ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF ALLIED HEALTH SCIENCES

DEPARTMENT OF MEDICAL LABORATORY SCIENCES

EVALUATION OF NEPHROTOXICITY AMONG CERVICAL AND OVARIAN CANCER PATIENTS TREATED WITH CISPLASTIN BASED CHEMOTHERAPY AT TIKUR ANBESSA SPECIALIZED HOSPITAL CHEMOTHERAPY AND RADIOTHERAPY CENTER, ETHIOPIA.

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A research Thesis submitted to the department of Medical Laboratory Sciences, School of Allied Health Sciences, College of Health Sciences, School of graduate studies, Addis Ababa University. In partial fulfillment of the requirements for the degree of Master in clinical laboratory sciences (CLS), clinical chemistry specialty Track.

Feb, 2016

Addis Ababa, Ethiopia

DECLARATION

Assurance of Principal Investigator

I the undersigned was conducted this research by adhering with all responsibilities for the scientific and ethical conduct of the research. I was provided a timely progress report to my advisors and got the necessary advice and approval from them in the course of the research. I was communicated timely to my advisors and all stakeholders involved in the study including any source of funding for this research.

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Acknowledgment

I offer my adoration to the Almighty God who created me, gave me the strength and courage to complete my theses and gave me the opportunity to thank all those people who gave me their unreserved support for the completion of the work.

I take it as a privilege to sincerely express my deep sense of gratitude and thank to my advisor: Jigssa Girma, Dr. Dagnachew and Dr. Wondemagegnhu Tigeneh whose meticulous guidance, valuable suggestions, constant motivation and dynamic approach enabled me to complete the theses work.

I would like also to thank staff members of the oncology unit of TASH whose support is greatly appreciated. I would like to acknowledge Addis Ababa University for sponsoring my postgraduate study .I would also like to thank all my friends and others who are directly or indirectly involved in motivating, encouraging and supporting me all through my career.

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Abbreviations

AC	Adriamycin + Cisplatin
AAU	Addis Ababa University
ADR	Adverse Drug Reaction
AIDS	Human Immunodeficiency Virus
AKI	Acute Kidney Injury
ARF	Acute Renal Failure
BUN	Blood Urea Nitrogen
CIN	Cisplatin Induced Nephrotoxicity
CTC	Common Toxicity Criteria
CG	Cockcroft-Gault
CrCl	Creatinine clearance
CP	Cisplatin + Paclitaxel
CTRL1	Copper Transporter
CDDP	Cis-diaminedichloroplatinum II (Cisplatin)
DNA	Deoxyrebose Nucleic Acid
DRPs	Drug Related Problems
DLT	Dose Limiting Toxicity
ERC	Ethics and Research Committee
EGFR	Estimated glomerular filtration rate
5-FU	5- Fluorouracil
EOC	Epithelial ovarian cancer
ESRD	End Stage Renal Diseases
FDA	Food Drug Administration
FIGO	International Federation of Obstetrician and Gynecologists
GFR	Glomerular Filtration Rate
GI	Gastro-intestinal
GN	Gynecology
HPV	Human Papilloma Virus
ICU	Intensive Care Unit
IFO	Ifosfamide

IV	Intravenous
KCl	Potassium Chloride
KD	Kidney Diseases
MOH	Ministry of Health
MTX	Methotrexate
NAC	N-acetylcyctine
NCI	National Kidney Institute
NSAIDs	Non Steroidal Anti-inflammatory Drugs
OC	Ovarian Cancer
OG	Oncology
ROS	Reactive Oxygen Species
RT	Radiotherapy
STD	Sexually Transmitted Diseases
SPSS	Statistical Package for Social Sciences
TASH	Tikur Anbessa Specialized Hospital
TB	Tuberculosis
UEC"s	Urea, Electrolytes, Creatinine
WHO	World Health Organization

Abstract

Background: Cancer is potentially fatal diseases; it can be caused by mainly environmental factors that mutate genes encoding critical cell-regulatory proteins. Cisplatin is a potent and an effective chemotherapeutic agent used to treat cervical and ovarian cancer, but is associated with the risk of nephrotoxicity. The prevalence of cisplatin based chemotherapy induced nephrotoxicity was not assessed in Ethiopia.

Objective: To assess the magnitudes of Cisplatin-based chemotherapy induced nephrotoxicity among cervical and ovarian cancer patients underwent cisplatin treatment at the oncology unit of Tikur Anbessa Specialized Hospital (TASH).

Materials and Methods: A prospective cross-sectional study has been conducted on 76 cervical and ovarian cancer patients who received cisplatin based chemotherapy. Clinical and laboratory data including kidney function tests were recorded at baseline and 21 days after treatment with cisplatin based chemotherapy. Serum creatinine, urea, uric acid and calcium have been analyzed using automated clinical chemistry analyzer (Mindray02) and estimated creatinine clearance has been calculated based on Cockcroft-Gault formula. Toxicities were classified according to the common toxicity criteria (CTC) scale set by (NCI CTC AE V4.0).

Results: Serum creatinine, uric acid levels increased significantly during the 1 cycles of chemotherapy, whereas eGFR levels decreased significantly. Accordingly, the results were (1.0854 ±0.781SD), (5.9 ±2.7SD) and (50.217±14.0SD) respectively where the (P. value 0.001), (p.value 0.00) and (p. value 0.00). On the other hand, serum urea and calcium levels showed no statistical significant difference have been shown where (p. value>0.05). According to Pearson‟s correlation analysis showed pre and post chemotherapy there was a strong negative correlation between the eGFR and serum creatinine level correspondingly (rho: –0.150 Vs -0.136, $P < 0.001$), and Spearman‟s correlation analysis showed that there was a strong negative correlation between the eGFR and uric acid level after treatment (rho: –0.500, $P < 0.05$).

Conclusion and Recommendation: Significant changes have been observed after the 1 cycle of cisplatin based chemotherapy treatment on the levels of serum creatinine, uric acid levels and decreased glomerular filtration rate. To effectively monitor nephrotoxicity, renal parameters and electrolyte levels should be measured before and after each cisplatin based chemotherapy cycle. More investigations are required to evaluate this method with higher doses of cisplatin.

Keywords: Cisplatin; 5Fluorouracil; Nephrotoxicity; chemotherapy; Tikur Anbessa Specialized Hospital.

1.0. Introduction

1.1. Background

Cancer is potentially fatal diseases; it can be caused by mainly environmental factors that mutate genes encoding critical cell-regulatory proteins, Genetic factor, Chemical factor, Physical factor, viral factors, Immune factors and Endocrine factors (1`). The cancer-causing agents (carcinogens) can be present in food and water, in the air, and in chemicals and sunlight that people are exposed to (1). More significantly, a globalization of unhealthy lifestyles, particularly cigarette smoking and the adoption of many features of the modern Western diet (high fat, low fiber content) will increase cancer incidence all over the world (2).

According to Global Cancer Network (GLOBOCAN) 2012 report, an estimated 14.1 million new cancer cases and 8.2 million cancer-related deaths occurred in 2012, compared with 12.7 million and 7.6 million, respectively, in 2008. Prevalence estimates for 2012 show that there were 32.6 million people alive who had cancer diagnosed in the previous five years (3). The prevalence of cancer is expected to increase, it has been estimated that by the year 2030, there will be 22.2 million new cancer cases and over 13.1 million cancer deaths will occurs annually in the world (3).

In Africa, the burden of cancer has been estimated to increase from 715,000 new cases and 542,000 deaths in 2008, to double by the year 2028 (4). Despite this growing burden, cancer continues to receive low public health priority in Africa, largely because of limited resources and other pressing public health problems, including communicable diseases such as Acquired Immune Deficiency Syndrome (AIDS)/Human Immunodeficiency Virus (HIV) infection, malaria, and tuberculosis (4). It may also be in part due to a lack of awareness about the magnitude of the current and future cancer burden among policy makers, the general public, and international private or public health agencies (5).

Cervical cancer is the second most common malignancy in women worldwide, and it remains a leading cause of cancer-related death for women in developing countries. Cervical cancer, a complication of Human Papilloma virus (HPV) infection, is the second most common cancer

next to Breast cancer in women with 529,000 new cases each year worldwide (6). There are several established risk factors for cervical cancer, with the strongest related to sexual behavior. Patients with a history of sexually transmitted diseases (STDs), as well as those who started having sexual intercourse early in life and/or have had multiple sexual partners and/or a promiscuous partner, are at increased risk for cervical cancer (6). The HPVs that infect the human cervix fall into 2 broad categories. The low-risk types, HPV 6b and 11 are associated with low-grade SILs but are never found in invasive cancer. The high-risk types, mostly HPV 16 and 18 are found in 50-80% of SILs and in up to 90% of invasive cancers (7).

Cancer of the cervix has a devastating impact on women‟s health around the world, especially in developing countries, where it is the most common cancer and the leading cause of death of cancer in women. Cervical cancer is the second most common cancer in women following breast cancer in developing countries like Ethiopia (6).According to the 2009 World Health Organization (WHO) report, the age-adjusted incidence rate of cervical cancer in Ethiopia is 35.9 per 100,000 patients with 7619 annual number of new cases and 6081 deaths every year (7).

According to Wondemagegnhu Tigeneh the pattern of Cancer in Tikur Anbessa Specialized Hospital Oncology Center in Ethiopia from 1998 to 2010found that 72.8% are females and the rest 27.2 % are males. Among all patients only 10% of patients did come to the center in early stage I and II (8). The most common malignancy in female was gynecological malignancy 47% followed by breast carcinoma 26%. Ca uterine cervix found the most common malignancies among all gynecological malignancies. Head and Neck malignancy is found to be the leading malignancy in male 22% followed by sarcoma 15%, Gastrointestinal 12%, Hematology malignancies and urogenital 9% each and Thyroid 5% (8).

