Journal Homepage: - www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI: 10.21474/IJAR01/20280
DOI URL: http://dx.doi.org/10.21474/IJAR01/20280

RESEARCH ARTICLE

THE USE OF COMPLETE BLOOD COUNT AS INFLAMMATORY BIOMARKERS IN PATIENTS WITH GASTRIC CANCER IN ENUGU STATE UNIVERSITY OF SCIENCE AND TECHNOLOGY TEACHING HOSPITAL, PARKLANE ENUGU

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Manuscript Info

Manuscript History
Received: 20 November 2024
Final Accepted: 24 December 2024
Published: January 2025

Key words:-
Gastric Cancer, Inflammation, CBC

Abstract

A complete blood count (CBC) is a standard investigation required from all gastric cancer patients before treatment and during treatment. Poor CBC parameters may negatively affect cancer outcomes. This present study investigated the use of Complete Blood Count (CBC) and Erythrocyte Sedimentation Rate (ESR) as an assessment of inflammation in these subjects. The study comprised of 54 male and female subjects and 54 controls with ages between 21-70 years. A longitudinal study method was used. The samples were collected from apparently healthy individuals as control, pre-treatment and the treatment samples at different stages. Questionnaire used obtained other demographic information. The data was analyzed with IBM SPSS PC. Version 20.0; SPSS Inc., Chicago, III., USA. Results showed decreased Lymphocyte/Monocyte ratio(LMR) were significantly increased hazard ratio (HR) and decreased OS at $p<0.05$.While increased Neutrophil/Lymphocyte ratio(NLR) and Platelet/Monocyte ratio(PLR) had no significant difference at $P>0.05$. In CBC and ESR, control, pre-treatment and treatment period, RBC parameters and TWBC parameters showed a significant decrease at $p<0.05$ in treatment results compared to the pre-treatment and control results while others showed no significant increase at $p<0.05$ in treatment results compared to pre-treatment results. Treatment RDW and MPV observed a significant increase ($p<0.05$) compared to the control and pre-treatment results. Age group 21-30 years showed more susceptibility than other age groups with lowest mean±SD in CBC and ESR but with no significant difference at $p>0.05$.This present study

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supports the concept that biomarkers such as CBC and ESR can be used as a prognostic tool in early detection, treatment and monitoring the disease progression in these subjects.

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Introduction:-

Hematopoietic stem cells (HSCs) maintain lifelong hematopoiesis via their ability to self-renew and differentiate into all blood cell lineages in humans [1]. HSCs are an extremely rare population of cells that usually reside in the highly organized bone marrow architecture (also called niche) [2]. Any perturbation of the bone marrow niche affects the hematopoiesis process [3]. Under physiological conditions, a small number (1%–5%) of hematopoietic stem and progenitor cells (HSPCs) regularly enter circulation and travel through peripheral blood [4]. HSPCs sense stress signals and are capable of converting environmental cues into versatile cytokine signals to regulate hematopoiesis [5]. Multiple factors, including growth factors, chemokines, and adhesion molecules, can influence HSPC circulation and activity. Extensive attention has been paid to the emergence and evolution of tumors, yet how the growth of malignant clones affect normal hematopoiesis is poorly understood. However, circulating HSPCs are highly enriched in tumor tissues and correlate with tumor progression [6]. Furthermore, tumor progression is manifested by alterations in intra- and extramedullary hematopoiesis (EMH), which supports a systemic tumor-promoting myeloid response [7]. Therefore, understanding the process by which tumors interrupt normal hematopoiesis is an important question that is highly relevant to tumor progression. A reviewed work was done on normal hematopoiesis in the context of hematopoietic malignancies. In this review, it outlined the impact of solid tumors on hematopoiesis and summarizes their underlying mechanism. In clinical observations, the progression of different types of solid tumors has resulted in an increased peripheral neutrophil-to-lymphocyte ratio [8], [9] and circulating granulocyte–macrophage progenitors (GMPs) [10]. HSPCs, which are upstream of these cells, have been increasingly recognized as playing key roles in tumor growth and metastasis progression. It has been well-established that elevated levels of HSPCs correlate with higher tumor stage and decreased progression-free survival [11]. Tumors usually accumulate immune-suppressive hematopoietic lineages at primary sites. HSPC production and circulation are elevated in cancer patients before detectable metastases [10]. The number of circulating HSPCs decreases if tumor-mediated mobilization is inhibited, whereas the pharmacological mobilization of HSPCs increases metastasis [11].

The relationship between cancer and the immune system has been increasingly recognized over the past three decades. While immune-surveillance is a strong line of defense by which transformed cells are cleared by cells like lymphocytes and natural killer cells, chronic inflammation is an established risk factor for developing several types of solid cancers [12]. In addition, the tumor microenvironment is infiltrated by a heterogeneous population of immune cells, each playing a different role in the cross-talk between cancer cells and the host, either favoring or suppressing tumor progression. For example, a subset of myeloid cells which is expanded in cancer patients are myeloid-derived suppressor cells (MDSCs). These are immature myeloid cells of granulocytic or monocytic lineages are elevated in cancer. MDSCs are capable of suppressing anti-tumor T cell activity and promoting tumor angiogenesis [13]. In fact, higher numbers of circulating MDSCs is a poor prognostic indicator in gastric cancers [14]. On the other hand, higher lymphocyte infiltration in the tumor (tumor-infiltrating lymphocytes, TILs) is a good prognostic indicator in this cancer [15]. In turn, cancer cells modify the behavior of neutrophils by inducing the release of cytokines and metalloproteinases, increasing their chemotactic potential and inhibiting apoptosis, which perpetuates cancer-associated inflammation [16]. This suggests that different subsets of the inflammatory arsenal play opposing roles in shaping cancer behavior [16]. It is clear that components of the CBC can provide important prognostic information in solid tumors and haematologic malignancies that are not only limited to survival predictions or assessment of disease progression, but also are important tools when evaluating response to treatment. Thus, true assessment of the utility of the CBC as an inexpensive, established, and globally accessible prognostic factor in many malignancies requires careful studies of the sample results obtained. It is likely that other prospective studies examining the biology behind the prognostic value of the different components of the CBC would later yield significant therapeutic progress and a thorough understanding of disease pathogenesis.

Aim:-

The aim of this study is to use peripheral blood cells as an inflammation biomarker in gastric cancer in patients attending Surgery Department at ESUT Teaching Hospital, Parklane Enugu.

Specific Objective

1. To calculate the neutrophil to lymphocyte ratio (NLR), lymphocyte to monocyte ratio (LMR) and platelet to lymphocyte ratio (PLR) in the subjects and access their use as prognostic biomarkers.
2. To determine the complete blood count and erythrocyte sedimentation rate of the subjects at their pre-treatment and treatment period.
3. To determine age group susceptibility in this solid cancer for proper treatment and management in these patients.

Justification Of The Study

Though biomarkers are organ specific, most are not cost effective and takes days for result to be available. Interestingly, recent studies shows that NLR, LMR, PLR has predictive value in accessing inflammation in systemic disorders. These indices can be obtained from simple complete blood counts. The relevance of this study lies in exploring the possible use of these simple, costs effective and less laborious indices in the diagnosis and treatment of cancer cases especially in resource poor settings.

Scope Of The Study

The economic and psychological challenges posed by cancer is profoundly overwhelming in our society nowadays, so this work focused on the use of complete blood cells for the assessment of inflammation in some solid cancers studied in this work. The assessment of inflammation involved the use of these ratios: NLR, LMR and PLR simple and cost effective biomarkers for the prediction of hazard ratios and overall survival in these patients. The CBC result obtained using autohaemoanalyzer monitored the efficacy of the chemotherapeutic plans and treatment during the different stages of these solid cancers. This work obtained the specific age group susceptibility of these patients in some solid cancer while in some specific age group susceptibility was not ascertained. This specific age group susceptibility creates better awareness, treatment and management for the patients, their families and society at large.

Statement Of Problems

The encumbrances in the early detection, diagnosis and treatment of cancer has led to early deaths, so employing simple, cost effective, fast and non-invasive method will timely eradicate the delays in treatment hence ensuring chances of long time survival. Also determining the specific age group that is more susceptible will increase awareness and promote screening of the age group.

Limitation Of Study

Some of the subjects died during the course of this work. Follow-up proved difficult due to subjects' unavailability for their scheduled chemotherapy due to economic constraints.

Literature Review:-

Gastric Cancer

Gastric cancer also known as Stomach cancer is a cancer that develops from the lining of the stomach [17]. Early indications may incorporate acid reflux, upper stomach torment, queasiness and misfortune of craving. Afterward signs and indications may incorporate weight misfortune, yellowing of the skin and brightening of the eyes, spewing, trouble gulping and blood within the stool among others. The cancer may spread from the stomach to other parts of the body, especially the liver, lungs, bones, lining of the midriff and lymph hubs [18]. The foremost common cause is contamination by the bacterium Helicobacter pylori, which accounts for more than 60% of cases. Certain sorts of H. pylori have more prominent dangers than others [19]. Smoking, dietary components such as salted vegetables and weight are other chance variables. Around 10% of cases run in families, and between 1% and 3% of cases are due to disorders acquired from a person's guardians such as genetic diffuse gastric cancer. Most cases of stomach cancers are gastric carcinomas. This sort can be separated into a number of subtypes. Lymphomas and mesenchymal tumors may moreover develop within the stomach. Most of the time, stomach cancer develops in stages over a long time. Conclusion is as a rule by biopsy done amid endoscopy. This is often taken after, by restorative imaging to decide in the event that the illness has spread to other parts of the body. Japan and South Korea, two nations that have increased rates of the illness, screen for stomach cancer [20]. A Mediterranean diet brings down the hazard of cancer as does the ceasing of smoking. There is tentative evidence that treating H. pylori diminishes future hazard. On the off chance that cancer is treated early, numerous cases can be cured. Medications may incorporate a few combinations of surgery, chemotherapy, radiation treatment and targeted treatment. In the event that it is treated late, palliative care may be exhorted [21].

