PREVALENCE, DISEASE SEVERITY, TREATMENT OPTIONS AND MEDIAN SURVIVAL OF PATIENTS WITH APLASTIC ANEMIA WHO ATTENDED MUHIMBILI NATIONAL HOSPITAL FROM 2018 TO 2023

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By

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A Dissertation Submitted in (partial) Fulfillment of the Requirements for the Degree of Master of Medicine (Haematology and Blood Transfusion) at

Muhimbili University of Health and Allied Sciences

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CERTIFICATION

The undersigned certifies that they have read and hereby recommend for examination by the Muhimbili University of Health and Allied Sciences a dissertation entitled: **"Prevalence, disease severity, treatment options and median survival of patients with aplastic anemia who attended Muhimbili National Hospital from 2018 to 2023",** in (Partial) fulfillment of the requirement for the degree of Master of Medicine (Haematology and Blood Transfusion) of Muhimbili University of Health Allied Sciences.

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DECLARATION AND COPYRIGHT

I, **Gladys N. Kaaya**, declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature…… Date…….....….....

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DEDICATION

This dissertation is dedicated to my beloved sons, **Hallelujah** and **Jedediah**. Your smiles, laughter, and energy inspire me daily. I hope this work inspires you to chase your dreams and strive for excellence. You are my greatest accomplishments and deepest pride.

ABSTRACT

Background: Aplastic anemia (AA) is a rare bone marrow failure disorder characterized by pancytopenia and hypocellular marrow, primarily due to immune-mediated hematopoietic stem cell destruction. Its prevalence varies globally, and survival outcomes have improved with immunosuppressive therapy and bone marrow transplantation. However, recent data on AA prevalence and survival in Tanzania are scarce.

Aim: This study aimed to determine the prevalence, severity, treatment options, and factors influencing the median survival of AA patients treated at MNH from 2018 to 2023.

Method: In this retrospective cohort study, AA patients diagnosed and treated at MNH between January 2018 and December 2023 was reviewed. Clinical, laboratory, and demographic data were extracted from medical records. Descriptive statistics analyzed AA prevalence, demographics, disease severity, and treatment options. Kaplan-Meier curves and log-rank tests estimated survival. Cox regression assessed mortality risk factors, with statistical significance set at $p < 0.05$.

Results: Among 577 pancytopenia patients, 156 (27%) had idiopathic AA, with a median age of 23 and a male-to-female ratio of 1.5:1. Severe AA was present in 85.9%. Treatments included cyclosporine (59.8%), supportive care (21.8%), and intensive IST (14.1%). The median survival was 158 days, with intensive IST showing the best outcomes, while supportive care increased mortality.

Conclusion: Intensive IST significantly improves survival in AA patients. However, many patients still rely on supportive care due to socioeconomic barriers, impacting outcomes. This study provides critical data on AA demographics, treatment, and survival in Tanzania, contributing valuable insights for healthcare practitioners and policymakers.

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LIST OF ABBREVIATIONS

AA	Aplastic Anemia
ALC	Absolute Lymphocyte Count
ANC	Absolute Neutrophil Count
ARC	Absolute Reticulocyte Count
ATG	Antithymocyte globulin
BMA	Bone Marrow Aspirate
BMF	Bone Marrow Failure
BMT	Bone Marrow Transplant
CBC	Complete Blood Count
CsA	Cyclosporine A
EBMT	European Society for Blood and Marrow Transplantation
FA	Fanconi Anemia
GvHD	Graft vs Host Disease
HID	Haploidentical Donor
HLA	Human Leucocyte Antigen
HR	Hazard ratio
HSCT	Hematopoietic Stem Cell Transplant
IBMFS	Inherited Bone Marrow Failure Syndromes
Intensive IST	Antithymocyte globulin (ATG) plus Cyclosporine A (CsA)
IST	Immunosuppressive Therapy
MDS	Myelodysplastic syndrome
MNH	Muhimbili National Hospital
MUHAS	Muhimbili University of Health and Allied Sciences
PBS	Peripheral Blood Smear
PLT	Platelets
PNH	Paroxysmal Nocturnal Hemoglobinuria
SAA	Severe Aplastic Anemia
VSAA	Very Severe Aplastic Anemia
WBC	White Blood Cells

DEFINITION OF TERMS

Bone Marrow Failure: Deficient or decreased hematopoiesis leading to pancytopenia

Pancytopenia: Decrease in all three hematological cell lines i.e. less than 10 g/dl of hemoglobin, 1.5 X 10^9/L of neutrophils, and 100 X 10^9/L of platelets are the minimum requirements.

The modified Camitta criteria (1) used to evaluate the severity of AA (2,3):

Severe AA (SAA); Marrow cellularity <25% (or 25–50% with <30% residual hematopoietic cells), plus at least 2 of:

(i) neutrophils <0.5 x 10^9/L,

(ii) platelets <20 x 10^9/L

(iii)reticulocyte count <20 x 10^9/L (manual counting) or <60 x10^9/L (Automated analyzer)(4)

Very Severe AA (VSAA); As for SAA but neutrophils <0.2 x 10^9/L

Non-severe AA (NSAA); AA not fulfilling the criteria for SAA or VSAA

Median Survival: The period of time after a disease has been diagnosed or after treatment has begun during which half of the patients with the disease are still alive(5).

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Aplastic anemia is an infrequent but diverse medical condition characterized by pancytopenia, which means a shortage of blood cells, without the presence of marrow fibrosis or abnormal infiltration, and it typically involves a bone marrow with reduced cellularity (2,3). While there are instances of inherited cases, the predominant causes are acquired and immune-mediated. Environmental factors such as drugs, infections, and toxins can trigger the condition, yet the majority of cases are considered idiopathic, constituting about 70-80% of all instances (2,3,6,7)

The prevalence of acquired aplastic anemia (AA) varies depending on age and geographic location (8). In Europe and North America, the annual incidence is approximately 2-3 cases per million individuals, while in East Asia, it is notably higher, 2-3 times that rate (8,9). The gender distribution of AA cases is nearly equal, with a ratio of almost 1:1 between men and women (2,3). The occurrence of AA follows a biphasic pattern, with peaks observed in two age groups: one between the ages of 10 and 25, and another in individuals aged 60 and above (3,8–10). While data on the incidence of AA in Africa is limited, cases have been reported in various regions of the continent, including Northern Africa, Western Africa, Eastern Africa, and Southern Africa (10–13).

The common symptoms include tiredness and easy bleeding or bruising, and while infections are occasionally present, there is typically no history of chronic sickness (14). Although almost all of the cases are idiopathic, special attention to medication, occupation, and family history ought to be taken (3). Young people with Fanconi Anemia (FA) are likely to have short stature, hyper- or hypopigmented regions of the skin, and skeletal anomalies, notably those affecting the thumb (15). Dyskeratosis congenita is characterized by the triad of oral leucoplakia, reticular skin pigmentation, and nail dystrophy (15).

To diagnose AA, a complete history and physical examination, a full blood picture with differential, a peripheral smear, a reticulocyte count, bone marrow aspirate with a core biopsy, as well as ancillary tests; cytogenetics and fluorescence in situ hybridization to rule out Myelodysplastic syndrome (MDS) is required (14). It is important to rule out other causes of bone marrow failure (BMF) syndromes (14).

At least two of the following must be present to diagnose AA; Platelet count less than 50 x 10^9/L, neutrophil count less than 1.5 x 10^9/L, and hemoglobin concentration less than 10 g/dl (1). The severity of AA, as determined by the Camitta criteria, serves as the treatment's guiding principle when the diagnostic evaluation is complete (14).

The choice of therapy is influenced by the severity of the AA, the patient's age, the accessibility to the best therapy, and the availability of matched donors (14). All pediatric patients with newly discovered severe aplastic anemia, as well as younger adult patients when a matched sibling donor is available, should undergo a bone marrow transplant (BMT) (14). Immunosuppressive therapy (IST) with horse antithymocyte globulin (ATG) and cyclosporine A (CSA) is the first line of treatment for patients who are older adults and for all patients who do not have a sibling donor who is a match (14). There is a growing advantage of eltrombopag being paired with the first IST (14).

In Tanzania, there is a shortage of up-to-date information on currently available treatment options and survival outcomes of patients with aplastic anemia, hence the purpose of this study.

1.2 Problem statement

Aplastic Anemia (AA), a rare and life-threatening hematological disorder, has a significant impact on the well-being of affected individuals. Previous research at Muhimbili National Hospital has contributed insights into the prevalence of AA, clinical characteristics and certain treatment options (12,16). However, a substantial knowledge gap remains as existing studies provide only fragmented insights into the disease. They fall short of conducting a comprehensive analysis of disease severity, the effectiveness of diverse treatment modalities, and the complex factors influencing patient survival and specific survival rates.

The last study conducted at Muhimbili National Hospital, covering the period from 2016 to 2017, reported a high annual prevalence of 34 cases, which exceeded the rates in many other nations (8,17–19). However, the study also revealed substandard treatment practices compared to the recommended guidelines (3), with a significant number of patients receiving only supportive management. Since then, new treatment modalities have become available, but also the median survival of AA patients has not been assessed, hence the focus of this study.

This research aims to address critical knowledge gaps through a retrospective cohort analysis of Aplastic Anemia (AA) patients at Muhimbili National Hospital. Previous studies have only provided fragmented data on the prevalence of AA, and the effectiveness of diverse treatment modalities has not been fully evaluated, especially after 2017, when new treatment options became available. Earlier research also revealed many patients received only supportive care, falling short of recommended treatment guidelines. Additionally, the outcome of treatments, particularly the median survival rates of AA patients, remains unclear. This study will provide a comprehensive understanding of AA's clinical profile, disease severity, treatment outcomes, and survival rates to guide future care strategies.

1.3 Conceptual framework

Patients with pancytopenia, who underwent BMA at MNH, will be evaluated and out of those, only those diagnosed to have AA by BMA will be enrolled into the study. The hypothesis is that a number of socio demographic characteristics, including age, gender, insurance status, disease severity at the time of diagnosis, and treatment regimen, serve as independent variables that affect the dependent variable of patient outcome including median survival.