Epithelial ovarian cancer (EOC) is the most common cause of death from gynecological cancers, affecting approximately 1 in 75 women in the developed world. It accounts for about 4% of all cancers in women in the United States, with over 23,000 cases diagnosed annually. In most cases (>75%), the disease is disseminated beyond the ovary at diagnosis (9).

Ovarian cancer spreads early in the disease into the abdomen. At surgery, large pelvic tumor lesions are found together with multiple tumor lesions involving the omentum, bowel, and mesentery together with a diffuse peritoneal carcinomatosis and diaphragmatic involvement. Unfavorable prognostic factors include stage IV disease (9).The Ethiopian oncology service in

organized way was started in Tikur Anbessa Specialized Hospital since 1998 Ethiopian calendar (6).In Ethiopia where oncology practice is so young, awareness‟ even among medical professionals about oncology is much inferior than expected.

In Ethiopia like most of sub-Saharan Africa countries doesn‟t have cancer registry. As far as we know there is no study or report done mentioning the type and pattern of malignancy in Ethiopia. The use of widespread screening programs and modifying of the risk factors can be used as a tool to prevent cervical cancer (8). Additionally, a recent availability of vaccines against Human papilloma virus (HPV) can play a role in controlling cervical cancer. The treatment protocol for optimum outcome is the combination treatment including chemotherapy, surgery as well as radiotherapy, though at TASH patients gets largely chemotherapy and only few get combination therapy and hence poor outcome.

Tikur Anbessa Specialized Hospital (TASH), is the only cancer therapy center in Ethiopia, and serves as the national referral Hospital for all regions of Ethiopia. Annually treats 4800 follow-up and 480 new patients with cervical cancer and therefore often congested with many patients (10). Cancer chemotherapy first emerged in the 1960s, prior to which surgery and radiation therapy formed the only means of cancer treatment. Since the advent of chemotherapy, over 50 different drugs have become available. These drugs are administered by a number of different methods, including oral, topical and intravenous (IV) administration, and are usually given over different time cycles and in combinations to form specific treatment regimens and schedules (10).

Generally, chemotherapy can be given alone or in a neo-adjuvant (pre-surgery), adjuvant (post-surgery) or palliative manner. Chemotherapeutic drugs are such that it presents with extremely high toxicity to non-cancerous tissues, has a 30% success rate and varies greatly in patient response (10).The treatment protocol for optimum outcome may often involve multiple modalities including surgery, radiotherapy, chemotherapy, though at TASH patients gets largely chemotherapy and only few get combination therapy(9,10).

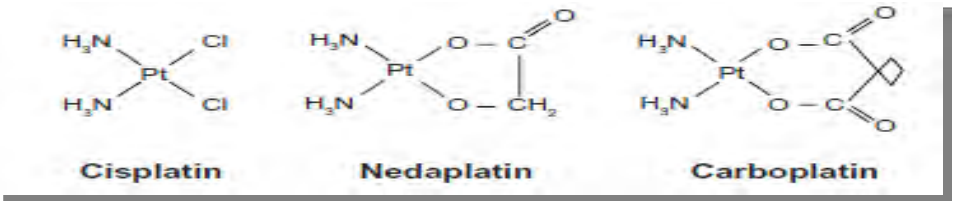
Table 1.Common chemotherapeutic drugs implicated in causing nephrotoxicity

ildlynephrotoxic	oderatelynephrotoxic	ghlynephrotoxic
luorouracil clitaxel thotrexate	Carboplatin Oxorubicin	splatin clophosphamide sfamide

Currently, Cisplatin is one of the most widely used and most potent chemotherapy drugs (11). However, side effects in normal tissues and organs, notably nephrotoxicity in the kidneys, limit the use of cisplatin and related platinum-based therapeutics (12). Cisplatin predominantly accumulates and is excreted through the kidneys (12). The limited possibility of increasing drug dosage posed by dose-dependent renal toxicity may compromise the effectiveness of treatment. Toxic effects occur primarily in the proximal tubule, particularly in the tubule epithelium cells on segment S-3 (12). Distal tubules and glomerular are involved at a later stage (13).

Clinically, cisplatin nephrotoxicity is often seen after 10 days of cisplatin administration and is manifested as lower glomerular filtration rate, higher serum creatinine, and reduced serum magnesium and potassium levels (14). Most chemotherapy drugs used to treat metastatic or recurrent cervical cancer are given on a 21-day schedule (14). This means that one cycle of chemotherapy is given over the course of a day on the first day of treatment and then the second cycle will not be given until 3 weeks later, or on day 22. Blood tests will be performed between treatments to monitor renal function (15).

Figure 1: Chemical structure of cisplatin, Nadaplatin and Carboplatin (12)



Mechanisms of action and metabolism of CDDP: Cisplatin enters renal epithelial cells via the OCT2 and, to a lesser extent, Ctr1 transporters. Cisplatin causes damage to nuclear and mitochondrial DNA and production of reactive oxygen species (ROS) which lead to activation of both mitochondrial and non-mitochondrial pathways of apoptosis and necrosis (12). Cisplatin is

one of the most commonly used drug for the treatment of carcinoma of ovary, and carcinoma of cervix etc. and it is associated nephrotoxicity (12, 13).

5-Fluorouracil (5-FU) is one of the most commonly-used chemotherapeutic drugs for the treatment of a wide variety of malignancies, including breast, gastrointestinal, esophageal, cervical, skin and lung cancer (16). The drug was synthesized over 50 years ago, upon the discovery that fluorine markedly inhibited tumors in mice (12).

5-FU is administered orally, topically, by IV injection or by slow IV infusion, either alone or in combination with other drugs. For example, 5-FU forms part of the ECF (Epirubicin + Cisplatin + 5-FU) regimen for pre- and post-operative chemotherapeutic treatment of Cervical and ovarian cancer patients. One of the predominant toxic effects of 5-FU in patients is myelo-suppression, which manifests as neutropenia, anemia or thrombocytopenia, consequently raising the risks of infection and bleeding (16).

Clinical manifestations of kidney damage include an elevation of serum creatinine, blood urea nitrogen (BUN), serum uric acid and / or decrease in glomerular filtration rate (GFR) (17)**.** Kidney damage is defined by structural or functional abnormalities of the kidney, with or without decreased GFR, which can lead to nephrotoxicity (17).The Oncology Group (OG) guideline recommends baseline screening for asymptomatic survivors of potentially nephrotoxic therapy (18).

For years the issue of monitoring nephrotoxicity, particularly late-onset, has been controversial. It remains inconclusive how often and which parameters should be assessed in long-term cancer survivors. Asubstantialnumberofcancer patientshaveunrecognized renal impairment, as indicated by reduced eGFR in the presence of serum creatinine (SCr) levels within the reference value (19). Despite this finding, most oncologists still rely on SCr when assessing whether chemotherapy dosage adjustment for renal impairment is required. This is the case for cisplatin, for which indications for safe administration include normal renal function (SCr levels <1.5 mg/dL).Nonetheless, cisplatin administration is associated with a significant vascular toxicity and increased CIN incidence (11, 12).

Based on these considerations, we hypothesized that reduced eGFR might represent a novel risk factor for CINonset in cancer outpatients receiving platinum-based regimens. Accordingly, a prospective cross sectional study was designed to assess the value of pretreatment eGFR in the risk prediction of a first CIN episode in cancer outpatients without previous history of renal failure who were scheduled for platinum-based chemotherapy. Toxicities were classified according to the National Cancer Institute common toxicity criteria (NCI CTC AE V4.0) (20). Specific conditions and symptoms may include biochemical laboratory values or descriptive comments for each level, but the general classification is: Mild, moderate, severe, life-threatening and death (20).

The assessment of kidney function during active antineoplastic treatment and after termination of the therapy is one of the key diagnostic elements permitting the prompt diagnosis of the side-effects of the therapy. Hence, early prediction of predisposition to renal function impairment and taking precautions early are crucial. Evaluation of nephrotoxicity is important as long term users of cisplatin continue to increase. The finding of significant abnormal glomerular filtration rate (GFR) is most often detected by elevated serum creatinine concentrations. Even mild elevations should be noted since as much as 50% of renal parenchyma loss may occur before detectable changes in the creatinine occur. Since early renal insufficiency is often asymptomatic, screening for proteinuria and or measurement of creatinine may be the only way to detect its presence (14).

Finally, “therefore” this project was aimed at addressing the magnitude of nephrotoxicity among patients undergoing cisplatin50Mg/m^2 / 5Flourouracil 500Mg/m^2 treatments. Diagnostic parameters performed in this study was; serum calcium, serum creatinine, urea, uric acid level and estimated glomerular filtration rate (eGFR), were used as indicator of renal insufficiency.

1.2. Statement of the Problem

Worldwide, cervical and ovarian cancer is the most common cause of cancer-related morbidity and mortality among women in the world (6, 9). In Ethiopia, invasive cervical and ovarian malignancies are the most common gynecological disease (8). Cisplatin use is limited by its dose limiting nephrotoxicity. Different measures such as fractionation of the dose, slower rate of infusion, forced diuresis with diuretics and hydration are used to counter this side effect (12-14). Nevertheless, the amount and duration of hydration is still controversial.