Outcomes are often poor with a less than 10% five-year survival rate globally [22]. This is largely because most people with the condition present with advanced disease [22]. In the United States, five-year survival is 28%, while in South Korea it is over 65%, partly due to screening efforts [22]. Globally, stomach cancer is the fifth leading type of cancer and the third leading cause of death from cancer, making up 7% of cases and 9% of deaths [23]. In 2012, it newly occurred in 950,000 people and caused 723,000 deaths. Before the 1930s, in much of the world, including most Western developed countries, it was the most common cause of death from cancer [24). Rates of death have been decreasing in many areas of the world since then. This is believed to be due to the eating of less salted and pickled foods as a result of the development of refrigeration as a method of keeping food fresh. Stomach cancer occurs most commonly in East Asia and Eastern Europe. It occurs twice as often in males as in females [25].

Malignant lesions of the stomach exhibit a wide geographical variation in prevalence. While the prevalence was initially high in the developed countries such as the United Kingdom and the United States of America, recent findings have indicated a significant drop in incidence rates in these countries which are attributed to better living conditions and dietary changes[26]. Conversely, in spite of poorer living conditions, malignant lesions of the stomach have always enjoyed a comparatively low prevalence in Africa . With the advent of modernization and adoption of Western-type lifestyles in most countries in Africa, malignant diseases hitherto rare in the native African are on the increase [27]. A 16 years survey done from 1989 to 2005 at IIe-Ife, on stomach cancer reported peak age of between 41-60 years with male to female ratio of 1.5:1. [28]. At Lagos and Shagamu from 1995 to 2006 reported male to female ratio of 1.8:1 with peak age of 60-70 years [29]. At Ibadan from 2004-2009, male to female ratio of 1.45:1 and peak age of 60-70 years [30]. At IIe-Ife, male to female ratio of 1.2:1 with peak age of 50-59 [31] .At Zaria from 1995 to 2009, male to female ratio was reported as 1.4:1 and peak age of 51-60[32]. Recent study at Ibadan form 1990 to 2008, male to female ratio of 1.4:1 with peak age of 61-70 years [27].

Relative to older patients, young patients have a female preponderance, a more frequent occurrence of diffuse cancer and less intestinal metaplasia [33]. This predominance of females is considered by some to be due to hormonal factors [33]. Cancers in young patients are more often multifocal than in older patients [34]. Approximately 10% of young gastric cancer patients have a positive family history, some of which are accounted for by inherited gastric cancer predisposition syndromes [35]. Although the underlying genetic events are not always known [35].

Full Blood Count In Gastric Cancer

Anemia caused by bone marrow infiltration, called leucoerythroblastic anemia, is well described in various solid malignancies and causes an impaired hematopoiesis, which is evident on the peripheral blood smear.

Full blood count is a prerequisite examination asked from all cancer patients some time before surgery, utilize of chemotherapy and/or radiotherapy. Decreased parameters antagonistically impact the result of cancers. [36] Hematological parameters and markers of the systemic inflammation reaction have been connected with prognosis in a few strong cancers [37].Anemia is a common morbidity experienced in most strong cancer patients and, as a result, cancer patients endure from shortness of breath, weariness, and diminished vitality, among other side effects. Iron deficiency of cancer may too be apparent at introductory determination. Activation of the immune system appears to be the driving drive for a worldwide decrease of erythropoiesis, closely resembling to chronic inflammatory conditions observed in anemia of persistent illness [38]. It is hypothesized that the immune system may be mobilized to fortify generation of inflammatory cytokines that can obstruct erythropoiesis. Thus, there's deficiently separation and expansion of erythroid antecedents, driving to anaemia [39]. Anemia caused by bone marrow infiltration, called leucoerythroblastic anemia, is well depicted in different strong malignancies and causes an impeded hematopoiesis, which is clear on the peripheral blood smear.

Other variables that will specifically influence the bone marrow incorporate past or concurrent treatments, such as nearby radiation to bone marrow, systemic utilization of radiopharmaceuticals (strontium-89), systemic chemotherapy, and long-term use of combined androgen blockade. [40]. Inflammatory cytokines can also impair iron metabolism which can result in reduced serum iron levels and iron retention within the reticuloendothelial system. Tumors can also produce cytokines, which induce iron sequestration, thereby decreasing RBC production. Shortened RBC survival may also result from over expression of inflammatory cytokines [39]. Furthermore, chronic blood loss at tumor sites can exacerbate anemia from cancer [41]. Anaemia can result from bone marrow invasion by solid tumors. Myelophthisis, resulting from bone marrow replacement by solid tumors or haematologic malignancies, may manifest as anaemia or pancytopenia. While anaemia in patients with cancer is often produced by

the cancer itself; the addition of chemotherapy significantly increases the proportion of patients with anaemia. [42]. The myelosuppressive effects of cytotoxic chemotherapy agents on erythropoiesis are generally cumulative in nature and up to 50% of patients with cancer may develop chemotherapy-induced anaemia over the course of chemotherapy [43]. A steady increase in the rate of anaemia occurs with additional cycles of chemotherapy as evidenced by data from the European Cancer Anaemia Survey (ECAS). This study showed that the rate of anemia (haemoglobin [Hb] <12 g/dL) increased from 19.5% in cycle 1 to 46.7% by cycle 5. The percentage of patients with more severe anaemia (grades 2 and 3) also increased with greater numbers of chemotherapy cycles 44. Patients can also become anaemic within the first 2 cycles of chemotherapy as evidenced by data from a separate analysis of ECAS data in patients who were not anaemic (Hb >12 g/dL) prior to initiating chemotherapy. In this analysis, 62% of patients experienced an Hb decline by 1.5 g/dL within a median time of 6.1 to 7.2 weeks and 51% experienced an Hb decline by 2 g/dL within a median time of 7.3 to 8.9 weeks [45]. Depending on the chemotherapeutic agent or regimen, anemia may be mild in degree (grade 1 or 2) in about 10%–85% of patients. Moderate or severe anemia will develop in about 2%–55% of patients and require intervention [46]. Chemotherapy may cause anaemia in multiple ways. First, some chemotherapeutic agents will affect the production of new RBCs by damaging normal bone marrow precursor hematopoietic cells. When these cells are damaged, the ability of the bone marrow to produce new RBCs is impaired. Some drugs, such as platinum-containing agents, are nephrotoxic, and also affect the development of new RBCs by interfering with erythropoietin production by the kidneys [41].

Patients with cancer may develop anaemia secondary to poor nutrition in general or due to reduced function in the gastrointestinal (GI) tracts to absorb nutrients [39].Folate deficiency may develop in anorexic patients with cancer, while vitamin B_{12}deficiency can arise in patients who have undergone gastric or small bowel resection or bypass or have atrophy of stomach parietal cells, which produce intrinsic factor necessary for vitamin B_{12} absorption [47]. Iron deficiency anaemia due to blood loss or the inability to absorb iron in the GI tract often occurs in patients with malignancies of the GI tract, including colorectal cancers. [43]. Nutrient deficiencies in folate, vitamin B_{12} or iron may lead to anaemia because all of these nutrients are essential to red blood cell (RBC) production and development. [48].

Therefore, the hemoglobin concentration in peripheral blood was also studied as a prognostic factor in malignant disorders [49]. The role of hemoglobin levels in clinical outcomes has been extensively examined in other solid cancers, such as cervical, ovarian, breast, prostate, renal, liver, and endometrial cancer. Researchers' studies established an association between hemoglobin levels and survival in solid carcinoma [50]. Similar results have been described for other solid malignancies, including cervical, prostate, esophageal, and lung cancer, reported that a low haemoglobin count is an indicator of poor prognosis [51]. Because of these studies done, close attention should be paid to anaemia before and during treatment, with the goal of maintaining adequate haemoglobin levels and, as a consequence, ideally improving cancer outcomes and quality of life.

Red cell distribution width (RDW) is a measure of the range of variation of red blood cell (RBC) volume that is reported as part of a standard complete blood count. More often than not red blood cells are a standard measure of almost 6–8 μm in diameter. Certain disorders, however, cause a significant variation in cell size. Higher RDW values indicate greater variation in size [52]. If anaemia is observed, RDW test results are often used together with mean corpuscular volume (MCV) results to determine the possible causes of the anaemia. It is mainly used to differentiate anaemia of mixed causes from anaemia of a single cause [53]. RDW reflects variability in the size of circulating red blood cells (anisocytosis) [53]. Its inclusion in the complete blood count has made diagnosing certain anaemias easier, especially those that are microcytic (caused by iron deficiency), and those due to vitamin B_{12} or folic acid deficiencies [54]. An increased RDW can also result from conditions that alter the shape of red blood cells due to the untimely release of juvenile cells into the circulatory system (extreme blood loss), abnormal heamoglobin (e.g., sickle cell anaemia), heamolysis or haemolytic anaemias [53]. Red cell distribution width (RDW) is an index of the heterogeneity in the size of circulating erythrocytes and may be used to quantitate the amount of anisocytosis on peripheral blood [55]. Accordingly, it reflects impaired erythropoiesis and abnormal red blood cell survival but it correlates also with inflammation, under nutrition and impaired renal function, with inadequate production of erythropoietin (EPO) [56].

Quite recently, red cell distribution width (RDW), have also been shown to associate with survival of solid tumors [57]. Growing evidence indicated that high RDW is associated with systematic inflammation and elevated RDW harbored the potential to predict poor survival in a variety of solid cancers, consisting of breast cancer, lung cancer, prostate cancer, endometrial cancer, colon, esophageal cancer and upper tract urothelial carcinoma [58],[59]. A

report done by some researchers evaluated RDW in gastric cancer patients and healthy individuals in a retrospective study and concluded that gastric cancer patients had significantly higher mean RDW values (14.9 ± 3.9) than healthy individuals (12.2 ± 0.7) .Therefore, they suggested that an elevated RDW level in a patient with upper gastrointestinal symptoms may be utilized as an indication for upper gastrointestinal endoscopy to screen for probable gastric cancer [60].

