PLATELET COUNTS IN PATIENTS WITH RHEUMATOID ARTHRITIS AT THE KENYATTA NATIONAL HOSPITAL, NAIROBI, KENYA

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DECLARATION

STUDENT'S DECLARATION

I **Dr. Beth Muthoni Mbuthia** declare that this dissertation is my original work and that to the best of my knowledge it has not been presented to any other institution.

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This dissertation for Master of Medicine in Internal Medicine has been submitted to the University of Nairobi with our approval as supervisors.

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DEDICATION

This work is dedicated to my family who have been an inspiration for me to complete my studies. My husband Patrick has been an ever present support and my two children Michelle and Jeremy are always such a delight.

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LIST OF ABBREVIATIONS

ACPA: Anti-citrullinated protein antibody

ACR: American college of Rheumatism

CRP: C-reactive protein

DAS: Disease activity score

DAS 28: Disease activity score 28 joints

DMARDS: Disease modifying anti-rheumatic drugs

EPO: Erythropoietin

ESR: Erythrocyte Sedimentation Rate

HB: Haemoglobin

IL: Interleukin

JRA: Juvenile Rheumatoid arthritis

KNH: Kenyatta National Hospital

MCH: Mean cell haemoglobin

MCV: Mean corpuscular volume

MPC: Mean platelet count

NSAID: Non steroidal anti-inflammatory drugs

RA: Rheumatoid arthritis

RF: Rheumatoid factor

ROPC: Rheumatology outpatient Clinic

TPO: Thrombopoeitin

UON: University of Nairobi

ABSTRACT

***Background*:** Rheumatoid arthritis (RA) is a disease associated with significant morbidity and mortality. Thrombocytosis is one of the haematological manifestations of rheumatoid arthritis that occurs in active disease. Platelet counts may vary depending on disease activity. The variation has been shown to correlate with clinical and laboratory indices of disease activity in RA. Occasionally patients with RA may have drug induced thrombocytopenia.

Objectives of the study: To determine the relationship between platelet counts and clinical disease activity in patients with RA at Kenyatta National Hospital (KNH).

Study design and setting: A cross-sectional descriptive study conducted in patients with RA attending the KNH Rheumatology Outpatient Clinic (ROPC).

Methods: Patients presenting to the clinic were screened and those meeting the inclusion criteria recruited into the study. Consecutive sampling technique was done. *A* targeted history was obtained, following which a physical exam was done on the recruited patients. The patients' platelet counts were measured using Abbot Cell Dyn 1300 counter. The patients' erythrocyte sedimentation rate (ESR) was measured using the Wintrobe's method. The patients' clinical disease activity was assessed using the DAS 28 score and recorded.

RESULTS: One hundred and four patients were recruited over the 6 months period between November 2010 and April 2011. Females were 90(86.5%) and 14(13.5%) were males giving a male to female ratio of 1:6.4. The mean age of the patients was 48years. Regarding medication use, 75% of the patients were on disease modifying anti-rheumatic drugs (DMARDs), 72.1% on non-steroidal analgesics (NSAIDs) and 46.2% on steroids. The mean platelet count was 313.2 ±SD94 x 10^9/L with a range of 152-611 x 10^9/L. Only 15 (14.4%) had thrombocytosis (>400x 10^9/L). No case of thrombocytopenia was recorded. Ninety two patients had active disease (88.5%) while 10 (11.5 %) were in remission. Among those with active disease, 10(9.6%) had mild disease, 51(49%) moderate disease and 31(29.6%) high disease activity. The DAS28 score was not significantly different between those who had thrombocytosis and those who had normal platelet counts (p=0.413). However, HB, MCV and MCH were significantly lower in those with thrombocytosis (P = 0.02, 0.002, 0.03

respectively). No correlation was found between platelet counts and clinical disease activity (DAS28).

Conclusion. The prevalence of thrombocytosis was less than that reported in majority of the studies in other set-ups. Platelet counts are poor indicators of disease activity in our patients with RA as no relationship was found between platelet counts and disease activity in patients with RA in KNH.

1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 RHEUMATOID ARTHRITIS

Rheumatoid arthritis is a chronic systemic inflammatory disorder characterised by deforming symmetrical polyarthritis often leading to joint destruction, deformity and loss of function. Extra-articular features and systemic symptoms can commonly occur and may antedate the onset of joint symptoms **[1].** Chronic pain, disability and increased mortality are common sequelae. High standardised mortality rates have been observed in the RA population compared with the general population **[2,3].**

Rheumatoid arthritis has a worldwide distribution with an estimated prevalence of 1 to 2%. Prevalence increases with age, approaching 5% in women over age 55. Both incidence and prevalence of rheumatoid arthritis are two to three times greater in women than in men. Although rheumatoid arthritis may present at any age, patients most commonly are first affected in the third to sixth decades **[1].**

While no data is available on the prevalence of rheumatoid arthritis in Kenya; studies have shown an increase in the number of cases diagnosed over the years in Kenyatta National Hospital **[4,5].**

1.2 THROMBOCYTOSIS

Thrombocytosis is a platelet count exceeding the top of the normal range of 400-450 $x10^9$/L **[6].** However, several studies have shown Africans to have lower platelets compared to Caucasians **[7-10].** Bain *et al* in London found blacks to have lower mean platelet counts (MPCs) compared to Caucasians at 183 $x10^9$/L vs 211$x10^9$/L respectively ($P<0.001$) **[7].** Essein *et al* in Zambia found the MPC to be 199 $x10^9$/L with a range of 81- 324 $x10^9$/L in Africans and a MPC of 313 $x10^9$/L and range of 193-433 $x10^9$/L in Caucasians living in a similar environment **[8].** Mukibi *et al* in Kenya found the MPCs in normal healthy adults to be 211 $x10^9$/L with a 95% range of 114- 300 $x10^9$/L **[9].** More recently in a study of healthy blood donors in Kenya, Rajab *et al* found a MPC of 242±86 $x10^9$/L (95% range 68-414 $x10^9$/L) **[10].** These and various other studies have demonstrated that Africans have lower platelet counts. This maybe important in interpreting platelet counts in African population because platelet ranges considered to be normal may actually be elevated.

Thrombocytosis can either be primary or secondary. Primary thrombocytosis is due to a failure to regulate the production of platelets (autonomous production) and is a feature of a number of myeloproliferative disorders. Secondary (reactive) thrombocytosis is the most common cause of thrombocytosis in general medical populations and is secondary to a number of conditions. The most common causes are tissue damage due to major surgery, infection, cancer, and chronic inflammation **[11]**

Under normal conditions, the regulation of platelet production from bone marrow megakaryocytes involves the binding of free plasma thrombopoietin to megakaryocytes, a process that stimulates megakaryocytopoiesis and hence leads to platelet production. In secondary (reactive) thrombocytosis, the underlying disease stimulates the synthesis of increased amounts of thrombopoietin possibly mediated by other cytokines, such as interleukin-6, leading to increased megakaryocytopoiesis and platelet production **[12].**

1.3 THROMBOCYTOSIS IN RHEUMATOID ARTHRITIS

Thrombocytosis is among one of the haematological manifestations of rheumatoid arthritis. Studies have shown that the platelet count correlates with disease activity-being high in active disease and reducing as disease activity goes down. Thrombocytosis has also been shown to correlate with other markers of disease activity such as erythrocyte sedimentation rate (ESR), plasma viscosity and C-reactive protein (CRP) **[13,14,28]**

1.3.1 Prevalence of Thrombocytosis In patients with RA.

Studies have demonstrated thrombocytosis in RA with prevalence ranges from 16% to 51% in different studies. A study in Finland by Selroos found thrombocytosis in a third of 115 patients with rheumatoid arthritis **[13]** while Hutchingsons *et al* in Bristol England found a prevalence of 51% **[14].** Dixon et *al* found thrombocytosis in 45% of patients with RA **[15].** A more recent study in Saudi Arabia showed thrombocytosis to be the second commonest extra-articular manifestation of RA with a prevalence of 16% **[16].**

Notably, apart from the Saudi Arabia study, the other studies were done earlier before current widespread use of disease modifying anti-rheumatic agents (DMARDs). No other study has been done in the recent past in this era of early DMARD use in RA. A literature search did not reveal any study done in Africa on the same.