Due to the concern of renal failure following the use of cisplatin, either the dose of medicine is decreased, or doses are skipped and cycle intervals are prolonged, and as a result of these, the efficacy is diminished (5). Several studies have been conducted in different countries showed a high incidence of cisplatin related nephrotoxicity among cervical and ovarian cancer patients (Arjmandi-Rafsanjani K, Hooman N 2008)(25), Knijnenburg SL et al (26). Evaluation of nephrotoxicity has not been obtained either from retrospective or prospective studies in our setting. Therefore, this study was aimed at in determining the magnitude nephrotoxicity among of cervical and ovarian cancer patients who are managed at the TASH.

1.3 Literature Review

Cancer is a leading cause of death in both more and less economically developed countries; the burden is expected to grow worldwide due to the growth and aging of the population, particularly in less developed countries, in which about 82% of the world‟s population resides (1). The adoption of lifestyle behaviors that are known to increase cancer risk, such as smoking, poor diet, physical inactivity, and reproductive changes (including lower parity and later age at first birth), have further increased the cancer burden in less economically developed countries (2).

Cancer is predicted to be an increasingly important cause of morbidity and mortality in few decades, in all regions of the world (3). The forecasted changes in population demographics in the next two decades mean that even if current global cancer rates remain unchanged, the adoption of lifestyle behaviors that are known to increase cancer risk, such as smoking, poor diet, physical inactivity, and reproductive changes (including lower parity and later age at first birth), have further increased the cancer burden in less economically developed countries (4). The estimated incidence of 12.7 million new cancer cases in 2008 will rise to 21.4 million by 2030, with nearly two thirds of all cancer diagnoses occurring in low and middle income countries (3).

Worldwide, cervical cancer is the leading cause of death among women and is the most common cause of cancer-related morbidity and mortality among women (6). According to Addis Ababa Cancer Registry a total of 5701 cancer cases registered from September 2011 to August 2014. Among these 3820 (67%) were females and 1881 (33%) males. The most commonly leading cancers among females were cancers of the breast (33%), Cervix uterine (17%) and Ovary (6%) (10).

The association between sexual activity and cervical cancer has been known for over a century (6). Cervical cancer is largely sexually transmitted disease caused by HPV (6). Other risk factors include early age at first coitus, multiple sexual partners, low socio-economic status, a high risk sexual partner, excessive vaginal acidity and sexually transmitted infections (6, 7). Disease stage is the most important prognostic factor, followed by lymph node status (21). After radical hysterectomy and lymphadenectomy, women with stage IB or IIA disease who have negative pelvic lymph nodes have a five-year survival of 88–96% compared to 64–74% for those with similar stage disease and pelvic nodal metastasis (21). The five-year survival outcomes are far

worse for women with involvement of par aortic nodes (113). The presence of persistent human papilloma virus (HPV) and specific HPV subtypes may also impact on prognosis after surgery or radiation therapy (9).

1.3.1 Advanced stage cancer

The patients usually present with advanced stage cancer that may lead to obstructive nephropathy and metastatic infiltration. Malignancy manifestations such as, disseminated intravascular coagulation, amyloidosis, electrolyte abnormalities and the syndrome of inappropriate ADH secretion contribute to renal failure in patients with advanced cancer (18, 19). Patients with advanced cancer have a high tumour burden and acute renal failure may occur after administration of chemo radiotherapy, due to tumour lysis syndrome (9). These patients have limited access to fluids. They travel long distances to hospital and stand in long queues before they finally get treatment (5).

Diarrhea and vomiting also lead to renal failure due to intravascular volume depletion (19). Due to limited resources, the public hospitals cannot provide enough fluids and anti emetics to cope with problems of volume depletion in these patients (20). Chemotherapy is the treatment of cancer with drugs called anticancer drugs, which can destroy cancer cells by impeding their growth and reproduction (11). Normal cells grow and die in a controlled way. When cancer occurs, cells in the body that are not normal keep dividing and forming more cells without control. Anticancer drugs destroy them by stopping them from growing or multiplying. Healthy cells can also be harmed, especially those that divide quickly. Harm to healthy cells is what causes side effects. These cells usually repair themselves after chemotherapy (13).

Chemotherapy drugs interfere with cell division in various possible ways such as with duplication of DNA or the separation of newly formed chromosomes. Most forms of chemotherapy target all rapidly dividing cells and are not specific for cancer cells, although some degree of specificity may come from the inability of many cancer cells to repair DNA damage, while normal cells generally can. Hence, chemotherapy has the potential to harm healthy tissue, especially those tissues that have a high replacement rate, such as intestinal lining (12).

1.3.2 Cisplatin Use in Cancer Management

Cisplatin was first shown to inhibit cell division in 1965 (11). Cisplatin administration and exposure to kidney cells, especially the proximal tubule, are associated with the activation of inflammatory reactions, and vascular and ischemic injury to the kidney, involving multifactorial and multidimensional processes nephropathy comprising the activation of signal transduction pathways leading to the damage and cell death of the renal tubule epithelium (18). Cisplatin is an effective cytotoxic agent that is used as standard treatment of a variety of neoplasms. It is used in the management of various cancers including bladder cancer, cervical cancer, malignant mesothelioma, non small cell lung cancer, and ovarian cancer, Squamouse cell carcinoma of head and neck cancer and testicular cancer. The incorporation of cisplatin into combination regimens has resulted in high cure rates, for example, of advanced testicular cancer (11, 13).

A hospital-based study done at Kenyatta National hospital in Kenya assessing the outcome of treatment of cervical cancer showed that 76.9% of patients were treated by cisplatin alone, intra cavitary was added in 8.3% and concomitant chemotherapy in 4.2% while 7.2% had prior surgery. Tumor recurrence occurred in 17.7% with 9.4% presented with local involvement, 6.1% distant metastases and 2.2% combined metastases. About 45.7% had no disease symptoms at all. Stage II was found to have high recurrence rate (81.1%) as compared to the other stages (22).

A case control prospective study conducted in Sudan to evaluate the „Effects of chemotherapy on the levels of plasma urea, uric acid and creatinine as indicators of renal impairment in Sudanese cancer patients attending Radiation and Isotopic Center of Khartoum. The results showed cases had statistical significant higher plasma creatinine (1.1 ±.55SD) and uric acid (6.5 ±2.7SD) as compared to control (0.8±.15SD) ,(5±1.01SD), respectively for both parameters.(p. value<0.05), however plasma urea in cases showed no statistical significant difference (35.7±27SD) as compared to control group (30.8 ±8.5SD).(p.value>0.05) (21).

A retrospective study conducted in Turkey, showed cisplatin treatment effect seen by significantly increase, in blood urea nitrogen, creatinine, and cystitis C levels during the 3 cycles of chemotherapy, where as sodium and potassium levels decreased significantly. Magnesium and calcium levels decreased only during the first cycle of chemotherapy. Significant increases in uric acid level were observed during the 1st and 3rd cycles (22).

A retrospective study conducted in Kenya in 2014 by Geoffrey; The preventive strategies, risk factors and profile of nephrotoxicity. The result showed Nephrotoxic preventive strategies employed were change of dose of cisplatin to Carboplatin (3.5%) and postponement of dose because of deranged laboratory values (20 %), and hydration using normal saline (100 %). However, the doses of normal saline used did not seem to prevent the development of nephrotoxicity (p=0.486) (25).

A Japanese study on 110 patients with epithelial ovarian cancer using Carboplatin at a dose of AUC 5 and a dose escalation of paclitaxel at levels of 150, 175 and 200 mg/m2 observed grade 4 neutropenia in four of six patients in the paclitaxel 200 mg/m2 administration group. At the chosen 175 mg/m2 dose of paclitaxel in this regimen the response rate was 66.7% and the median progression-free survival was 432 days (27).

In a single centre Iranian study, reported a 25.2% rate of renal toxicity, including tubular disorders and hypertension (27). Similarly Knijnenbur reported a prevalence of 28.1% of therapy related renal dysfunction in childhood cancer survivors (28). In both studies, the proportions reflected at least one renal adverse effect or elevated blood pressure in the survivors. Gronroos documented a seven year follow up of 187 children post stem cell transplant in Finland and reported the finding of chronic kidney disease (CKD) in 41% at 1 yr, 31% at 3 yr, and 11% at 7 years (29).

In a retrospective study conducted in Egypt, the authors reported that about 10% of patients with acute kidney injury (AKI) developed CKD (30). Frequencies of renal impairment in patients treated for adult and childhood cancers have been documented in studies from various parts of the world but none reported from Ethiopia. Risk factors that increase kidney impairment after CDDP administration include previous or concomitant renal diseases, solitary kidney (nephrectomy), combined anticancer treatment with IFO and MTX, concurrent treatment with other nephrotoxic agents such as amino glycosides and amphotericin B, the cumulative dose of CDDP (≥ 200 mg/m2), radiation impacting the kidney (renal radiation dose ≥ 15 Gy), diabetes mellitus, hypertension, dehydration and hypo albuminaemia (14).

A phase II study of cisplatin plus 5-fluorouracil versus cisplatin plus 5-fluorouracil with interferon-a gave no response in the 5-FU/cisplatin arm and only 2 partial responses were

achieved in the interferon-arm, lasting 27 and 32 weeks, respectively (201). A high-dose 5-fluorouracil (5- FU) + leucovorin and bi-weekly cisplatin gave an overall response rate of 33% and a median survival of 7.9 months (202). In a phase II trial, 5-FU plus cisplatin (FUP) yielded a 26.5% response rate and a 29% survival rate at 1 year (15).

