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Use of Procalcitonin and Neutrophil to Lymphocyte Ratio in Evaluation of Inflammation in Chronic and Acute Kidney Disease

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Abstract

Background: This is a cross- sectional study that included biochemical markers comparative between Procalcitonin (PCT) , and Neutrophil to lymphocyte ratio (NLR) in chronic hemodialysis patients and acute kidney disease patients**.**
Objective: The purpose of this study was to clarify the diagnostic accuracy of the use of Procalcitonin (PCT) and NLR level and to prove the value of these markers in the diagnosis of inflammation in patients with chronic kidney disease and Acute kidney disease.
Methodology: Blood samples were collected from patients with chronic kidney disease and acute kidney disease, then approximately 5 ml with complete information about the patients, then the blood separate by the centrifuge and the serum was used to measurement the levels of Procalcitonin, and NLR.
Results: The study showed the highest means levels of PCT were found in patients with chronic kidney disease (CKD) (1.82 ng/ml), followed by patients with acute kidney disease (0.49 ng/ml), (P. value=0.0495) .The highest means level of NLR were found in patients with chronic kidney disease (4.35±4.07) mg/L , followed by patients with acute kidney disease (2.78±1.31) mg/L.
Conclusions:that CKD patients had higher levels of PCT and NLR than AKD patients.

Key words:PCT, NLR, CKD, AKD.

Introduction

The term renal failure denotes inability of the kidneys to perform excretory function leading to retention of nitrogenous waste products from the blood, function of kidney are: electrolyte regulation, excretion of nitrogenous waste, elimination of exogenous molecules(ex., drugs), synthesis of a variety of hormones (ex., erythropoietin), metabolism of low molecular weight protein (ex., insulin). (Pallos *et al.*, 2015).

Acute and chronic renal failure are the two kinds of kidney failure:

Acute kidney disease (AKD) is a heterogeneous disorder that is common in hospitalized patients and associated with short and long-term morbidity and mortality , that AKD is not a self- limited process, but is strongly linked to increased risk for chronic kidney disease (CKD) , and future mortality (Moore *et al* ., 2018).

Chronic kidney failure (CKF) also known as Chronic kidney disease (CKD) defined as a persistent abnormality in kidney structure or function (eg., glomerular filtration rate (GFR) < 60ml/min/1.73m or albuminurea ≥30 mg per 24 hours) for more than 3 months, CDK affects 8% to

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16% of the population worldwide.(Chen *et al.*, 2021). CKD is slowly progressive and leads to irreversible loss of nephrons, end stage renal disease and / or early death. Therefore. CKF represent a worldwide major concern and its prevalence continues to rise, also it is one of the most common diseases .(Ruiz-Ortegn *et al*., 2020)

One of the major complication of hemodialysis catheter use is bloodstream infection , which is associated with an increased risk of systemic infection complication , hospitalization , and death (Poinen *et al.,* 2019.

Procalcitonin (PCT), a protein that consists of 116 amino acids, is the peptide precursor of calcitonin, a hormone that is synthesized by the parafollicular C cells of the thyroid and involved in calcium homeostasis. Procalcitonin arises from endopeptidase-cleaved preprocalcitonin. The reference value of PCT in adults and children older than 72 hours is 0. 15 ng/mL or less.(Giannetta *et al* ., 2020)

Neutrophil to Lymphocyte ratio (NLR)is inexpensive, convenient, and measured easily and have demonstrated utility in stratifying mortality from cardiac events , and prognostic factor for cancer , and it is reported that the NLR predicts the progression rate of stage 4 chronic kidney disease to dialysis (Brito *et al* ., 2021). Studies suggested that NLR was linked to inflammation and could predict mortality among hemodialysis(HD) patients (Catabay*et al* ., 2017).

Material and method

Determination of Procalcitonin (PCT)

1:- Intended use

The fluorecare PCT is application to the quantitative detection of the concentration of PCT in human serum and plasma.

2:- Principle:

The fluorecare PCT , based on the principle of the immunochromatographic assay , is used to detect the concentration of PCT in human serum or plasma by double antibody sandwich method.

3:- Requirements of Specimens

1- The serum and plasma are obtained from the whole blood collected by the conventional method , the hemolysis and severe jaundice sample should not be used during the whole process. All specimens should be treated as infection factors.

2- The plasma specimens are allowed to be treated with heparin sodium, citrate and EDTA.

