataa kupeana kibali cha kuhusishwa kwa utafiti huu haitaathiri matibabu anayostahili.

Matokeo ya utafiti huu kwa jumla utachapishwa katika jarida la kisayansi au utabibu ama upasuaji kuweza kuchangia maarifa ya "**UPUNGUFU WA DAMU KUGANDA KATIKA WAGONJWA WALIOUMIA MIFUPA SANA KATIKA HOSPITALI YA KENYATTA"**

- Nimehakikisha kwamba mhusika amepewa fursa kamili ya kuuliza maswali kuhusu kuhusika kwake kwa utafiti huu na kwamba kwa kadiri ya uwezo wangu nimemuelewesha ipasavyo.

Ninahakiki kwamba mhusika hajalazimishwa kupeana kibali kuhusika kwenye utafiti huu bali amekubali kwa hiari.

Nakala ya kibali hiki kimewasilishwa kwa mhusika naye akatia sahihi ipasayvo.

Jina la mtafiti aliyepewa kibali cha mhusika……

Sahihi ya mtafiti mhusika.....……

Tarehe……

C. DATA COLLECTION SHEET

Date……..	NO…….	AGE… …	Gender……. .	Mechanism of Injury…….…….…. ….

Date and time if injury ……. Duration before presenting to KNH……..	Mode of arrival to the hospital: 1. Referral from another facility…….. 2. Brought by paramedics…….. 3. Brought by police…….. 4. Brought by relatives……..
Vital signs at first contact; Temperature…….. Blood pressure…….. Pulse rate…….. Respiratory rate……..	

Type of Injury: Blunt force……. Penetrating force……..		
Coagulation profile at admission: APTT- PT- INR- Hb-	AIS SCORE at admission:	Type of fluid(s) received prior to blood sample collection…….. …. Amount of fluid received……..

Outcome:	Day 0	Day 7	Day 14
Blood transfusion and amount			
Creatinine level			
Heaemoglobin level			
Other			
NOTES:			

D. ABBREVIATED INJURY SCALE

Regions	AIS	AIS meaning
Head, neck and C-spine	1	Minor
Face including nose, mouth, eyes, ears	2	Moderate
Thorax, thoracic spine, diaphragm	3	Serious
Abdomen and lumbar spine	4	Severe
Extremities including pelvis	5	Critical
External soft tissue injury	6	Maximal (untreatable)

Calculate AIS for most severely injured body part in each region. ISS is calculated as sum of square of AIS for the 3 most injured body regions. Maximum score is 75. If any body region is assigned a 6, the overall ISS is automatically 75.
Legend: AIS – abbreviated injury scale