In spite of the fact that the components causing increased RDW remain vague, several other components, including inflammation and malnutrition, may be involved. It is reported that inflammation and oxidative stress influenced RDW [61]. Furthermore, it was observed that RDW also reflected the increase in the cytokines such as IL6, TNF-a and hepcidin circulating in blood [62];[63]. Solid cancer, on the other hand is characterized with increased inflammation and RDW which were rarely examined in solid cancers [64],[65],[66],[67],[68],[69].

The white blood cell count (total and differentials) and packed cell volume predict disease severity and mortality risk [70]. For example, elevated WBC counts predict a worse prognosis in patients with cancer and anaemia predicts increased risk of death of solid cancer patients [71]. Solid cancer patients with an absolute granulocyte count of 6000/mm^3 or more were observed to have a shorter survival than the ones with less than 6000/mm^3. A similar phenomenon was observed independently in patients with advanced solid carcinoma [72]. A significantly worse 5-year cancer-related survival for patients with peripheral blood monocyte count>300/mm^3 than for patients with a count<300/mm^3 was observed in Japan [73].The prognostic significance of neutrophils, lymphocyte, platelet, mean platelet volume, platelet-lymphocyte ratio and neutrophils-lymphocyte ratio in patients with locally and advanced gastric cancer were assessed in Turkey and found to influence overall survival [74]. Total leucocyte count (TLC), if elevated, predicts poorer prognosis [75]. The white blood cell count (total and differentials) and platelet count predicts disease severity and mortality risk. White blood cell (WBC) count, an inflammatory biomarker, has become a useful predictor of certain diseases as well as a marker of infection [76]. An elevated WBC count, even within the normal range, has been associated with breast cancer incidence and mortality rate [77]. The role of WBC count as a surrogate for inflammation has not been examined in the context of well-known effect modifiers for breast cancer development [53]. Several studies have attempted to identify the association between WBC counts and solid cancer risk especially in gastric cancer, but no consistent evidence has been found [78].

The role of neutrophils in human cancers is relatively small [79]. From an initial interest in the 1980s, the number of publications on neutrophils in cancer-related studies has been steadily going down [79]. However, this trend is now beginning to change with the realization that neutrophils are indeed important players in cancer development, as reflected by several recent reviews [80]. Also the role of neutrophils in cancer is multifactorial and not fully understood. Neutrophils reflect a state of host inflammation, which is a hallmark of cancer [81]. They can participate in different stages of the oncogenic process including tumor initiation, growth, proliferation or metastatic spreading [82]. The various roles of neutrophils in cancer development and progression, by several groups have recently explored the role of neutrophils and other markers of host inflammation on clinical outcomes [83]. Furthermore, most data are available for the ratio of neutrophils to lymphocytes measured in the peripheral blood, the so-called neutrophil-to-lymphocyte ratio (NLR)[84]. An elevated NLR is associated with worse outcomes in many solid tumors, both in early and advanced stage of cancer [84]. In contrast a rising NLR during the first weeks of treatment had the opposite effect [85]. These findings make NLR a biomarker easy to evaluate, and that have potential for the identification of early responders.

Peripheral blood absolute neutrophil counts are increased in patients with cancer. Tumours produce granulocyte colony-stimulating factor (G-CSF) which skews the neutrophil retention/release balance in bone marrow, leading to this increase in blood neutrophils [86]. In direct contrast, neutropenia in patients undergoing chemotherapy has been shown (by meta-analysis) to be beneficial to survival [87].

This may of course just be a reflection of satisfactory toxicity quality of the drug being accomplished to kill tumor cells. It must too be recalled that blood neutrophil levels increases beneath other conditions, such as diseases. Inside the same patient, neutrophils may show varying parts at diverse sites. Besides, suitable inflammatory reactions are dependent upon a working balance of neutrophil generation, release from bone marrow, recruitment to the location of damage and clearance. Dysregulation of this homeostatic process, for instance, by tumour-derived G-CSF, might propagate harm. In numerous patients with progressed cancer, increased counts of neutrophils in blood are found. How cancers initiate neutrophilia is vague, but generation of granulocyte-macrophage colony-stimulating figure (GM-CSF) could be a conceivable instrument in a few sorts of cancer [88]. In addition, other cytokines such as

granulocyte colony-stimulating factor (G-CSF), interleukin- (IL-) 1, and IL-6 produced by tumors seem to contribute to elevated neutrophil numbers in blood [89]. This neutrophilia is associated with poor prognosis in several types of other solid cancers, such as lung, melanoma, and renal carcinomas [90]. In agreement with this; the presence of neutrophils within certain tumors seems also to be an indicator of poor prognosis [90]. Because neutrophilia is frequently associated with inflammatory responses to infections and tissue damage, neutrophilia represents evidence for the concept of cancer-related inflammation inducing tumor progression [91]. Not only elevated numbers of neutrophils in peripheral blood as reflected by NLR are of prognostic relevance, but also their presence in the tumor can be associated with clinical outcome [92]. In this context, it should be noted that what mainly affect the worse outcome is the presence of inflammation within the tumor, and the assessment of neutrophils is an indirect measure of this and can differ among tumor types.

Lymphocytes represent a vital component of the inflammatory microenvironment favoring the start and progression of malignancies. On the other hand, lymphocytes are key effectors of antitumor immune reactions, for instance as they sense senescent cells ($CD4^+$ T lymphocytes), as they release cytokines and stimulate other immune cells (NKT cells) or as they exert direct cytolytic activities against transformed cells (NK and $CD8^+$ T lymphocytes). Elimination and equilibrium are achieved via lymphocytes, mainly the T cell subpopulation [93]. In cancer patients the "healthy" reaction against the tumor is counteracted by a suppressive, tumor-driven effect. This hypothesis is strengthened by recent studies showing that the absence or presence of T cells in colorectal cancer specimens more accurately predicted the outcome than using standard prognostic factors [94]. Other studies in different types of cancer, mainly cervical and breast cancer have also shown similar results [95]. These studies further confirmed the importance of the immune response in prognosis alongside other more established factors [96]. Recent studies also support the case of immunoediting by observing that tumor infiltration by lymphocytes is linked to tumor-associated immune response, mainly showing that the presence of tumor infiltrating[97] lymphocytes may be associated with improved prognosis and clinical outcome in solid cancer patients [97]. The composition of lymphocytic populations in blood, ascites and tumors is regulated by various cytokines and chemokines produced by the tumors or the components of the immune system [98].

The higher the absolute lymphocyte count (ALC), the better the overall survival, the lower the platelet- lymphocyte ratio, the better the overall survival. Works done by some researchers analyzed the correlation between curability by conventional treatment of the 589 cases of the different types of solid cancer with reasonable possibilities of cure, and the total number of leukocytes in peripheral blood[99]. A positive significant correlation was found between gastric cancer curability and the total number of peripheral ALC, a negative correlation was found between the total number of peripheral absolute neutrophils (segmented and none segmented) and gastric cancer curability. No correlation was found between curability of gastric cancer and absolute monocytes (AMC), absolute eosinophil (AEC), or absolute basophils (ABC). The molecular mechanisms by which cytotoxic drugs actuate exhaustion of lymphocytes have not been characterized and may include proliferative capture in lymphocyte precursor compartments or, on the other hand, coordinate acceptance of apoptosis in mature cells. Their findings indicate that the immunologic activity of peripheral lymphocytes may be a favorable factor in the cure of cancer by conventional treatment [99].

It has been hypothesized that monocytes advance tumor progression and support antitumor insusceptibility. Moreover, an increased monocyte count in the peripheral blood is considered a predictive factor of poor prognosis in solid cancer patients [100]. Elevated pre-treatment monocyte counts in a multivariate analysis were found to be an independent prognostic factor for gastric cancer-related survival. A high peripheral AMC (alone or combined with neutrophil count) has also been associated with adverse outcomes in other solid cancers such as cervical and ovarian cancer [101].

An increased pre-treatment platelet count has been identified as an adverse prognostic indicator in gastric and gynecological malignancies [102]. A high platelet count is associated with tumor progression and poor survival in patients with solid cancers [103].The relationship between cancer and thrombosis was established in the late 19th century by Armand Trousseau [104]. Since then, thrombocytosis has been associated with cancer prognosis. Clinical studies have investigated the frequency of high platelet count in patients with cancer and the role of high platelet count in patient outcomes [105]. The overall survival (OS) of patients with solid cancers especially gastric, ovary cancer, lung cancer, and breast cancer has been related to thrombocytosis at the time of diagnosis [105]. Some workers reported that platelet count is a predictor of metastasis and venous thromboembolism in patients with solid cancer [106].

Penetration of the bone marrow by metastatic tumour cells can result in bone marrow failure and resultant hematologic abnormalities. As cancer cells attack the healthy marrow, they supplant hematopoietic stem cells, leading to the depletion of multiple cell lines. A work done in 2010 describes a typical pattern of anemia, thrombocytopenia, and increased mortality. With advanced age comes immune system dampening and modulation that could potentially predispose to both malignancy and thrombocytopenia [107]. Other theories include an increase in anti-platelet antibody with carcinoma, as well as the presence of immune-modulating oncogenic viruses [108].