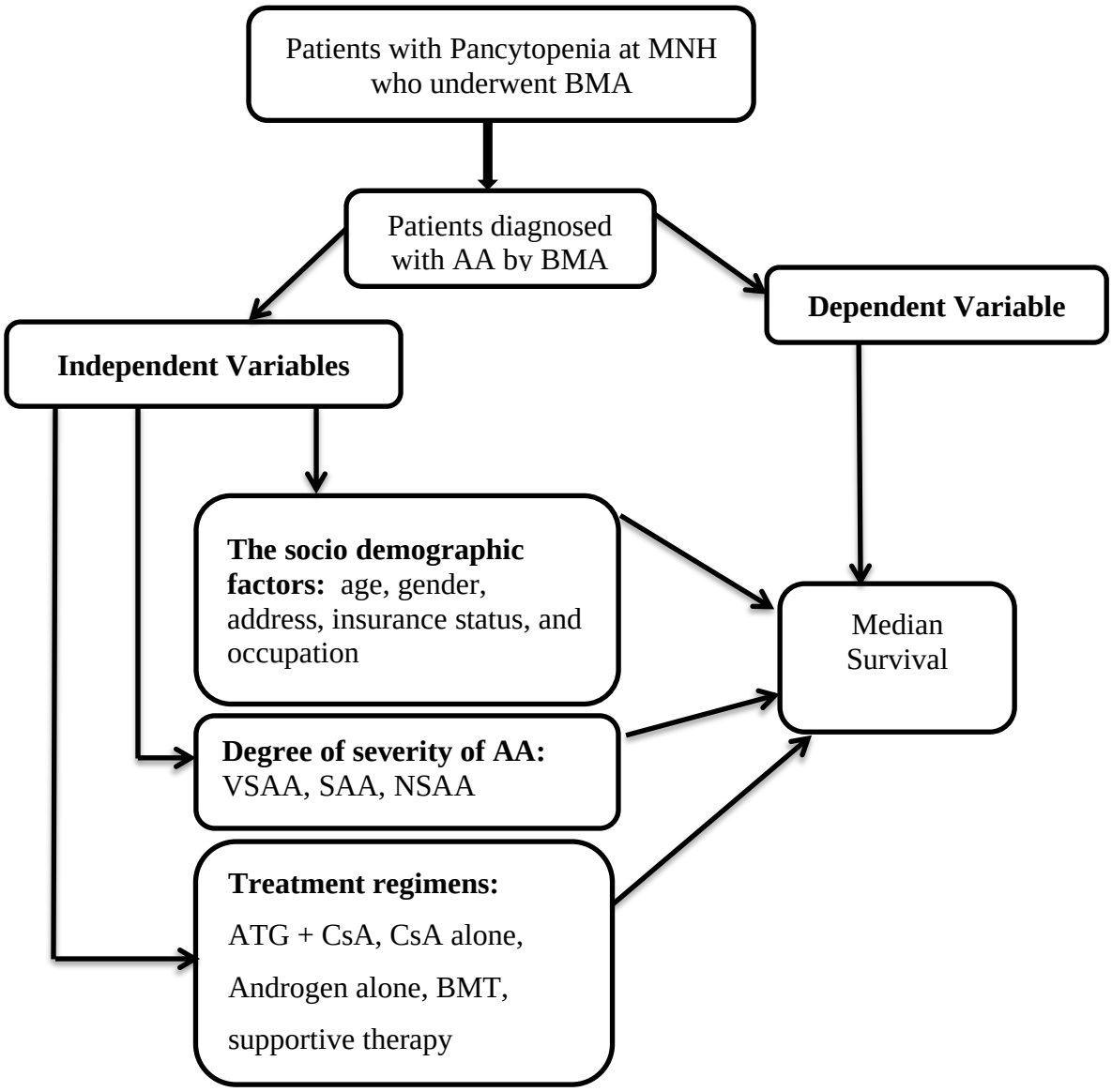


Figure 1: shows conceptual framework of the study

1.4 Rationale

This study will give a general overview of the impact of AA, contribute to a better understanding of the illness and its clinical course, and analyze the survival outcome of people who have been diagnosed with AA. Consequently, this will lead to advancements in the disease's therapy. This study will serve as a springboard for additional investigation of the range of AA diagnoses, therapies, and other patterns across time at MNH.

Comprehensive information about the outcomes of treatment of aplastic anemia in Tanzania is lacking. Only a few studies have reported on the subject. The results obtained from this study will help identify regulatory gaps and challenges in the current system; this will enable the development of better regulation, interventions and effective monitoring of strategies for treating aplastic anemia.

1.5 Research Questions

The overall research question is: What are the prevalence, disease severity, treatment options and factors associated with median survival of patients with aplastic anemia who attended MNH from 2018 to 2023?

1.5.1 Specific research questions

i. What percentage of pancytopenia patients who underwent BMA at MNH from 2018 to 2023 had aplastic anemia?
ii. What is the degree of severity of AA patients at time of diagnosis at MNH?
iii. What therapies did the patients with Aplastic anemia receive at MNH from 2018 to 2023?
iv. What are the factors associated with median survival of patients diagnosed to have Aplastic anemia at MNH?

1.6 Broad Objective

To determine prevalence, disease severity, treatment options and factors associated with median survival of patients with aplastic anemia who attended MNH from 2018 to 2023

1.6.1 Specific Objectives

i. To determine the prevalence of aplastic anemia in pancytopenia patients who underwent BMA at MNH between 2018 and 2023
ii. To describe the disease severity among AA patients who visited MNH from 2018 to 2023 at the time of diagnosis.
iii. To describe the treatment options offered to aplastic anemia patients who visited MNH between 2018 and 2023
iv. To determine the factors associated with median survival of patients diagnosed to have Aplastic anemia at MNH from 2018 to 2023.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Aplastic Anemia Prevalence in pancytopenia patients

Globally, the occurrence of aplastic anemia has been estimated to be fewer than 3 cases for every million individuals annually, mirroring the incidence rate observed in Europe (6). In Europe, the yearly incidence is approximated to be around 2 cases per million in the population, a figure consistent with reports from Latin America (6,20). While precise data on the incidence in the United States are unavailable, insights from various retrospective studies indicate that it ranges between 0.6 and 6.1 cases per million people, similar to the European estimate (6). Notably, in Eastern Asia, AA stands out as significantly more prevalent, manifesting 2 to 3 times more frequently than in other regions (20).

In Asia, the annual incidence varies, with urban Thailand showing a rate of 4 cases per million population, while rural areas in Thailand may have a higher incidence, possibly reaching 6 cases per million population; while in Africa, aplastic anemia is predominantly associated with severe anemia, as indicated by population-based studies (11,21).

Aplastic anemia may affect people of all ages; however, it is most usually seen in people between the ages of 15 and 25, with a subsequent peak occurring between the ages of 65 and 69 (18). Although some data indicate a male predominance in Malaysia and Thailand, the ratio of men to women for AA is often around 1:1 (11,21).

In an observational study conducted in MNH, Tanzania; from September 1, 2016, to August 31, 2017, 19 patients were from the Dar es-Salaam region which had a population of about 5 million which means a crude minimum figure for acquired AA in Dar es Salaam region is 19/5 million, or 3.8 cases per million per year (12). However, this data may be an underestimate since it only captured 1 year.

This study aims to retrospectively assess the prevalence of AA within a pancytopenia patient cohort, where AA is identified as the primary cause of pancytopenia, utilizing BMA as a recognized diagnostic tool (22).

2.2 Disease severity of patients with Aplastic Anemia

The most commonly reported symptoms were symptoms of anemia which included fatigue, palpitations, and dizziness, often followed by fever and a propensity for bleeding. To confirm empty marrow, a bone marrow biopsy is essential. This procedure is crucial for excluding conditions like MDS, leukemia, and solid malignancy metastases. Diagnosing AA necessitates both a trephine biopsy and a bone marrow aspirate (3,16,23).

The Camitta criterion should be used to determine the severity of AA whereby, AA is classified clinically by the extent of the peripheral blood count suppression (including Absolute reticulocyte count, absolute neutrophil count and absolute platelet count) (3). Nevertheless, patients meeting the criteria for severe or very severe AA according to Camitta's classification are often guided by this categorization method, which is strongly associated with prognosis, toward a treatment approach that may involve early bone marrow transplantation (3,24).

Fatty bone marrow remains a crucial diagnostic indicator for aplastic anemia (25). However, advanced testing can now differentiate various pathophysiological abnormalities and distinguish between diseases with similar and sometimes overlapping symptoms, including PNH, MDS, and telomere diseases (25).

The disease severity of AA is an important part of this study, and it is important to assess it because it will give an impression of whether there is an improvement in awareness and early diagnosis hence affecting the prognosis of patients with AA as compared to the study done by Mwashungi *et al* in 2017 as survival of AA depends also on disease severity (12,26).

2.3 Treatment offered to patients with Aplastic Anemia

In the early days of transplantation, occasional autologous bone marrow recovery, despite graft failure, hinted at a potential positive impact of antilymphocyte globulin used in conditioning regimens (25). Presently, both BMT and IST serve as primary treatment approaches for both children and adults, achieving success rates between 60% and 80% (27).

The decision regarding whether to opt for immunosuppression or BMT primarily hinges on the presence of a sibling donor and the patient's age (28). In numerous medical facilities, individuals aged over 45-50 years are not typically considered candidates for BMT as the initial treatment choice. Conversely, there is no age restriction for immunosuppressive therapy, and the decision to treat older patients currently depends on their overall health and performance status (28). The enhanced outcomes observed in unrelated donor transplants have led to survival rates comparable to those of matched sibling donor grafts, albeit with an elevated risk of GvHD (23).

Combined with cyclosporine, ATG leads to hematologic responses in about two-thirds of patients. IST is recommended for the treatment of SAA patients who are not eligible for HSCT (21). Patients treated with IST are not cured of their disease and are at risk for 3 major complications: no response, relapse, and clonal evolution (23). Most cases of AA following autoimmune disease benefitted from IST or HSCT if a matched donor was available. Further prospective investigation is needed to assess the effects of IST on the outcome of underlying autoimmune disease (27).