3- The serum or plasma specimens cannot be placed over 1 day under room temperature (20-25 ^{o}C) , sample cannot be stored over 3 days within 2-8 ^{o}C, or no more than 3 times, after being thawed, the specimens should be fully mixed.

4- The specimens containing visible particles should be treated by centrifugation, and the supernatant fluid is to be tested.

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5- Before being tested, the sample must be recovered to room temperature. Frozen preserved specimens that are to be detected need to be completely malted, rewarmed and mixed well.

4:- Test Setup

1- Take out the test card from refrigerator and leave it at room temperature (20-25^{o}C), turn on the instrument according to the instructions.(**Figure 1**)

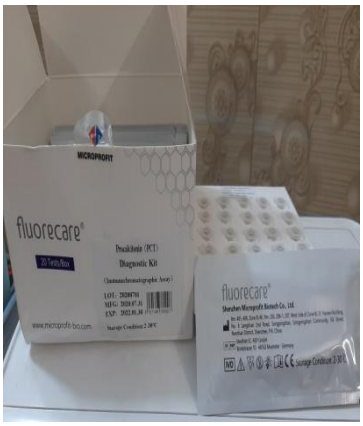
2- Check the consistence of the ID chip and the lot number or the diagnostic kits, do not touch the insertion end of the ID chip when it is inserted.

3- Open the foil pouch by tearing along the splice and place the test card on the flat operation table , the test card should be used within 1 hour.

4- Holding the pipette vertically, add 20µL serum and plasma sample or the reference product without air bubbles to the 180 µL diluents solution (the diluents is along with the kit box) tube and mix , mixing procedure should be 2 minutes , and then apply 70 µL mixture to the specimen well on the test card.

5- Being placed at the room temperature for 15 minutes, and then insert it into test card holder of analyzer and start to test according to the analyzer instruction manual, few seconds later , the result will be automatically displayed on the screen , the result can be kept and printed out as well.

NOTE: The experiment should be done at 20-25 ^{o}C , humidity 35%-85%.



1 Kit contents

2 Check whether the code of ID chip is consistent with the reagent batch number

3 Turn on the machine , press the [Test] button on screen

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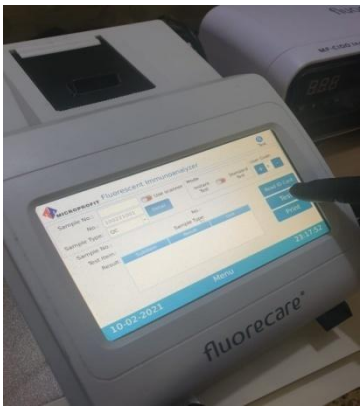
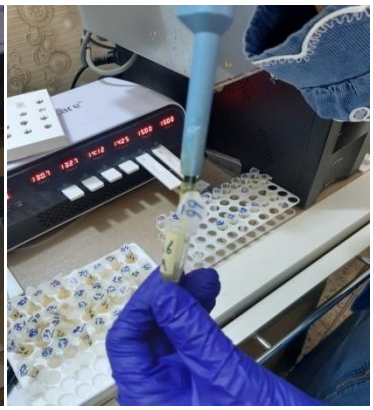
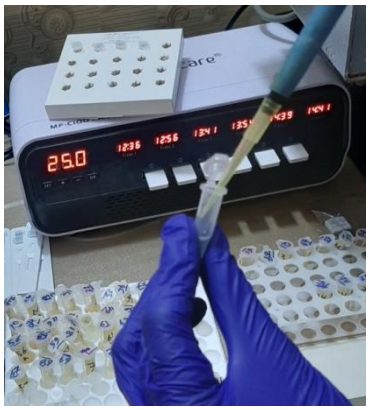


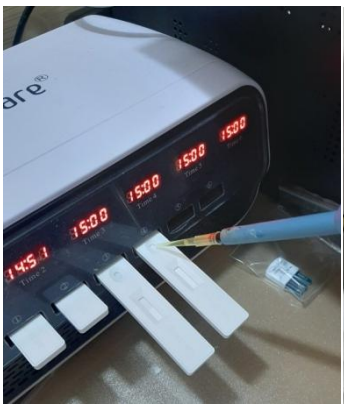
4 Insert the ID chip, and press [Read ID