Mean platelet volume (MPV), the most commonly used measure of platelet size, represents a surrogate marker of platelet activation [109]. Large platelets have been proposed to be more reactive and more likely to aggregate which leads to their faster utilization. MPV is inversely proportional to the platelet count, which is associated with haemostasis maintenance and preservation of constant platelet mass [110]. This means that the increased production of platelets is accompanied by a reduction in their mean volume. In various pathologies, this physiological proportion is disturbed[111]. Markedly enhanced or abnormal thrombocytopoiesis, increased wear, or the effect of activating factors on blood platelets may lead to changes in the proportions between MPV and PLT [112]. As of late, increasing consideration has been paid to the evaluation of MPV in cancer patients. Neoplastic transformation is associated with a chronic inflammatory process, which may also influence platelet parameters. The observation of decreased platelet size in cancer patients has been explained by an increased cancer-associated platelet activation and exhaustion [113]. In this context, a low MPV may reflect degranulated “exhausted” platelets that have already secreted their potentially tumor growth-promoting cytokines, and thus are associated with a worse outcome in cancer patients [114]. In addition, an increased release of small platelets from the bone marrow may be the result of enhanced megakaryopoiesis triggered by tumor-related cytokines [115]. Altered MPV levels have previously been analyzed as a prognostic and predictive biomarker in cancer patients and have been associated with prognosis in several solid cancer entities such as gastric, bladder, renal, endometrial, non-small cell lung cancer, and hepatocellular carcinoma [116]. Gastric cancer is another gastrointestinal injury accompanied by changes in the platelet parameters. It is characterized by early metastasis formation and high mortality [117]. Work in 2013, reported that in patients with primary gastric cancer, MPV was considerably higher before treatment as compared to healthy subjects [118]. After treatment, the level of MPV underwent a significant reduction to the values comparable to control. Research conducted in 2016 confirmed earlier reports on MPV in gastric cancer patients [114]. The researchers also observed a high pre-treatment level of MPV in patients and its significant decrease when the treatment was applied. The development of gastric cancer has been known to be closely associated with chronic inflammation accompanied by significantly elevated IL-6 concentration [119]. The authors suggest that the increased MPV in gastric cancer patients can be a sequel of inflammatory condition and the accompanying elevated level of IL-6 [120]. Likewise, in 2013, researchers observed that MPV and PLT in patients in an early stage of cancer were similar to those found in healthy subjects and increased with the disease progression [121]. Therefore, a comprehensive evaluation of the literature is warranted. Routine peripheral blood counts may be useful prognostic factor for evaluating the accuracy of risk stratification in patients with solid cancers. Since chemotherapy and other solid cancer treatment affect the full blood count, it is important to know the extent of these effects by comparing the full blood count results before and during treatment in these subjects.

Erythrocyte sedimentation rate (ESR) is the most widely used laboratory test for evaluating the inflammatory status in clinical practice, including infection, autoimmune and malignant diseases [122]. Increased ESR is habitually experienced in patients with cancer. The outcome in various malignancies depends on the type of the underlying disorder, the stage and duration of the disease, and the regimen and intensity of the antitumor treatment [123]. In addition, an elevated ESR level has also been identified as a prognostic factor adversely affecting survival in cancer patients [124]. A number of studies indicated that an increased ESR level is associated with worse survival; patients with higher ESR values was observed in gastric cancer and other solid cancer such as: colorectal cancer [125], renal cell cancer, head and neck cancer, soft tissue sarcoma , breast cancer, and prostate cancer [123], had a shorter survival compared with those with normal ESR levels. However, serum CRP levels are not routinely assessed in the pre-treatment assessment, hence the use of ESR is more readily available and inexpensive compared to CRP.

Total blood counts are routinely performed amid chemotherapy and other solid cancer treatments to check the number of each sort of blood cell circulating within the body [126]. Complete blood counts are routinely performed during chemotherapy and other breast cancer treatments to check the number of each type of blood cell circulating in the body. The complete blood count too helps to check for different side effects of chemotherapy. Blood counts are monitored regularly before each cycle of treatment in breast cancer patients, since cancer treatments affect the bone marrow’s ability to make blood cells. Chemotherapy medications and radiation exposure can significantly

reduce the levels of blood cells. This reduction increases the risk of infection, fatigue and bleeding. Complete blood count especially lymphocytic count reflects the response of cellular immunity in a cancer patient. The alteration in hematological parameters influences the disease progression. Hemoglobin (Hb) and packed cell Volume (PCV) are indirectly associated with increased risk of cardiac failure in cancer patients [126].

It is evident that components of the CBC count can provide valuable prognostic information in solid tumors and hematologic malignancies that are not only limited to survival predictions or assessment of disease progression, but also are important tools when evaluating response to treatment. Thus, true assessment of the utility of the CBC count as an inexpensive, established, and globally accessible prognostic factor in many malignancies requires careful studies of the sample results obtained. It is likely that future planned studies considers analyzing the science behind the prognostic value of the distinctive components of the CBC count would afterward yield significant therapeutic advances and a thorough understanding of disease pathogenesis. of illness movement, but too are vital instruments when assessing reaction to treatment.

In this present study, complete blood count was studied in order to determine and compare their pre-treatment and treatment CBC results for prognostic values during the courses of chemotherapy to prevent the risk of unpleasant and life threatening side effects such as anaemia, fatigue, infections and bleeding. Also to prevent disruption of delivery of the treatment, due to none efficient monitoring of the CBC which can result in change to the planned dose and time.

Materials and Methods:-

Study Site

The study was conducted in ESUTH Teaching Hospital Parklane GRA Enugu, Enugu State. Enugu was created on 27th August 1991. Enugu State is one of the five states in the South Eastern geopolitical zone of Nigeria and was the administrative capital of the former East Central State. It has an area of 8727.1 square kilometers. It is bounded by Anambra State on the west, Imo and Abia States on the south, Kogi state on the north and Ebonyi and Benue States on the east. The state has a projected population of over 3.5 million people. The major municipal cities are the capital, Enugu and Nsukka.

Study Design

This was a longitudinal study. The control samples were collected from sex and age matched apparently healthy individuals. The pre-treatment samples were collected at diagnosis and the treatment samples collected at different stages [stage 1(localized); 11 (tumour); 111(lymph node); 1V (metastasis)] of the treatment. The controls, pre-treatment and treatment samples collected were compared and changes reported. The treatment samples were collected from seven days to at least a day before the next treatment. The study lasted for 14 months (August 2019 to December 2020) and a total of 4 subjects were lost to death.

Study Population

This study comprised of fifty-four (54) gastric cancer subjects. The subjects used in this study were adults between the ages of 21years to70years. There was no ethnicity differentiation. Questionnaires were used to obtain other demographic characteristics, clinical/provisional diagnosis, their life styles, and the staging of these solid cancers. Follow up the subjects began at entry of this study. Subjects were followed monthly for a period of fourteen months depending on the scheduled clinical appointments of the subjects by their clinician

Criteria

Exclusion criteria:

Subjects suffering from other types of health problems like liver cirrhosis, active bleeding, intestinal obstructions, diabetes, hyper blood pressure, non-solid cancers examples leukemia, lymphomas, myelomas and soon on, mixed cancers like adenosquamous carcinomas, mixed mesodermal tumors, and other types of solid cancers. Also subjects with the presence of any haematological system diseases. These subjects will be excluded based on the clinical diagnosis already made by the clinician's report

Inclusion criteria:

All subjects suffering from all forms of gastric cancer, which has been diagnosed by their clinician at the different stages of the illness. Also subjects with life expectancy of more than three years.

Ethical Consideration/Informed Consent

All subjects gave a verbal consent and they study protocol were approved by the Ethics Committee of Enugu State University of Science and Technology Teaching Hospital Park Lane G.R.A. Enugu-North Local Government Area. The subjects attending surgical out-patient (SOP) clinic at ESUT Teaching Hospital Parklane GRA Enugu State were used.

Data Collection

Subjects' data including demographics (example ages, sexes, level of education occupation and soon on) and clinicopathological features (cancer location, and stages) were all obtained using questionnaires. The cancer staging was performed according to the 7th edition of the Union for International Cancer Control- American Joint Committee on Cancer Association on cancer classifications. Blood sampling were performed to measure erythrocyte sedimentation rate (ESR), total and differential leucocytes counts, platelet counts for the calculation of neutrophil/lymphocyte ratio (NLR), platelet / lymphocyte ratio (PLR), lymphocyte / monocyte ratio (LMR). These ratios are defined as the total number of neutrophils, platelets, monocytes divided by the total number of lymphocytes.

Sample Processing

Sequestrated sample of a total four milliliters of blood were collected by venipuncture at the antecubital vein from all the subjects at different stages (pre-treatment and treatment). The blood samples were collected in dipotassium ethylenediaminetetraacetic acid (K_2EDTA) containers commercially prepared and processed immediately. Stored blood samples were not used in this research work. The complete blood count (CBC) and ESR were done as soon as possible or at least within thirty minutes to one hour from the time of collection. The sample collections and processing were done at all the different stages of cancer in this research work and results analyzed.

Determination Of Haematological Parameters

Haematological parameters such as; haematocrit (HCT), haemoglobin concentration (Hb), total white cell count (TWCC), differential white cell count, total platelets count, MCHC, MCV, MCH were immediately analyzed on samples collected in EDTA tubes by a haematological analyzer "Be-5300 – Mindray" Japan. Determination of erythrocyte sedimentation rate was done using Westegren method.

Statistical Analysis

Sample size was calculated using Graphpad Prism of Statmate Software version 2.0. A sample size of 54 has 90% power to detect a difference between means of 0.33 with significant difference level (alpha) of 0.05 (two-tailed). The mean and standard deviation (mean value ± SD) of the data were tabulated for each group. The data was analyzed with IBM Statistical Package for Social Sciences (SPSS PC. version 20.0; SPSS Inc., Chicago, III., USA). The ROC curve was used to determine the different cut-offs in the ratios (NLR, LMR and PLR). Cox proportional-hazards regression analysis was used to evaluate the prognostic factors (ages, duration, ratios and their cancer diagnosis). Overall survival (OS) was defined as the duration from diagnosis to death or last follow-up. The ANOVA and Tukey HSD post- hoc test were used to compare the results obtained within controls, pre-treatment and treatment result; age groups and the age group susceptibility.

Results:-

Table 1: Demographic table of the Gastric cancers.

Sample sizes of twenty-six female and twenty-eight male subjects with age range mean±SD of 43.±21.0 were studied. Educational qualifications were: primary, 0(0%); secondary, 40(74%) and tertiary, 14(26%). There occupations were: civil servants, 10(19%); business, 44(81%) and students, 0(0%). The duration was calculated from the onset of diagnosis to the end of this research and it was calculated in months. The duration was grouped into three categories in this work. The duration on each of the cancer were reported in mean±SD. The total number and percentage was reported for gastric Cancer. Average treatment intervals in weeks (mean±SD) were: gastric cancer (13.0±8.0). The controls of fifty-four subjects used in this work were apparently healthy individuals.