1.3.2 Mechanisms of Thrombocytosis In RA

The exact pathogenetic mechanism(s) that cause increased platelet counts in RA are still unknown. However several possible mechanisms have been proposed as possible causes of the increased platelet count.

1.3.2.1 Decreased Platelet Survival

Some studies have shown decreased platelet survival in RA due to increased platelet destruction and consumption. In 1971, Garg and Amorosi *et al* demonstrated compensated thrombocytolytic states in which shortened platelet survival were accompanied by increases in megakaryocyte maturation **[17]**. Hutchingson *et al* studied selenomethionine labelled platelets and found the platelet survival to be decreased in RA **[14]**. While using a different technique of indium labelled platelets, Farr *et al* also demonstrated decreased platelet survival **[18]**. While one would expect to find a low platelet count with the decreased platelet survival; paradoxically these patients' bone marrow overcompensate leading to levels of platelets counts of upto $1{,}000\times10^9$/L. Platelets are found localised in regions of actively inflamed joints but not in inactive ones. Notably, patients with thrombocytosis have more platelets in their synovial fluid compared to those without **[19]**. Thus, the increase in platelet count probably represents marrow overproduction in response to the increased consumption. The decreased platelet survival is not seen in other inflammatory conditions with reactive thrombocytosis and thus this maybe specific for RA **[18]**.

1.3.2.2 Increased Erythropoeitin Levels

Thrombocytosis in RA could also be related to the anemia of chronic disease found in RA. An inverse correlation has been found between high platelet count and low haemoglobin levels **[13,14]**. It has been argued that thrombopoeitin maybe related chemically to erythropoietin as chronically anaemic patients with persistent reticulocytosis and increased EPO levels have higher than normal platelet counts**[20]**. Similiarly, if EPO levels are increased in anemic rheumatoid patients, then thrombocytosis could result.

1.3.2.3 Role of Cytokines

Cytokines are thought to play a major role in the thrombocytosis of RA. Particular interleukins, namely interleukin IL-6, IL-4 and IL-1, with pro-inflammatory mediator activities have also been shown to be involved in the regulation of megakaryocytopoiesis **[12,21]**.A Turkish study which compared cytokine levels of patients with thrombocytosis due to myeloproliferative disorders, polycythemia vera and RA; serum interleukin

concentrations in patients with MPD and thrombocythemia were either suppressed or similar to those of normal subjects, whereas IL-6, IL-1 beta and IL-4 levels were increased in RA patients with reactive thrombocytosis **[22]**. Hollen *et al* also compared mean serum IL-6 levels in patients with primary thrombocytosis and those with reactive thrombocytosis and found a marked difference (2.19U/ml versus 38.3U/ml;p <0.001) **[23]**. Ceresa *et al* in a study of thrombocytosis of inflammatory disorders found serum IL-6 levels positively correlated with IL-6 demonstrating the important role IL-6 plays in reactive thrombocytosis **[24]**.

1.3.2.4 Role of Thrombopoeitin

Thrombopoietin also plays a minor role in the thrombocytosis of RA. Thrombopoietin levels are usually elevated mildly in patients with mild thrombocytosis but suppressed in patients with marked thrombocytosis. In patients with markedly increased platelet count serum TPO levels might be regulated by increased platelet mass via receptor-mediated uptake and metabolism **[25]**. Thus its role is limited. IL-6, whose levels are elevated in RA has been found to up-regulate the expression of thrombopoietin messenger RNA (mRNA) in the liver and thus plays a role in the elevation of thrombopoietin **[25]**.

1.3.2.5 NSAID-induced gastrointestinal bleeding

Thrombocytosis is a feature of chronic blood loss and could be secondary to analgesic-induced occult gastrointestinal bleeding, particularly in patients with active disease. However, Hutchinson *et al* found that, although there was an inverse correlation between high platelet counts and low haemoglobin, thrombocytosis was not necessarily associated with gastrointestinal blood loss. Patients that had positive occult blood did not all have thrombocytosis **[14]**.

1.3.3 Relationship of thrombocytosis to disease activity

Thrombocytosis has been shown to have consistent correlation with disease activity in different studies. Hutchingson *et al* in a study of 75 patients with RA of whom 39 had thrombocytosis, compared those with normal platelet count to those with thrombocytosis. Disease severity and activity was assessed by presence of morning stiffness, grip strength joint score and presence of extra-articular manifestations. The laboratory tests included peripheral blood count, rheumatoid factor and plasma viscosity. Platelet and fibrinogen kinetics were also studied. Plasma viscosity, haemoglobin levels and disease activity were compared to the platelet count. The mean plasma viscosity was significantly increased in

patients with thrombocytosis ($p<0.01$) while there was a highly significant inverse relationship between platelet count and haemoglobin concentration ($p<0.001$) **[14].**
A direct correlation between platelet levels and disease severity was found ($p<0.001$). Further evidence that thrombocytosis is related to disease activity was seen in some patients by a fall in platelet levels to normal when the disease was suppressed by steroids. It was noted that extra-articular manifestations tended to occur in patients with thrombocytosis **[14].**

In addition to correlation with disease activity, Selroos in a similar study also observed that platelet count also correlated with anemia, leucocytosis and rheumatoid factor in these patients **[13].**

Later,Farr *et al* conducted two cross-sectional studies and one longitudinal study that also showed that platelet counts correlated with both clinical and laboratory parameters of disease activity. The first cross-sectional study examined the relationship between platelet count and the following parameters of disease activity: total articular index,erythrocyte sedimentation rate (ESR),haemoglobin (Hb) level, white cell count (WBC),albumin and immunoglobulins in 130 patients. The results showed a statistically significant correlation between platelet count and 8 of the 9 parameters such as ESR ($r=0.407;p<0.01$) and HB (-0.405; $p<0.01$) among others **[18].**

The second cross-sectional study involving 131 patients also included other acute phase proteins in addition to those above. This too showed a statistically significant correlation between 11 of the 14 laboratory tests studied such as ESR ($r=0.61$ or more;$p<0.001$), plasma viscosity ($r=0.53$ or more;$<p<0.001$) and CRP ($r=0.71$ or more;$p<0.001$) **[18]** .

In the longitudinal study, 15 patients were followed up for 3-4 years. The platelet counts were followed in relation to changes in disease activity using total articular index,rheumatoid factor levels, serum alkaline phosphatase, ESR and CRP. In 9 of the patients the platelet counts also correlated with the various markers as above. The correlation between platelet count and ESR was $r=0.36$ or more;$p<0.05$ **[18].**

It has also been shown that during clinically active stages of RA, patients may present with relatively increased platelet counts, which may decline in remission period by different treatment modalities. In a recent Turkish study by Yacizi *et al*, 97 patients were followed up for 6 months after diagnosis of RA. Their platelet counts and inflammatory markers were taken before and after the treatment and disease activity assessed with the DAS28. Notably,

at baseline values their platelet counts were significantly higher than the controls at 307±99 $\times 10^9$/L in RA and 258±58$\times 10^9$/L in controls. At the end of the treatment the mean platelet count was 275 $\times 10^9$/L but unchanged in the control group. The mean DAS28 score was 5.96±0.95 at baseline and decreased to 3.87±1.63 ($p<0.001$) **[27].** Yacizi also correlated platelet counts and mean platelet volume to disease activity. In contrast to earlier studies, he found no correlation between platelet counts and disease activity but the mean platelet volume positively correlated with disease activity. Notably Yacizi used the DAS 28 to assess disease activity in contrast to earlier studies where no standardised measure of disease activity existed.