5 Drop 20 µL of serum



6Add the serum to the dilute tube and mix well for 2minutes

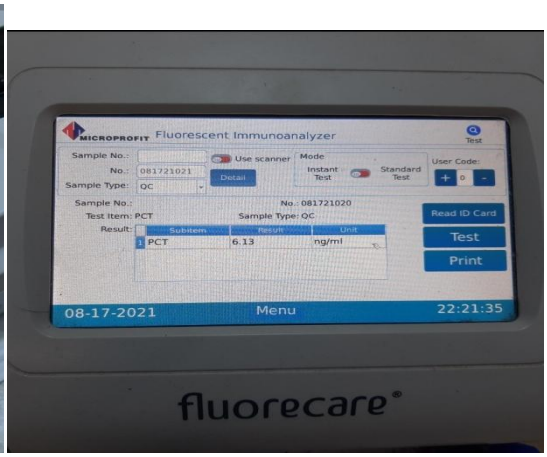


7 Drop 70 µL of mixture to the sample well on testing

8 Keep the cassette at room temperature 15 minutes for chromatographic reaction.

9 Take out the cassett, and insert into the analyzer.

10 Press [Test]



11 get the result , and press [Print] to print out the result from inner printer

Figure (1) PCT test steps

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Determination of Complete Blood Count (CBC)

1:- Principle

The Sysmex XN-350 is multi-parameter quantitative automated hematology analyzesr for in vitro diagnostic use in determining whole blood diagnostic parameters, examination of the numerical and / or morphological findings of the complete blood count by the physician are useful in the diagnosis of disease states such as anemia , leukemia, allergic reactions, viral, bacterial, and parasitic infections, the devices perform hematology analyses based on the hydrodynamically focused impedance measurement , the flow cytometry method (using a semiconductor laser) and the SLS- hemoglobin .

2:- Method.

The device counts and sizes red blood cells (RBC) and platelets (PLT) using hydrodynamic impedance counting (sheath flow DC method). At the same time the hematocrit (HCT) is measured as a ratio of the total RBC volume to whole blood via the RBC pulse height detection method. Cytometry is used to analyze physiological and chemical characteristics of cells and other biological particles. Flow cytometry is a method used to analyze those cells and particles as they pass through extremely small flow cells. The Data Innovations Instrument Manager (DI) is a Data Innovations computer program which is used to manage data coming from the XN-350 analyzers and sends that data to the Laboratory Information System (LIS)(Ehrmeyer, 2011). (**See figure (2).** Sets of WBC, RBC, and PLT rules determine how positive parameter flags are handled by the instrument and/or operator and which samples are auto-validated by the DI. Manual differentials and RBC/Platelet morphology is entered via the DI. Pending Orders are checked via the Outstanding List in EPIC.

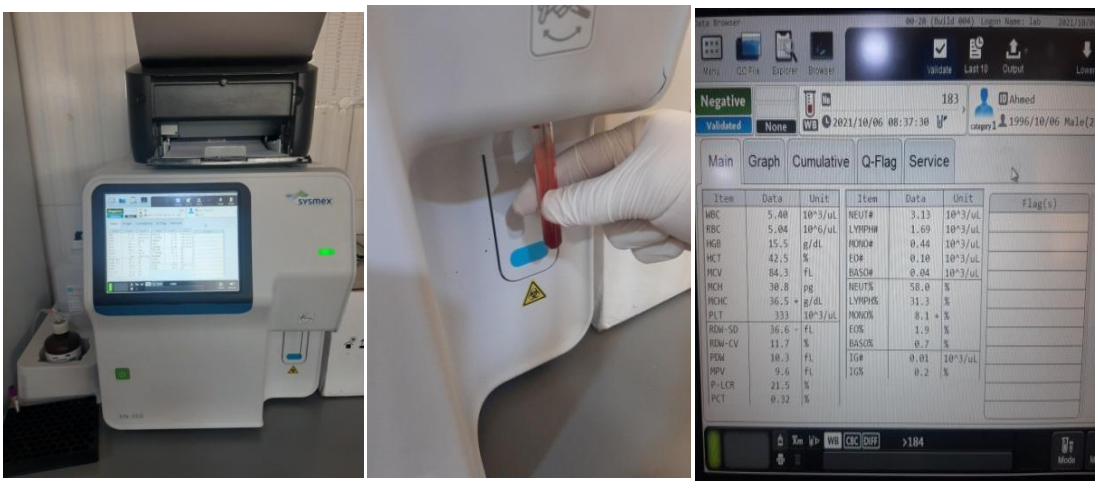

Figure (2) Sysmex XN-350 , Complete Blood Count and Parameters – Whole Blood

3:- Specimens:

- Whole blood anticoagulated with a potassium EDTA is preferred.