Eltrombopag could potentially reshape non-transplant therapy and treatment strategies if the reported response and survival rates are verified (25). Androgens have been frequently used in IST-resistant patients and have shown notable response rates (23). When eltrombopag was incorporated into the initial standard IST, it significantly boosted the overall response rate to approximately 80% and the complete response rate to around 50%, often resulting in swift hematologic recovery (25). So far, the rates of relapse and progression to myeloid cancers with this approach appear to be on par with

or even lower than those observed in historical controls treated with immunosuppression alone (25).

Androgens, traditionally considered less effective than immunosuppressive approaches for severe aplastic anemia, have been used in marrow failure syndromes and are standard for various constitutional syndromes (25). Sex hormones boost telomerase gene expression in cell cultures and mice (25). High danazol doses, a synthetic androgen, enhanced blood counts and reversed telomere attrition in patients with telomere disease (25).

HSCT is the recommended treatment for patients under 40-50 years old. In Tanzania, due to limited government support, only a few eligible patients can afford this expensive procedure. Treatment for AA in Tanzania was suboptimal in 2017. This study aims to evaluate whether there has been any improvement in the availability of recommended treatments since then (12).

2.4 Median Survival Outcome of patients with Aplastic anemia

In the 1970s, acquired SAA had a mortality rate of 80% to 90%, but today we're witnessing an impressive 80% to 90% survival rate, thanks to global research efforts (23). A study in Thailand found no significant difference in survival between genders, with a 2-year overall survival rate for both males and females (21). Unfortunately, current population-based data on incidence and survival are limited (8). Among 342 AA patients, the median overall survival was 19.2 months, with a 2-year survival rate of 48.1%. When categorized by disease severity, the 2-year survival rates for NSAA, SAA, and VSAA were 65.5%, 49.3%, and 20.1%, respectively (21).

In a Chinese study comparing immunosuppressive therapy (IST) and haploidentical donor (HID) hematopoietic stem cell transplantation (HSCT) for severe aplastic anemia, 10-year overall survival rates were 86% for IST and 95% for HID transplant. However, failure-free survival was significantly lower with IST (62.7%) compared to HID transplant (94.8%) (29).

A comprehensive Swedish population-based study on AA patients diagnosed between 2000 and 2011 found that 5-year survival rates for younger patients (up to age 40) were around 90%, similar to rates reported in clinical trials with ATG or HSCT registry data. This study also revealed no survival difference between IST and HSCT as the primary treatment in younger patients, consistent with data from the European Society for Blood and Marrow Transplantation (EBMT) registry. Patients aged 40-59 had a 5-year survival rate of about 70% (8).

In a Nigerian study, the median survival was 6.5 weeks, with the longest-surviving patient monitored for 55 weeks. Late presentation was a common issue, and higher platelet counts at diagnosis were positively correlated with survival (r=0.53), as were younger ages at diagnosis (r=0.52) (11).

Infection emerged as the primary contributor to mortality in patients subjected to either bone marrow transplantation (BMT) or immunosuppressive therapy, with adults experiencing a higher incidence of infections, leading to their elevated mortality rates compared to children (28). According to a study done in Tanzania, out of the 40 patients involved in the study, 17 individuals (43%) succumbed during the research period, with sepsis and bleeding being the predominant causes of death. These findings align with existing literature, emphasizing that untreated AA can result in a fatal outcome (12). Notably, there is currently no study in Tanzania that has examined the median survival of AA patients over an extended timeframe.

CHAPTER THREE

3.0 METHODOLOGY

3.1 Design and Study Issues

The study was a retrospective cohort design enrolling all patients with AA from January 2018 to December 2023, following them until death, with those who did not die by the end of the follow-up period being declared censored.

3.2 Study Location and Study Population

Muhimbili National Hospital, a tertiary national hospital that treats patients from around the nation and also functions as a teaching hospital for MUHAS, will be the area of study. MNH has two facilities one at Mloganzila in the Ubungo area and another at Upanga in the Ilala district. The hematology and blood transfusion department of MNH Upanga, which treats both adult and pediatric patients, will serve as the site of this study. Not only is it linked to the Central Pathology Laboratory, which handles all hematological laboratory analysis as well as blood donation and transfusion services, but it also operates adult hematology clinics twice a week (Tuesday and Friday) and pediatric hematology clinics (Thursday), where Aplastic Anemia patients are seen alongside others with hematological conditions. These clinics see an average of 300 hematology patients per week. The hematology section is managed by six hematologists and two certified hematology nurses, providing care for both inpatient and outpatient AA patients.

The study's target population was patients who sought treatment services for aplastic anemia at MNH at pediatric and general clinics and wards. This study recruited all patients found to have AA, who underwent BMA and trephine biopsy at MNH from January 2018 to December 2023.

3.3 Study duration

The data collection took place for three months from January 2024 to March 2024

3.4 Inclusion and Exclusion Criteria

3.4.1 Inclusion criteria

All patients with pancytopenia who underwent BMA and Trephine biopsy and was confirmed to have idiopathic AA from January 2018 to December 2023

3.4.2 Exclusion criteria

Twenty patients were excluded from the study due to suspected IBMFS or known/suspected secondary causes of AA. These causes included viral infections such as HIV (3 patients), Hepatitis B (9 patients), and Hepatitis C (1 patient). Although the study included exclusion criteria for patients with more than 10% missing or incomplete data, no patients met this criterion. Therefore, no patients were excluded from the analysis due to missing or incomplete data

3.5 Sample size calculation

The sample size for this study was estimated using the following parameters: a previous study conducted in Tanzania reported a prevalence of 28.6% of AA patients(12). Assuming a variation of 10% prevalence from the true population value, an alpha of 0.05 to address type I error, and a power of 80%, the study would require **168** patients to estimate their survival outcome. The following formula was used to estimate the sample size:

$$n = \frac{P_o Q_o \left\{ Z_{1-\alpha/2} + Z_{1-\beta} \sqrt{\frac{P1Q1}{PoQo}} \right\}^2}{(P_1 + P_0)^2}$$

Q0=1-P0

Q1=1-P1

Proportion

P0=Proportion (incidence) of population

P1=Proportion (incidence) of the study group

N = sample size for this study

Alpha=probability of type I error

Beta = Probability of type II error

Z=Critical value corresponding to a given value for alpha and beta

3.6 Sampling design and recruitment process

We recruited all patients with pancytopenia who had undergone BMA and trephine biopsy between January 2018 and December 2023 and were confirmed to have idiopathic AA, obtaining additional details by contacting the patients or their next of kin in case of discrepancies in patient records.

3.7 Variables

3.7.1 Independent variables

Patient demographics such as age, gender, address, occupation, and insurance status; disease severity (extracted from laboratory characteristics ARC, ANC, Platelet count, BMA and Trephine biopsy and clinical characteristics of fever, bleeding tendencies and anemia) such as SAA, NSAA, VSAA, types of treatment received such as Supportive therapy, CsA alone, androgen alone, intensive therapy and BMT.

3.7.2 Dependent variables

Survival outcomes

3.8 Data collection methods

Clinical information on patients with AA who visited MNH from January 2018 to December 2023 was collected from hardcopy and electronic records (JEEVA system). Data was also gathered from the bone marrow registry, a counter book documenting all bone marrow procedures at CPL. The information included demographics (age, gender, and insurance status), symptoms, hematological parameters, and results from BMA and trephine biopsy. BMA was performed using a Jamshidi needle inserted into the superior posterior iliac crest, while trephine biopsy involved removing a core of bone marrow tissue. The bone marrow aspirate is usually stained by either Leishman or Giemsa stain. Trephine biopsies of bone marrow are typically stained using Hematoxylin and Eosin (H&E) stain. Treatment plans and contact details for patients and their next of kin were recorded for follow-up.

3.9 Data Collection Tools

To gather information on the socio-demographic profile, disease severity (including clinical background and laboratory features), and treatment methods, we employed a standardized data abstraction form. Patient information and survival outcomes were accessed from hospital registers. For additional data cleaning and analysis, information from the data abstraction form was entered into the statistical program STATA version 17.

3.10 Data management and analysis

The data we extracted from the JEEVA system and patient file records using a data extraction form was entered into Microsoft Excel version 2010 before being imported into STATA version 17. Data cleaning was conducted in STATA version 17 to check for missing or inconsistent data and address any issues before analysis. Descriptive statistics were used to estimate the number of aplastic anemia cases each year and the overall prevalence, as well as to analyze patient demographic characteristics (age, gender, etc.), disease severity, and treatment options. Survival analysis was conducted to estimate the median survival time from diagnosis to death. The Kaplan-Meier survival curve was used to visualize survival data, and the log-rank test compared survival distributions based on disease severity and treatment options. We used the Cox regression model to assess factors associated with mortality risk, with hazard ratio (HR) = 1 suggesting no difference in risk, HR < 1 indicating a lower risk, and HR > 1 indicating a higher risk compared to the reference group. Statistical significance was set at a p-value < 0.05. Results are presented using tables and figures.

3.11 Ethical issues

Ethical clearance for the study was obtained from the Institutional Review Board (IRB) at MUHAS (MUHAS-REC-11-23-1981). Authorization to collect data was granted by the MNH Clinical Research, Training and Consultancy Unit for access to patient files. Verbal consent was sought from family members to fill in missing details. Confidentiality was maintained by omitting patient identities from data collection tools and restricting data access to research personnel. The collected information will be used solely for research purposes and subsequent publications.

CHAPTER FOUR

4.0 RESULTS

4.1 Prevalence of Aplastic anemia in pancytopenia patients who underwent BMA at MNH

Between January 2018 and December 2023, we recruited 577 patients with pancytopenia from the bone marrow registry. The most common cause of pancytopenia was bone marrow failure syndromes, affecting 189 (32.8%) of the cases, which included both inherited and acquired forms of aplastic anemia (AA). Among these, 156 patients (27%) were diagnosed with idiopathic AA and included in the study. However, 20 patients (3.5%) exhibited signs of IBMFS, such as short stature, café au lait spots, and absent radii, and were excluded. Additionally, 13 patients (2.3%) had viral infections at the time of diagnosis (3 with HIV, 9 with Hepatitis B, and 1 with Hepatitis C) and were excluded because these infections could have caused their aplastic anemia (Figure 2).

The second most common cause of pancytopenia was hematological malignancies (30.5%), followed by peripheral consumption (15.9%), cases where no diagnosis was established (non-diagnostic) (6.6%), Myelodysplastic syndrome (5.9%), nutritional deficiencies (5.7%), and myelofibrosis (2.6%).

