

Correlation of Serum Calcium and Phosphorus with the Degree of Coronary Artery Complexity in Patients with Chronic Kidney Disease

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Abstract

Background: Cardiovascular disease is the leading cause of mortality and morbidity among patients with chronic kidney disease. This is attributed not only to traditional, but also non-traditional risk factors, of which the altered calcium-phosphorus homeostasis is of interest in this study. A recently studied tool in evaluating the degree of coronary artery complexity in patients who have undergone coronary angiography is the Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score.

Objective: This study aimed to determine if the serum calcium and phosphorus are correlated with the SYNTAX score in patients with CKD stages III, IV and V

Materials and Methods: This is a retrospective correlation study, which included 79 patients with CKD stages III, IV, V not on dialysis and on dialysis, who have undergone invasive coronary angiography at the National Kidney and Transplant Institute (NKI) Catheterization Laboratory. The SYNTAX score was computed via an interactive web program with the help of an interventional cardiologist. This score was then correlated with serum calcium and phosphorus using Pearson's Correlation Test.

Results: Among the 79 subjects included in the study, 7.6% are at Stage III, 11.4% at Stage IV, 5.1% at Stage V but not yet on dialysis, and 75.9% are on dialysis. A statistically significant inverse correlation was noted between SYNTAX score and total EGFR (R coefficient -0.230, p-value 0.04). But when analyzed per stage of CKD, there was no statistically significant correlation. There were positive but weak correlations between the SYNTAX score and the serum calcium (R coefficient 0.135, p-value 0.231) and phosphorus values (R coefficient 0.044, p-value 0.696) but these were not statistically significant.

Conclusion: Among CKD Stages III, IV, V and dialysis patients, there is a positive but weak and insignificant correlation between the SYNTAX score and the levels of calcium, and phosphorus. A robust and equal number of cases among the different stages of CKD have to be analyzed in order to generate statistically significant data with regards the correlation of declining kidney function and the SYNTAX score.

Keywords: SYNTAX score, Coronary artery complexity, Coronary angiography, Chronic kidney disease, EGFR

Introduction

The prevalence of Chronic Kidney Disease (CKD) in the Philippines is staggering, with a rate of 2.6 per 100,000 people in 2003 to 9.75 per 100,000 in 2008.¹ Data from the World Health Organization in 2011 estimated that the death rate from renal disease in the Philippines is about 23.3% per 100,000.¹² Cardiovascular disease (CVD) remains to be the major cause of mortality and morbidity in these patients. In the US Renal Data System, cardiovascular disease accounts for 45% of all-cause mortality in End-stage renal disease (ESRD) patients, with sudden cardiac death as the leading cause (26%).²

The factors that increase the risk for CVD have been grouped into traditional and non-traditional. The former includes older age, male gender, white race, hypertension, elevated LDL, decreased HDL, DM, tobacco use, physical

inactivity, menopause, psychosocial stress and family history of CVD.³ However, because these traditional risk factors fail to fully account for the elevated CV risk in CKD, there has been a great deal of interest lately in emerging "non-traditional" risk factors such as inflammation, C-reactive protein, oxidative stress, nitric oxide, hyperhomocysteinemia, hyperphosphatemia, vascular calcification, increased vascular stiffness, LVH, anemia, endothelial dysfunction, volume overload and electrolyte imbalance and timing of dialysis.²

Of particular interest is the phenomenon of accelerated atherosclerosis and vascular calcification in CKD patients which is linked to hyperphosphatemia. These patients have alterations in their calcium and phosphorus homeostasis that ultimately result in bone disorders and soft tissue and vascular calcifications. With declining GFR, there is reduced excretion of phosphate causing increased synthesis of PTH which in turn mobilizes calcium from the bone.¹² The increased calcium and phosphate in the blood favors the development of vascular calcification, and this mechanism can be explained by the differentiation of vascular smooth muscle cells (VSMC) into osteo/chondrocytic-like cells in the setting of chronic

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kidney disease, diabetes, aging, inflammation, and multiple other toxins, by the upregulation of transcription factors such as RUNX-2 and MSX2. These osteo/chondrocytic-like VSMC then become calcified in a process similar to bone formation. These cells lay down collagen and noncollagenous proteins in the intima or media and incorporate calcium and phosphorus into matrix vesicles to initiate mineralization into hydroxyapatite. Although there are inhibitors of this process such as fetuin-A in the blood, the levels of these inhibitors go down during inflammation and in dialysis patients.¹³ In a study by Adeney et al in 2009, which included 439 participants from the Multi-Ethnic Study of Atherosclerosis (MESA) who had moderate CKD and no clinical CV disease, it was noted that each 1.0-mg/dl increment in serum phosphate concentration was associated with a 21% (P 0.002), 33% (P 0.001), 25% (P 0.16), and 62% (P 0.007) greater prevalence of coronary artery, thoracic, aortic valve, and mitral valve calcification, respectively as determined through electron-beam or multi-detector row computed tomography.¹⁶