Table 1:- Demographic Table of the Gastric Cancers.

	Total number		**Percentage**	
	Test Subjects	Control	Test Subjects	Control
Gender	54	54	100	100

Females Males	26 28	30 24	48 52	56 44
Level of Education				
Primary	0	0	0	0
Secondary	40	45	74	83
Tertiary	14	9	26	17
Occupation				
Civil Servants	10	20	19	37
Business	44	34	81	63
Students	0	0	0	0
Age(years)Mean±SD	**43.0±21.0**			
Age Groups				
21-30	34	40	63.0	74.0
51-60	10	8	19.0	15.0
61-70	10	6	18.0	11.0
Duration (months)mean±SD	**23.6 ±9.4**			
11-30	22	0	44.0	0
31-50	20	0	40.0	0
51-70	8	0	16.0	0

Table 2: High and Low optimal cut-off values in the Gastric cancers with their total number and percentages respectively.

Receiver Operating Characteristic (ROC) curve calculated using Youden index for AUC (area under the curve) were constructed between death events and censors. The optimal cut-off values of pretreatment NLR, LMR, and PLR were calculated using ROC curve. According to these optimal cut-off values, the 54 subjects were classified into two groups: high and low NLR, LMR, and PLR with their respectively percentage.

Table 2:- High And Low Optimal Cut-Off Values In Gastric Cancers With Their Total Number And Percentages Respectively.

	NLR	**LMR**	**PLR**
Optimal cut-off	2.65	5.75	3550.0
Sensitivity	100	100	100
specificity	0.0	0.0	0.0
AUC	1.0	1.0	1.0
p-value	0.07	0.05	0.000
High (N %)	34(62%)	10(19%)	12(22%)
Low (N %)	20(38%)	44(81%)	42(78%)

Table 3: The prognostic purposes of NLR, LMR and PLR in Gastric cancer

A total of 20(38%) of Gastric Ca subjects had low NLR (<2.65) while 34(62%) had high NLR (>2.65). In LMR, 44(81%) had low ratio (5.75) and 10(19%) had high ratio (>5.75). 42(78%) had low PLR (<3550.0) while 12(22%) had high PLR (>3550.0). In GCa, the coefficient (B) NLR (2.0) and LMR (0.30) have a positive value. HR for NLR is 7.20 (95%CI: 0.90-60.05; p=0.07 and LMR is 1.30 (95%CI: 1.00-1.70; p=0.05). In NLR, there was no significant difference at p>0.05 meaning that there was no evidence of risk of death observed in either group (high NLR and low NLR). Lower LMR ratios are associated with increased HR and shortened survival time in the subjects with significant difference at p≤0.05 meaning that low LMR ratios are associated with increased HR and decreased survival time in the subjects. A unit decrease LMR by 1.0 increase HR of the ratio values by 1.30 (LMR) folds. Also a unit decrease in LMR decreases the survival time in the subjects by 1.70 months. But in PLR, there was no significant difference at p>0.05 meaning that there was no evidence of risk of death observed in either group (high PLR and low PLR).

Table 3:- The Prognostic Purposes Of Nlr, Lmr And Plr In Gastric Cancer.

Covariates (mean/N)	Coefficient (β)	Standard error	P-value	Exp(B) (Hazard ratio)	95% CI for Exp(B)	
					Lower	Upper
NLR(3.20)	2.00	1.10	0.07	7.20	0.90	60.05

[:0 <3.20(34); 1>3.20(20)							
LMR [0:<5.31(10);1>5.31(44)]	(5.65)	0.30	0.10	0.05*	1.30	1.00	1.70
PLR (0:<87.0(12);1>87.0(42)	(87.0)	0.22	0.20	0.30	1.25	0.81	1.92

P<0.05*-signifies a significant difference.

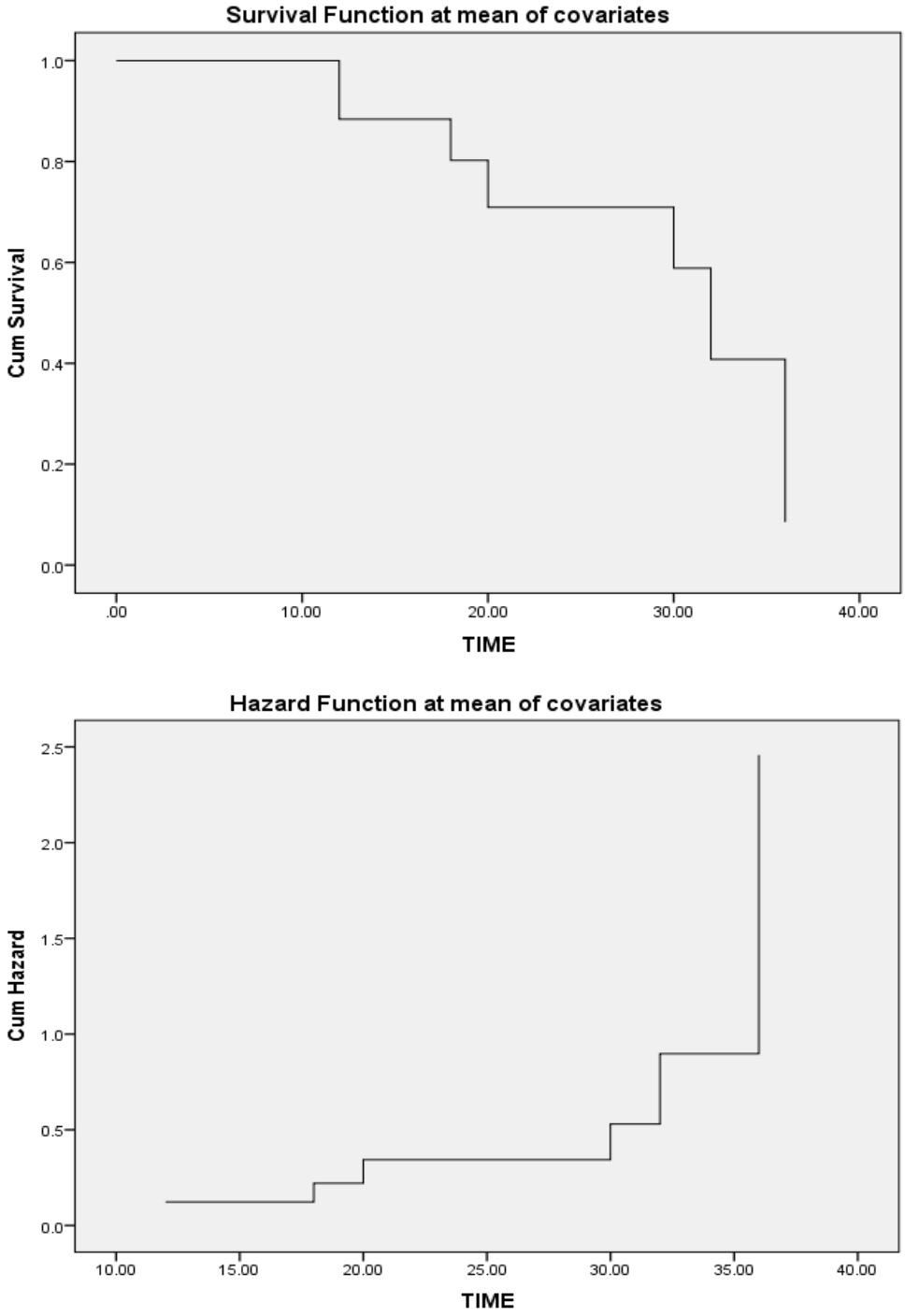

Figure 1:- The Prognostic Purposes in GCa Showing Nlr Survival And Hazard Function.