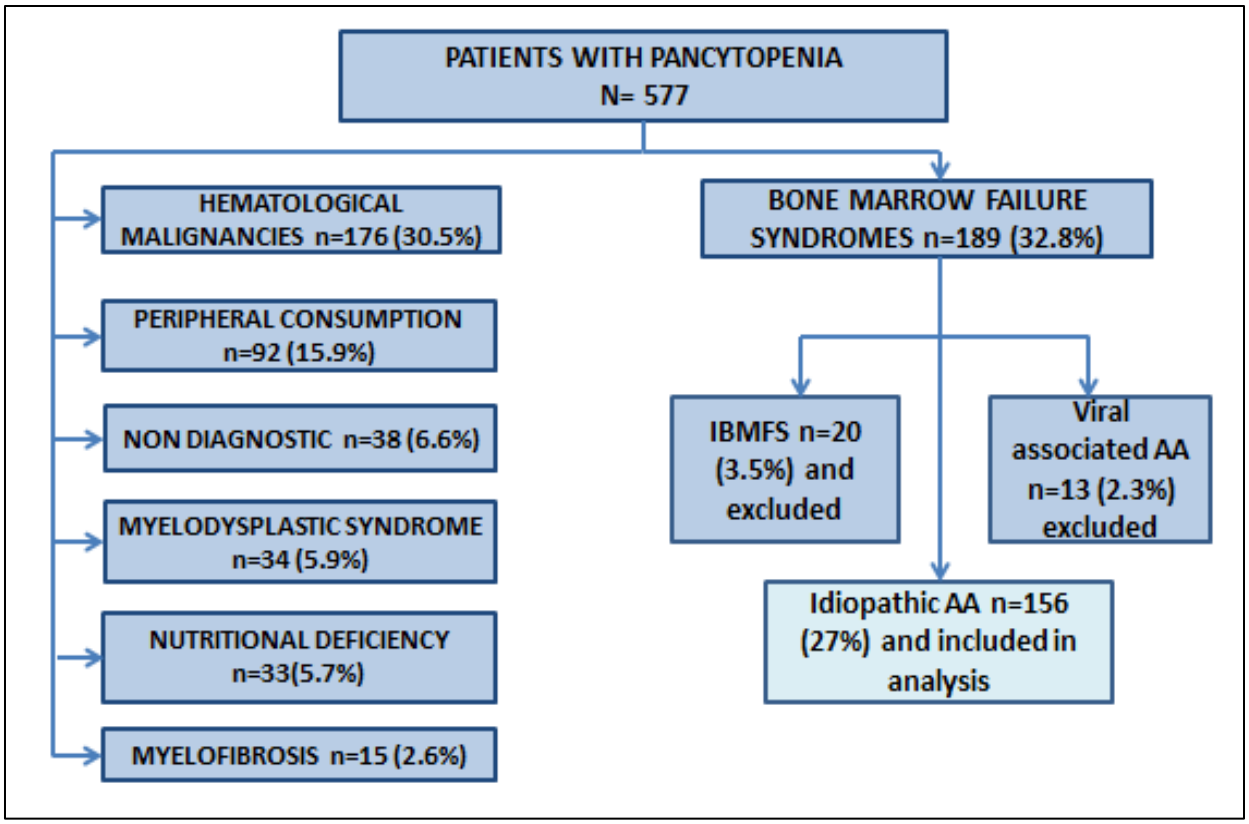


Figure 2: Showing flow chart and prevalence of AA in pancytopenia patients who underwent BMA at MNH

4.2 Socio-demographic characteristics

The study included 156 patients with AA, comprising 94 males (60.3%) and 62 females (39.7%), with a male-to-female ratio of 1.5:1. The age distribution showed that the majority were young, with a median age of 23 years. Among them, 54 patients (34.6%) were below 18 years old, and 52 patients (33.3%) were aged 18-29. Most patients (57.7%) came from outside Dar es Salaam, even though Dar es Salaam itself had the highest number of patients from a single location, as shown in Table 1 and Figure 3. A significant portion of the patients were students (28.9%), and 59 patients (37.8%) had insurance coverage, leaving the majority (62.2%) without insurance.

Table 1 .Socio-demographic characteristics of patients diagnosed with AA (n=156)

Variable	Frequency (n)	Percentage (%)
Sex		
Male	94	60.3
Female	62	39.7
Age group (years)		
Below 18	54	34.6
18-29	52	33.3
30-39	17	10.9
40 and Above	33	21.2
Median and IQR	23 (15,33)	
Place of residence		
Dar es Salaam	66	42.3
Out Dar es Salaam	90	57.7
Occupation		
Employed	10	6.4
Self employed	23	14.7
Student	45	28.9
Unemployed	20	12.8
Missing	58	37.2
Insurance status		
Insured	59	37.8
Not insured	97	62.2

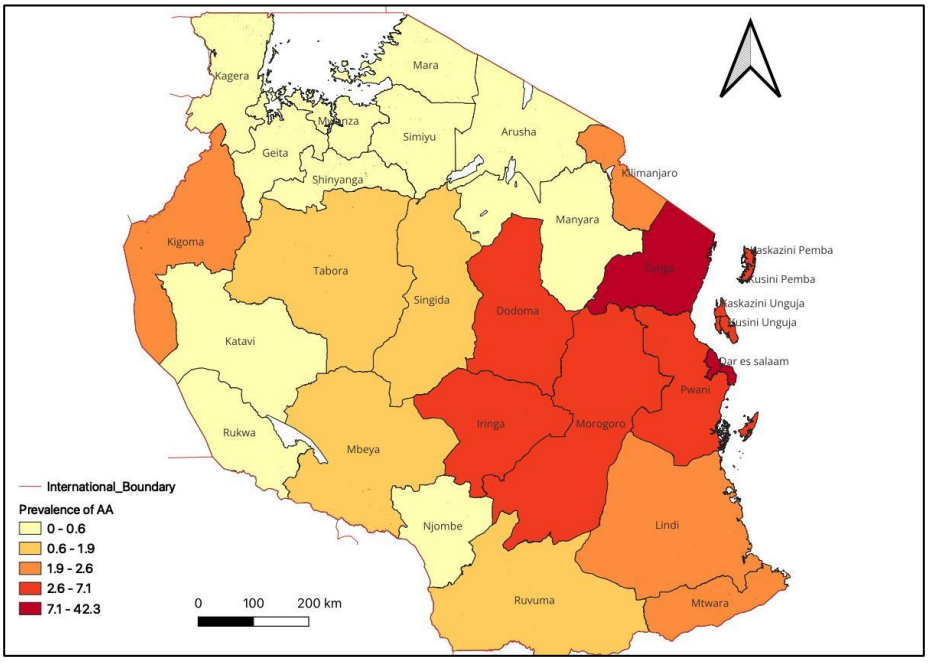


Figure 3: Map of Tanzania showing AA cases by regions of residence

4.3 Disease severity among AA patients who visited MNH

Out of 156 patients, 49.4% presented with severe aplastic anemia (SAA), 36.5% with very severe aplastic anemia (VSAA), and 14.1% with non-severe aplastic anemia (NSAA) (Figure 4). Almost all patients (99.4%) exhibited features of anemia, 63.5% had bleeding tendencies, 41.0% experienced fevers, and 4.5% showed signs of jaundice (Figure 5). At diagnosis, 97.4% had already received red cell transfusions, and 66.7% had received packed platelet transfusions, indicating they were transfusion-dependent. The mean hemoglobin level was 6.3 ± 2.3 g/dL (Table 2). Additionally, 36.5% presented with very severe neutropenia, 88.5% had reticulocytopenia, and 66% had very severe thrombocytopenia.

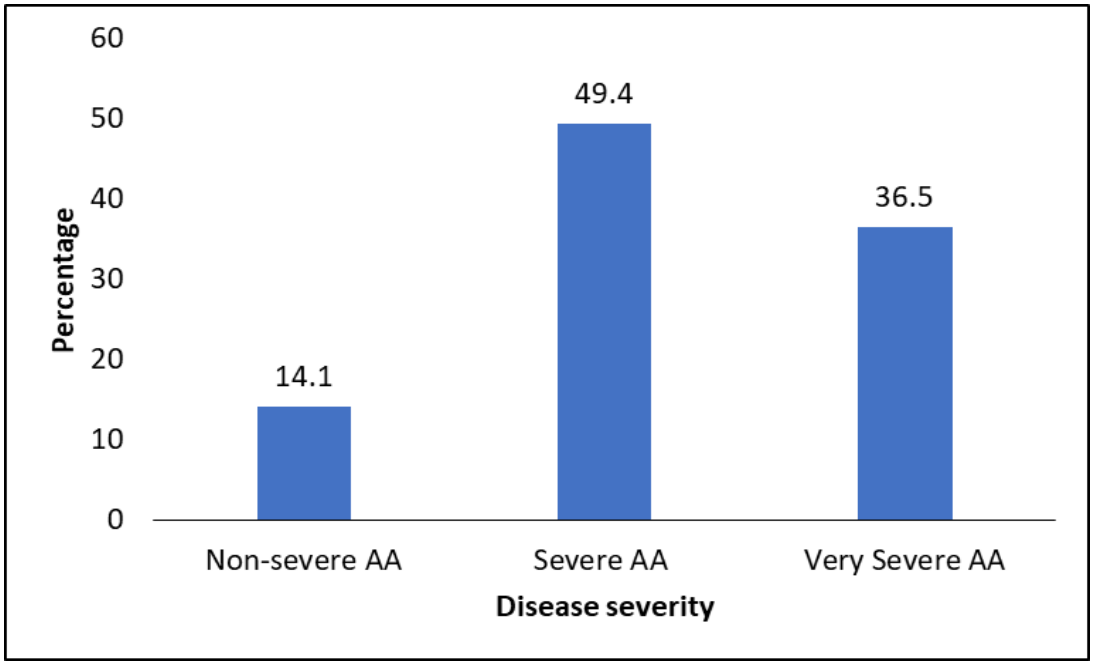


Figure 4: Disease severity at time of diagnosis (n=156)