In Sweden, Milavonic carried out a longitudinal study over 2 years in RA patients on treatment. Platelet counts and other markers of disease activity such as CRP were recorded at the start of the study. The patients were put on treatment and these parameters repeated after two years during disease remission. The initial platelet counts were 365±78$\times 10^9$/L and after two years they were 312±55$\times 10^9$/L. He also found that platelet count and CRP levels correlated in active disease (r 0.7;$p<0.01$)**[28]**.

A recent Chinese study found the platelet count correlated with the severity of cartilage erosions in RA. Four hundred and thirty six patients with RA had their wrist joints X-rayed and cartilage erosions graded. This was correlated to platelet count among other factors. Results showed that age, disease course, red blood cell (RBC) and platelet (PLT) counts were found to be correlative factors with cartilage erosion in multiple linear regression analysis **[29].**

Platelet count has also been found to be a useful parameter in JRA. In Norway, Endressen *et al* did a study on children with JRA. They correlated platelet count with disease activity and the presence of amyloidosis. The median platelet count in patients with active disease was 327$\times 10^9$/L (173-937$\times 10^9$/L) while in those with inactive disease it was 271$\times 10^9$/L (88-779$\times 10^9$/L); $p<0.05$. A high platelet count was also associated with the presence of amyloidosis. The mean platelet count in these patients was 495$\times 10^9$/L (288-937$\times 10^9$/L); $p<0.01$. Significant positive correlation was found between the platelet count and ESR ($r=0.57;p<0.0001$) while the platelet count and Hb were negatively correlated ($r=-0.60;p<0.0001$).It was found that platelets can also serve as an additional parameter of disease activity in these patients and could predict the development of amyloidosis **[30].**

A more recent study was carried out in Taiwannese children with the aim of finding out factors affecting clinical and therapeutic outcomes in JRA. Various laboratory parameters including platelet count were recorded at diagnosis. After a period of treatment with NSAIDs and DMARDs, the patient were classified into groups as follows; those who went into remission (Group 1), those who relapsed (Group2) and those who were drug dependent (Group3). A comparison of the groups revealed the initial mean platelet count in Group1 was 369×10^9/L while in Group 3 it was 467×10^9/L ($p<0.026$) at diagnosis. It was therefore concluded that among other factors thrombocytosis at diagnosis was related to response to treatment in JRA **[31]**.

1.3.4 Consequences of thrombocytosis in RA

Though rare, there have been few cases of thromboembolic phenomenon complicating thrombocytosis in RA. A case was reported in Israel of a patient with rheumatoid arthritis complicated by excessive thrombocytosis and recurrent thromboembolic events. The platelet count correlated well with disease activity and thrombosis occurred when thrombocytosis was marked. The patient died from massive thrombosis of the aorta despite treatment with anticoagulants, corticosteroids, and azathioprine **[32]**.

Pines *et al* too reported a 71-year old patient suffering from long-standing seropositive and nodular rheumatoid arthritis with severe pulmonary involvement who during an exacerbation of her disease and following the appearance of thrombocytosis, several episodes of transient ischemic attacks occurred. The neurological manifestations were right facial nerve paralysis, paraesthesia of the right cheek and dysarthria. The patient was treated successfully with antiaggregants, anticoagulants and busulfan **[33]**.

1.3.5 Management of thrombocytosis in rheumatoid arthritis

Effective treatment and control of disease is associated with decrease of platelet count or return to normal in cases of thrombocytosis **[13]**. Anticoagulants may be necessary rarely in cases of embolic phenomenon as cited above **[32, 33]**.

1.4 PLATELETS AND DRUGS USED IN TREATMENT OF RHEUMATOID ARTHRITIS

Drugs used in treatment of rheumatoid arthritis may cause thrombocytopenia (platelets less than 150×10^9/l). This is especially seen with DMARDs **[34]**. The drug most implicated is

methotrexate. Methotrexate causes bone marrow suppression and thrombocytopenia may occur in isolation or as part of a pancytopenia.

The prevalence of thrombocytopenia induced by methotrexate in RA has been found to be low as the doses used in RA are very low. In an Indian study by Buhroo *et al*, only 2 out of 245 patients had thrombocytopenia and this occurred as part of a pancytopenia. The patients had been on methotrexate for a period ranging from 6 months to 7 years **[33]**.

Another Japanese study looking at cytopenias associated with low dose methotrexate found only 0.8% patients had thrombocytopenia **[36]**. On the higher side, Franck *et al* in a retrospective study reviewed the records of 315 patients with rheumatoid arthritis (RA) treated with low-dose methotrexate (MTX) and found a prevalence of 3.1%. The age of these patients (51 +/- 12.6 years) did not correlate with thrombocytopenia ($r = 0.211$, $p > 0.05$)**[34]**.

Gold salts can cause an immune mediated thrombocytopenia by inducing autoantibody production. The induced antibody reacts with platelets even in the absence of the drugs. They cause thrombocytopenia in 1% of the patients on gold therapy **[37]**

Though rare, NSAIDs can cause thrombocytopenia by inducing a drug dependent antibody that binds to membrane protein only in the presence of soluble drug **[38]**. NSAIDs may increase the occurrence of thrombocytopenia when co-administered with other agents such as methotrexate **[34]**.

Sulphasalazine may also rarely cause thrombocytopenia through bone marrow depression or auto-antibody production **[39]**.

1.5 COMMONLY USED DISEASE MARKERS IN RA

1.5.1 Erythrocyte Sedimentation Rate (ESR)

The test measures the distance that erythrocytes have fallen after one hour in a vertical column of anticoagulated blood under the influence of gravity **[40]**. The ESR is largely a measure of fibrinogen and globulins in the blood. The amount of fibrinogen in the blood directly correlates with the ESR **[41]**

In rheumatoid arthritis, the ESR tends to reflect clinical disease activity in the absence of other co-morbidities. Monitoring ESR levels thus helps in assessing response to therapy. Persistently raised ESR levels are associated with severe disease and progressive joint damage **[42]**.

ESR is considered a less specific measure of the acute-phase response than CRP because it is influenced by many factors other than systemic inflammation, including age, sex, red-blood-cell morphology, hemoglobin concentration, and serum levels of immunoglobulins and rheumatoid factor. Thus, the trend in the recent years has been in favour of CRP. However,ESR is less expensive, widely available and less time consuming compared to CRP **[43,44]**. It thus remains a useful test especially in poor resource set-ups.

The ESR is useful in calculating the DAS score **[45].** Positive correlation has been found between platelet counts and ESR levels in patients with active RA **[18]**.

1.5.2 C-Reactive Protein (CRP)

C - reactive protein belongs to the pentraxin family of proteins, so-called because it has five identical subunits, encoded by a single gene on chromosome 1, which associate to form a stable disc-like pentameric structure. CRP is an acute-phase protein produced by the liver in response to various cytokines, including interleukin IL-6, IL-1 and tumor necrosis factor (TNF)-alpha during acute injury, infections, inflammatory stimuli, and malignant disease **[46]**.

Though considered to be more specific than ESR, studies have shown that both test complement each other in monitoring disease activity. This is because one test maybe normal while the other is abnormal despite clinically active disease **[47,48]**

Farr *et al* and Milavonic correlated CRP levels and platelet counts and found significant correlation in active disease **[18, 28].**

1.6 CLINICAL ASSESSMENT OF DISEASE ACTIVITY

DISEASE ACTIVITY SCORE 28 JOINTS (DAS 28)

In rheumatoid arthritis (RA), inflammatory activity cannot be measured using one single variable. Notably, earlier on no standard measure of disease activity existed with various studies using different measures of disease activity **[13,14].** For this reason, the Disease Activity Score (DAS) was developed. The DAS is a clinical index of RA disease activity that combines information from swollen joints, tender joints, the acute phase response and general health. The DAS 28 is a modification of the original DAS that assessed 44 joints to assessing 28 joints **[45]**.