The 2009 Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical practice guidelines, recommends maintaining the levels of serum calcium and phosphorus within the normal range in patients with CKD Stage 3-4, and toward the normal range in patients on dialysis. The calcium-phosphorus product is largely driven by serum phosphorus and generally does not provide any additional information beyond that which is provided by individual measures, hence it is of limited use in clinical practice.²¹

The phenomenon of accelerated vascular calcification in CKD increases the risk for coronary artery disease (CAD) and subsequently, mortality from such disease. The correlation between CAD and worsening CKD status was demonstrated by an unpublished local study done by Dr. Malasig in 2012 at NKTl, wherein an anatomic scoring system based on invasive coronary angiography was used to evaluate the complexity of the coronary arteries of CKD patients at the National Kidney and Transplant Institute (NKTl). The SYNTAX score was developed and validated in the Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) trial. It is a score for the severity of coronary artery disease (CAD) based entirely on angiographic characteristics including presence of total occlusion, bifurcation or trifurcation, angle and involvement of branch vessels, calcification, lesion length >20mm, ostial location, tortuosity, presence of thrombus and diffuse disease (Appendix). It is computed during visualization of the patient's coronary angiogram. A computer program calculates the SYNTAX score after answering a set of interactive, self-guided questions. A higher SYNTAX score means a more complex and severe coronary artery disease. Dr. Malasig's study in 2012 entitled "The Complexity of Coronary artery Disease using the SYNTAX Score in Patients with Chronic Kidney Disease as compared to patients without Chronic Kidney Disease" demonstrated that with decreasing GFR, there is an increasing trend in the SYNTAX score, hence an increasing severity of coronary artery disease.

This research aims to correlate the serum calcium, phosphorus and calcium-phosphorus product with the degree of coronary artery complexity assessed by invasive coronary angiography with the use of the SYNTAX scoring system. A positive relationship between these variables is a significant finding that will support aggressive management, monitoring and maintenance of these two elements at a normal range in CKD patients, with the long-term goal of decreasing cardiovascular morbidity and mortality.

Objectives

To determine if serum calcium and phosphorus are correlated with the SYNTAX score in patients with chronic kidney disease

Methodology

Research Design and Study Population

This is a retrospective correlational study which included all patients with CKD stages III, IV, V and on dialysis, who underwent coronary angiography from 2011 to 2014 at the NKTl Catheterization Laboratory.

Inclusion criteria:

- CKD stages III, IV, V not on dialysis and on dialysis
- With serum creatinine, calcium, and phosphorus determination within three months prior to coronary angiography

Exclusion criteria:

- Patients who had coronary artery bypass surgery or PTCA
- Post kidney transplant patients with stable graft
- Patients with diseases that can alter the calcium or phosphorus levels other than CKD such hypercalcemia of malignancy or primary hyperparathyroidism

Data Gathering:

The diagnostic angiograms of all patients with CAD were retrieved from the catheterization laboratory of the NKTl. Subjects were selected based on the inclusion and exclusion criteria. All the angiographic variables pertinent to calculating the SYNTAX score were obtained by an interventional cardiologist by reviewing the diagnostic angiograms. Each coronary lesion producing >50% luminal obstruction in vessels more than or equal to 1.5mm was separately scored and summated to provide the overall SYNTAX score. The SYNTAX score was calculated by a computer program consisting of sequential and interactive self-guided questions. The algorithm consisted of 12 main questions (Appendix). The first three determine the dominance, the total number of lesions and the vessel segments involved per lesion. The last nine questions refer to adverse lesion characteristics. With the exception of

the selection of the type in case of a bifurcation or a trifurcation lesion all the other questions of the algorithm can be answered by selecting "yes" or "no". After the completion of the algorithm a report was automatically generated summarizing all the adverse characteristics, and the individual scoring of each lesion as well as the total SYNTAX score.

The clinical characteristics of the subjects were obtained through chart review at the Medical Records Section. Descriptive statistics such as mean and standard deviation were presented for quantitative data, and proportions for the qualitative data.