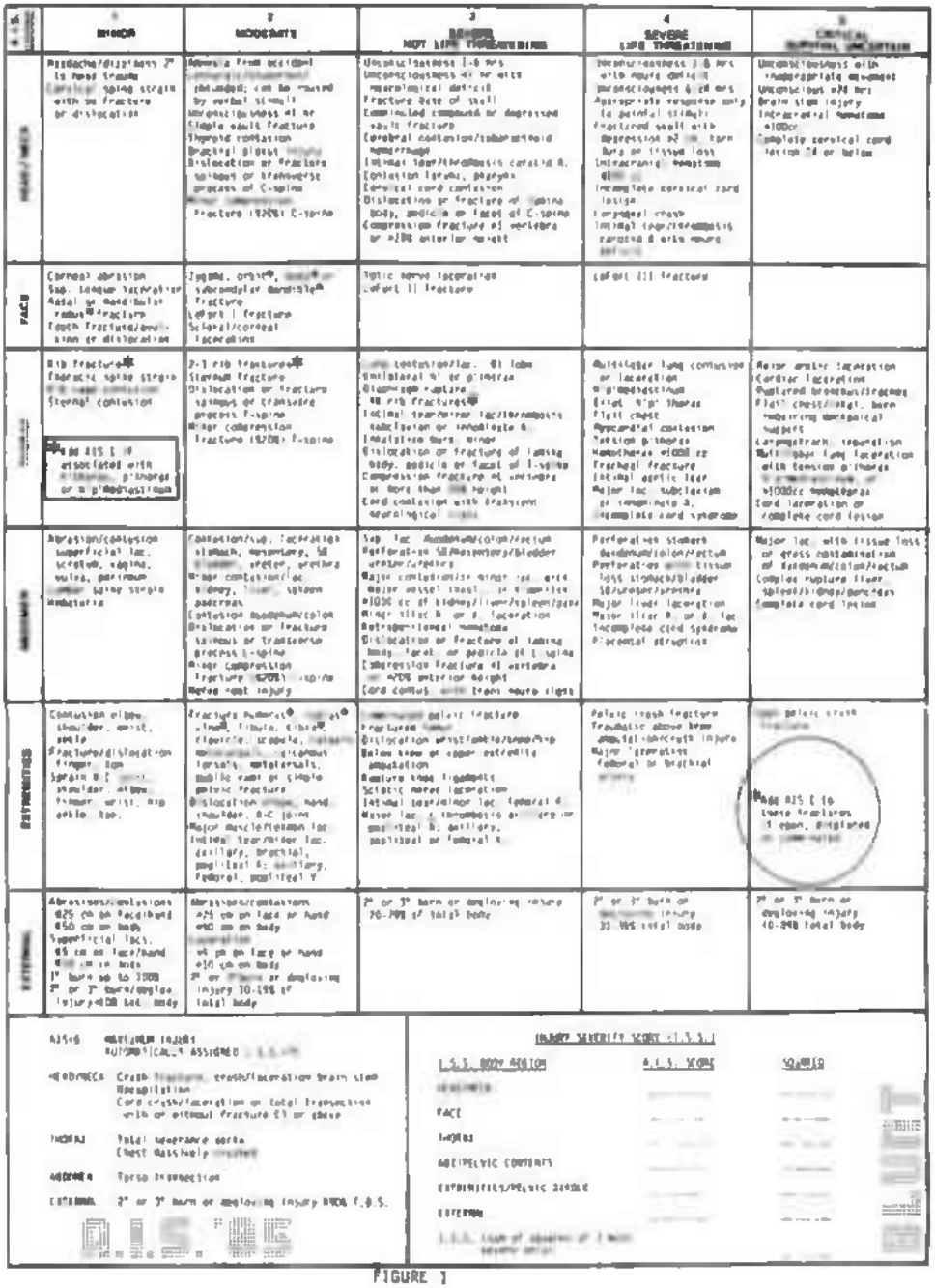


FIGURE 1

E. STUDY TIME FRAME: GNATT CHART

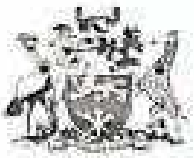
Activity	June 2020	July 2020	Aug 2020	Sept 2020	Oct 2020	Dec 2020	Jan 2021	Feb 2021	March 2021	April 2021
Proposal development										
Ethical Approval										
Data collection										
Data Analysis										
Dissertation Writing and presentation										

F. STUDY BUDGET

Funded by principal researcher

ITEM	COST (KSH)
Research fee (KNH/ERC)	2500/=
Stationery, printing and binding	10,000/=
Laboratory charges	120,000/=
Statistician plus Assistant	50,000/=
Contingencies	10,000/=
Total	**192,500/=**

G. KNH/ UON ETHICS AND RESEARCH COMMITTEE APPROVAL



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KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 7252529
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/425

30th November 2020

Dr. Kelvin Yuti Maweu
Reg. No:H58/86375/2016
Dept.of Orthopaedic Surgery
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Maweu

RESEARCH PROPOSAL – ACUTE TRAUMATIC COAGULOPATHY IN MAJOR TRAUMA ORTHOPAEDIC PATIENTS AT KENYATTA NATIONAL HOSPITAL (P425/09/2020)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and approved your above research proposal. The approval period is 30th November 2020 –29th November 2021.

This approval is subject to compliance with the following requirements:

a. Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b. All changes (amendments, deviations, violations etc.) are submitted for review and approval by KNH-UoN ERC before implementation.
c. Death and life threatening problems and serious adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH-UoN ERC within 72 hours of notification.
d. Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH- UoN ERC within 72 hours.
e. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*)
g. Submission of an executive summary report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/ or plagiarism.