Major advantages of the DAS are that its more valid than single measures alone, it has a continuous scale with a Gaussian distribution. Moreover its values are clinically interpretable and it's sensitive enough to assess small effects **[49]**. DAS28 is based on counts of the number of painful joints (NPJ28) and the number of swollen joints (NSJ28) out of 28 joints:

$$DAS28 = 0.56\ (\sqrt{NPJ28}) + 0.28\ (\sqrt{NSJ28}) + 0.70\ (\text{In ESR}) = + 0.014\ (PGA)$$

The joints assessed are: proximal inter-phalangeal (PIP) and metacarpa-phalangeal (MCP) joints of both hands, wrists, elbows, shoulders and the knees. The Erythrocyte Sedimentation Rate (ESR) should be measured (in mm/hour). In addition, the patients' general health (GH) or global disease activity measured on a Visual Analogue Scale (VAS) of 100 mm must be obtained **[45]**.

The score for the complete DAS28 can range from 0 to 10. A DAS28 above 5.1 means high disease activity whereas a DAS28 below 3.2 indicates low disease activity. Remission is achieved by a DAS28 lower than 2.6 **[45]**.

Studies have shown the DAS28 to be quite reliable in assessment of disease in RA **[50, 51]**.

Serial measurements of DAS28 are strong predictors of physical disability and radiological progression **[52]**

2.0 STUDY JUSTIFICATION

RA is a disease with significant morbidity and mortality. Monitoring of disease activity in patients with rheumatoid arthritis is important as it allows for assessment and appropriate modification of treatment.

Studies done elsewhere have shown association between platelet counts and disease activity. There is a need to validate the findings in our set-up as no local data exists on platelet abnormalities in our patients with RA. It is also notable that most of the earlier studies are few and old, and were conducted before the current widespread use of DMARD and when no standard measure of disease activity existed.

Use of platelet count as an indicator of disease activity can provide an affordable, quick and rapid assessment of disease activity in our patients in the routinely done full hemogram (FHG).

It was hoped that data from this study would sensitize the clinicians attending to patients with RA to monitor their platelet counts to provide useful information on disease activity.

2.1 RESEARCH QUESTION

What is the relationship between platelet counts and clinical disease activity in patients with rheumatoid arthritis at KNH?

3.0 OBJECTIVES

3.1 Broad Objective

To determine the relationship between platelet counts and clinical disease activity in patients with rheumatoid arthritis at Kenyatta National Hospital.

3.2 Specific Objectives

1. To describe platelet counts in patients with rheumatoid arthritis.
2. To document the clinical disease activity in patients with RA using the disease activity score 28 joints (DAS-28).
3. To correlate platelet count with disease activity score (DAS-28) in patients with RA.

4.0 MATERIALS AND METHODS

4.1 Study Design and Location

This was a cross-sectional descriptive study that was carried out in Kenyatta National Hospital Rheumatology Out-patient Clinic. KNH is a teaching tertiary hospital and is the largest referral hospital in Kenya. KNH mainly draws patients from the environs of Nairobi but also receives referrals from all over the country

4.2 Study Population

Patients with RA on follow up at the KNH ROPC.

4.3 Patient Selection

4.3.1 Inclusion Criteria

1. Patients aged 18 years and above with rheumatoid arthritis attending the ROPC
2. Patients who gave informed consent

4.3.2 Exclusion Criteria

1. Patients who had acute febrile illnesses or other acute co-morbid conditions e.g post-surgery, bleeding disorders
2. Hematological conditions such as cryoglobulinemia, plasma cell disorders, chronic myeloid leukemia, idiopathic thrombocytopenia purpura,thrombotic thrombocytopenic purpura,haemolytic uremic syndrome,disseminated intravascular coagulation,primary thrombocythemia.
3. Patients known to have malignancies
4. RA with mixed connective tissue disease.

4.4 CASE DEFINITION/ MAIN OUTCOME VARIABLES

4.4 1 Case Definition

Rheumatoid arthritis- patient with signs and symptoms that satisfy the American College of Rheumatology (ACR) 1987 criteria or ACR/European League Against Rheumatism (EULAR) 2010 criteria for RA and confirmed by rheumatologist **[53,54].** (Appendix 1)

4.4.2 Main outcome Variables

4.4.2.1 Clinical Disease Activity

Clinical disease activity as per DAS28 scores were classified as follows:

Remission.....≤ 2.6

Mild.....2.6-3.2

Moderate..... >3.2-5.1

High..... ≥ 5.1

4.4.2.2 Platelet Count Grading

- <150 $\times 10^9$ /l Thrombocytopenia
- 150– 400 $\times$ 10^9/l Normal platelet
- 400-600 $\times$ 10^9/l Mild Thrombocytosis
- 650-800 $\times 10^9$ /l Moderate thrombocytosis
- >800 $\times$ 10^9/l Marked thrombocytosis

4.5 SAMPLING

4.5.1 Sample Size Estimation

The study was time bound and patients were recruited consecutively at the rheumatology clinic for a period of 6 months from November 2010 to April 2011. This time period allowed for recruitment of all patients with RA attending the ROPC estimated to be 95 at the time of proposal writing. All new patients referred to the clinic at this time who were diagnosed with RA by the rheumatologist were also recruited in the study. Thus, 104 patients were recruited in the 6 month study period.

4.5.2 Sampling Method

Patients were enrolled consecutively in the ROPC clinic during the period of data collection

4.6 SCREENING AND RECRUITMENT

In the ROPC, all patients on follow up for RA were screened for recruitment into the study. Screening entailed assessment of eligibility by reviewing the patient's files. The principal investigator reviewed the files of all patients with RA who had attended ROPC on that day. The files of patients who met the inclusion criteria were selected and consecutively sampled for study.

Of the eligible patients, informed consent (Appendix 2) was obtained from them to participate in the study. Once consent was given, history was taken, physical examination performed and blood collected from them for laboratory investigation as outlined below.

4.7 CLINICAL METHODS

The principal investigator explained the purpose of the study, obtained consent and after assurance of confidentiality conducted a face to face interview. The principal investigator obtained socio-demographic data which included age, gender, marital status, place of residence, and occupation from both the patients and/or the patients' records. Disease history obtained included duration of illness, when first diagnosed, whether on any treatment, response to treatment and any current concurrent illness. This was recorded in the study proforma (Appendix 3).

4.7.1 Clinical Evaluation

Physical examination was carried out with emphasis on features of active RA. All joints were examined for swelling and tenderness. The number of joints swollen and/ tender was recorded on the DAS28 score sheet (Appendix 4). The patient was asked to assess his/her general well being using the visual analog scale (VAS) and this was also recorded in the DAS28 score sheet.

4.8 LABORATORY METHODS

4.8.1 Specimen Collection and Handling

Three millilitres of venous blood was drawn aseptically from the forearm and collected in an EDTA bottle for a full blood count and ESR estimation in consenting patients.

4.8.2 Laboratory Analysis

Full blood count: The blood was analyzed using Abbot Cell Dyn 1300 counter in the Department of Pathology, Haematology Unit University of Nairobi **[57]**. A peripheral blood count was done to rule out pseudothrombocytopenia and confirm findings.

The ESR was measured using the Winthrobe's method **[58]**. The ESR level was then recorded in the DAS score sheet.

4.9 QUALITY ASSURANCE

Internal quality control was performed to ensure precision of results and hence their reliability. A portion of the specimen of every 10^{th} sample was sent to the Pediatric department haematology laboratory to double check the platelet count twice per month. The standard operating procedures were adhered to.

4.10 DAS 28 SCORE

The total DAS score was then calculated using the DAS28 calculator downloaded from the DAS website **[45]**. This was then recorded in the study proforma for each patient.

5.0 DATA MANAGEMENT AND ANALYSIS

5.1 Data Organization

All data was collected on the study proforma and entered into a computer data base MS Access. The data was then cleaned, verified and imported into a computer statistical software. Statistical analysis was done using statistical package for social sciences (SPSS) version 17.0 software.