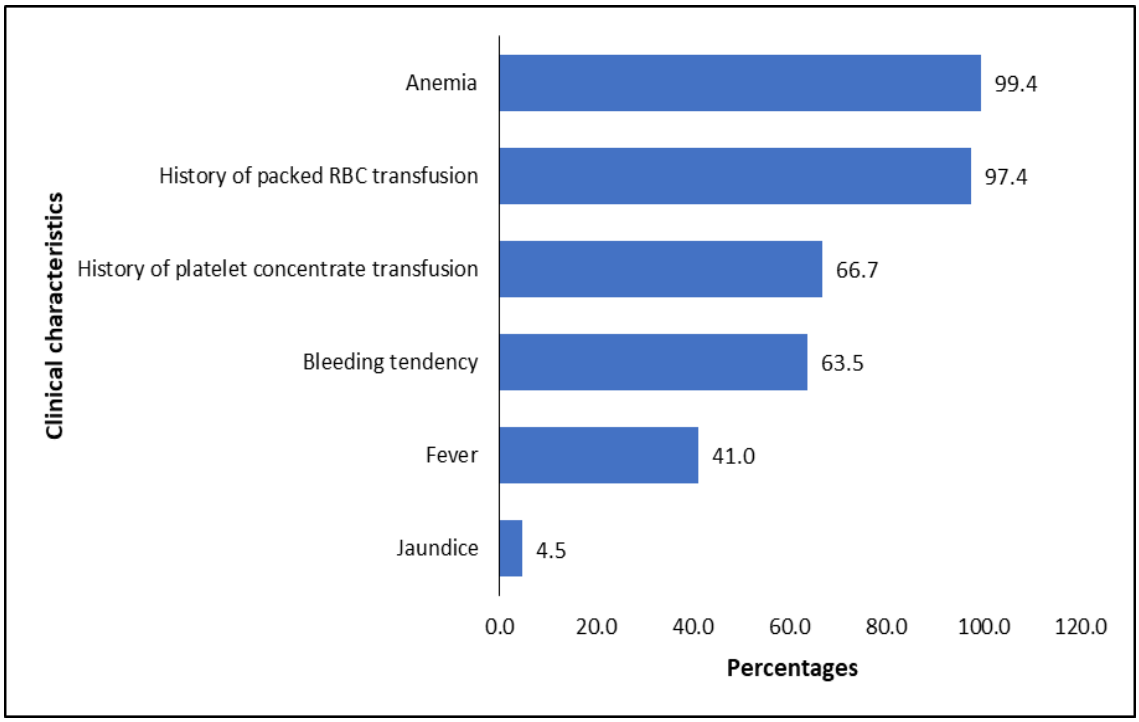


Figure 5: Clinical characteristics of patients with AA at diagnosis (n=156)

Table 2: Laboratory characteristics of patients with AA at diagnosis (n=156)

Variable	Reference range	Frequency (n)	Percentage (%)
Hb (g/dl)			
Mean SD		6.3+2.3	
ANC (x10^9/L)			
Very severe	<0.2	57	36.5
Severe	0.2-0.49	51	32.7
Moderate	0.5-0.9	31	19.9
Mild	>1.0	17	10.9
ARC (X10^9/L)			
Reticulocytopenia	<60	138	88.5
Normal	>60	18	11.5
PLT (x10^9/L)			
Very severe	<20	103	66
Severe	20-49	39	25
Mild to Moderate	>50	14	9

4.4 Treatment options offered to AA patients who visited MNH

The majority of the patients (59%) received Cyclosporine A (CsA) with supportive management, while 21.8% received only supportive treatment, including blood product transfusions and antimicrobial management (Figure 6). Intensive immunosuppressive therapy (IST) with ATG and CsA, along with supportive care, was administered to 14.1% of the patients. Additionally, 4.5% of patients received other treatments, such as androgens with or without CsA, and Eltrombopag, combined with supportive management. Only 1.9% of the patients underwent a bone marrow transplant (BMT), which was performed abroad.

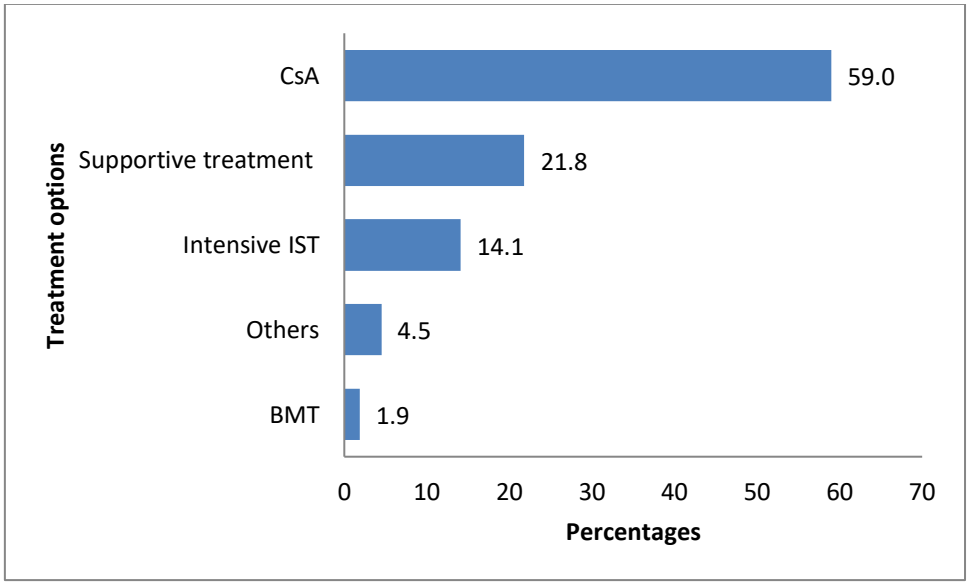


Figure 6: Treatment options that were offered to AA patients (n=156)

Key: Others* include patients who received Androgen with or without CsA and eltrombopag.

Supportive treatment* included only blood transfusion products and antimicrobial medications.

All patients received supportive treatment in addition to the treatment received.

4.5 Factors associated with Median survival of AA patients at MNH

The overall survival rate over the 6-year study period was 27.6%, with a median survival time of 158 days (5.2 months), as seen in Figure 7. The survival analysis indicates that individuals with NSAA have significantly longer survival times than

those with SAA or VSAA ($p < 0.001$). For patients with NSAA, the median survival time is 695 days, with 75% surviving at least 100 days. In contrast, SAA patients have a median survival of 389 days, with 75% surviving at least 75 days. Those with VSAA fare the worst, with a median survival of just 46 days, and only 75% surviving beyond 15 days (Figure 8).

Examining the impact of different treatments, those receiving supportive treatment alone had a median survival of 48 days. In comparison, patients treated with CsA and supportive management exhibited an improved median survival of 155 days, with 25% surviving after 852 days. Intensive IST (ATG plus CsA) showed a significant benefit, with more than 50% of patients surviving up to the end of the study period, indicating that the median survival time for intensive IST exceeds the observation period (Figure 9). Three patients underwent BMT abroad; one patient succumbed to acute transplant-related complications two weeks post-transplant, while the remaining two patients were declared cured.

Cox regression analysis was used to assess factors influencing survival in AA patients, using Intensive IST plus supportive treatment as the reference. Results showed that supportive treatment alone (aHR = 6.40, 95% CI: 2.61-15.73, $p < 0.001$), CsA plus supportive treatment (aHR = 3.25, 95% CI: 1.42-7.45, $p = 0.005$), and other treatments that included Androgen with or without CsA and/or eltrombopag (aHR = 4.20, 95% CI: 1.51-11.69, $p = 0.006$), significantly increased the hazard of death compared to Intensive IST. BMT done abroad did not significantly affect survival (aHR = 0.41, 95% CI: 0.05-3.70, $p = 0.428$), likely due to the small sample size. VSAA markedly increased the hazard of death (aHR = 4.77, 95% CI: 2.23-10.22, $p < 0.001$), while SAA did not (aHR = 1.67, 95% CI: 0.82-3.43, $p = 0.159$). Sex, age, and residence were not significant. These findings underscore the superior survival benefits of Intensive IST and the heightened risk with VSAA (Table 3).

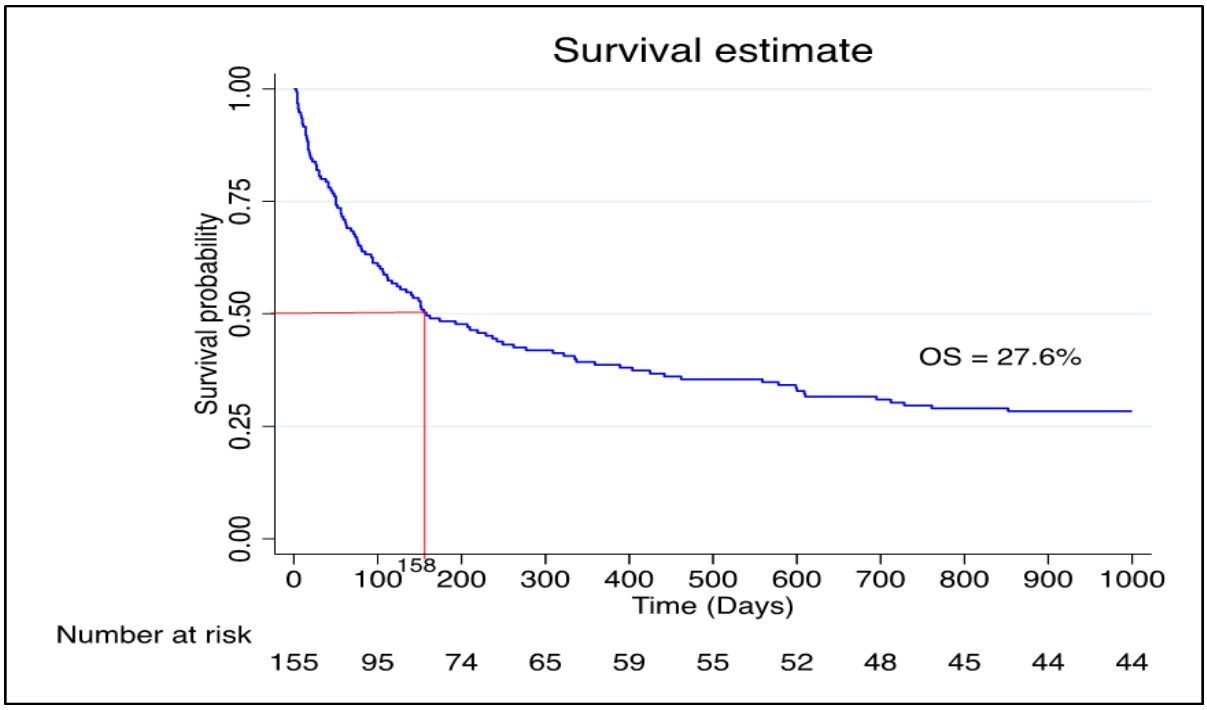


Figure 7: Kaplan Meier curve indicating overall survival estimate for AA patients