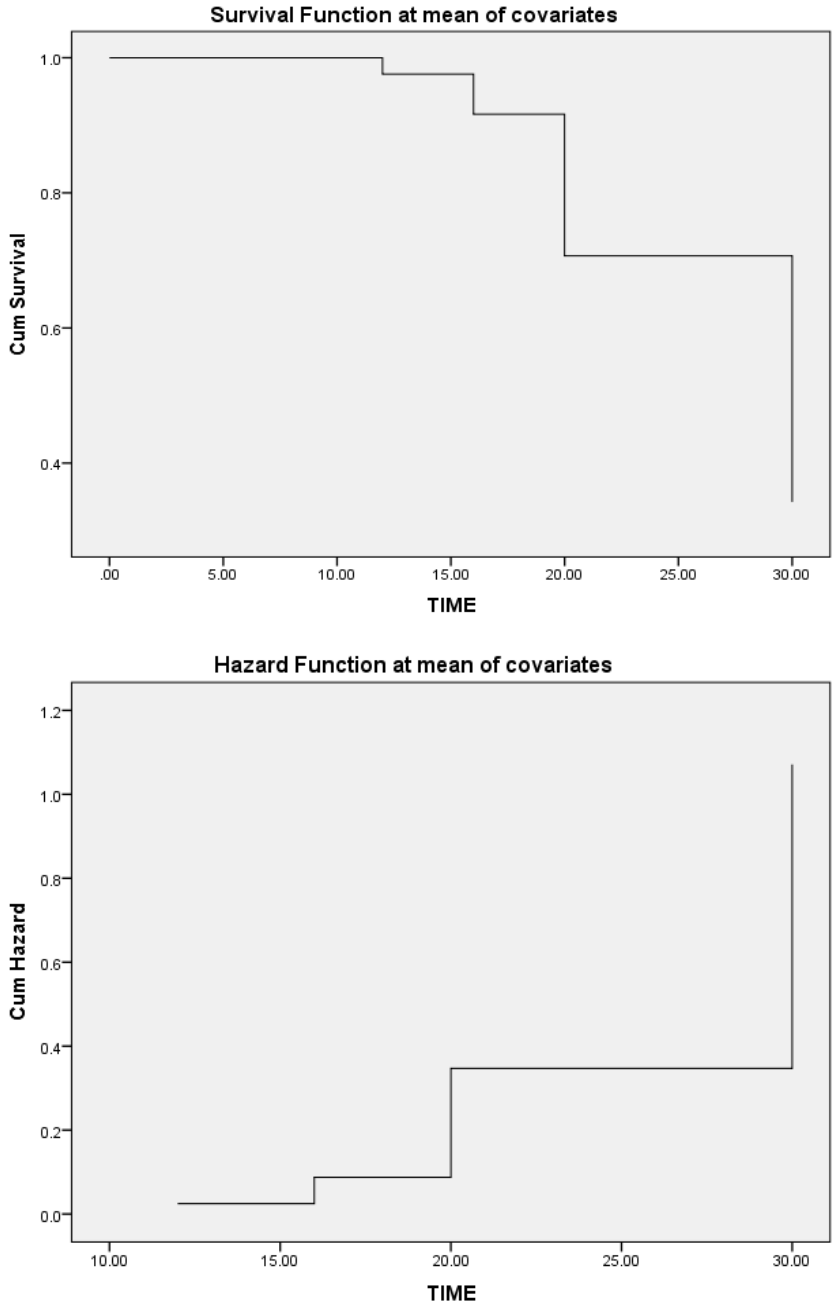

Figure 2:- The Prognostic Purposes in GCa Showing Lmr Survival And Hazard Function.

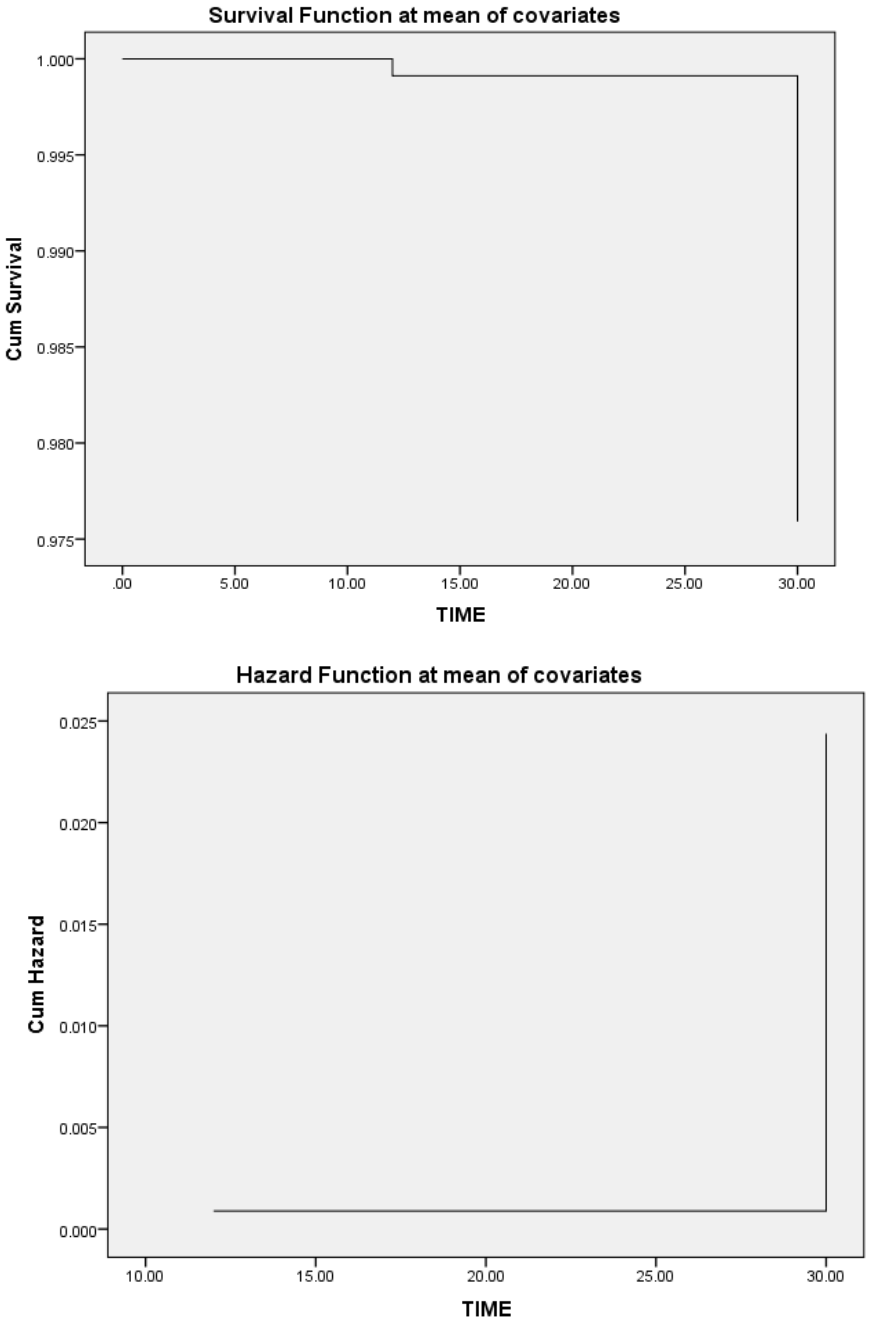

Figure 3:- The Prognostic Purposes In GCa Showing Plr Survival And Hazard Function.

Table 4: ANOVA showing the CBC and ESR results in controls, pre-treatment and treatment in Gastric Cancer (GCa) subjects

Analysis of Variance (ANOVA) was used to calculate the difference between and within the controls, pre-treatment and treatment CBC and ESR result in gastric cancer subject. A significant difference at $P \leq 0.05$ between and within the RBC, TPLT and some WBC parameters were observed. A Turkey post-hoc of the mean±SD was carried out on the RBC parameters, ESR, TPLT, TWBC, ANC, ALC and AMC within and between the control, pre-treatment and treatment results. In TRBC, a significant decrease control (4.5±0.5) and pre-treatment (4.74±0.6) at p=0.01; control (4.5±0.5) and treatment (3.98±0.7) at p=0.002; pre-treatment (4.74±0.6) and treatment (3.98±0.7) at p= 0.02 was seen. In HB, a significant increase control (13.1±0.2) and pre-treatment (12.03±0.9) at p=0.01; control (13.1±0.2) and treatment (10.20±1.1) at p=0.0001; pre-treatment (12.03±0.9) and treatment (10.20±1.1) at p=0.0001 was

observed. In HCT, a significant increase control (39.5±0.7) and pre-treatment (36.20±2.7) at p=0.02; control (39.5±0.7) and treatment (30.70±3.1) at p=0.0001; pre-treatment (36.20±2.7) and treatment (30.70±3.1) at p=0.0001 was observed. In MCHC, a significant increase control (33.2±0.5) and treatment (29.60±2.0) at p=0.001; pre-treatment (32.0±2.8) and treatment (29.60±2.0) at p=0.04 was observed. In MCV, a significant increase control (88.5±2.9) and pre-treatment (80.0±5.0) at p=0.01; control (88.5±2.9) and treatment (74.30±8.0) at p=0.0001; pre-treatment (80.0±5.0) and treatment (74.30±8.0) at p=0.03 were observed. In MCH, a significant increase control (29.6±1.9) and pre-treatment (25.30±1.8) at p=0.00001; control (29.6±1.9) and treatment (23.00±1.6) at p=0.0001; pre-treatment (25.30±1.8) and treatment (23.00±1.6) at p=0.02 was observed. In RDW, a significant decrease control (11±0.9) and pre-treatment (14±1.6) p=0.0005; control (11±0.9) and treatment (15.8±2.0) at p=0.00001; pre-treatment (14±1.6) and treatment (15.8±2.0) at p=0.05 was observed. In TPLT, a significant increase control (235000±41700) and pre-treatment (205.200±89.227) at p=0.03; control (235.000±41.700) and treatment (208.000±61.076) at p=0.04 was observed .In TWBC, a significant decrease control (3.9±0.7) and pre- treatment (9.22±2.8) at p=0.0001; control (3.9±0.7) and treatment (7.10±1.2) at p=0.001; significant increased pre-treatment (9.22±2.8) and treatment (7.10±1.2) at p= 0.04 was observed. In ANC, a significant decrease control (3.7±0.5) and pre-treatment (8.5±2.5) at p=0.00001; control (3.7±0.5) and treatment (6.7±1.8) at p=0.00001; pre-treatment (8.5±2.5) and treatment (6.7±1.8) at p=0.04 was observed. In ALC, a significant decrease control (2.1±0.4) and pre-treatment (2.6±0.6) at p=0.03; control (2.1±0.4) and treatment (2.1±0.7) at p=0.0001. In AMC, a significant increase at p=0.05 was observed between control (0.28±0.02) and pre-treatment (0.13±0.2); control (0.28±0.02) and treatment (0.04±0.07) at p=0.002. In ESR, control (12.2±5.0) and pre-treatment (29.0±14.4), p=0.05; control (12.2±5.0) and treatment (62.0±24.0), p=0.0001; pre-treatment (29.0±14.4) and treatment (62.0±24.0) observed a significant difference at p=0.0002.

Table 4:- Anova Showing The Cbc And Esr Results In Controls, Pre-Treatment And Treatment In Gastric Cancer (Gca) Subjects.