Protect to discover

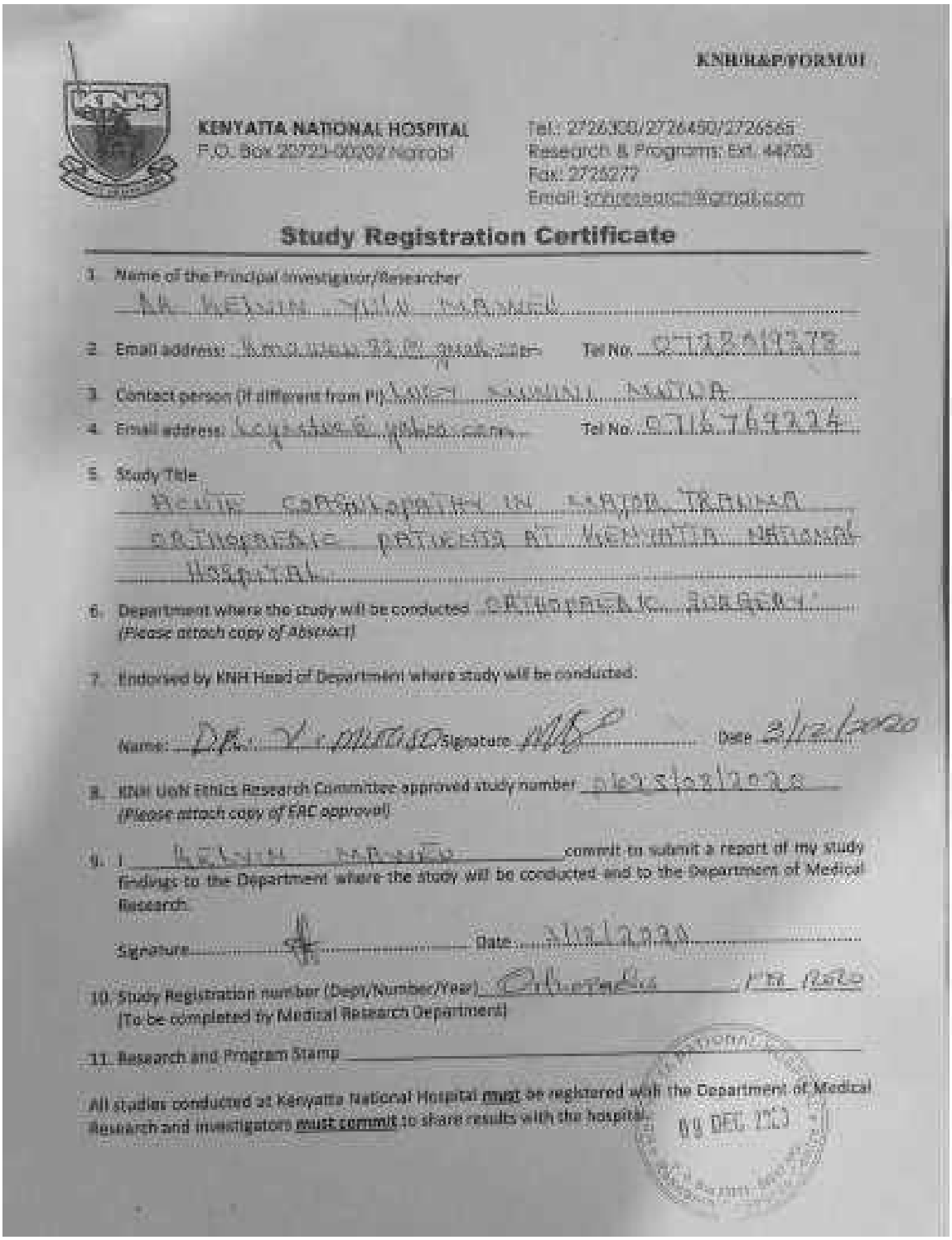
For more details consult the KNH- UoN ERC website http://www.erc.uonbi.ac.ke

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Senior Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information Dept, KNH
The Dean, School of Medicine, UoN
The Chair, Dept. of Orthopaedic Surgery, UoN
Supervisors: Dr. Vincent Mucki Mutiso, Dept. of Orthopaedic Surgery, UoN
Dr. Edward Gakuya, Division of Orthopaedics, Kenyatta N. Hospital

H. KNH STUDY REGISTRATION CERTIFICATE



KNH/R&P/FORM/01

KENYATTA NATIONAL HOSPITAL
P.O. Box 20723-00202 Nairobi

Tel.: 2726300/2726450/2726565
Research & Programs: Ext. 44705
Fax: 2725277
Email: knhresearch@gmail.com