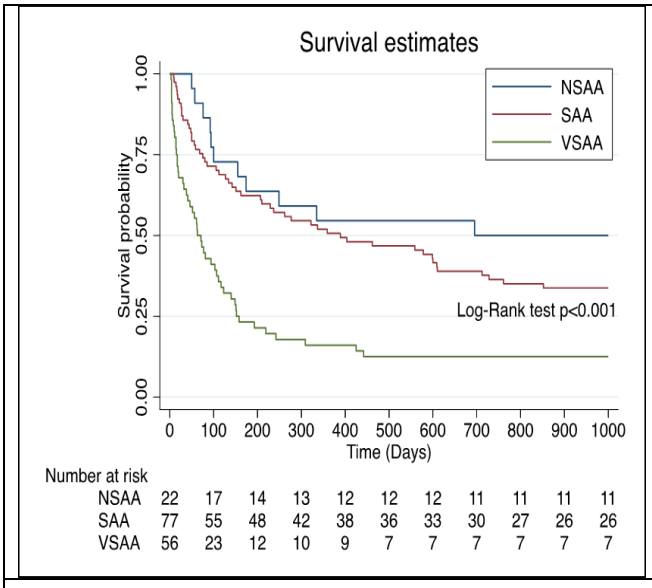


Figure 8: Kaplan Meier curve indicating overall survival of AA patients stratified by disease severity

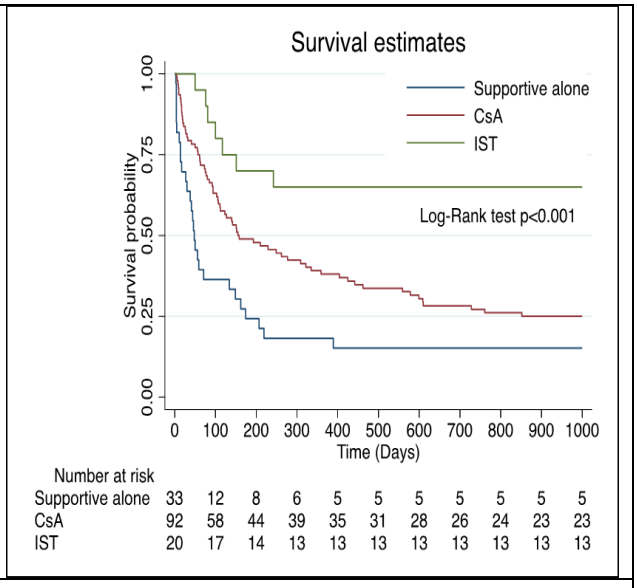


Figure 9: Kaplan Meier curve indicating overall survival of AA patients stratified by Treatment option.
Key: IST-Intensive IST with supportive treatment, CsA-Cyclosporine A with supportive treatment.

Table 3: Cox regression for factors associated with the survival of AA patients

Variable	cHR	*p*-value	aHR(95% CI)	*p*-value
Sex				
Female	Ref		Ref	
Male	1.05(0.72-1.54)	0.784	0.72(0.48-1.08)	0.112
Age group				
Age (per year)	1.00(0.99-1.01)	0.745	1.00(0.99-1.01)	0.929
Place of residence				
Dar es Salaam	Ref		Ref	
Out Dar es Salaam	1.01(0.68-1.48)	0.978	1.26(0.83-1.91)	0.278
Treatment options				
Intensive IST* + Supportive treatment	Ref		Ref	
Supportive treatment alone	5.48(2.25-13.37)	<0.001	6.40(2.61-15.73)	<0.001
CsA** + Supportive treatment	3.06(1.38-6.79)	0.006	3.25(1.42-7.45)	0.005
BMT*** (Abroad)	0.79(0.12-4.98)	0.800	0.41(0.05-3.70)	0.428
Others****	2.91(1.14-7.41)	0.026	4.20(1.51-11.69)	0.006
Disease severity				
Non severe Aplastic anemia	Ref		Ref	
Severe Aplastic anemia	1.37(0.73-2.57)	0.325	1.67(0.82-3.43)	0.159
Very Severe Aplastic anemia	3.31(1.75-6.25)	<0.001	4.77(2.23-10.22)	<0.001

Key:
cHR: crude Hazard Ratio, aHR: adjusted Hazard Ratio, Ref: Reference group
Intensive IST* include ATG and CsA, CsA**: Cyclosporine A, ATG: Antithymocyte globulin
BMT***: Bone marrow transplant
Others****include patients who received Androgen with or without CsA and eltrombopag

CHAPTER FIVE

5.0 DISCUSSION STRENGTHS AND LIMITATIONS

5.1 Discussion

This study is the first study to assess median survival in East Africa and Central Africa in a resource-limited setting for patients with idiopathic aplastic anemia (AA). It has highlighted the significant impact of intensive IST on improving patient outcomes. The findings underscore the critical benefits of intensive IST compared to supportive care alone in this region.

One of the key demographic observations in our study was the relatively young age of the patient cohort, with most individuals being under 30 years old and a median age of 23. This is similar to a South African study with a median age of 24.5 years (17). Unlike the biphasic age distribution seen in European countries, our findings suggest an unimodal distribution, similar to the Asian population (8,30,31). This difference can be attributed to the younger demographic structure of Tanzania, where the median age is around 18 years, while the median age in Europe is 44.5 years (32,33). This demographic skew means that any medical condition, including aplastic anemia, is more likely to be observed in younger individuals simply because they make up a larger portion of the population.

Our study also revealed a gender disparity, with a male-to-female ratio of 1.5:1. This is consistent with findings from other studies conducted in Sub-Saharan Africa and parts of Asia (11,13,34). However, the gender variance in AA is not universally consistent, as some studies have reported a nearly equal sex ratio, while others indicate a male predominance (18,30). The reasons behind this disparity remain unclear and warrant further investigation.

A significant finding in our study was the high prevalence of idiopathic AA, which constituted 27% of the cases. This prevalence is comparable to that reported in South Asian countries but differs from the lower rates (11% to 12.8%) observed in North America and Western India (35–37). The variance in prevalence may be influenced by

geographical and environmental factors, as well as the single-center nature of our study, which could have led to an underestimation.

The severity of AA at the time of diagnosis was another crucial aspect, with the majority of patients presenting with SAA or VSAA. This trend aligns with previous studies from the region but contrasts with findings from high-income countries where NSAA is more common at diagnosis (12,17,38). The predominance of severe cases in our study likely reflects late presentation, limited access to healthcare, socio-cultural beliefs and financial constraints faced by patients.

Over the past five years, treatment options for AA in Tanzania have improved significantly (12). Intensive IST is now available locally, although its use is still limited, with only 14.1% of patients receiving this regimen. Most patients continue to receive cyclosporine (CsA) with supportive care, and a significant proportion relies solely on supportive treatment. In Sub-Saharan Africa, South Africa is the only documented country offering ATG as intensive immunosuppressive therapy (13,17). In other countries, the cost and availability of ATG remain challenging (19,39,40). Since 2021, BMT procedures have been conducted at MNH, initially focusing on autologous stem cell transplants, while Benjamin Mkapa Hospital performs allogeneic BMT for sickle cell anemia (SCA) patients (41,42). In Sub-Saharan Africa, only 3 countries inclusive of Tanzania, South Africa and Nigeria have BMT centers but due to high cost, access to BMT services for the management of hematological conditions is limited (42–44).

The study's findings on median survival underscore the disparities in healthcare outcomes between resource-limited settings and high-income countries. The median survival time in our study was 158 days, significantly lower than the survival times reported in upper-middle and high-income countries, where median survival ranges from 19.2 to 150 months (8,21,45,46). The stark difference in survival outcomes is primarily due to the availability of definitive treatments in more developed regions, highlighting the need for improved access to advanced therapies in resource-limited settings.

Additionally, the study observed that patients receiving supportive treatment alone had the lowest median survival time, comparable to findings from Nigeria (11). Although not formally assessed, it was observed that some patients struggled with drug adherence to cyclosporine due to financial challenges, which may have contributed to the lower survival rates in patients receiving CsA alongside supportive care.

Patients diagnosed with NSAA demonstrated significantly longer survival times compared to those with SAA or VSAA. This trend aligns with similar observations from international studies, such as research conducted in China, where patients with NSAA also experienced better overall survival outcomes (38). The notable survival difference emphasizes the importance of disease severity in prognosis and treatment response

5.2 Strengths

- This study delves deeper into treatment modalities and their impact on survival outcomes. It provides valuable insights into the evolution of treatment options over time, particularly the availability of advanced therapies like intensive IST, highlighting their significant contributions to improved survival rates.
- The study goes beyond mere description and incorporates a longitudinal survival analysis and examines factors influencing survival outcomes. By providing detailed survival data it offers a more robust understanding of treatment outcomes, thereby enhancing the clinical relevance and applicability of the findings.

5.3 Limitations:

- As a single-center study conducted in Tanzania, the findings may not fully represent aplastic anemia treatment outcomes across diverse populations with different demographic and environmental contexts.
- The study does not systematically assess the impact of socioeconomic factors on treatment access and outcomes, and differences in treatment availability and accessibility over the study period may introduce variability in treatment effectiveness, complicating the interpretation of outcomes. Additionally, the fact that not all patients regularly adhered to treatment due to financial constraints, which could impact treatment outcomes, was not systematically addressed.

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

The findings highlight a predominantly young patient population with notable gender differences and a high prevalence of severe aplastic anemia at diagnosis. Despite advancements in treatment options, including the availability of intensive immunosuppressive therapy, the study shows that survival rates remain suboptimal, especially for those receiving supportive care alone and cyclosporine monotherapy. The results suggest further improvements are needed in treatment outcomes, particularly for severe cases, and emphasize the importance of early diagnosis and access to intensive therapies in improving patient survival.