5.2 Data Analysis and Presentation

Continuous variables such as age, DAS 28 scores, platelet counts and ESR are summarized into means, median, and ranges. Comparison of means was done using Student's t test for normally distributed data and Mann Whitney U test for non-normal data. Platelet count was correlated to DAS28 score using the spearman Rho coefficients. Bivariate analysis was done using the Man Whitney U test.

Multivariate analysis done by linear regression was used to determine the relationship between platelet count and DAS28 adjusting for various factors.

Comparisons were considered statistically significant at a P value ≤ 0.05. Ninety five percent confidence limits were used as a measure of certainty. Results are presented in form of charts, graphs and tables.

6.0 ETHICAL CONSIDERATIONS

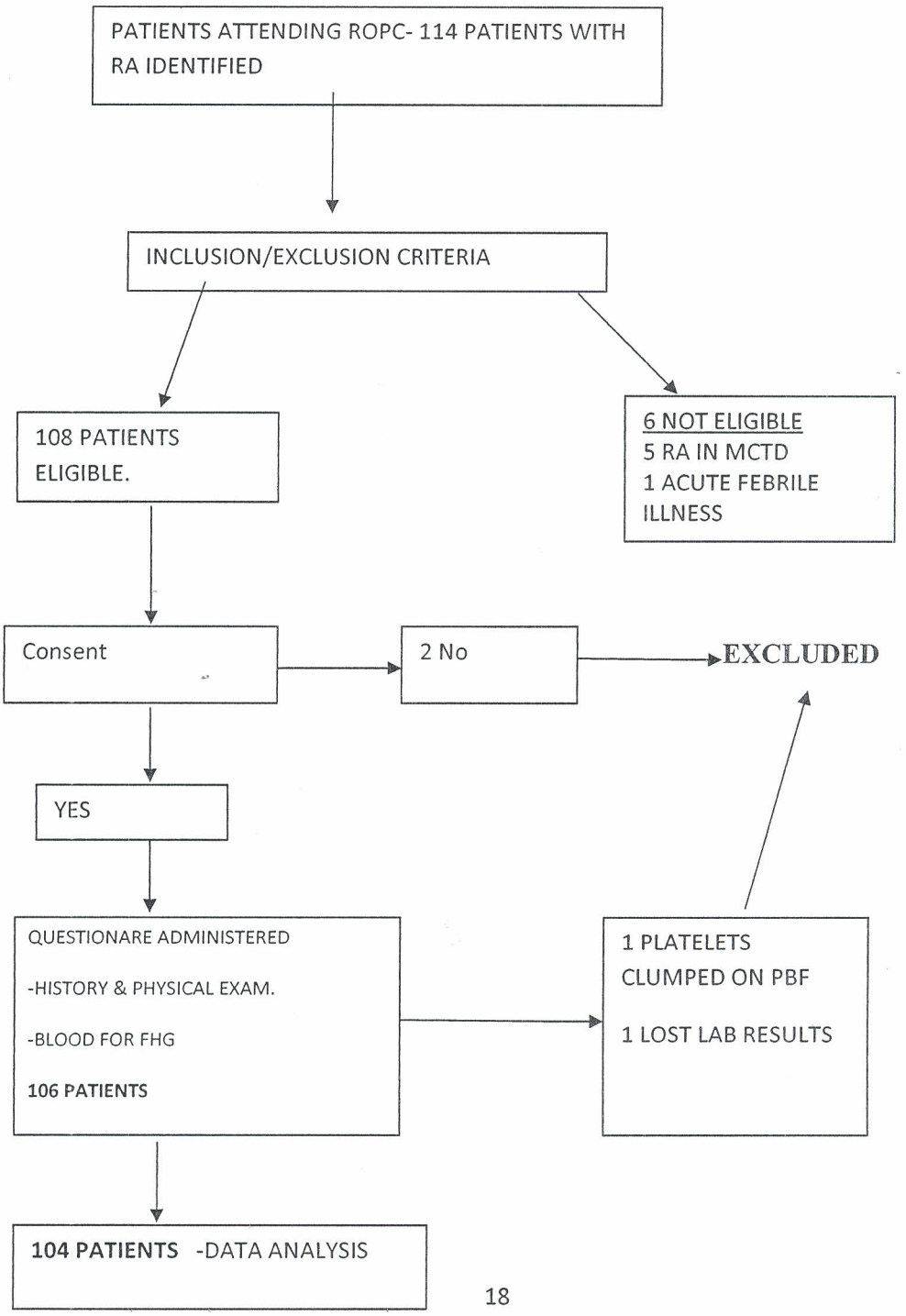
1. The study was carried out upon approval by the department of clinical medicine and therapeutics (UON) and KNH Ethics and Research committee.
2. Patients were included in the study after being explained the purpose of the study and giving informed consent.
3. Patients were not coerced to be included in the study.
4. The patient's right to privacy was respected.
5. Study results needing attention such as low haemoglobin levels were communicated to doctors taking care of the patients to allow for appropriate management.

7.0 RESULTS

7.1 PATIENTS FLOW CHART

In a period of 6 months, among the patients attending ROPC, 114 patients with RA were identified. These were screened and recruited into the study.

Figure 1: Patients flowchart



7.2 BASELINE CHARACTERISTICS OF THE STUDY POPULATION

Table 1: Selected demographic and other characteristics of the study participants

Variables	N=104	%
Age in years		
<30 years	13	12.5
30 - 39 years	14	13.5
40 - 49 years	24	23.1
50 - 59 years	30	28.8
60 or more	23	22.1
Sex		
Male	14	13.5
Female	90	86.5
Duration of disease		
<1 year	25	24.0
1 - 5 years	45	43.3
>5 years	34	32.7
Type of medication		
NSAIDs	75	72.1
DMARDs	78	75.0
Steroids	48	46.2
Type of DMARDS		
Methotrexate	72	69.2
HCQ	20	19.2
Sulphasalazine	3	2.9
Leflunomide	1	1.0

7.2.1 Demographic characteristics.

Demographic characteristics of the study population are shown in the table 1 .

Most of the patients (53.9%) were aged between 40 to 59 years. The mean age was 48±14 years with a median age of 49 years (18-79years). Most of the population was female with a male to female ratio of 1: 6.4.

7.2.2 Clinical characteristics

Selected clinical characteristics of the study population are shown in table 1.

Most of the patients (43.3%) had been diagnosed with RA over the last 1 to 5 years while in 25 (24%) patients the diagnosis had been made over the last one year. Majority of the patients (75%) were on DMARDs while only 48 (46.2%) were on steroids. The most commonly used DMARD was methotrexate in 69.2% (72) of the patients while only one patient was on leflunomide.

7.3 PLATELET COUNTS IN STUDY POPULATION

Table 2: Platelet counts in study population

	N/ (%)
Median	294 $X10^9$/L
Mean	313.2±94 $X10^9$/L
Range	152-611 $X10^9$/L
Normal platelet counts (150- 400x10^9/L)	89 (85.6%)
Thrombocytosis (mild) (Above 400x10^9/L)	**15 (14.4%)**

Platelet counts of the study population are shown in table 2.

The platelet count varied between 152 to 611 x10^9/L with a mean of 313.2±94.0 x10^9/L and a median of 294.5 x10^9/L. Eighty nine (85.6%) had normal platelet counts while 15 (14.4%) **[95% C I: 8.9-22.4]** had thrombocytosis. No case of moderate (> 650 x10^9/L) or severe

thrombocytosis (>800 x10^9/L) was recorded. Among those with thrombocytosis, 12 (80%) were female and 3 (20%) were male.