A randomized trial comparing 5-FU with 5-FU plus cisplatin in advanced pancreatic carcinoma gave a superior response rate in the 5-FU plus cisplatin. The survival rates at 6 months were 28% and 38% for the FU and FUP arms, respectively, and 1-year survival rates were 9% and 17% (20). S1, a newly developed oral fluoropyrimidine derivative gave response rates of 20%; when S1 was combined with weekly cisplatin response rates of 57% were achieved in patients with pancreatic cancer; CA19-9 serum concentration was reduced by more than 50% in a significant fraction of patients (26).

A retrospective study by Asangansi, patient related factors, and drug related factors as well as drug interactions play a role in nephrotoxicity. These include age, sex, race, specific diseases (diabetes mellitus, hypertension, sickle cell disease, multiple myeloma, proteinuria disease, Systemic Lupus Erythromatosus) Sodium-retaining states (cirrhosis, heart failure, and nephritis) dehydration and volume depletion, acidosis, potassium and magnesium depletion, hyperuricemia, hyperuricosuria, sepsis, shock and renal transplantation (31).

The use of cisplatin in cancer management is so far immense. However, clinical application is limited because of serious and sometimes irreversible toxicity, including gastrointestinal (GI), neurotoxicity, nephrotoxicity, myelosuppression, and ototoxicity (22). Forced diuresis pre- and post cisplatin infusion limits nephrotoxicity, and with current supportive medication, GI toxicity is manageable in the majority of patients.

However, despite extensive research, no therapeutic intervention of proven benefit has been found to prevent neurotoxicity and ototoxicity. The most commonly used protective measure against renal toxicity is to establish solute dieresis (13). There is evidence that the therapeutic efficacy of cisplatin increases with increasing dose. However, cisplatin-induced nephrotoxicity has also been shown to be dose-related in both animals and humans, as the kidney is the primary excretory organ for cisplatin (12).

Other renal manifestation of cisplatin toxicity include hypomagnesaemia, Fanconi-like syndrome distal renal tubular acidosis, hypocalcaemia , renal salt wasting, renal concentrating defect, hyperuricemia, transient proteinuria, erythropoietin deficiency, thrombotic microangiopathy and chronic renal failure (18). Biotransformation of cisplatin could play an important role in renal toxicity. A decrease in sulphydryl groups in the kidney may be a primary event, and reactive metabolites may be formed. However, the incidence of cisplatin nephrotoxicity has been observed to decrease when patients are rehydrated. The clinical recommendations are to avoid rapid cisplatin infusion rates (over 1 mg/kg per hour) and to induce hydration at least during and after cisplatin administration (17).

1.3.3 Clinical Characteristics of Cisplatin Nephrotoxicity

Early clinical use of cisplatin results in dose-related cisplatin-induced AKI in 14 to 100% of patients, with the incidence varying with the cumulative dose (32). The incidence of renal insufficiency in more recent experience using saline hydration and diuresis is in the range of 20.30% of patients and is revealed by increases in the serum creatinine and blood urea nitrogen concentrations (33). The urine output is usually preserved (non-oliguric) and the urine may contain glucose and small amounts of protein, indicative of proximal tubular dysfunction (22). Hypomagnesaemia is also common, particularly after repeated doses of cisplatin, even in the absence of a fall in the GFR. Recovery of renal function usually occurs over a period of 2.4 weeks, though more protracted courses, as well as lack of recovery are reported. Progressive and permanent nephrotoxicity can result with successive treatment courses despite preventative measures (28). Studies have revealed that the prevalence of cisplatin nephrotoxicity is high, occurring in about one-third of patient undergoing cisplatin treatment (30).

Clinically, cisplatin nephrotoxicity is often seen after 10 days of cisplatin administration and is manifested as lower GFR, higher serum creatinine, and reduced serum magnesium and potassium levels (12). On the other hand, the long-term effects of cisplatin on renal function are not completely understood, but it is believed that cisplatin treatment may lead to subclinical but permanent reduction in GFR (21). Nephrotoxicity increases with the dose and frequency of administration and cumulative dose of cisplatin .High peak plasma free platinum concentration has been correlated with nephrotoxicity (16), and one study suggested GFR and plasma

magnesium concentrations decreased after cisplatin doses of higher than 50 mg/m2 body surface area, but were unchanged if the dose was below 20 mg/m2 (19).

1.3.4 Risk Factors for Cisplatin Nephrotoxicity

Risk factors that increase kidney impairment after cisplatin administration include previous or concomitant renal diseases, solitary kidney (nephrectomy), combined anticancer treatment with IFO (Ifosfamide) and MTX (Methotrexate), concurrent treatment with other nephrotoxic agents such as amino glycosides and amphotericin B, the cumulative dose of cisplatin (200 mg/m2), radiation impacting the kidney (renal radiation dose), diabetes mellitus, hypertension, dehydration and hypoalbuminaemia (26). Hypocalcaemia is another common electrolyte disturbance related to cisplatin treatment and hence also a risk factor. It may be caused by various mechanisms, but even the cisplatin-induced hypomagnesaemia itself may lead to hypocalcaemia (11).

1.3.5 Cytoprotective. Therapy to Prevent the Nephrotoxicity of Platinum Derivatives

Intensive hydration simultaneous to cisplatin administration, osmotic diffusion, magnesium supplementation, increasing duration of infusion and dividing the dose of cisplatin within the cycle all decrease the nephrotoxicity of this cytostatic agent (26, 25). Hydration and intravenous mannitol administration reduce the incidence of cisplatin nephrotoxicity by decreasing the exposure of the renal tubular cells to the drug (21). Cisplatin is less nephrotoxic when administered in a long infusion compared to a bolus. This is because endogenous sulphydryls present in renal tubules neutralize cisplatin at lower concentrations but are less efficient at higher concentrations achieved by a cisplatin bolus (28).

Moreover, N-acetylcysteine (NAC) has been considered to be cisplatin-nephroprotective (34). It inhibits apoptosis caused by cisplatin by interfering with caspase signaling. A liposomal formulation of cisplatin, lipoplatin, has been intensely studied over the recent years. It is regarded as equally effective but much less nephrotoxic which has been confirmed in animal studies as well as in clinical trials in adult patients with advanced pancreatic cancer, non-small cell lung carcinoma, head and neck neoplasm and metastatic breast cancer (32).

A research done by Luzonckzy came up with recommendations to be followed on administering cisplatin. Renal function should not be evaluated by serum creatinine concentration and should

be based on calculated creatinine clearance (for example, by the Cockcroft-Gault equation) and patients to be treated by high-dose cisplatin should be euvolemic and should have saline diuresis (urine NaCl concentration ~1%) of at least 100 ml/hour prior to, during and several days following the administration of cisplatin. Keeping these recommendations ensures prolonged cisplatin treatability of lung cancer patients. Moreover, decreased renal function will not limit the full dose administration of several other cytotoxic agents (37).

1.3.6 Use of Cisplatin in Cancer Management in TASH

Cisplatin forms the backbone of various cancer treatment protocols in TASH. It is used alone in treatment of cervical cancer at a dose of 50mg/m2. It is also combined with paclitaxel at a dose of 50-75 mg/m2 for each cycle of chemotherapy. In esophageal cancer, it is combined with 5-FU given as 80mg/m2 IV infusion. A higher dose of 150mg/m2 is used in combination with docetaxel and 5FU in treating esophageal cancer. For germ cell tumors, cisplatin (100mg/m2) is combined with etoposide and bleomycin. Doxorubicin and cisplatin at 100mg/m2 is given as continuous infusion for treating osteosarcoma. For head and neck cancer, it is combined with 5FU at a dose of 100mg/m2 (5).

1.3.7 Pre-Treatment/Preventive Measures of Nephrotoxicity in TASH

General preventive measures include using alternative non nephrotoxic drugs whenever possible, correcting risk factors, assessing baseline renal function before initiation of therapy, followed by adjusting the dosage, monitoring renal function and vital signs during therapy and avoiding nephrotoxic drug combinations. Adequate hydration is also important to maintain renal perfusion and to avoid drug-induced renal impairment (37). In TASH, hydration is maintained by administering at least 2L of Normal Saline during treatment with cisplatin (8). Prevention still relies on decreases in drug dosage, hydration measures, and active screening for renal abnormalities as part of the usual pre therapeutic biological work-up in patients treated with anticancer drugs. The European Society of Clinical Pharmacy Special Interest Group on Cancer Care suggested that hydration should be maintained for at least 3 d after the chemotherapy course, and by IV or oral route when feasible (38).

1.3.9 Causes of Nephrotoxicity

Drugs cause approximately 20 percent of community- and hospital acquired episodes of acute renal failure (11). Among older adults, the incidence of drug-induced nephrotoxicity may be as high as 66 percent. Compared with 30 years ago, patients today are older, have a higher incidence of diabetes and cardiovascular disease, take multiple medications, and are exposed to more diagnostic and therapeutic procedures with the potential to harm kidney function. Most drugs found to cause nephrotoxicity exert toxic effects by one or more common pathogenic mechanisms (17).

Two similar definitions based on SCr and urine output (RIFLE and AKIN) have been proposed and validated. (24) AKI is defined as any of the following: Increase in SCr by X0.3 mg/dl (X26.5 mol/l) within 48 hours; or Increase in SCr to X1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or Urine volume o0.5 ml/kg/h for 6 hours serum creatinine or GFR Risk; Increase in serum creatinine x1.5 or GFR decrease 25%, Injury; Serum creatinine x2 or GFR decreased 50%, Failure; Serum creatinine x3, or serum creatinine 44 mg/dl (4354 mmol/l) with an acute rise 40.5 mg/dl (444 mmol/l) or GFR decreased 75%, Loss; Persistent acute renal failure=complete loss of kidney function 4 weeks End-stage kidney disease ESRD 3 months (39,40).