The serum calcium and phosphorus of all the included patients were determined through chart review (DocuView) and through the "Communications" of the NIKI. The values for serum calcium were non-ionized, and so the serum albumin was reviewed to compute for the corrected calcium. Pearson's correlation statistics was used to determine the correlation of each independent variable (EGFR, corrected calcium and phosphorus) with the dependent variable (SYNTAX score). A p value of <0.05 was considered statistically significant.

Data and Results

From August 2011 to July 2014, there were a total of 310 patients who underwent coronary angiogram with or without Percutaneous transluminal coronary angioplasty. Of those who underwent coronary angiography, 173 patients had CKD Stages III, IV and V. However, seven of these patients already had a prior PTCA and five patients had prior CABG, while two patients were post-KT with stable graft at the time of coronary angiogram. Eighty patients had incomplete data, resulting in 79 remaining patients for analysis.

Among the remaining population with complete data, the average age was 61 years (≤ 11), with a male:female ratio of 3:1. Majority of the population were CKD on dialysis (75.9%), while 5.1% were at Stage V but were not yet on dialysis; 11.4% were at Stage IV and 7.6% were at Stage III as shown in Table I. The etiologies of CKD among these patients are shown in Figure 2, with Diabetic nephropathy as the leading cause, followed by hypertensive nephrosclerosis and chronic glomerulonephritis. The total mean EGFR of these subjects (computed via CKD-EPI) was $9.99 \leq 9.17$ ml per minute/ 1.73m^2 . When computed per stage of CKD, those at Stage III had a mean EGFR of $34.6 \leq 7.4$; those at Stage IV had mean EGFR of $20.46 \leq 5.87$; those at Stage V but not yet on dialysis had a mean EGFR of $10.4 \leq 2.5$ and those who were on dialysis had a mean EGFR of $5.97 \leq 8.77$. More than half (56%) of the subjects were smokers.

For these subjects, the mean calcium level was $9.23 \leq 0.73$ mg/dl and about 30% of the subjects had serum calcium more than recommended range set by KDOQI. The mean phosphorus level was $5.72 \leq 2.2$ mg/dl and about 47% of the subjects had more than the range recommended by KDOQI. The SYNTAX score ranged from 0 to 60 with a mean of 21.81

≤ 14.46 .

The Pearson's correlation test was used to analyze if the SYNTAX score was correlated to the EGFR and if the SYNTAX score was correlated to the calcium, and phosphorus. The SYNTAX score in this study was inversely correlated to the total EGFR (R coefficient of -0.230), and this was statistically significant with a p-value 0.04. However, when analyzed per stage of CKD, there seems to be no statistically significant correlation. In Stage III and V CKD not on dialysis, there was a trend towards a positive correlation but this was not significant. In Stage IV and dialysis group, there was trend towards an inverse correlation but this was also not significant. The serum calcium was noted to be positively correlated to the SYNTAX score (R coefficient of 0.135) but this was not statistically significant (p-value 0.231). The serum phosphorus was also positively correlated to the SYNTAX score (R coefficient of 0.044) but this was also not statistically significant (p value 0.696).

Discussion and Analysis of Data

In this study, the most common cause of chronic kidney disease remains to be diabetic nephropathy and males were noted to be of greater proportion than females. Diabetes is one of the traditional risk factors for developing renal disease, along with hypertension, male gender and smoking. Smoking appears to induce functional abnormalities of the renal vasculature and shorten the interval from microalbuminuria to overt nephropathy in diabetic patients.¹⁹

When analyzed altogether, the EGFR was noted to be inversely correlated with the Syntax score. However, when analyzed per stage of CKD, there seems to be no significant correlation between the EGFR and the Syntax score. This is contrary to the findings of a study by Coskun et al. in 2013, wherein 217 patients underwent coronary angiography and it was noted that the risk of significant lesion complexity based on Syntax score increased progressively with decreasing kidney function. This discrepancy might be explained by the small population of the study, as a result of the exclusion of some cases due to incomplete data obtained from records of the subjects. A head to head comparison of the Syntax scores among the different stages of CKD cannot be done due to the big difference in sample size per stage.