Study Registration Certificate

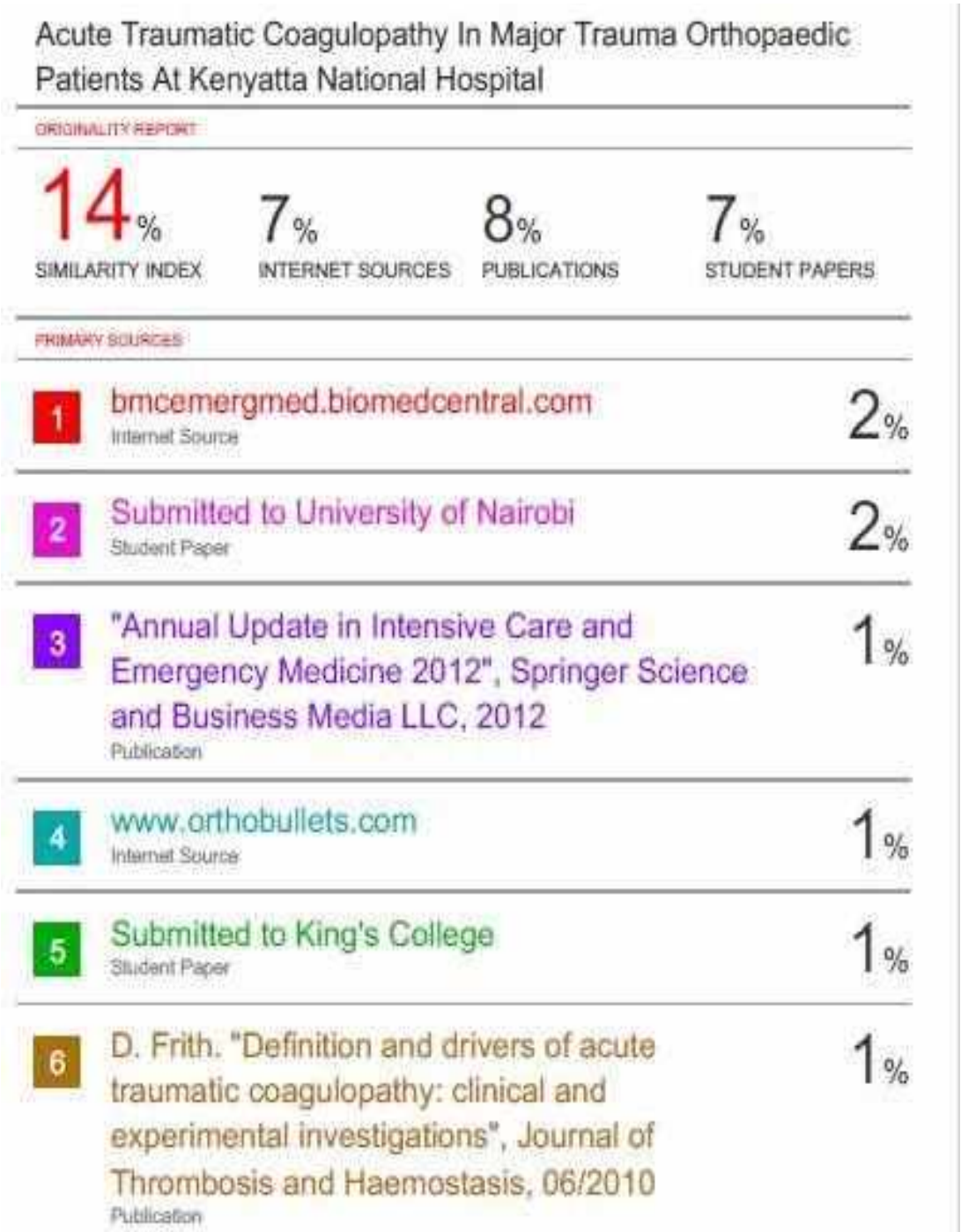
1. Name of the Principal Investigator/Researcher
2. Email address: Tel No.
3. Contact person (if different from PI)
4. Email address: Tel No.
5. Study Title
6. Department where the study will be conducted
   (Please attach copy of Abstract)
7. Endorsed by KNH Head of Department where study will be conducted.

   Name: Signature Date
8. UoN Ethics Research Committee approved study number
   (Please attach copy of ERC approval)
9. I commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Medical Research.

   Signature Date
10. Study Registration number (Dept/Number/Year)
    (To be completed by Medical Research Department)
11. Research and Program Stamp

All studies conducted at Kenyatta National Hospital must be registered with the Department of Medical Research and investigators must commit to share results with the hospital.

I. ORIGINALITY REPORT



Acute Traumatic Coagulopathy In Major Trauma Orthopaedic Patients At Kenyatta National Hospital

ORIGINALITY REPORT

14%	7%	8%	7%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	bmcemergmed.biomedcentral.com Internet Source	2%
2	Submitted to University of Nairobi Student Paper	2%
3	"Annual Update in Intensive Care and Emergency Medicine 2012", Springer Science and Business Media LLC, 2012 Publication	1%
4	www.orthobullets.com Internet Source	1%
5	Submitted to King's College Student Paper	1%
6	D. Frith. "Definition and drivers of acute traumatic coagulopathy: clinical and experimental investigations", Journal of Thrombosis and Haemostasis, 06/2010 Publication	1%