Other patient variables that increases the risk of nephrotoxicity, including female sex, older age, smoking, and hypoalbuminemia. In addition, pre-existing renal dysfunction increases the risk for AKI (30). In the specific case of cisplatin, however, there are limited data on the incidence of nephrotoxicity in populations with chronic kidney disease since many trials exclude patients with renal insufficiency (29). Diabetes decreases the risk of cisplatin nephrotoxicity in animal models, but clinical studies have not found any impact of diabetes on nephrotoxicity in humans (18).

Grading nephrotoxicity

Chemotherapy toxicity was graded using the CTC (Common Toxicity Criteria) method formulated by the NCI (National Cancer Institute) (40) and biochemical profile was assessed, prior to each chemotherapy cycle (41). A reduction in creatinine clearance to less than 60 m/min was also viewed as a DLT, although it does not form part of the CTC criteria (41).

This is based on the fact that creatinine clearance has to be calculated before administration of Cisplatin. Entry criteria mandated serum creatinine within normal limits for the NCI of Canada, or not greater than 2.0 mg/dl in the GOG 123, and treatment with Cisplatin was withheld where the creatinine clearance fell to less than 50 ml/min (42).

The methodology used by Cockcroft and Gault has, however, been criticized as only data relating to males was used. The use of a factor of 0.85 to allow for the difference in mass between males and females in extrapolating estimates for females was based on expert opinion only, and not on actual data. Creatinine clearance is a more effective way of assessing renal function than serum creatinine. The use of endogenous serum creatinine to assess renal function is simple and is widely accepted. A limiting factor, however, is that creatinine is not filtered by the glomerular alone, but is also secreted by the renal tubular cells. The rate of secretion by the renal tubular cells is highly variable and is individual specific and time specific. This may lead to inaccurate prediction of GFR. The serum creatinine concentration also depends on lean body mass (muscle), which varies according to age and body size (as assessed by body weight) and sex (43, 44).

1.4 Significances of the study

Cancer is a known leading cause of morbidity and mortality in Kenya and the world at large. Treatment modalities available to manage cancer include radiation therapy, surgical therapy and chemotherapy. The use of cisplatin based regimen, in particular, causes renal dysfunction. Continued use of cisplatin may lead to toxicity and impede optimal use of ancillary and supportive measures. Therefore, early prediction of predisposition to renal function impairment and taking precautions early are crucial (17).

Evaluation of nephrotoxicity is important as long term users of cisplatin continue to increase. This is because both acute life threatening adverse effects and long term toxicity on the kidneys impacts negatively on the quality of life of the survivors, and therefore need to be controlled Several studies conducted in different countries showed a high incidence of chemotherapy related nephrotoxicity among cancer patients (24). But studies related to chemotherapy induced nephrotoxicity are limited in Ethiopia and so this study is expected to add information regarding chemotherapy induced nephrotoxicity in Ethiopian tertiary care hospital settings. This study

determined the prevalence of cisplatin based chemotherapy induced nephrotoxicity on patients put on cisplatin based regimen. By analyzing RFT and eGFR as a marker.

The findings of this study might provide information on the challenges during cisplatin-based chemotherapy treatment and used as baseline for next studies since it was not done previously. The information generated from this study will help the clinicians treating the patients to consider other saver options of treatment, to consider a better preventive protocol and appropriate intervention to be undertaken as early as possible, this also help patient to be protected from adverse effect of the drug and for immediate recovery. Also help in influencing the development of appropriate policies, plans and intervention programmers for the prevention and management of chemotherapy related renal problems. This in turn, might improve the quality of care for patients treated in TASH.

2.0. Objectives

2.1. General Objective

To evaluate the prevalence of ciplastin based chemotherapy induced nephrotoxicity among cervical and ovarian cancer patients undergoing first cycle chemotherapy treatment at Tikur Anbessa Specialized Hospital (TASH), Addis Ababa Ethiopia.

2.2. Specific Objectives

- To compare parameters renal function test values before and after treatment among cervical and ovarian cancer patients.
- To measure serum creatinine concentration before and after treatment among cervical and ovarian cancer patients.
- To determine serum urea levels before and after treatment among cervical and ovarian cancer patients.
- To assess serum uric acid concentration before and after treatment among cervical and ovarian cancer patients.
- To determine serum calcium concentration before and after treatment among cervical and ovarian cancer patients.
- To assess eGFR before and after chemotherapy

3.0. Materials and Methods

3.1. Study Design

A prospective cross-sectional study design was used to assess the prevalence of cisplatin-based chemotherapy induced Nephrotoxicity in the oncology wards of Tikur Anbessa Specialized Hospital.

3.2. Study Area

The study was conducted at oncology unit of TASH. TASH is a large referral teaching hospital, under the administration of Addis Ababa University, located in Addis Ababa, Ethiopia. The hospital has 800 beds and give diagnostic and treatment service for about 370,000-400,000 patients per year (10). The oncology unit of TASH is the only oncology unit for the country and has an outpatient department, which gives service to new and follow-up patients and an in-patients department, which has 19 beds. Professionally, the unit has 3 oncologists with palliative specialist, 1 general practitioner, 6 residents, and 12 nurses. KNH is Kenya‟s national referral hospital and would give results which can be extrapolated to the whole country. TASH offers comprehensive cancer treatment within the country. Being a public hospital, TASH offers the lowest cost for these services when compared to the private hospitals.

3.3.1 Source Population

All cancer patients referred to Tikur Anbessa Specialized and Referral Hospital chemotherapy department for treatment during the study period was included in the study.

3.3.2. Study subjects

Cervical and ovarian cancer patients evaluated and treated with cisplatin based chemotherapy at TASH between June, 2015- Oct, 2015 that were met the eligibility criteria**.**

3.3.3. Study Period

This study was carried from June, 2015 to December 2015.

3.4. Inclusion and Exclusion Criteria

3.4.1 Inclusion criteria

- Biopsy-proven untreated invasive carcinoma of the cervix and ovary

- Patients, who were agreed to give the consent.
- Patients over 18 years of age.
- Patients adequate renal function (calculated creatinine clearance of >60 mL/min according to the Cockcroft and Gault (CG) formula were included.

3.4.2 Exclusion Criteria`

- Patients with the history of systematic hypertension
- Patients with pre-existing renal failure
- Patients with diabetic patients
- Patient‟s medical contraindications to chemotherapy
- Patients who received treatment prior to the study period were excluded.

3.5 Sample size and sampling method

Convenience sampling method was applied to recruit study subjects. In this study 76 consecutive cervical and ovarian cancer patients who were evaluated and treated with cisplatin based chemotherapy during the study period were included.

3.6. Study variables

3.6.1. Dependent variables

- Renal Function Test results (RFTs normal/higher)
- Post serum creatinine level
- Post serum urea level
- Post serum uric acid level
- Post serum calcium level
- Post eGFR

3.6.2. The independent variables included

- Socio demographics
- Type of therapy
- Type of cancer
- Baseline RFT values
- Age

- Smoking
- Alcohol usage

3.7 Data Source

The study instruments consisted of files and a survey form which is divided into the following sections:

- ✓ Socio-demographic characteristics
- ✓ Reproductive data
- ✓ Stage, treatment and follow up.

3.8 Data collection procedure

In this study, quantitative and qualitative, data was collected prospectively using structured self-administered questionnaire and concerning clinical a well as patient history were collected from patient card by the oncology nurses. The data collections were mainly focus on the objective of the study. The first Primary data sources were baseline information about each patient like patient characteristics; physical examination (height and weight), current medications, co-morbidities, relevant previous medical and medication histories were recorded using data abstraction format through reviewing patients‟ medical chart.

For the evaluation of serum renal function tests and electrolyte determination. Blood sample were collected under aseptic conditions; skin over the vein were cleaned by 70% alcohol then specimens were transferred to serum separator container and centrifuged at 3000 rpm for 5 minutes. Serum were separated into a clean and sterile container and stored at – 20°C. The parameters were measured by calibrated automated Mind ray, clinical chemistry analyzer in central laboratory of Tikur Anbessa Specialized.

3.9 Data quality assurance

In order to assure its quality, data was collected by two oncology nurses who had basic knowledge on cancer therapy care services. The blood samples for biochemical assay were collected by adherence with standard operation procedures (SOP) and measurement of analyses were carried out after running quality control samples by the investigator.

3.9.1 Statistical Analysis

The data was analyzed using statistical Package for Social Sciences (SPSS) Vs 20 and parametric data were expressed as mean ± standard deviation. The comparison of the mean values within the group was done using paired samples t test. The correlation between the glomerular filtration rate (GFR) and creatinine was based on Pearson‟s correlation analysis, whereas Spearman‟s correlation analysis was used to determine the correlation between the GFR and uric acid values that were not normally distributed. The level of statistical significance was set at $P < 0.05$.