Approximately 30-50% of the study population had levels of calcium and phosphorus greater than the range recommended by KDOQI. It is said that hemodialysis patients are generally in a net positive calcium balance because of dietary intake of calcium, ingestion of calcium-based phosphate binders, calcium absorption from dialysate, and abnormalities in bone buffering and turnover which all contribute to the calcium burden in these patients.²⁰ In this study, there is note of a positive trend in the calcium and phosphorus values when correlated with the syntax score though not proven to be statistically significant. Nevertheless, these variables have to be aggressively managed because elevated levels of these variables have been implicated in

the accelerated atherosclerosis and inflammation in CKD patients. Serum phosphorus and mortality risk have been analyzed in multiple observational studies. In ESRD patients on hemodialysis, those with serum phosphorus $> 6.0 - 7.0\text{mg/dl}$ had a relative risk of death 1.25 times that of those with serum phosphorus $\leq 5.0\text{mg/dl}$.¹⁵ A systematic review and meta-analysis of studies involving serum phosphorus, parathyroid hormone and calcium and risks of death and CVD in individuals with chronic kidney disease by Palmer et al in 2011 showed that the risk of death increased by 18% for every 1.0mg/dl increase in serum phosphate concentration.¹⁸

CKD is a major risk factor for cardiovascular morbidity and mortality. It is associated with accelerated atherosclerosis which further causes vessel calcification. According to a study by Coskun et al. in 2013, which included 217 patients who underwent coronary angiography, the risk of significant lesion complexity based on SYNTAX score increased progressively with decreasing kidney function. The study demonstrated that eGFR was a strong predictor of higher SYNTAX Score.²³ Again, this can be explained both by traditional (diabetes, hypertension, male gender and smoking) and non-traditional factors (calcium and phosphorus). Of the traditional factors, diabetes mellitus still is the leading cause of CKD in this study followed by hypertension, and males are noted to have a higher prevalence of CKD. A greater proportion of the subjects are exposed to smoking, which appears to induce functional abnormalities of the renal vasculature and shorten the interval from microalbuminuria to overt nephropathy in diabetic patients.¹⁹

When analyzed altogether, the EGFR was noted to be inversely correlated with the SYNTAX score. However, when analyzed per stage of CKD, there seems to be no significant correlation between the EGFR and the SYNTAX score. This might be explained by the small population of the study, as a result of the exclusion of some cases due to incomplete data obtained from records of the subjects. A head to head comparison of the SYNTAX scores among the different stages of CKD cannot be done due to the big difference in sample size per stage.

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This study is limited by the fact that levels of calcium and phosphorus have diurnal and postprandial variations and

may have been already affected by intake of phosphate binders, which were not considered in this study. Serum phosphorus levels reach a nadir in the early hours of the morning, increasing to a plateau at 1600 hours, and further increasing to a peak from 0100 to 0300 hours. Serum phosphorus levels reach a nadir in the early hours of the morning, increasing to a plateau at 1600 hours, and further increasing to a peak from 0100 to 0300 hours.²¹ Another limitation is the inadequate data regarding the duration, frequency and adequacy of dialysis in a subset of the study population, as well as information regarding the comorbidities and body mass index of the patients.

Conclusion

Among CKD Stages III, IV, V and dialysis patients, there is a weakly positive but insignificant correlation between the SYNTAX score and the levels of calcium, and phosphorus. A robust and equal number of cases among the different stages of CKD have to be analyzed in order to generate statistically significant data with regards the correlation of declining kidney function and the SYNTAX score.

Recommendations

For future studies, a good topic would be to compare the use calcium-based and non-calcium-based phosphate binders among CKD patients and to correlate it with the degree of coronary artery disease. A study on the correlation of statins (duration, dose, and type of statin) and the SYNTAX score is also suggested. It is recommended that all CKD patients be tested for serum calcium and phosphorus, and also be screened for cardiovascular disease even at early stages of CKD. Aggressive management of the calcium and phosphorus levels is also recommended because of their role in the acceleration of CVD.

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Appendices

Table I. Baseline Characteristics of Subjects

Characteristics	Data	
Population (N)	79	
Age in years (x ± SD)	61 ± 11	
Gender		
Male (%)	60 (76%)	
Female (%)	19 (24%)	
Etiology of CKD		
DM Nephropathy (%)	42 (54.4%)	
HPNNS (%)	28 (35.4%)	
CGN (%)	6 (7.6%)	
Urate Nephropathy (%)	1 (1.3%)	
NSAID nephropathy (%)	1 (1.3%)	
ADPKD (%)	1 (1.3%)	
Stages of CKD		Mean EGFR (x ± SD)
III (%)	6 (7.6%)	34.6 ± 7.4
IV (%)	9 (11.4%)	20.46 ± 5.87
V not on Dialysis (%)	4 (5.1%)	10.4 ± 2.5
V on Dialysis (%)	60 (75.9%)	5.97 ± 8.77
Total	79	9.999.99 ± 9.17
Smoking history		
Yes (%)	44 (56%)	
No (%)	35 (44%)	