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- A minimum of 1 mL of whole blood is required for sampler analysis

- If stored at 4-8o C within 6 hours of collection, EDTA blood samples with normal results may be analyzed up to 48 hours without significant loss of differential stability. The stability may be increased to 72 hours if results do not show a loss of specimen integrity.

- Sample stability at room temperature is 8 hours. Samples stored at room temperature may exhibit an increase in MCV after 24 hours; this may be minimized by refrigeration.

- Allow refrigerated samples to come to room temperature for 30 minutes and mix by hand inversion before analysis.

- Do not place samples on a mechanical rocker. Constant rocking may cause PLT clumping and alter white cell membranes resulting in false interpretive messages. inversion before analysis.

4:- Reagents / Materials:

a. Supplies: Lint-free lined lab wipes, Gauze, Test tubes, CELLCLEAN® AUTO, Sysmex reagents (listed below), and Commercial controls; XN CHECKTM

b. Sysmex Reagents: Sysmex reagents and CELLCLEAN AUTO are used on the Sysmex XN-350 Series modules, all reagents are used at room temperature and are to be used within the manufacturer's expiration date on each container, date received and date opened on container, Record, and all reagents are azide free and are intended for in vitro diagnostic use only. Do not ingest.

Reagent	Volume	Open Expiration
CELLPACK DCL	20L/10 L	60 days
SULFOLYSER	5.0 L	90 days
Lysercell WDF	2 x 4L	90 days
Fluorocell WDF	2 x 42 mL	90 days

4.1. Distribution of the study groups

In the present study, groups were distributed according to the type of group, number of persons ,age, and gender, as shown in the table (1).

Table (1): Distribution of the current study groups .

Type of group	Number	Age (Years)	Gender	
			Male	Female
Chronic kidney disease (CKD) patients groups	128	15-84	80	48
Acute kidney disease patients groups	60	15-90	30	30
Total number	188	-	110	78

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(AKD) patient

The study showed the mean level of PCT that there is a significant statistically difference between in patients with chronic kidney disease (CKD) (1.82 ng/ml), compared with patients with acute kidney disease (0.49 ng/ml), (P. value=0.0495), (Table 2 and Figure 3**).**

Table 2: Level of Procalcitonin (PCT) in patients with chronic and acute kidney disease .

Parameter / **Groups**		**PCT** ng/ml
CKD	Mean ± SD	1.82 ± 5.17
AKD	Mean ± SD	0.49 ± 0.5
P. value		0.0495

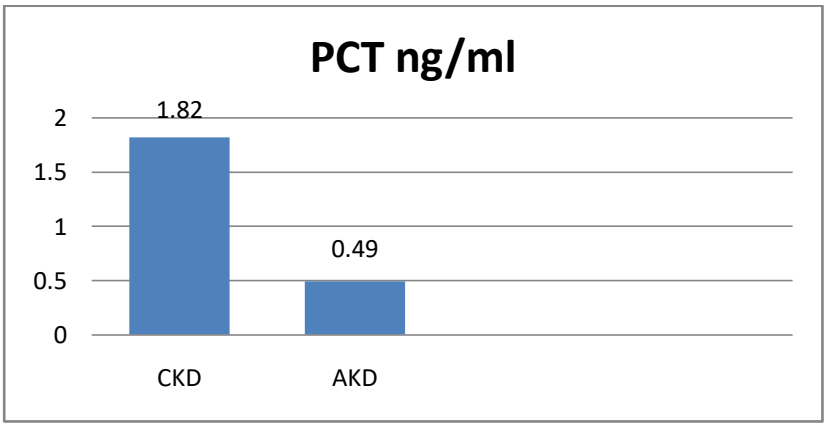

Figure (3):- Levels of Procalcitonin (PCT) ng/ml in patients with chronic (CKD) and acute kidney disease (AKD) .

In the current study , we found that CKD patients had significantly higher serum PCT levels than AKD patients. Since the renal clearance ability of PCT decreased in both AKD and CKD, these results might reflect the higher amount of PCT production induced by the more inflammatory characteristic of CKD when compared to AKD.