6.2 Recommendations

- Given the availability of Intensive IST, we recommend its use as the definitive treatment for eligible AA patients. Additionally, hematopoietic stem cell transplantation (HSCT) should be considered for those meeting the criteria.
- Peripheral hospitals should promptly refer suspected AA cases to specialized centers for timely diagnosis and treatment.
- Future prospective studies should focus on assessing possible risk factors for AA, treatment outcomes, and factors influencing treatment choices to further enhance patient care and survival rates.

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APPENDICES

APPENDIX 1: FORM OF CONSENT

CONSENT TO TAKE PART IN THE RESEARCH ON PREVALENCE, DISEASE SEVERITY, TREATMENT OPTIONS AND MEDIAN SURVIVAL OF PATIENTS WITH APLASTIC ANEMIA WHO ATTENDED MUHIMBILI NATIONAL HOSPITAL, TANZANIA

NAME_____

MR NO: _____

AGE: _____

Greetings Sir/Madam

Gladys Nicholas Kaaya is my name, and I work as a resident practitioner in the MUHAS department of haematology and blood transfusion. I am conducting research on the prevalence; clinical, laboratory, therapy, and prognosis of aplastic anemia patients who visit MNH. I hereby ask for your cooperation.

The goal of this study: The purpose of the study is to determine the prevalence, disease severity, treatment options and median survival of patients with aplastic anemia who attended muhimbili national hospital

How to participate: Patients or a patient's relative who are willing to participate must sign a consent/assent form indicating that they are willing to do so. Patients or their next of kin will be given a brief interview to ask questions regarding the missing data from the records.

Confidentiality: Information extracted will be kept private and will only be used for this study and to provide future patients with Aplastic anemia with better care.

Costs: You won't be charged anything for taking part in this study.

Participation freedom and liberty to opt out of the study: Because participation in the study is voluntary, you are free to withdraw at any time.

Risk: Involvement in this study is not considered to pose any potential risks.

Benefits: Your participation will contribute to research on the prevalence of AA, the severity of the condition at diagnosis, available treatments, and the effectiveness of those treatments. This research will help us better understand the scope of the disease and advance the standard of care for AA patients as a whole.

STATEMENT OF THE INVESTIGATOR:

I, as the investigator, have informed the research subject about the significance and potential applications of this investigation.

Dated..... Signed……..

STATEMENT OF THE PARTICIPANT:

I voluntarily consent to participating in this study. I do this knowing exactly what the goals of the study are, as Dr. Gladys Kaaya has described to me.

Signed by the patient…….

Witness's signature……

Dated……

During the study, you can get in touch with the following people if you have any questions or concerns:

Muhimbili University of Health and Allied Sciences (MUHAS)

Department of Hematology & Blood Transfusion

P.O. Box 65001 Dar es Salaam

Principal Investigator: Dr. Gladys N. Kaaya.

Phone number: 0754296636

OR

The study's supervisor

Dr. Mwashungi Ally

Department of Hematology and BT

Mobile +255 653986798

Please get in touch with Dr. Nahya Masoud, Acting Director of Research and Publication (DRP) of MUHAS, P. O. Box 65001, Dar es Salaam, Tanzania, if you have any questions about your rights as a participant.

Email: drp.muhas.ac.tz, Fax: +255-022-2152489, and Telephone: +255-022-2152489.

Appendix 2: Fomu Ya Kuridhia Ushiriki

KURIDHIA KUSHIRIKI KATIKA UTAFITI KUHUSU WINGI, UKUBWA WA UGONJWA, UTARATIBU WA TIBA NA MATOKEO BAADA YA TIBA, KWA WAGONJWA WENYE APLASTIC ANEMIA WANAOTIBIWA MNH

MAJINA_____ NAMBA YA FAILI_____ UMRI WA MSHIRIKI_____

Kwako Bwana/Bibi, Majina yangu ni Gladys Nicholas Kaaya, daktari na pia ni mwanafunzi katika shahada ya uzamili kutoka chuo cha afya na sayansi shirikishi Muhimbili, ninafanya utafiti kuhusu wingi, ukubwa wa ugonjwa, utaratibu wa tiba na matokeo baada ya tiba, kwa wagonjwa wenye ugonjwa wa aplastic anemia wanaotibiwa MNH.

Nia ya utafiti: Utafiti huu unalenga kuangalia wingi, ukubwa wa ugonjwa, utaratibu wa tiba na matokeo baada ya tiba, kwa wagonjwa wenye aplastic anemia, hii itasaidia kutambua ukubwa wa tatizo hilo hivyo kuboresha mfumo wa matibabu.

Namna ya Kuwa mshiriki: Utahitajika kujaza fomu ya kuridhia ushiriki, au kupatiwa msaada wa kujaza na ndugu (wale watakaoshindwa au walokuwa washafariki), Utafiti huu utahusisha mahojiano mafupi kwa wagonjwa au ndugu kwa ajili ya kupatikana kwa taarifa zitakazo kosekana kwenye rikodi.

Kutunzwa kwa Siri: Usiri utazingatiwa katika utunzaji wa taarifa zote zitakazohusika kwenye utafiti huu nakutumika kuboresha huduma za wagonjwa wenye aplastic anemia.

Gharama za Ushiriki: Mshiriki hatatozwa gharama yeyote katika kushiriki kwenye utafiti huu

Uhiari wa Kushiriki/Kujitoa: Ushirika wako na uwezo wa kujitoa ni wa hiari. Maamuzi yako hayatazuia haki yako ya matibabu

Athari za ushiriki: Mshiriki hatopata athari yeyote kwa kushiriki kwenye utafiti.

Faida za ushiriki: Kushiriki kwako kutasaidia kutambua ukubwa, stage ya ugonjwa wanayogundulika nayo wagonjwa, utaratibu wa tiba na matokeo baada ya tiba, kwa wagonjwa wenye aplastic anemia wanaotibiwa MNH. Hili itasaidia katika kuboresha huduma za tiba

TAMKO LA MTAFITI Mimi kama mtafiti nimempa maelezo mshiriki juu ya utafiti huu.

Sahihi (Mtafiti)……. Tarehe……..

TAMKO LA MSHIRIKI

Nimesoma na kuelewa yaliyoko kweye fomu hii na nakubali kushiriki utafiti huu.

Sahihi (Mshiriki)……

Sahihi (Shahidi)……

Tarehe……

Mawasiliano ya Wahusika kama kutakuwa na swali ama mapendekezo juu ya utafiti huu.

Dr. Gladys Nicholas Kaaya

Chuo kikuu cha afya na sayansi Shirikishi Muhimbili

Idara-Hematolojia

SLP 65001 DSM

SIMU: 0754296636

AU

Dr. Mwashungi Ally
Msimamizi wa utafiti huu.
Chuo kikuu cha afya na sayansi shirikishi Muhimbili
Idara-Hematolojia
SLP 65001 DSM
SIMU 0653986798

Endapo utakuwa na maswali juu ya haki zako kama mshiriki wa tafiti hii, wasiliana na:

Kaimu mwenyekiti wa kamati ya tafiti na matoleo chuoni
Dr Nahya Masoud
Chuo Kikuu cha afya na sayansi shirikishi Muhimbili
SLP 65001 DSM
SIMU 022-2152489

Appendix 3: Data collection tool for aa (English Version)

Study No …… Patient Reg No……..

DEMOGRAPHIC HISTORY

1. Date of birth…..……
2. Age at Diagnosis …….....
3. Gender……..
4. Address ……..
5. Profession/Occupation …….
6. Insurance status (insured/not insured)……

CLINICAL CHARACTERISTICS;

1. Date of diagnosis of AA ……
2. Anemia ……..…..(yes/no)
3. Fever…….....(yes/no)
4. Tendencies to bleed …….(yes/no)
5. Jaundice……..(yes/no)
6. Other (be specific)…….....
7. History of packed red cell transfusion……(yes/no)
8. History of platelet concentrate transfusion……. (yes/no)

LABORATORY TESTS

1. HB……
2. ANC……
3. ARC ……
4. PLT Count ……
5. Viral Screen: Human Immunodeficiency virus…… Hepatitis B.....…(Positive/Negative)

BMA Report…….Trephine biopsy Report…….

TREATMENT OFFERED

1. Supportive treatment(Blood transfusions, Antimicrobials) alone
2. CsA with supportive management
3. Androgen with supportive management
4. Intensive IST (CsA and ATG with supportive management)
5. BMT
6. Other (be specific)……

SURVIVAL OUTCOME:

1. Alive
2. Dead – Date……

Appendix 4: Data Collection Tool for Aa (Swahili Version)

Dodoso ya…… Namba ya faili…….

TAARIFA ZA MGONJWA:

1. Tarehe ya kuzaliwa…….
2. Umri wakati wa kugundulika ugonjwa……..
3. Jinsia……..
4. Mahali unapotoka…….
5. Kazi yako……..
6. Bima ya afya (ndiyo/hapana)…….

TAARIFA ZA UGONJWA:

1. Tarehe ya kugundulika ugonjwa wa AA……..
2. Kupungukiwa damu……..(ndiyo/hapana)
3. Homa……(ndiyo/hapana)
4. Dalili za kutokwa na damu……(ndiyo/hapana)
5. Manjano…….(ndiyo/hapana)
6. Nyingine(Elezea)……
7. Historia ya kuongezewa damu nyekundu…….(ndiyo/hapana)
8. Historia ya kuongezewa chembe sahani……(ndiyo/hapana)

VIPIMO VYA MAABARA:

1. HB…….
2. ANC……
3. ARC……..
4. PLT …….....
5. Uchunguzi wa virusi: Virusi vya UKIMWI……Virusi vya homa ya ini……..(Ipo/haipo)

Ripoti ya BMA…….Ripoti ya Trephine Biopsy…….