7.4 OTHER LABORATORY PARAMETERS.

Table 3: Other laboratory parameters

LABORATORY PARAMETERS	n	Mean	SD	Median	Minimum	Maximum
ESR(mm/hr)	104	34.9	14.8	36.0	2.0	63.0
HB (g/dl)	104	12.5	2.1	12.8	4.4	16.3
MCV (fl)	104	80.3	8.8	81.5	55.0	101.0
MCH (pg)	104	26.0	3.5	26.0	15.6	34.0
WBC x10^9/L	104	6.8	2.2	6.3	3.0	13.6

Other laboratory parameters are depicted in table 3.The mean ESR was 34.9±14.8 mm/hr with a median haemoglobin of 12.8g/L. The mean MCV and MCH were 80.3±8.8fl and 26±3.5pg respectively. The WBC range was 3.3 to 13.6 x10^9/ L with a median of 6.3 x10^9/L

7.5 COMPARISON OF VARIOUS PARAMETERS BETWEEN HIGH AND NORMAL PLATELET COUNT.

Table 4: Comparison of various parameters in those with normal Vs high platelet counts

Laboratory parameters	Platelet count (>400x10^9) n	Median (Range)	Platelets count (150 – 400x10^9) n	Median (Range)	P value
DAS28 Score	15	4.6 (2.2-7.1)	89	4.2 (1.7-8.4)	0.413
Age (years)	15	46.0 (25.0 - 76.0)	89	50.0 (18.0 - 79.0)	0.715
ESR(mm/hr)	15	40.0 (6.0-60.0)	89	35.0 (2.0-63.0)	0.185
HB(g/dl)	15	11.5 (4.4-13.9)	89	12.8 (7.4-16.3)	**0.020**
MCV(fl)	15	72.0 (56.0-87.0)	89	83.0 (55.0-101.0)	**0.002**
MCH(pg)	15	22.8 (15.6-28.9)	89	26.8 (16.0-34.0)	**0.001**
WBC x10^9/L	15	7.6 (4.8-13.6)	89	6.1 (3.0-12.2)	**0.030**

Table 4 shows comparison of various parameters between those with thrombocytosis and those with normal platelet counts. Comparison between those with normal versus elevated platelet counts showed that the median DAS28 score was slightly lower in those with normal platelet scores at 4.2 versus 4.6 in those with thrombocytosis but insignificant (p=0.413). Differences in the median age and ESR levels were also insignificant with P values of 0.715 and 0.185 respectively. Significant differences in the median of the haemoglobin levels, RBC indices and WBC counts were found between the two groups. Lower HB, MCV and MCH were associated with elevated platelet counts while higher WBC was associated with thrombocytosis.

7.6 MULTIVARIATE ANALYSIS.

The significant values were then subjected to a multivariate analysis by linear regression as shown in the table 5. While haemoglobin lost significance, MCV remained significant demonstrating that the MCV is independently associated with platelet levels.

Table 5: Multivariate analysis of Platelet count and various parameters

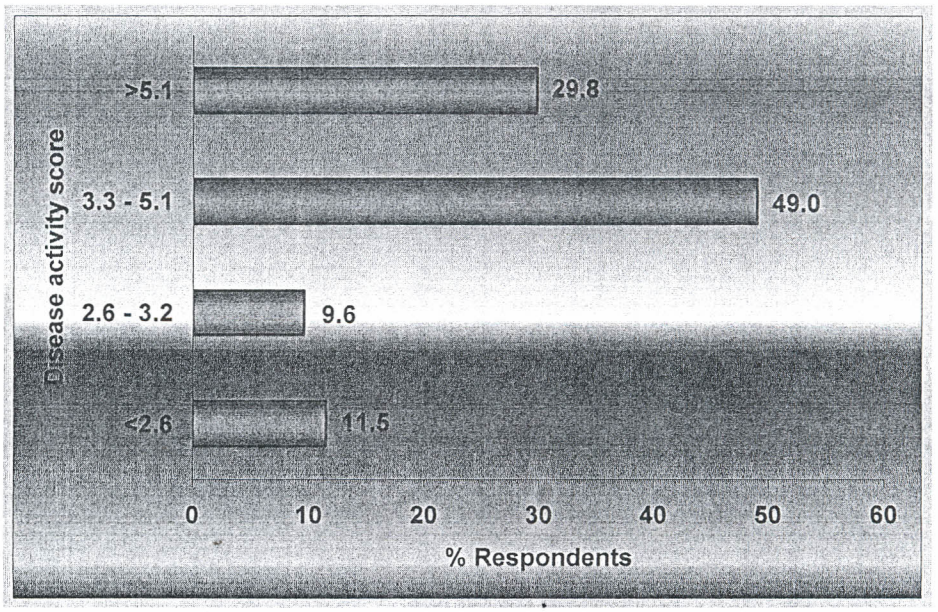
Variable	ß	s.e. (ß)	t - value	P – value	R – square
Full model					
(Constant)	622.33	82.38	7.56	<0.001	
HB	-1.41	5.97	-0.24	0.815	
MCV	-6.79	3.13	-2.17	0.032	0.285
MCH	5.64	8.39	0.67	0.503	
WBC	15.71	3.83	4.10	<0.001	
Reduced model					
(Constant)	599.03	73.85	8.11	<0.001	
MCV	-4.86	0.91	-5.33	**<0.001**	0.282
WBC	15.34	3.67	4.18	**<0.001**	

7.8 CLINICAL DISEASE ACTIVITY (DAS 28 SCORE).

The clinical disease activity of the study population is shown in the figure 2

The mean DAS28 score was 4.5±1.5 with a median of 4.3 and a range of 1.7-8.4. Majority (49%) of the patients had moderate disease activity while only 12 (11.5%) had their disease in remission. Thirty (29.8%) had high disease activity and 10 (9.6%) mild disease as shown in figure 2.

Figure 2: Distribution of clinical disease activity



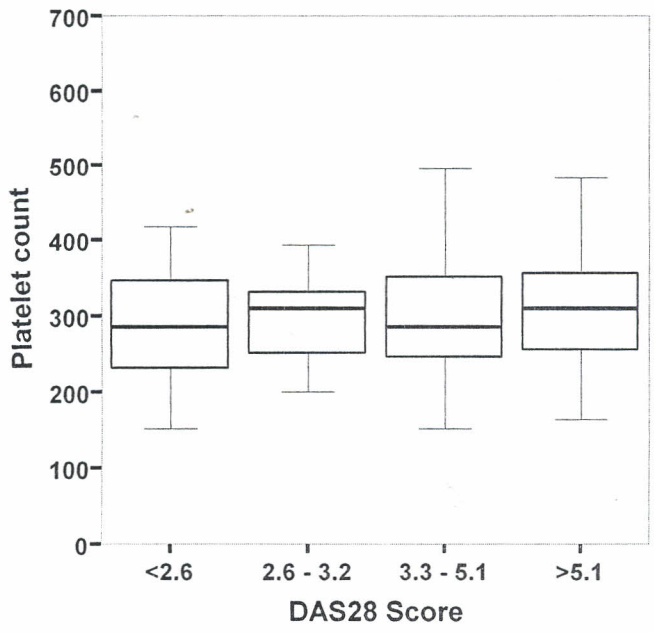
7.9 PLATELET COUNT AND DISEASE ACTIVITY.

Table 6: Platelet counts at various levels of disease activity

DAS28 Score	n	Mean	SD	Median	Minimum	Maximum
<2.6	12	285	82	285	152	416
2.6 - 3.2	10	300	55	310	201	393
3.3 - 5.1	51	311	90	285	152	606
>5.1	31	332	113	311	164	611
Total	**104**	**313**	**94**	**295**	**152**	**611**

Table 6 shows the distribution of the platelet counts in the various levels of disease activity and is best illustrated in figure 3 .The median platelet count for those in remission was 285x 10^9/L, 310x10^9/L for mild disease, 285x10^9/L for moderate disease and 311x10^9/L for those with high disease activity.