3.9.2 Evaluation of Toxicity

National Cancer Institute Common Toxicity Criteria for Adverse Events Version 4.0 (NCI CTCAE v4.0) were used to assess (pre-sRFT) and on the 21 day of the first cycle of chemotherapy (post-sRFT). CrCl was calculated using the Cockcroft-Gault formula (40, 41).

$$\text{Estimated creatinine clearance (ml/min/0.85m}^2\text{)} = \frac{[140 - \text{Age}] \times \text{Weight} \times 1.02}{(72) \times \text{Serum Creatinine}}$$

3.9.3 Operational Definitions:

- **Grade 1:** GFR _90 ml/min: Normal kidneys function with markers of kidney damage.
- **Grade 2**: GFR 60–89 ml/min: mild reduction of GFR with markers of kidney damage.
- **Grade3**: GFR 40–59 ml/min: moderate reduction of GFR.
- **Grade4**: GFR 20–39 ml/min: severe reduction of GFR.
- **Grade5**: GFR <15 ml/min: kidney failure.

Nephrotoxicity: It‟s the elevation of serum creatinine or blood urea nitrogen, uric acid or decreased glomerular filtration rate (12).

Neoadjuvant chemotherapy is the use of chemotherapy alone prior to definitive surgery or radiation therapy. It‟s given before primary therapy.

Adjuvant therapy: Is the additional cancer treatment after primary treatment to lower the risk of reemergence.

Table 2: Grading of nephrotoxicity (40, 41, 42)

phrotoxicity	rade	tal score (Ns) (sum of GFR)
R >90 Ml/min/0.85m^2		No nephrotoxicity
60-89 Ml/min/0.85m^2		Grade 1 nephrotoxicity
-59 Ml/min/0.85m^2	≤3	Grade 2 nephrotoxicity
-39 Ml/min/0.85m^2		Grade 3 nephrotoxicity

3.9.4 Ethical consideration

Ethical clearance was obtained from AAU, ethical Committee of department of Medical Laboratory and School of Allied Science prior to the study. Then a letter informing the department of radiotherapy and chemotherapy about the study were written from ethical Committee of department of Medical Laboratory and permission was obtained from department of chemotherapy and radio-therapy unit to access data from study population.

4.0 Result

4.1 Demographics characteristics

Between, July 2015 to December 2015, a total of 76 consecutive eligible patients had been enrolled. The age of the study subjects ranged from 24 to 79 years, with a mean age of 51 years (± 13.02 SD); majority of the study subjects (34.2%) were in the age group 35-44 years **(table 1).** The greater part of the patients (51.31%) was married, and the divorced comprised 30.2% of all women **(table 2).** Mean Minimum, Maximum and Standard Devotion of the study subjects were summarized in **(Table 3).**

Table 1: Socio-demographic characteristics of study subjects (N=76)

ge group	**N**	**%**
-34	11	14.47
-44	26	34.2
-54	23	30.2
-64	7	9.2
-74	8	10.5
4	1	1.31
tal	**76**	**100**
sidence		
ban	56	73.68
ral	20	26.31
lucation		
mary	41	53.94
condary	26	34.21
gher education	7	9.21
her	2	2.63
tal	**76**	**100**
arital Status		
rried	39	51.31
vorced	23	30.2
married	14	18.42
tal	**76**	**100.0**

Table 2: Mean and standard deviation (SD) of Age and Weight of the total participants

(year),Weight(kg)	nge	nimum	aximum	ean	d. Deviation
Age 1*	55.00*	24.00*	79.00*	51.21*	13.02060*
Age 2**	55.00**	24.00**	79.00**	51.7**	13.02060**
Weight1*	39.00*	38.00*	77.00*	54.86*	8.77472*
Weight 2**	37.00**	39.00**	76.00**	54.84**	8.15361**

Age 1*; and Weight 1*; before treatment, Age 2** and Weight 2**; after treatment at TASH, Ethiopia, 2016.

4.2 Clinical features of the study subjects.

As indicated in table 5 the disease distribution of the study subjects showed a higher incidence of cervical cancer (69.73%) followed by ovarian cancer (29.36%), Commonly prescribed drug classes in the study subjects were cisplatin is where the most frequently prescribed regimens (69.73%) followed by 5-Fluorouracil (5-FU) plus cisplatin (29.36%).

Table 3: Clinical characteristics of the study subjects

Type of cancer	Number of Patients	Percent (%)
rvical cancer	53	69.73
arian cancer	23	29.36
tal	**100.0**	**100.0**
pe of chemotherapy		
splatin 50mg/m^2	53	69.73
splatin 50mg/m^2 + 5-fu 500mg/m^2	23	29.36
tal	**100.0**	**100**

4.3 Evaluation of the Renal Functions at Baseline

Prior to the start (Day 0) of treatment with cisplatin based chemotherapy, renal function test has been performed on 76 subjects. Accordingly, mean serum creatinine (0.759 ±.0.1954), urea

(31.723±15.677), uric acid (4.3579±1.01065), and calcium (8.725±1.27050) for serum creatinine, urea, uric acid and calcium where the (p.value>0.05). Mean estimated creatinine clearance was where (82.1589 ± 21.5005SD). Mean/SD of pre and post treatment renal function of the recruited patients is reported in **(Table 4).**

4.4 Change in Renal Function/Nephrotoxicity

After the first course of treatment (Day 21) renal function /nephrotoxicity has been assessed by measuring the level of serum creatinine, urea, uric acid, calcium, and estimated glomerular filtration rate (eGFR) were measured.

Accordingly, serum creatinine and uric acid levels increased significantly, the results where (1.08 ±0.78) and uric acid levels (5.90 ±2.40) where the (P.value 0.001) and (p.value0.00) respectively. However, serum urea and calcium levels has been shown no statistical significant change after treatment where the (p. value>0.05).On the other hand estimated creatinine clearance was assessed according to the Cockcroft-Gault formula. Accordingly, the eGFR following the 1st cycles of chemotherapy were significantly lower than those before the start of chemotherapy correspondingly, where the results (82.16 ±16.50) Vs (50.22 ±14.04) where the ($P < 0.01$). The comparison between pre and post treatment values of sCr, urea, uric acid, ca^2 and CrCl **(Table 4).**

Pearson‟s correlation analysis was performed between the eGFR and serum creatinine level, the result showed there is a strong negative correlation correspondingly, (rho: –0.150 Vs -0.136, $P < 0.001$) and Spearman‟s correlation analysis showed that there was a strong negative correlation between the eGFR and uric acid level (rho: –0.018, $P < 0.05$).

Table 4: Comparison of biochemical parameters between before and after the 1st courses of cisplatin-based chemotherapy

rameters Mg/dl	inimum	axim	ean	d. Deviation	P. value
fore Treatment					
eatinine*	40	10	7595	0.195	0.72*
ea*	)	9.0	.7	11.67	0.119*
ic acid*	20	20	3579	1.01	0.605*
lcium*	30	.00	7250	1.27	0.637*
R*	.00	8.0	.1589	12.50	0.185*
ter Treatment					
eatinine **	**)**	**50**	**0754**	**0.78**	**0.001***
ea **	**000**	**7.0**	**.77632**	**11.22**	**0.335****
ic acid **	**50**	**.90**	**0000**	**2.39**	**0.00****
lcium **	**00**	**.80**	**0145**	**1.70**	**0.207****
R **	**.0**	**111.00**	**.2170**	**14.0**	**0.00****

**Before therapy: 0 days before chemotherapy; **after therapy: 21 days after chemotherapy; † (mean ± SD). Addis Ababa Ethiopia 2015*

Table 5: Mean of creatinine, urea, uric acid, calcium serum level and glomerular filtration rate (eGFR) of before and after cisplatin and or cisplatin and 5 Fluorouracil treatment of the 1St cycle alone nephrotoxicity outcome (Paired T-test)

Parameters Mg/dl		Sig.2tailed
Pair 1	Creatinine1 Creatinine2	*.001
Pair 2	Urea 1 Urea 2	.335
Pair 3	Uric acid 1 Uric acid 2	*.000
Pair 4	Calcium 1 Calcium2	.207
Pair 5	GFR 1 GFR 2	*0.000

Values are compared before1* and after2* treatment and expressed as Mean ± SEM (n=76). *P<0.05 is considered as significant. Addis Ababa Ethiopia 2015

4.5 Grading of Nephrotoxicity

Nephrotoxicity were graded according to the National Cancer Institute, Common Terminology Criteria for Adverse Events (NCI CTCAE, version 4.0), during the first course of cisplatin chemotherapy (39).

When eGFR used alone as nephrotoxicity marker, no nephrotoxicity (Grade 0) was observed in 18 patients (24.3%). Grade 1 nephrotoxicity was observed in 43 patients (56.53%), Grade 2 in 11 patients (14.4%), and Grade 3 in 3 patients (5.26%). None had Grade 4 nephrotoxicity. Only 41 patients showed an increase in serum creatinine, 23 of them 1.5 to 1.9 from baseline and 12 of them 2.0-2.9 only 6 patients >3.0 times **(Table 6).**

Table 6: Grading of nephrotoxicity according to the estimated glomerular filtration rate

Parameters	**No nephrotoxicity***	**Grade1***	**Grade2***	**Grade3***
EGFR ml/m	18 (24.3%)	43 (56.53%)	11 (14.4%)	4 (5.26%)
Classifications	*>90ml/min**	*60-89ml/min**	*45-59ml/min*30-44ml/min**	

Table 7: Grading of nephrotoxicity according to measured serum creatinine levels after the1st cycles of chemotherapy

rameters	**No nephrotoxicity***	**Grade1***	**Grade2***	**Grade3***
r mg/dl	35 (46.03%)	23 (30.25%)	12 (15.78%)	6 (7.89%)

*Scr1.5;*1.5-1.9;*2-2.9,*3 times the baseline were considered as having nephrotoxicity. Addis Ababa Ethiopia 2015.