Table II. Descriptive statistics of variables being studied

Variable	Minimum	Maximum	Mean ± SD
Calcium (x ± SD) in mg/dl	7.18	12	9.23 ± 0.73
Phosphorus (x ± SD) in mg/dl	1.4	12.5	5.72 ± 2.2
SYNTAX Score	0	60	21.81 ± 14.46

Table III. Correlation of EGFR, Calcium and Phosphorus and SYNTAX score

Variable	SYNTAX score R coefficient	p-value
EGFR in all Subjects	0.230	0.04
EGFR at CKD Stage III	0.085	0.872
EGFR at CKD Stage IV	-0.295	0.441
EGFR at CKD Stage V not on dialysis	0.300	0.700
EGFR at CKD Stage V on dialysis	-0.089	0.498
Calcium	0.135	0.231
Phosphorus	0.044	0.696

Table IV. SYNTAX score algorithm

1. Dominance
2. Number of lesions
3. Segments involved per lesion Lesion Characteristics
4. Total occlusion i. Number of segments involved ii. Age of the total occlusion (>3 months) iii. Blunt Stump iv. Bridging collaterals v. First segment beyond the occlusion visible by antegrade or retrograde filling vi. Side branch involvement
5. Trifurcation i. Number of segments diseased
6. Bifurcation i. Type ii. Angulation between the distal main vessel and the side branch <70°
7. Aorto-ostial lesion
8. Severe tortuosity
9. Length >20mm
10. Heavy calcification
11. Thrombus
12. Diffuse disease/small vessels

Table V. Definition of SYNTAX Score Components

Dominance	a) Right dominance: the posterior descending coronary artery is a branch of the right coronary artery (segment 4). b) Left dominance: the posterior descending artery is a branch of the left coronary artery (segment 15). Co-dominance does not exist as an option at the SYNTAX score.
Total occlusion	TIMI 0 flow: no perfusion; no antegrade flow beyond the point of occlusion Bridging collaterals: Small channels running in parallel to the vessel and connecting proximal vessel to distal and being responsible for the ipsilateral collateralization
Trifurcation	A junction of three branches, one main vessel and two sidebranches. Trifurcations are only scored for the following segment junctions: 3/4/16/16a, 5/6/11/12, 11/12a/12b/13, 6/7/9/9a and 7/8/10/10a
Bifurcation	A junction of a main vessel and a side branch of at least 1.5mm in diameter. Bifurcations are only scored for the following segment junctions: 5/6/11, 6/7/9, 7/8/10, 11/13/12a, 13/14/14a, 3/4/16 and 13/14/15. Bifurcation lesions may involve one segment (types A, B and E), two segments (types C, F and G) or three segments (type D).
Aorto-ostial	A lesion is classified as aorto-ostial when it is located immediately at the origin of the coronary vessels from the aorta (applies only to segments 1 and 5, or to 6 and 11 in case of double ostium of the LCA).
Severe tortuosity	One or more bends of 90° or more, or three or more bends of 45° to 90° proximal of the diseased segment.
Length >20mm	Estimation of the length of that portion of the stenosis that has ≥50% reduction in luminal diameter in the projection where the lesion appears to be the longest. (In case of a bifurcation lesion at least one of the branches has a lesion length of >20mm).
Heavy calcification	Multiple persisting opacifications of the coronary wall visible in more than one projection surrounding the complete lumen of the coronary artery at the site of the lesion.
Thrombus	Spheric, ovoid or irregular intraluminal filling defect or lucency surrounded on three sides by contrast medium seen just distal or within the coronary stenosis in multiple projections or a visible embolization of intraluminal material downstream.
Diffuse disease/ small vessels	More than 75% of the length of the segment has a vessel diameter of 2mm, irrespective of the presence or absence of a lesion.