Chronic CKD is associated with an impaired renal clearance of PCT from the circulation, which indirectly keeps the serum PCT levels high.

Inflammation is a necessary component of chronic kidney disease (CKD) that can be attributed to an accumulation of toxins and a reduced clearance of pro-inflammatory cytokines, procalcitonin

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(PCT) is a widely applied biomarker in the diagnosis of infection, and considering the presence of pre-existing inflammation in CKD patients, the PCT level could be high in such a population ; however, no reference value for PCT in CKD patients has been available to date . May be Use the PCT levels in predicting renal outcome and mortality in these patients .taking PCT as an applicable biomarker for AKD

The elevated serum PCT level we observed in CKD patients can be attributed to the following reasons. First , persistent and low-intensity inflammation has been recognized as an important component of CKD pathology, and the intensity of inflammation, including IL-1β, IL-1 receptor antagonist, IL-6, TNF-α, and CRP levels, was inversely associated with residual renal function (Gupta *et al* ., 2012). With the accumulation of dysfunctional proinflammatory cytokines, which are produced by lymphocytes and various tissues (Iglesias& Díez, 2010) it is reasonable that PCT is elevated under such circumstances. The second probable cause of increased PCT levels is that impaired renal function could not provide sufficient clearance of circulating PCT. Third, Renal function degenerated significantly and caused massive accumulation of toxins and proinflammatory cytokines; consequently , an elevation in PCT emerged.

The data of the present study demonstrate that assessment of PCT kinetic can also be used for diagnostic and prognostic reasons in patients with renal dysfunction.

Our study agree with Wu *et al* .,2020 were reached the level of PCT was higher in CKD patients (0.50 ± 0,73 ng/mL) than in ACD patients(0.20 ± 0.31ng/mL).

The kinetics of PCT, including the elimination route or mechanism, are not fully known. However, considering its low molecular weight of 13.600 Da, impaired renal function is thought to affect PCT levels. In previous studies, end-stage renal disease patients had a mean serum PCT value of 0.69±0.81 ng/ml before dialysis and presented higher than the standard value of 0.5 ng/ml in 57% of patients (Level *et al*., 2001). The mean serum PCT level decreased significantly to 83±25% after high-flux dialysis, whereas no change in PCT concentration occurred after low-flux dialysis (Herget-Rosenthal *et al* ., 2001).In addition , PCT was elevated in patients on continuous ambulatory peritoneal dialysis (median of 1.18 ng/ml) (Steinbach *et al*., 2004).

Several studies have demonstrated a significant positive correlation between PCT and estimated glomerular filtration rate (eGFR) (Nakamura *et al*., 2015; Park *et al* ., 2014). These finding suggest that PCT is partially removed via the kidney and is therefore dependent on renal function .

The pathophysiological mechanism explaining the relationship between serum concentrations of PCT and AKD is still unclear. Various inflammatory responses have been suggested as a possible mechanism for the development of AKD (Lemay *et al* ., 2000; Okusa, 2002).Experimental data have confirmed that bacterial toxins and other mediators can induce PCT(Araujo *et al*., 2013).PCT acts as a chemo attractant in the inflammatory area, directly attracting more monocytes, PCT is initially produced in adherent monocytes that later contribute to the marked increase in circulating PCT by recruiting parenchymal cells when they are in direct contact with activated monocytes, the expression of PCT mRNA by peripheral blood mononuclear cells is stimulated by LPS or other toxins released by microbes (Wiedermann *et* al., 2002 ;Linscheid *et al* ., 2004; Chang *et al* ., 2013) . Additionally , it is suggested that an indirect pathway induced through cell-mediated host responses

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caused by inflammatory cytokines (e.g., IL-1β, IL-6, and TNF-α) plays a pivotal role in AKD (Ramesh & Reeves, 2002). Another possible mechanism represent the direct toxic effect of PCT on mesengial cells (Araujo et al., 2013).That mesangial cells could be destroyed by PCT through increased synthesis of IL-6, iNOS, and TNF- α, inducing disruption of actin microfilaments and apoptosis, this reflects the possibility of PCT as a toxic mediator of AKD (Chun *et al*., 2019)

Neutrophil/ Lymphocyte Ratio (NLR) in Chronic Kidney Disease (CKD) and Acute Kidney Disease (AKD) patient.