5.0. Discussion

The goal of drug therapy is to achieve defined therapeutic outcomes and improve the patient‟s quality of life while minimizing patient risk. However, inappropriate use of drugs during disease management may lead to drug therapy problems. This study was carried out to assess the prevalence of CIN among cervical and ovarian cancer patients treated at oncology ward of TASH in Ethiopia. The present study was undertaken to evaluate pre and post-cisplatin induced nephrotoxicity among cervical and ovarian cancer patients by measuring biochemical parameters including serum creatinine, urea, uric acid, calcium and estimated creatinine clearance.

In the current study we found increased level of serum creatinine when compared with the baseline value, the results where (1.08 ±0.78SD), (0.7595±0.195) respectively. These results disagree with the results of Takako O *et al* (42) who conducted a prospective cross sectional study among 46 ovarian cancer patients treated with cisplatin based chemotherapy in Japan. He reported post-sCr value shown no statistical significant difference between pre and post sCr value, the result where (0.77 ± 0.19Vs0.83 ± 0.19) this could be patients in Japan may taken adequate fluid before and after treatment. On the other hand the value of post-CrCl significantly decreased compared to pre-CrCl ($p < 0.001$ and $p > 0.031$, respectively). This results directly in agreement with the current study. This may be due to the drug effect, cisplatin directly affect the renal tubular cell damage.

In our study the levels of GFR has been calculated using cockroft-gault equation. The levels of GFR were found to be decreased significantly after the course of cisplatin-based chemotherapy treatment. Accordingly, the results where (82.158 Vs 50.217 SD) where the (p.>0.05 Vs <0.05) respectively. These results agree with the finding of Songül Tezcan et al (32) who conducted prospective cross sectional study in Turkey in 2013 he reported the level of GFR decreased significantly after the first cycle of cisplatin-based chemotherapy. Accordingly the results where (GFR: 109.62 ± 5.12 vs. 99.99 ± 4.7 n = 43; $P < 0.01$).

The result of the current study showed an increased level of serum creatinine. Accordingly, the resulted where (1.0854 ±.781 SD) and uric acid level (5.9 ±2.7SD) were statistically significant (p. value<0.001), (p. value=0.00) respectively for both parameters after treatment as compared to the base line (0.759 ±.0.1954), (4.3579±1.01065) where the (P.value>0.05) for both parameters respectively., This is in agreement with a prospective cross sectional case control study

conducted by Ameer (24) in Sudan. He documented different manifestations of renal dysfunctions. Accordingly cases had statistical significant higher serum creatinine (1.1 ±.55SD) and uric acid (6.5 ±2.7SD) as compared to control(0.8±.15SD) ,(5±1.01SD), respectively for both parameters.(*p.* value<0.05), however serum urea and calcium after treatment showed no statistical significant difference (35.7±27SD) as compared to control group (30.8 ±8.5SD).(p.value>0.05) (26).

Chemotherapy-related kidney toxicity was more frequent in patients with reduced eGFR values, even in the presence of SCr levels within the normal range. Nephrotoxicity rates increased from 2% in patients with normal kidney function to approximately 7% in patients with moderate renal dysfunction. Although the difference was not significant, possibly because of the low number of toxic events, this observation is in agreement with recent findings suggesting that the presence of unrecognized renal impairment could be responsible for chemotherapy-associated adverse effects (29) and highlights the significance of eGFR assessment before the initiation of anticancer therapy.

Climaco A J 2015 Canada cohort study (43) in this study nephrotoxicity was observed in 41 subjects (75.9%). Grade 1 nephrotoxicity was observed in 18 patients (33.3%), Grade 2 in 5 patients (9.2%), and Grade 3 in 18 patients (33.3%). None had Grade 4 nephrotoxicity.

These patients have limited access to fluids. They travel long distances to hospital and stand in long queues before they finally get treatment. Diarrhea and vomiting during treatment which lead to volume depletion and eventually to renal dysfunction. Mild dehydration induces an increase in vasopressin secretion, which in turn leads to morphologic and functional changes in the kidney leading to acute renal failure. Diarrhea and vomiting also lead to renal failure due to intravascular volume depletion (38, 34, and 35).

The present study also monitored serum creatinine levels and determined its correlation with the GFR among cervical and ovarian cancer patients. Pearson‟s correlation analysis showed that pre and post chemotherapy there was a strong negative correlation between the eGFR and serum creatinine level correspondingly (rho: –0.150 Vs -0.136, P < 0.001) and Spearman‟s correlation analysis showed that there was a strong negative correlation between the eGFR and uric acid level after the first cycle of chemotherapy (rho: –0.018, P < 0.05). This result agrees with the study carried out by Mohammad AM, (44) reported that there was stronger negative correlation

between creatinine clearance and serum creatinine levels creatinine and the GFR: rho: –0.701, P < 0.001).

Serum urea result was reported to differ according to the age of the patient, this agrees with the findings reported by Gnohaar K et al (27) who concluded that the increase in plasma urea levels are associated with the age of the patient. While plasma creatinine showed different results based on the age of that undergoing chemotherapy treatment, this agrees with the findings of Genohaar. Koichi (). The difference in plasma uric acid levels between those aged less than 50 year and those aged 50 years and more goes in concordance with the result conducted by American association for cancer research

Although the detailed mechanism underlying this effect is not clear, recent reports have shown that the human organic cation transporter 2 (OCT2) is predominantly expressed in the human kidney at the basolateral membrane of renal proximal tubules (43) (28). These findings suggest that pre-cisplatin dosing among patients with renal impairment in our hospital was not calculated based on CrCl results even though the physicians‟ interview revealed GFR is used to adjust cisplatin dose in oncology medicine wards of TASH. Our patients had decreases in GRF and increases in serum creatinine after each treatment session with cisplatin, thus validating the use of these tests to verify altered kidney function only after and never before exposure to the drug (first cycles).

The present study resulted with various manifestation of nephrotoxicity which is in line with In a single centre Iranian study, reported a 25.2% rate of renal toxicity, including tubular disorders and hypertension (25). Similarly Knijnenbur reported a prevalence of 28.1% of therapy related renal dysfunction in childhood cancer survivors (26). In both studies, the proportions reflected at least one renal adverse effect or elevated blood pressure in the survivors. Gronroos documented a seven year follow up of 187 children post stem cell transplant in Finland and reported the finding of chronic kidney disease (CKD) in 41% at 1 yr, 31% at 3 yr, and 11% at 7 years (27).Evidence strongly suggests the involvement of inflammatory mechanisms in the pathogenesis of cisplatin nephrotoxicity (14).

In this study, a CIN was observed at a Cisplatin dose of 50 mg/m2. The CIN consisted of elevated serum creatinine and low calculated creatinine clearance. Although most studies do not

use GFR as a CIN, it was felt to be justified in this study, as chemotherapy could not be given when the creatinine clearance was low.

Adequate renal function was an eligibility criterion for all patients participating in the clinical trials using Cisplatin. In a phase I study reported by Nyongesa et al, (40) Cisplatin was withheld because of transient rises in BUN and creatinine. In a phase I/II study reported by Thigpen (20) Cisplatin was discontinued if the creatinine exceeded 2.0 mg %. In further phase III studies, including the NCI of Canada and the GOG 120, (28, 33) Cisplatin was discontinued, if the serum creatinine exceeded 140 μmol/ml (2.0 mg /dl).

In a study from Roswell Park, reported by Jeffrey Bell, (36) patients received Cisplatin only if the urine creatinine clearance was greater than 60ml per min. In this particular study one patient developed a drop in creatinine clearance to 30ml per min. The serum creatinine of this patient also rose to 1.7 mg % and Cisplatin was discontinued. In two other studies, reported by Pujol JL and Daures JP, (37) Cisplatin was discontinued if creatinine clearance fell to <50 ml /min.

Based on the findings of this study, post chemotherapy hydration may be necessary even at these low doses of Cisplatin. Creatinine clearance should be obtained both at baseline and before each cycle of Cisplatin chemotherapy. Renal function (Urea and Creatinine) as well as serum electrolytes (Na, Mg, Ca and K) should be monitored carefully during treatment. The fluid status of the patient is critical. The recommended approach is to give at least 1 liter before and 1 liter after Cisplatin treatment of 0.9 % sodium chloride with 20 mEq of KCL. Glomerular filtration rate (GFR) is the best index of kidney function. Mathematical estimations of GFR, based on serum creatinine, are clinically useful methods to follow renal function (42).

6. Conclusion

There was deterioration in renal function among cervical and ovarian cancer patients undergoing one cycle(1st cycle) of cisplatin alone and Cisplatin with 5-Flourouracil chemotherapy treatment after adequate rehydration when, creatinine, plasma urea glomerular filtration rate and uric acid were used as indicators to assess the renal function. In the present study we have found that Cisplatin induces nephrotoxicity possibly by disturbing significant elevations in serum creatinine and uric acid and also decreased creatinine clearance observed, if no corrective measures are initiated. Frequency and severity of cisplatin nephrotoxicity may be reduced by slow intravenous electrolyte infusions and maintaining the hydration; before, during and immediately after the administration of cisplatin.

7. Limitation of the study

Some limitations must be acknowledged.

- The study was cross-sectional and the size of the population of individuals studied was small.
- Since the study has been conducted in one hospital the results may not represent the national figure
- Some risk factors were not assessed in these particular studies like psychological factors for instance the extent of anxiety.
- Therefore the finding may not reflect the situation in other towns or at the national level.

8. Recommendations

- Oncology unit of TASH should consider using the recent chemotherapy guidelines to improve the management of CIN.
- To effectively monitor nephrotoxicity, renal parameters and electrolyte levels should be measured before and after cisplatin based chemotherapy treatment.
- More investigations are required to evaluate nephrotoxicity with higher doses of cisplatin.