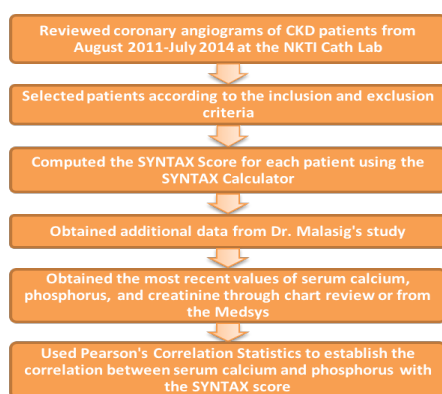


Figure 1. Flow diagram of Methodology

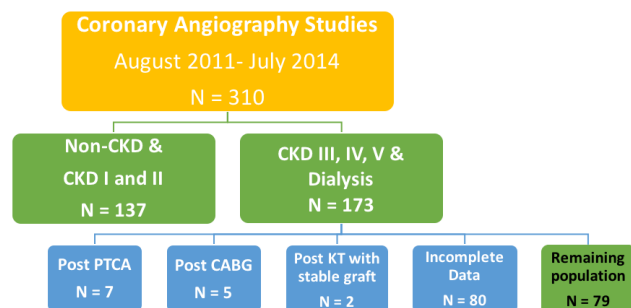


Figure 2. Flow Chart of Data Collection

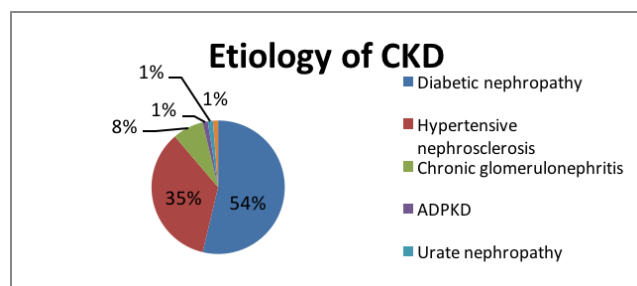


Figure 3. Etiologies of Chronic Kidney Disease

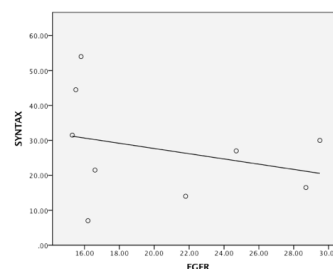


Figure 6. Linear Regression of EGFR and Syntax score in CKD Stage IV

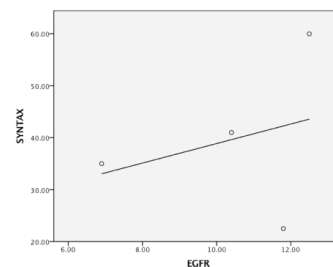


Figure 7. Linear Regression of EGFR and Syntax score in CKD Stage V Not on dialysis

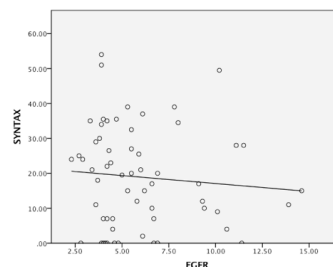


Figure 8. Linear Regression of EGFR and Syntax score in CKD Patients on dialysis

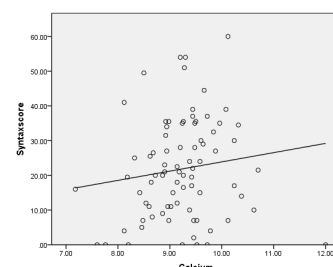


Figure 9. Linear Regression of Serum Calcium and Syntax Score

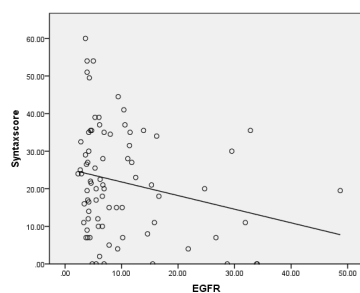


Figure 4. Linear Regression of EGFR and Syntax Score among CKD stages III, IV, V and on Dialysis

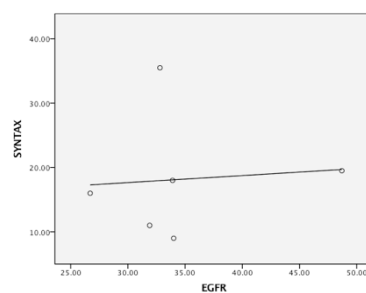


Figure 5. Linear Regression of EGFR and Syntax score in CKD Stage III

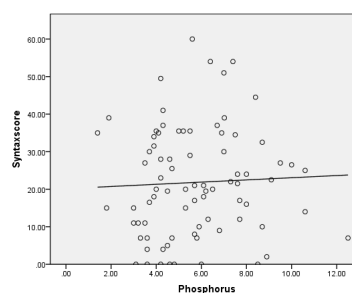


Figure 10. Linear Regression of Serum Phosphorus and Syntax Score