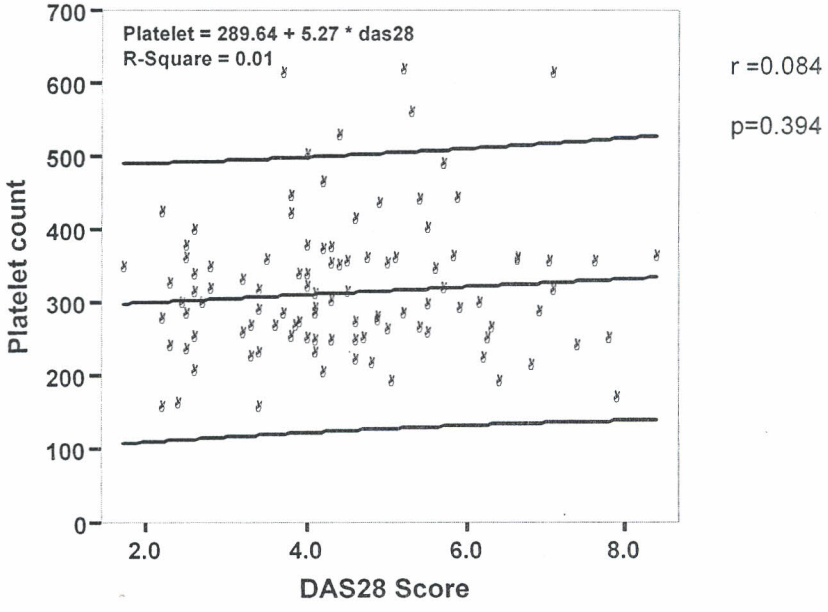
Figure 3: Box plot of various DAS scores and respective platelet counts.



7.10 CORRELATION BETWEEN PLATELET COUNTS AND DISEASE ACTIVITY.

Correlation between platelet counts and DAS28 scores revealed a correlation coefficient of r=0.084 which is statistically insignificant at p=0.394 as shown in the scatter plot (figure 4)

Figure 4: Scatterplot on platelet count in correlation to disease activity score (DAS28 score)



8.0 DISCUSSION

The aim of this study was to determine platelet counts in patients with RA and to describe their relationship to the clinical disease activity as assessed using the DAS 28 score in patients with RA attending KNH ROPC.

The total number of patients identified with RA for period of 6 months was 114 which is almost double that seen in 2008 by Owino *et al* **[5]** who managed to recruit only 60 patients in KNH medical outpatient clinics within the same duration of time. This indicates that there is an increase in the numbers of patients with RA being seen in KNH probably attributable to the recent establishment of a dedicated Rheumatology outpatient clinic.

The mean age of the study population was 48 years. This is because RA is a disease with onset from the third to fifth decades of life. The male to female ratio was 1:6.4.Though this was higher than commonly reported (usually 1:3), RA, like majority of other connective tissue diseases predominantly affects females **[1].**

In the therapy of RA, majority of the patients (75%) were on DMARDs. It was noted that majority of the patients not on DMARDS were patients newly referred to the ROPC and diagnosed with RA during the study period. They were later put on DMARDs. Forty six percent of the patients were on steroid therapy. It was noted that some patients continued to be on steroid therapy even with inactive disease in contrast to current guidelines of therapy **[55].**

The mean platelet count in the study population was 313.2 ±94 $x10^9$/L, a median of 294 $x10^9$/L and a range of 152-611$x10^9$ /L. These figures are much higher than platelet counts in normal healthy adults. In 1981, Mukibi *et al* found a mean platelet count of 200$x10^9$/L in healthy Kenyan adults. A more recent study by Rajab *et al* on haematological parameters in healthy Kenyan blood donors found a mean platelet count of 241.2±86.6 $x10^9$/L and median of 235.1 $x10^9$/L **[10].** Bain found even lower platelet counts of a mean of 183 $x10^9$/L in black females and 207 $x10^9$/L in black males in a study comparing ethnic and gender differences in healthy adults though in a different set up **[7].** It can therefore be inferred from these previous studies that patients with RA have higher platelet counts. Our results are comparable to a Turkish study by Yacizi *et al* who found mean platelets of 307±99 $x10^9$/L in patients with active RA compared to a mean of 258 ±58 $x10^9$/L. in healthy controls **[27].**

It is worth noting that despite the significant use of DMARDs, no case of thrombocytopenia was recorded. The prevalence of thrombocytopenia in various studies ranges from 0.8 to 3.1% in patients using DMARDs **[34, 35].** Buhroos *et al* in a study in India found only 2 out of 245 patients (0.8 %) had thrombocytopenia. This is close to our study that recorded no case of thrombocytopenia **[35].** The consistent concurrent use of folate in our patients may account for this finding as folate has been shown to reduce the adverse effects of methotrexate **[56].**

Thrombocytosis was found in only 14.4% (15) of the study population. Studies elsewhere have recorded higher prevalences of thrombocytosis. Selroos and Hutchingsons found prevalences of 33% and 51% respectively **[13,14].** Notably these studies were done in the 70s and 80s when use of DMARDs was not widespread. A higher prevalence of thrombocytosis in Caucasians could also be attributable to the fact that Caucasians have been shown to have higher levels of platelets compared to Africans in several studies [7,8]. Therefore a relatively lower baseline platelet count to start with will result to fewer cases of thrombocytosis when using the same cut-off as the Western studies despite a similar increase in platelet counts. A case control study in future may bring out these differences. A more recent Saudi Arabia study found a prevalence of 16% **[16].** This is comparable to the findings of this study. No similar study has been done in Africa to which the findings can be compared.

Most of the patients (88.5%) had active disease (DAS28 scores >2.6). The majority of these had moderate disease activity (49%) while 29.7% had high disease activity and only 9.6% with mild disease activity. These results are comparable to the findings by Owino *et al* who found 88% with active disease. However the different categories varied in that 18% had mild disease,38% moderate disease and 32% severe disease **[5].**While we expected less active disease with the more use of DMARDs in our patient population that was not the case. This is probably because a significant number of the patients (24%) were diagnosed during the study period and had previously not been on treatment and therefore had high disease activity. Another possible explanation is that more aggressive treatment maybe needed for these patients such as anti-TNF antagonist or use of biologicals of which none of the patients was on. The study did not assess compliance to treatment which could also affect the levels disease activity seen in the study population.

While comparing different parameters in those with thrombocytosis versus normal PCs, no significant difference was found in the median DAS28 scores between the groups i.e 4.6 versus 4.2 (p=0.413). This precludes any meaningful relationship between platelet counts and disease activity in this study. The Hb ,MCV and MCH were however noted to be significantly lower in the group with thrombocytosis with p values of 0.20,0.002 and 0.001 respectively. This is similar to what other studies have reported. Hutchingsons found higher platelet counts in those with lower Hb mean of 12.47 ±0.10g/dl in platelets <450 $x10^9$/L and 11.27± 0.77g/dl in >450 $x10^9$/L **[13].** The lower Hb was noted to be mainly microcytic hypochromic. This was confirmed by the multivariate analysis that showed MCV to be an independent contributor to platelet counts.

Microcytic anemia is usually due to either iron deficiency anemia (IDA) or less commonly anemia of chronic disease ACD. IDA is usually associated with a reactive thrombocytosis. ACD may also be associated with a reactive thrombocytosis secondary to chronic inflammation **[20].** This can explain the association between thrombocytosis and low MCV. The association between low Hb and thrombocytosis could also be due to possible chronic GIT blood loss in these patients of whom majority were on NSAIDs. NSAID induced GIT bleeding is thought to contribute to the thrombocytosis of active disease in patients using NSAIDs **[14]**.

Correlation between disease activity and platelet count revealed no significant correlation (p=0.394). These findings are in contrast to earlier studies by Hutchingsons and Farr *et al* who both found a positive correlation. However, they used different measures of disease activity with Hutchinson including a presence of extra-articular manifestations, morning stiffness and grip strength which are not assessed in the DAS 28 score. Farr *et al* used the total articular index i.e summation of pain on movement, stiffness, swelling, heat and tenderness of each joint. Notably, the other studies had recorded higher levels of thrombocytosis to start with **[14,18]**.