MATIBABU ULIOPATA:

1. Kupunguza athari za ugonjwa(mfano kuongezewa damu, kupewa dawa za kuua vinyemelea vya maambukizi) peke yake
2. Cyclosporin na za kuimarisha matibabu
3. Androgen (dawa za homoni) na za kuimarisha matibabu
4. Tiba ya Kina (Cyclosporin na ATG na za kuimarisha matibabu)
5. Kupandikizwa uroto au kupewa rufaa kwenda nje ya nchi kwa ajili ya kupandikiza uroto
6. Nyingine (Elezea)

MATOKEO:

1. Hai
2. Kifo….. Tarehe ya kifo……

Appendix 5: Approval for Clearance

UNITED REPUBLIC OF TANZANIA

MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

OFFICE OF THE DIRECTOR – RESEARCH, PUBLICATIONS AND INNOVATION

Ref. No.DA.282/298/01.C/1981 Date: 28/11/2023

MUHAS-REC-11-2023-1981
GLADYS NICHOLAS KAAYA
COLLEGE OF MEDICINE
MUHAS

RE: APPROVAL FOR ETHICAL CLEARANCE FOR A STUDY TITLED: PREVALENCE, DISEASE SEVERITY, TREATMENT OPTIONS AND MEDIAN SURVIVAL OF PATIENTS WITH APLASTIC ANEMIA WHO ATTENDED MUHIMBILI NATIONAL HOSPITAL

Reference is made to the above heading,

I am pleased to inform you that the Chairman has on behalf of the University Senate, approved ethical clearance of the above-mentioned study, on recommendations of the Senate Research and Publications Committee meeting accordance with MUHAS research policy and Tanzania regulations governing human and animal subjects research.

APPROVAL DATE: 28/11/2023
EXPIRATION DATE OF APPROVAL: 28/11/2024

STUDY DESCRIPTION:
Purpose:

The purpose of this retrospective cohort study is to to determine prevalence, disease severity, treatment options and median survival of patients with aplastic anemia who attended MNH from 2018 to 2023

The approved protocol and procedures for this study is attached and stamped with this letter, and can be found in the link provided:
https://irb.muhas.ac.tz/storage/Certificates/Certificate%20-%2014801.pdf and in the MUHAS archives.

The PI is required to:

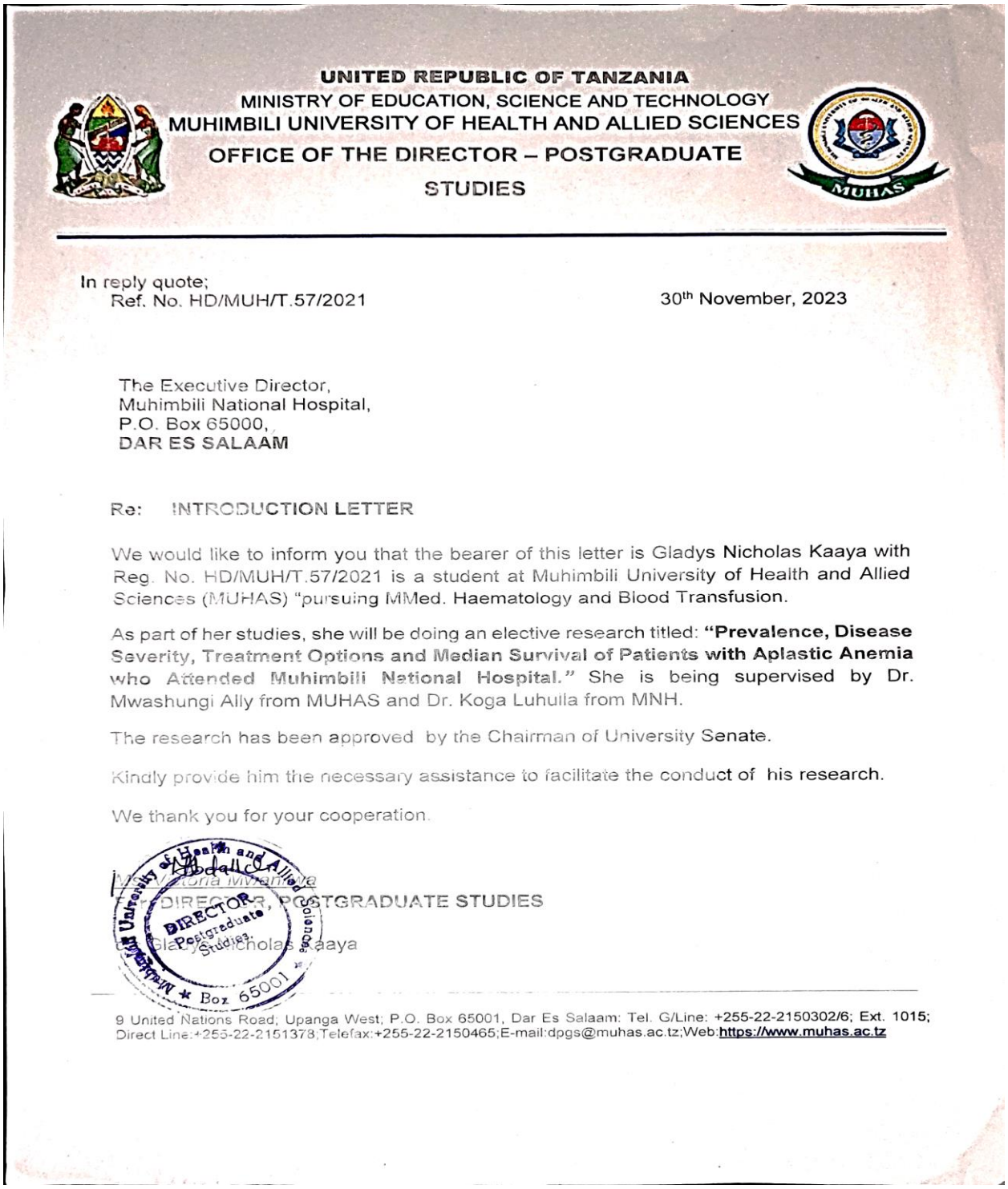
1. Submit bi-annual progress reports and final report upon completion of the study.
2. Report to the IRB any unanticipated problem involving risks to subjects or others including adverse events where applicable.
3. Apply for renewal of approval of ethical clearance one (1) month prior its expiration if the study is not completed at the end of this ethical approval. You may not continue with any research activity beyond the expiration date without the approval of the IRB. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.
4. Obtain IRB amendment (s) approval for any changes to any aspect of this study before they can be implemented.
5. Data security is ultimately the responsibility of the investigator.
6. Apply for and obtain data transfer agreement (DTA) from NIMR if data will be transferred to a foreign country.
7. Apply for and obtain material transfer agreement (MTA) from NIMR, if research materials (samples) will be shipped to a foreign country,
8. Any researcher, who contravenes or fail to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine as per NIMR Act No. 23 of 1979, PART III section 10 (2)
9. The PI is required to ensure that the findings of the study are disseminated to relevant stake holders.
10. PI is required to be versed with necessary laws and regulatory policies that govern research in Tanzania. Some guidance is available on our website https://drp.muhas.ac.tz/.

Dr. Nahya Salim Masoud,

Chairperson, MUHAS Research and Ethics Committee



Appendix 6: Introduction Letter



UNITED REPUBLIC OF TANZANIA
MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY
MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
OFFICE OF THE DIRECTOR – POSTGRADUATE STUDIES

In reply quote;
Ref. No. HD/MUH/T.57/2021

30th November, 2023

The Executive Director,
Muhimbili National Hospital,
P.O. Box 65000,
DAR ES SALAAM

Re: INTRODUCTION LETTER

We would like to inform you that the bearer of this letter is Gladys Nicholas Kaaya with Reg. No. HD/MUH/T.57/2021 is a student at Muhimbili University of Health and Allied Sciences (MUHAS) "pursuing MMed. Haematology and Blood Transfusion.

As part of her studies, she will be doing an elective research titled: **"Prevalence, Disease Severity, Treatment Options and Median Survival of Patients with Aplastic Anemia who Attended Muhimbili National Hospital."** She is being supervised by Dr. Mwashungi Ally from MUHAS and Dr. Koga Luhuila from MNH.

The research has been approved by the Chairman of University Senate.

Kindly provide him the necessary assistance to facilitate the conduct of his research.

We thank you for your cooperation.

Mary Viola Mwaiteleke
FOR: DIRECTOR, POSTGRADUATE STUDIES

Ms. Gladys Nicholas Kaaya

Muhimbili University of Health and Allied Sciences
DIRECTOR
Postgraduate Studies
Box 65001

9 United Nations Road; Upanga West; P.O. Box 65001, Dar Es Salaam: Tel. G/Line: +255-22-2150302/6; Ext. 1015; Direct Line:+255-22-2151378;Telefax:+255-22-2150465;E-mail:dpgs@muhas.ac.tz;Web:https://www.muhas.ac.tz

Appendix 7: Permission to Collect Data

THE UNITED REPUBLIC OF TANZANI

MINISTRY OF HEALTH

MUHIMBILI NATIONAL HOSPITAL

In reply please quote;

Ref. No.: MNH/CRTCU/Perm/2023/571 Date: 06th December, 2023

Head of Department
- Medical Records
-Central Pathology Laboratory
Muhimbili National Hospital

RE: PERMISSION TO COLLECT DATA AT MNH

Name of Student	**Gladys N. Kaaya**
Title	**" The Prevalence , Disease Severity, Treatment Options And Median Survival Of Patients With Aplastic Anaemia Who Attended MNH"**
Institution	Muhimbili University of Health and Allied Scie
Supervisor	Dr. Mwashungi Ally (MUHAS)
Co-supervisor	Dr. Koga Luhulla (MNH)
Period	06th December, 2023 to 06th March, 2024

Approval has been granted to the above principal investigators to collect data at MNH. Dissemination of study findings at MNH shall be overseen by **Dr. Koga Luhulla (MNH)** supervisor.

Kindly ensure the named principal investigator abide to the ethical principles and other conditions of the research approval.

Sincerely,

Dr. Charles Pallangyo
For: Head of Clinical Research, Training and Consultancy Unit

HEAD, TEACHING, RESEARCH & CONSULTANCY UNIT * MUHIMBILI NATIONAL HOSPITAL * DAR-ES-SALAAM

c.c DICT
cc DCSS
c.c **Gladys Kaaya**
c.c **Dr. Koga Luhulla**

Upanga West, Kalenga Street, Plot No. 10480/3, P.O. BOX 65000, Dar es Salaam, Tanzania.
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