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ADDIS ABABA UNIVERSITY

SCHOOL OF GRADUATE STUDIES

DEPARTEMENT OF MEDICAL LABORATORY

Annexes:

Annex-I: Consent Form

Addis Ababa University School of Allied Department of medical laboratory since and clinical chemistry truck Prospective cross-sectional study on assessment of drug related problems in medical wards of Tikur Anbessa Specialized Hospital

Greeting:

Hello, My name is_____. I am here today to collect data to asses drug related problems in medical wards of Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. The study is being conducted by Mr. FasilTefera from Addis Ababa University, school of Allied Science, department of clinical chemistry, post graduate program. The objective of this study is to determine the prevalence of chemotherapy related nephrotoxicity to identify predictors of occurrence of drug related nephrotoxicity. This is prospective cross-sectional study so I request you to take part in this study. Your cooperation and willingness is greatly helpful in assessing drug therapy problems in Tikur Anbessa Specialized Hospital.

PARTICIPATION: Without your participation and voluntarism the feasibility of this research are under question, so we asking you and all other to voluntary participant in this study. What we expect from you is your willingness to give blood to be examined for renal function status. The examination involves laboratory procedure with collection of 4 ml blood from vein. Sample will be collected using sterile and disposable needles and test tubes. RISKS: Taking 4ml of blood does not have any harm to your health but minor needle pain may last for seconds. If there comes any discomfort, we shall offer you necessary medical treatment freely.

BENEFITS: If we find any negative result possible medical care and treatments will be provided for participant by referring to local health service or Tikur Anbessa Specialize Hospital depending upon availability of possible treatment in local health service facility or severity of the finding.

CONFIDENTIALITY: Any information collected from you will be kept confidential. Your identity will not be disclosed in any situation and study results will be present by using different code number instead of your name. **Right to Refuse** Since your participation in this study is entirely depend your voluntarism you have right to refuse to accept this request.

Are you willing to participate in this study?

1. Yes - …….. Continue
2. No - …… Skip to the next participant

If you have questions regarding this study or would like to be informed of the results after its completion, please feel free to contact the principal investigator.

Address of the principal Fasil Tefera

Cell phone: +251- 948001746

E-mail: tassewfasil09@gmail.com

Annex II: Amharic version of participant's information sheet, consent and questionnaire

የተሳታፊዎች መረጃ ቅጽ

የአዲስ አበባ ዩኒቨርሲቲ ጤና ሳይንስ ኮሌጅ የህክምና ላቦራቶሪ ሳይንስ ዲፓርትመንት

አርስት፡የኬሞቴራፒ ህክምና በማህፀን ካንሰር ህመማን ላይ የሚያስከትለው የጉንዮሽ ጉዳት ለማወቅ

አጠቃላይ መረጃ፡ በጥናቱ በመሳተፍ ከልብ እያመሠገንኩ ከመሳተፎ በፊት ይህንን ቅጽበት ክክል እንብበው ወይም ሲነበብሎት በትክክል አድምጠው እንዲሁም ግልጽ ያልሆነልዎትን ነገር በሙሉ በግልጽነት ይጠይቁ፡፡

ጤና ይስጥልኝ ስሜ ---------- ይባላል፡፡

የመጣሁት ከአደስ አበባ ዩኒቨርሲሲ የህክምና ላቦራቶሪ የድህረ ምረቃ የትምህርት ክፍል ነው፡፡ የመጣሁበትም ዋናው ምክንያት በጥቁር አንበሳ ሆስፒታል በካንሰር ህክምና ክፈል ውስጥ ህክምናውን ከመሀጀመራቸው በፊትና መድሀኒቱን ከወሰዱ በኋላ ምን ያክሉ ታካሚዎች የጉንዮሽ ጉዳት እንደደረሰባቸው ለማወቅ ነው፡፡

ለጉንሽ ጉዳት ምርመራው ጥቂት የደም ናሙና ከክንዶት ላይ መውሰድ ያስፈልገኛል፡፡ ደም የምወስድበት መሳሪያ ንፁህ እና ሙሉ በሙሉ አስተማማኝ ሲሆን ከዚህ በፊት ጭራሽ ጥቅም ላይ ያልዋለና የእርስዎን ደም ምርመራ ካደረግን በኋላ የሚጣል ነው፡፡ ምንም ስም ስለማይያያዝ የምርመራ ውጤቱን ልንገግርዎት አንችልም ሌላ ማንም ሰው ቢሆን የእርስዎ የደም ውጤት ሊያውቅ አይችልም፡፡

<u>እርስዎ የሚያገኙት ጥቅም</u>

ከዚህ ጥናት ምንም አይነት የገንዘብ ክፍያ የማይከፈል ሲሆን ነገር ግን ለሚሰራው የደም ምርመራ እርስዎ ለደም ምርመራው ምንም አይነት ክፍያ አይከፍሉም፡፡ በተጨማሪም መንግሥት በዚህ ጥናት ላይ ተመርኩዞ እቅድ ለማቀድ ይረዳዋል፡፡ በዚህ ጥናት ላይ እንደሚሳተፉ ተስፋ አደርጋለሁ፡፡

አሁን ባለበብኩት ላይ ጥያቄ አለዎት

አሁን መጠይቁን እና የደም ናሙናውን መውሰድ እችላለሁ

የአጥኚው ፊርማ ----------ቀን ----------

ለማንኛውም ጥያቄ በሚከተሉት አድራሻዎች መጠየቅ ይችላሉ

ስልክ 0948001746

E-mail: tassewfasil09@gmail.com

Annex III: Data Collection Form

For The Study **"**Evaluation of nephrotoxicity among cervical cancer patients treated with cisplatin based chemotherapy at Tikur Anbessa Specialized Hospital"

Study ID…….. Study Serial Number**…….**

1.0 Participant Socio-demographic Data

Date of data collection: ……

Patient Code Number: ……. Data Collector"s initials: …….

1. Age: …….. Years …….

2. Weight: Kg ……

3. Height: ……. M ……

4. Place of residence: 0. Urban ( ) 1. Rural ( )

5. Highest level of Education

0. Informal ( ) 1. Primary ( ) 2. Secondary ( ) 3. College ( )

6. Marital Status

0. Married ( ) 1. Single ( ) 2. Divorced ( ) 3. Widowed ( ) 4. Separated ( )

7. Employment Status 0. Employed ( ) 1. Not Employed ( ) 2. Student ( ) 3. Retired ( )

Cancer specific information

What type of cancer was diagnosed? Duration since Diagnosis?

No Type of cancer	Tick as appropriate	Duration) since Diagnosis
1 Ovarian		
2 Cervical		
3 Esophageal		
4 Breast		

Specify other co morbidities present in the patient.

1. Cirrhosis □Yes □No

2. Diabetes Mellitus □Yes □No

3. Hypertension □Yes □No

4. Heart Failure □Yes □No

5. Nephritis □Yes □No

6. Hyperuricemia □Yes □No

10. Others (Specify)……
…….

Annex VI:

Laboratory testing method and principles

Creatinine Test method – Fixed time kinetic colorimetric method

Definition

Creatinine is a non protein end product of creatinin metabolism and it is excreted via kidney with minimal or no tubular re absorption creatinine level there for are directly related to the glomerular filtration rate.

Purpose; To asses renal glomerular filtration and to screen for renal damage

Creatinine Testing Principle

Creatinine under alkaline condition reacts with picrate ion forming a radish complex. The Formation rate of complex measured though the increase of absorbance in the prefixed interval of time is proportional to the concentration of creatinine in the sample.

Creatinine + Picric ⟶ read addition complex

Sample; Serum or Plasma (heparin as anticoagulant)

Normal values For Men up to 1.1**/.** For women up to 0.9

Urea test method – Berthelot enzymatic colorimetric method.

Definition

Hydrolysis of protein to amino acid occurs in the intestine. The absorbed amino acid are carried to the liver and other tissue were there may be utilized for the synthesis of new protein which is converted to other compound, or utilized for energy. When canalized the amino group end up in urea which is excreted by the kidney as a waist product.

Urea Testing Principle

Urea + grease $\longrightarrow$ (NH_4^+) 2 + CO_2

NH_4^+ + salycilate + NaC1O nitroprusside $\longrightarrow$ Indophenols

The intensity of the color formed is proportional to the urea concentration in the sample.

Sample Serum or Plasma, SpecimenqualitiesFresh, free from hemoliysis, non lipermic and non turbid**,** SpecimenstorageAnalyze as soon as possible if delayed store at 4-8^{0}c for 3 days.

Uric acid

- ✓ **Test method** – uricase - POD. Enzymatic colorimetric method

Definition

Uric acid is purine compound that circulates in plasma as sodium urea and is excreted by the kidney it is derived from the break downs of nucleic acid that are ingested or come from the destruction of tissues cell. It is also synthesized in the body from simple compound.

- ✓ **Purpose**

To detect hyperuricemia and hyperuricemia

- ✓ **Principle**

Uric acid is oxidized by uricase to allanotine and hydrogen peroxide which under the influence of POD, 4-aminophnazone and 2-4 dichlorophenol sulfanete forms a red quinonemine compound.

- ✓ Sample

Serum of plasma

Estimated glomerular filtration rate

Method: Cockcroft-Gault formula

EGFR (ml/min/0.85m^2) = $\frac{(140\text{-Age}) \times \text{weight (kg)}}{(72) \times \text{Scr}}$ **x 0.85m^2**