Our findings are more comparable to Yacizi's who used the DAS score in assessment of disease activity **[27].** The study demonstrated a fall in mean platelet counts after a period of treatment but the platelet counts did not correlate with disease activity however. Our study and the study by Yacizi demonstrated that the findings by the earlier authors cannot be generalised to all populations. Though this study, Yacizi's study and the older studies all demonstrate that a relative increase in platelets occurs in active disease, the change in platelet

counts is not a consistent variable as demonstrated by this study and Yacizi's study.As mentioned earlier, the older studies were done when use of DMARDs was limited to few cases with severe disease activity. In the recent times majority of the patients are on DMARDs and its possible that the DMARDs may blunt the full haematological response to disease activity. Another possible explanation is that because the populations studied were different, they may have different haematological response to disease activity. These findings can be interpreted to mean that platelet counts are poor indicators of disease activity in our population.

9.0 STUDY LIMITATIONS

- Relative increases or decreases in platelet count were missed as only a one time platelet count was done in the study.
- Possible occult gastro-intestinal bleeding which has the potential to raise platelet counts was not explored in this study.

10.0 CONCLUSION

- Patients with RA have relatively increased platelet counts compared to the general population in our Kenyan patients.
- The prevalence of thrombocytosis was less than that reported in majority of the other studies.
- Platelet counts are poor indicators of disease activity in our patients as demonstrated by lack of correlation between platelet counts and disease activity.

11.0 RECOMMENDATIONS

- A larger, longitudinal study to describe the changes in platelet count in individual RA patients. This may require a multicenter approach to avail sufficient number of patients.
- A study on the magnitude of anaemia and its causes as noted in the study population.

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13.0 APPENDICES

Appendix 1: The ACR Criteria for Classification of RA

1. Morning stiffness-Morning stiffness in and around joints, lasting at least one hour before maximal improvement.

2.Arthritis of three or more joint areas-At least three joint areas simultaneously have had soft tissue swelling or fluid[not bony overgrowth alone] observed by a physician.The fourteen possible areas are right or left PIP,MCP,wrist,elbow,knee,ankle and MTP joints.

3. Arthritis of hand joints-At least one area swollen[as defined above] in a wrist,MCP,or PIP joint.

4.Symmetric arthritis-Simultaneous involvement of the same joint areas[as defined above in 2] on both sides of the body[bilateral involvement of PIPs,MCPs or MTPs is acceptable without absolute symmetry].

5.Rheumatoid nodules-Subcutaneous nodules,over bony prominences,or extensor surfaces, or juxta-articular regions,observed by a physician.

6.Serum rheumatoid factor-Demonstration of abnormal amounts of serum RF by any method for which the result has been positive in <5% of normal subjects.

7.Radiographic changes-Radiographic changes typical of RA on postero-anterior hand and wrist radiographs,which must include erosions or equivocal bony decalcification localized in or most marked adjacent to the involved joints[osteoarthritis alone do not qualify].

For classification purposes,a patient shall be said to have RA if she /he has satisfied at least four of these seven criteria. Criteria 1 through 4 must have been present for at least six weeks.

Patients with two clinical diagnoses are not excluded.

Designation as classic, definite or probable RA is not to be made.

2010 RHEUMATOID ARTHRITIS CLASSIFICATION CRITERIA

Classification criteria for RA a score of >6/10 is needed for classification of a patient as having definite RA

A. Joint involvement

1 large joint -0

2-10 large joints -1

1-3 small joints (with or without involvement of large joints)- 2

4-10 small joints (with or without involvement of large joints)- 3

>10 joints (at least 1 small joint)-5

B. Serology (at least 1 test result is needed for classification)

Negative RF and negative Anti-citrullinated protein antibody (ACPA)- 0

Low-positive RF or low-positive ACPA -2

High-positive RF or high-positive ACPA -3

C. Acute-phase reactants (at least 1 test result is needed for classification)

Normal CRP and normal ESR -0

Abnormal CRP or abnormal ESR -1

D. Duration of symptoms

<6 weeks 0

>6 weeks 1

Appendix 2: Consent Form

Consent Explanation before Recruitment

I am Dr. Muthoni Mbuthia, a postgraduate student in Internal Medicine at the University Of Nairobi. I would like to inform you that I am conducting a study on 'Platelet counts in patients with rheumatoid arthritis at KNH'. The study aims at determining the relationship between platelet counts and disease activity in RA. If significant correlation is found, platelet counts will useful as part of monitoring disease activity. I would also like to inform you that:

Joining the study is voluntary and no payments will be charged to you due to participation in the study.

Participation in the study will not delay your treatment in any way and will be beneficial to you.

You may decline to participate in the study or drop out at will and this will not lead to any denial of treatment or any form of care in the hospital.

Once you agree to participate in the study, you will answer questions of personal nature as laid in the study proforma, I will carry out a full physical examination and take some blood for laboratory tests. You will feel a little pain as is normal with standard phlebotomy and the amount of blood drawn will not affect your health.

Any results obtained will be communicated to your primary physician for the appropriate therapy to be instituted.

The information obtained from you will be treated with utmost confidentiality. Any publications arising out of the study will not identify you. If you have understood the information that we have given you and you are willing to participate in the study, you will be required to sign a form indicating your willingness to be recruited.

If you have any questions about this study, you may contact

Dr. Mbuthia B.Muthoni. Tel: 0721449352

Dr. Omondi Oyoo. Dept of Int Medicine. Tel:020-2725452

The Chairman, KNH/UoN Ethics Research Committee. Tel: 020-2726300 Ext 44355

STATEMENT OF CONSENT BY THE PATIENT

The purposes of this study, procedure, study benefits and my rights have been fully explained to me. I hereby give my written consent to allow myself ..... to participate in the study.

NAME:..... SIGNATURE: .....

DATE: .....

WITNESS ..... SIGNATURE: .....

DATE: .....

INTERVIEWER'S STATEMENT

I have explained the purpose and benefits of this study to the respondent. To the best of my knowledge and conviction, he / she has understood and has given consent.

INTERVIEWER: ..... SIGNATURE: .....

DATE: .....

Appendix 3: Study Proforma

BASIC INFORMATION

1. Study No .....

2. Hospital No .....

3. Telephone contact .....

4. Address .....

5. Age .....

6. Sex Male1, Female 2 □

7. Marital status single□, married□, separated□ divorced□, widowed□

8. Residence Rural □ peri-urban □ urban□

9. Educational level none□ primary□, secondary□, tertiary□

10. Occupation .....

HISTORY

How long have you had the signs and symptoms of arthritis?

Less than 1yr □ 1-5yrs □ more than 5yrs□

When was the diagnosis of RA made?

Less than 1yr □ 1-5yrs □ more than 5yrs□

Are you on any medications? Yes□ No □

If so which? NSAIDS □ DMARDS□ steroids□

Have you seen any improvement since starting medication? Yes □ No□

Do you have any current illness apart from RA? Yes □ No□

If so, which? Fever □ R/s□ CVS□ CNS □ GIT□

Appendix 4: Das28 Form

Patient name..... Date of Birth .....-.....-.....

Observer name..... Date .....-.....-.....

	Left		**Right**	
	Swollen	tender	Swollen	Tender
Shoulder				
Elbow				
Wrist				
MCP 1				
2				
3				
4				
5				
PIP 1				
2				
3				
4				
5				
Knee				
Subtotal				
Total	swollen		Tender	

No disease activity high disease activity

Swollen (0-28)	
Tender (0-28)	
ESR	
VAS disease activity (0-100mm)	

DAS28 = 0.56*√(t28) + 0.28*√(sw28) + 0.70*Ln(ESR) + 0.014*VAS