Parameter	Control(A) (mean±SD) (N=54)	Pre-treatment(B) (mean±SD) (N=54)	Treatment(C) (mean±SD) (N=50)	f-value	p-value	A vs B	A vs C	B vs C
TRBC($\times10^{12}$l)	4.5±0.5	4.74±0.6	3.98±0.7	7.7	0.002*	0.01*	0.002*	0.02*
HB(g/dl)	13.1±0.2	12.03±0.9	10.20±1.1	31.3	0.0001*	0.02*	0.0001*	0.0001*
HCT (%)	39.5±0.7	36.20±2.7	30.70±3.1	34.1	0.0001*	0.01*	0.0001*	0.0001*
MCHC(g/dl)	33.2±0.5	32.0±2.8	29.60±2.0	8.3	0.002*	0.4	0.001*	0.04*
MCV(fl)	88.5±2.9	80.0±5.0	74.30±8.0	16.3	0.0001*	0.01*	0.0001*	0.03*
MCH(pg/cell)	29.6±1.9	25.30±1.8	23.00±1.6	35.8	0.0001*	0.0001*	0.0001*	0.02*
RDW (%)	11±0.9	14±1.6	15.8±2.0	23.0	0.0001*	0.0005*	0.0001*	0.05*
PLT($\times10^{9}$l)	235.000 ±41.700	208.000 ±61.076	205.200 ±89.227	4.6	0.02*	0.03*	0.04*	1.0
MPV (%)	11±2.1	12±2.5	10±0.9	2.2	0.13	0.5	0.6	0.1
TWBC($\times10^{9}$l)	3.9±0.7	9.22±2.8	7.10±1.2	21.9	0.0001*	0.0001*	0.001*	0.04*
ANC($\times10^{3}$l)	3.7±0.5	8.5±2.5	6.7±1.8	20.0	0.0001*	0.01*	0.0001*	0.04*
ALC($\times10^{3}$l)	2.1±0.4	2.6±0.6	2.1±0.7	61.5	0.0001*	0.0001*	0.0010*	0.2
AMC($\times10^{3}$l)	0.28±0.02	0.13±0.2	0.04±0.07	8.4	0.002*	0.05*	0.002*	0.4
AEC($\times10^{3}$l)	0.00±0.0	0.08±0.1	0.09±0.2	1.5	0.2	0.1	0.4	0.8
ABC($\times10^{3}$l)	-	-	-	-	-	-	-	-
ESR(mm/hr)	12.2±5.0	29.0±14.4	62.0±24.0	26.0	0.0001*	0.05*	0.0001*	0.0002*

P<0.05*-signifies a significant difference. A (control), B (pre- treatment), C (treatment)

Table 5a and 5b: showing the CBC and ESR results at different age groups in gastric cancer

There were no significant differences at p>0.05 in all the CBC parameters mean ±SD measured within and between the different age groups studied, except, RDW , ESR and ALC showed a significant difference at p≤0.05. A Turkey HSD post-hoc test was carried out on the different age group in the RDW, ESR and ALC. The RDW result observed a significant increase at p=0.03 between 21-30(15.6±0.7) and 51-60(13.1±1.0) also within 21-30(15.6±0.7) and 71-80(12.0±1.3) at p=0.002. In ESR, result indicated that there was a significant increase at p=0.002 between the age group 21-30 (75.0±7.1) and 71-80 (29.7±10.0).In ALC, a significant increase at p=0.04 between 21-30(2.8±0.2) and 51-60(2.1±0.4)

Table 5a:- Red Blood Cell Parameters Results At Different Age Groups In Gastric Cancer Using Anova With Tukey Hsd Post-HOC.

Age groups (years/N)	**TRBC $\times 10^{12}$l**	**HB g/dl**	**HCT %**	**MCHC g/dl**	**MCV fl**	**RDW %**	**MCH pg**	**ESR mm/hr**
(A)21-30 (n=34)	4.5± 0.9	11.3± 0.4	33.5± 0.7	30.8± 4.2	76.5± 12.0	15.6 ±0.7	24.5± 0.7	75.0± 7.1
(B)51-60 (n=10)	4.9± 0.6	12.3± 0.7	34.0± 2.8	31 .8± 2.5	80.0± 10.2	13.1 ±1.0	25.2± 1.5	45.0± 14.1
(C)71-80 (n=10)	4.8± 0.5	11.3± 7.1	36.2± 2.1	34.5± 0.7	80.0± 14.1	12.0 ±1.3	26.5± 3.5	29.2± 10.1
F (p) value	0.27 (0.9)	1.41 (0.3)	1.69 (0.3)	1.47 (0.3)	-	18.4 (0.003) *	0.62 (0.6)	14.31 (0.003) *
A vs B p-value	0.8	1.0	0.9	0.9	0.9	0.03*	0.8	0.2
A vs C p-value	0.9	-	0.1	0.5	0.9	0.002*	0.3	0.003*
B vs C p-value	1.0	1.0	0.3	0.6	-	0.4	0.7	0.06

P<0.05*-signifies a significant difference.

Table 5b:- Platelet And White Blood Cell Parameters Results At Different Age Groups In Gastric Cancer (GCa) Using Anova With Tukey Hsd Post-HOC

Age groups (years/N)	**PLT 10^9l**	**MPV %**	**TWBC 10^9l**	**ANC 10^9l**	**ALC 10^9l**	**AMC 10^9l**	**AEC 10^9l**	**ABC 10^9l**
(A)21-30 (n=34)	179.500± 97.291	13.7 ±5.2	10.6± 0.9	8.3 ±3.0	2.8 ±0.2	0.1 ±0.1	0.1 ±0.2	0
(B)51-60 (n=10)	207.500± 95.459	12.1 ±3.3	8.3± 4.6	7.4 ±5.0	2.1 ±0.4	0.2 ±0.3	0.05 ±0.07	0
(C)71-80 (n=10)	280.000± 7.071	9.9 ±0.1	9.1± 3.0	10.3 ±0.9	2.2 ±0.4	0.2 ±0.2	0.05 ±0.07	0
F (p) value	0.94 (0.4)	1.6 (0.2)	0.29 (0.8)	1.4 (0.3)	6.9 (0.02) *	1.7 (0.3)	1.8 (0.2)	0
A vs B p-value	0.9	0.9	0.5	0.9	0.04*	0.7	0.9	0
A vs C p-value	0.4	0.2	0.7	0.7	0.07	0.3	0.9	0
B vs C p-value	0.7	0.8	0.9	0.7	0.9	0.8	-	0

P<0.05*-signifies a significant difference.

Discussion:-

Complete blood count is a standard investigations required from all gastric cancer patients before surgery, use of chemotherapy and/or radiotherapy. Poor parameters adversely correlated with prognosis in several solid cancers [37].

The relationship between NLR,LMR and PLR and prognostic significance in patients with different solid cancers have been reported by many studies, however inconsistent results have been presented so far. No reference values have been established in Nigeria and Africa to the best of my knowledge. We made an attempt to determine different cut-off values for all the six solid cancers using the pre-treatment CBC results. And in addition, determine the NLR, LMR and PLR ratio with their respective percentage in each group using longitudinal approach. Previous studies determined these ratios in retrospective studies. The duration of the disease was used to determine the overall survival using the different ratio cut-off values.

In this study, the treatment red cell parameters results were significantly lower than the pre- treatment and control result. These results showed a classical case inflammation and anaemia in these subjects which can be caused by malnutrition, cytotoxicity of the chemotherapy drug. RDW reflects impaired erythropoiesis and abnormal red blood cell survival but it correlates also with inflammation, under nutrition and impaired renal function, with inadequate production of erythropoietin (EPO) [56].

Quite recently, red cell distribution width (RDW), have also been shown to associate with survival of solid tumors [112]. Growing evidence indicated that high RDW is associated with systemic inflammation and elevated RDW harbored the potential to predict poor survival in a variety of human solid cancers, consisting of breast cancer, lung cancer, prostate cancer, endometrial cancer, colon, gastric, esophageal cancer and upper tract urothelial carcinoma [58],[59]. Work done in 2005 reported anaemia in solid cancer patients, this work suggested that this anaemia which is mostly of iron deficiency may be due to the malignancy itself or a direct consequence of the treatment due to the decreased value in red blood indices [49]. Same work also reported that this anaemia in these cancers may be evident at initial diagnosis and develops due to activation of immune system which appears to be the driving force of global diminution of erythropoiesis [49]. In 2006, a work hypothesed that this immune system once activated stimulates the production of inflammatory cytokines that impedes erythropoiesis hence leading to insufficient differentiation and proliferation of erythroid precursors leading to anaemia [50]. Works done in 2005 reported that these inflammatory cytokines also impairs iron metabolism which results in reduced serum iron levels and iron retention within the reticuloendothelial system (RES) [38]. Another work done 2005, in their work reported that, these cytokines can be produced by the cancer cells themselves which then induces iron sequestration, thereby decreasing RBC production and over expression of these inflammatory cytokines causes shortened RBC survival [47]. Reported works observed that chronic blood loss at common sites can exacerbate anaemia from bone marrow invasion by these solid cancers causing myelophthisis resulting from bone marrow replacement causing pancytopenia [83, 84, 51]. This is work is consistence with works done by [50, 83, 84, 51, 38, 47].

In this present work, there is significant decrease of the treatment TWBC compared to the pre-treatment and control TWBC even though the TWBC are within the normal range. This change could be attributed to effect of chemotherapy which exerts cytotoxic destructive effect during treatment on the bone marrow. Studies done in 2017, 2015 and 2012 all reported leucocytosis in solid cancer subjects [77, 71, 72]. Several studies in 2019 and 2016 had attempted to identify the association between TWBC and solid cancer risk, but no consistent evidence has been found most reports were done on neutrophils/ lymphocytes ratios [76, 78]. This work reported leucopenia which is not consistent with other published works done in 2017, 2015 and 2012 [77, 71, 72]

In differential TWBC, most data were available for the ratio of NLR. The role of neutrophils in cancer is multifactorial and not fully understood. A work done in 2015 reported that neutrophils participate in different stages of the oncogenic process including tumor initiation, growth, proliferation or metastatic spreading [82]. The various roles of neutrophils in cancer development and progression by several researchers have recently explored the role of neutrophils and other markers of host inflammation on clinical outcomes. Works done 2009, reported also that an elevated absolute neutrophil count is an adverse prognostic factor incorporated in a contemporary prognostic score for metastatic carcinoma treated with targeted therapy [61]. A lot of controversies in neutrophil counts have been involved in neutrophil count report. Some works in 2011, reported that the expression of neutrophils in the tumour had been linked with detrimental outcome in some cancer examples include: head and neck cancer, esophageal cancer whereas in other cancers, it has been associated with better survival [81]. However, in 2016 reported works observed that neutrophils assessment can be used as indirect measurement of the tumor inflammation outcome [98].