The study showed the high significant difference in NLR between CKD and AKD, (P. value=0.004). The highest means level of NLR were found in patients with chronic kidney disease (4.35±4.07) mg/L , followed by patients with acute kidney disease (2.78±1.31) mg/L. (Table 3 and Figure 4).

Table (3): Level of NLR in patients with a chronic and acute kidney disease .

Parameter / **Groups**		**N/L ratio**
CKD	Mean ± SD	4.35 ± 4.07
AKD	Mean ± SD	2.78 ± 1.31
P. value		0.004

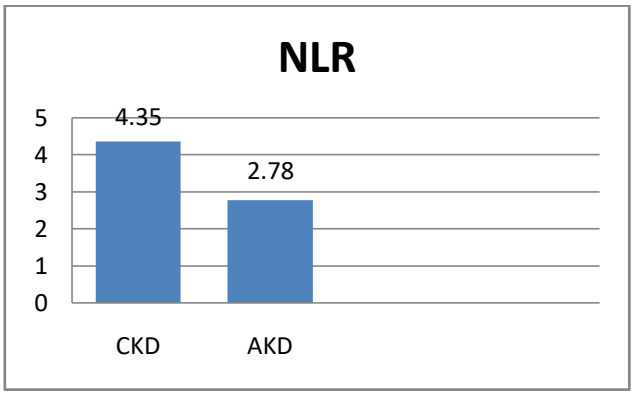

Figure (4):- Levels of NLR in patients with chronic (CKD) and acute kidney disease (AKD) .

Some studies that focused on NLR outlined its advantages compared to other inflammatory markers. Malhotra *et al*., 2015 concluded that NLR could be a potential substitute marker for CRP in hemodialysis patients, since it is a useful systemic inflammation test, especially in places with limited resources. Okyay *et al* ., 2013 stated that the determination of NLR values is easy and

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inexpensive and can provide significant information about the inflammatory state in CKD .

In some studies, NLR stood out as an inflammatory marker, reaching higher levels than other markers such as CRP and interleukins and in some outcomes as an indicator of acute kidney injury in patients with sepsis and as an indicator of cardiovascular events in patients with end stage renal disease (Abe *et al* ., 2015; Yilmaz *et al* ., 2015). Yoshitomi *et al* ., 2019 showed that higher NLR was associated with worse renal outcomes, indicating that it is useful as a prognostic marker. Yuan *et al* ., 2019 suggested that NLR could be used in risk assessment for stage 4 patients to progress to renal replacement therapy.Yoshitomi *et al*., 2019, demonstrated that NLR level as an independent risk factor for kidney disease progression in patients with CKD stages, the measurement of NLR might be useful for predicting kidney disease progression in CKD patients.

NLR was demonstrated deterioration in renal function and assessed as a predictor of worsening renal function in CKD patients, found NLR to be significantly higher in patients with CKD compared to controls, and also NLR was found associated with the stage of CKD , the NLR may constitute a practical predictor of CKD besides creatinine in patients who had undergone partial or radical nephrectomy (Tonyali *et al* ., 2018).

Some researcher have reported that NLR are positive correlated with inflammatory markers in patients with CKD (Turkmen *et al* ., 2012; Ahbap *et al* 2016), Ahbab *et al* ., 2016, reported that patients with higher CRP levels>3 mg/dL had higher NLR compared to patients with lower CRP levels.

Although avariety of markers have been introduced to measure inflammation , NLR is easy to calculate marker that are of great benefit to chronic hemodialysis population, therefore we encourage the use of this ratio to be included as marker to detect inflammation occurrence.

Considering the aforementioned facts, NLR can be considered a promising inflammatory biomarker in renal disease patients.

Conclusion

1- It is found that CKD patients had significantly higher serum PCT levels than AKD patients.

2- Highest means level of NLR were found in patients with chronic kidney disease (4.35±4.07) mg/L.

Recommendation

1- Higher cut-off values should be applied to patients with impaired renal function, suggest that serum PCT at a cutoff ≤ 2ng/ml is an appropriate indicator in chronic HD patients.
2- Expand in the study of markers in chronic renal failure patients and find the correlation between inflammatory markers and PCT. 3- Meta-analysis studies are recommended to evaluate the use of PCT as a predictor for the need of kidney transplantation in end stage renal disease patients.
4-we encourage the use of NL ratio to be included as marker to detect inflammation occurrence in chronic hemodialysis patients.

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