In this work, significant increases were observed in absolute neutrophil count (even though the values fell within the normal range) in their pre- treatment samples results compared with their treatment and control results. A work done in 2017 reported that peripheral bloods neutrophils are increased in subjects with solid cancer before treatment. This work suggested that this could be because tumors at initial stage produces granulocyte colony – stimulating factor (G-CSF) which skews the neutrophil retention or release balance in bone marrow, leading to this increase in circulating neutrophil [85] .However during treatment, reported work done in 2011 observed that reduced neutrophil count were seen in these subjects showing to be beneficial to the survival of the subjects and this may of course just be a reflection of adequate toxicity of the drug being achieved as it kills tumour cells [86]. The direct effect of toxicity during therapy on neutrophils should be closely monitored in order to prevent the occurrence of neutropenia. This work is however consistent with other works. [85, 86, 87, 88]

In absolute lymphocyte counts (ALC), a significant decrease value in the treatment sample result compared with their pre- treatment and control results all within the normal range were observed. The lymphocyte counts in this work may be within the normal range but the values obtained tend towards higher unit of the normal range. The decrease in this study may be as a result cytotoxicity of these drugs, could also be caused as a result of proliferative arrest in lymphocyte precursor or by direct induction of apoptosis in mature cells [62]. However the mechanisms by which cytotoxic drugs induce depletion of lymphocytes have not been defined. In this work, a decrease pre-treatment monocyte and eosinophil count were observed when compared with the treatment sample results, however with no significant difference.

In PLT count, an increase pre – treatment PLT count has been identified as an adverse prognostic indicator in some solid cancers such as bronchial cancer, gastric cancer and gynecological cancer [101]. Works in 2014, observed that high PLT is also associated with tumor progression and poor survival in patients with solid cancers especially in esophageal cancer [102]. Reported works in 2010 observed that thrombocytopenia increased mortality [106]. Another work also reported ITP in pre – treatment solid cancer subjects [107]. However the mechanism of cause associated with ITP has not yet been elucidated. In this present work, the chemotherapy PLT results were significantly increased when compared with pre- treatment and control results, however all result were all within normal range. The mean platelet volume (MPV) values obtained were significantly decreased in the treatment results compared to the pre- treatment and control results. Mean platelet volume (MPV), the most commonly used measure of platelet size, represents a surrogate marker of platelet activation [109]. Recently, increasing attention has been paid to the assessment of MPV in cancer patients. The observation of decreased platelet size in cancer patients has been explained by an increased cancer-associated platelet activation and exhaustion [112]. In this context, a low MPV may reflect degranulated "exhausted" platelets that have already secreted their potentially tumor growth-promoting cytokines, and thus are associated with a worse outcome in cancer patients [113]. Researchers in 2014, examined the effect of chemotherapy treatment on MPV levels in colorectal cancer patients. Pre-treatment MPV findings were similar in the whole study group, but decreases during treatment. They indicated that changes in MPV could be due to the effect of chemotherapy on the formation of blood platelets and cyclic drug administration [108]. Gastric cancer is another gastrointestinal lesion accompanied by changes in the platelet parameters. It is characterized by early metastasis formation and high mortality [116]. Two groups of researchers reported that in patients with primary gastric cancer, MPV was considerably higher before treatment as compared to healthy subjects. After treatment, the level of MPV underwent a significant reduction to the values comparable to control. They concluded that a significant decrease was observed during treatment but a high pre-treatment level of MPV in patients. Hence no thrombocytosis or thrombocytopenia was observed [117, 113]. All the literatures about PLT were of western countries origin none has been reported in Nigeria to the best of my knowledge. From the result of this work, it was observed that the solid cancers rarely affect the platelets as most of the subjects during treatment had no bleeding tendencies. So the result obtained in this study is not consistent or in agreement with other past researchers.

ESR is the most widely used laboratory test for evaluating the inflammatory status in clinical practice, including infection, autoimmune and malignant diseases [120]. In 2014, some works reported an elevated ESR in cancer patients could be as a result of underlying disorder, the stage and duration of the disease, the regimen and intensity of the antitumor treatment [121]. Another work in 2014, also reported on elevated ESR level as a prognostic factor adversely affecting survival in cancer patients [122]. This present work observed a significant increase of treatment ESR to pre- treatment ESR test and control results in all the in solid cancers. The result coincides with anaemia observed in these patients who may be caused by several factors including nutritional decline, bone marrow filtration, treatment – related toxicity and chronic inflammatory state. This work is in agreement with other works [120,12,126].

In this work, the cut-off values of NLR (2.65) and PLR (3330) were used to determine the prognostic factor in these GCa patients. The increased value of NLR and PLR were found to have no significant prognostic effect in the OS and HR in the progression of the disease in these subjects. The reason could be because the subjects in this work were in the early stages of the cancer development so their immune system had not been compromised. So the finding in this work is not in conformity with other reported works. In this work, there was a significant association between LMR and survival in these patients. It was observed that low LMR ($\leq$ 2.50) in these subjects were associated with increased HR and shortened OS. The LMR is the ratio of lymphocytes to monocytes and is a comprehensive index that may better predict long term prognosis in GCa patients, although the prognostic value will remain controversial.

Works done in 2013 reported that elevated pre-treatment LMR is associated significantly with favourable survival for GCa patients and some other solid cancers[69]. Two other works done in 2014 reported that increases pre-treatment LMR is associated significantly with poor prognosis in these patients [44], [76]. This works were supported by another work done in 2016 where same work were repeated and had same result [105]. In 2015, some works observed that increased monocyte counts are associated with poor survival in patients with solid cancer but the potential mechanism remains unknown [125]. Another work reported that monocytes inhibit the immune system and promote tumour proliferation angiogenesis and progression [114]. In 2013, further works reported that that monocytes also inhibit the immune system by releasing cytokines, chemokines and regulates tumour environment hence decreasing lymphocyte production causing this decrease in LMR seen in GCa patients. This work is consistent with other previous published works on GCa [79].

In this GCa work, it showed a higher female (52%) prevalence than male (48%) which contradicts other works done in Nigeria [28, 29]. Works did in 2011 observed a higher male to female ratio of 1.5:1, 1.8:1 and 1.45:1 respectively [30]. In this work, younger age prevalence was observed at age group 21 – 30. A decrease value in all RBC parameters and PLT were observed in age group 21 – 30. In the WBC parameters (especially in the ALC) and ESR increased values were observed showing that age group 21 – 30 are mostly affected by this cancer. However this contradicts earlier works done in other parts of the world and in Nigeria; age mostly affected 41 – 60 years at Ile – Ife for 16 years period, 1980 to 2005[28]; at Lagos, reported peak age as 40 – 59 over 11 years period 2004 to 2009[29]; at Ibadan, 60-70 years for a period of five years from 2004 to 2009 [30]; Zaria reported no specific age range was particularly affected for 15 years from 1995 to 2009; at Ibadan, 61 – 70 over 19 years period from1990 to 2008[27]. However studies in 2016 and 2014 reported a higher proportion of female especially in younger adults of below 40 years, although the reason for this is not clear [118, 80]. Another work done in 2012 and 2013 potentially explained that younger patients more frequently present with advanced and metastatic disease at diagnosis which was seen in the CBC and ESR result in this work [103,104]. Younger adults susceptibility works done 1999,2009, and 2016, all reported that 21 – 30 years age group tend to ingest high proportion of red and processed meat, smoking, alcohol which are some of predisposing factors for stomach cancer[40,46,84]. So this work is the first report on prevalence of stomach cancer in younger adults in Nigeria.

Summary, Conclusion and Recommendation:-

Summary Of Findings

1. Systemic inflammation and immune response are closely related to cancer prognosis which was observed between the CBC and ESR control, pre- chemotherapy and chemotherapy results obtained.
2. This works proved that pre- chemotherapy ratios of NLR, LMR and PLR should be introduced in clinical practice as a routine laboratory tests in order to improve early prognosis.
3. This work has shown once again that CBC and ESR is still the hallmark of medicine since the result is vital in predicting overall survival and monitoring of the therapy given to each patient.
4. This work observed that these ratios (NLR, LMR and PLR) can be used as inexpensive biomarkers in these cancers since these results are easily reproducible and accessible.

Conclusion:-

It is evident that components of CBC count in this study had provide valuable prognostic information in solid cancer that are not limited to survival predictions or assessment of diseases progression, but also were important tools when evaluating response to treatment. The findings of this work indicate that the use of CBC especially the pre-treatment NLR/ LMR/PLR score can be considered a valuable prognostic indicator in patients with these solid cancers. A close relationship between NLR/LMR/PLR and cancer progression was also observed in subject with these solid cancer. Thus, these ratios may be considered for routine clinical use as reliable and low-cost biomarkers.

Recommendations:-

1. Further studies is needed to fully understand the underlying biology of this effect of anaemia and to determine if reversing the anaemia can improve survival in these solid cancer patients.
2. Identification of adequate cut-off values in these ratios over a pre- chemotherapy and chemotherapy period of time could add more accurate information in the type of therapy for use in these patients.
3. Comparison of these ratios with the expression of other inflammatory biomarkers in the blood could help to improve prognosis and predictions in these patients.

4. Clinical psychologist should be provided to help these patients deal with the trauma and mental issues associated the breaking of news or result to these patients.
5. Awareness programmes should be created to all medical personals on the importance of these ratios for better treatment and management of these patients.

Limitation Of The Study

1. Some of the subjects died during the course of this work.
2. Follow-up proved difficult due to subjects' unavailability for their scheduled chemotherapy due to economic constraints since this is a third world country.
3. Some of the illiterate patients forgot the scheduled treatment day.

No Conflict of Interest and No Funding

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