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SYSTEMATIC REVIEWS: COMPLICATION OF DISEASE AND RISK OF DEATH ON CHRONIC KIDNEY PATIENTS NON-HEMODIALYSIS

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Abstract:

Introduction*: Chronic Kidney Disease (CKD) is a condition of reducing renal function in excreting metabolism residual. Dietary habit, using of drugs in a long time, losing of body fluid, infection, a complication of disease and family history are the factors of end-stage renal disease (ESRD), while ESRD becomes one of the largest public health problems in the world.*

Objective *: To evaluate the complication of disease and risk of death in chronic kidney disease (CKD) non-hemodialysis patients.*

Method *: literature review about studies that reported the risk of death from CKD. The accumulated risk is calculated using the ratio of confidence for the method of random effects meta-analysis of the data medium quality and high quality.*

Results *: Atherosclerosis is increased in CKD patients. It is known from Zahran, M.et.al study whereas they did research about risk factor of atherosclerosis by measuring Carotid Intima-Media Thickness (CIMT) for all subjects. Besides that, CKD changes the metabolism of vitamin D which is one of the most important factors in the pathogenesis of secondary hyperparathyroidism and chronic kidney disease-mineral bone disorder (CKD_MBD). Chronic kidney disease patients also cannot produce Erythropoietin Stimulating Agent (ESA) like normal patients, so it causes anemia. Diabetes mellitus, hypokalemia, and hyperkalemia also found in CKD patients.There are some complications of chronic kidney disease: cardiovascular disease, deficiency vitamin D, diabetes mellitus type II, hypokalemia, hyperkalemia, and anemia.*

Conclusion *: These complications will be a risk of death factors on CKD patients if the patients are not handled well.*

Keywords: *Chronic Kidney Disease, Risk of Death, Complications , Non-Hemodialysis, Anemia, Diabetes Mellitus*

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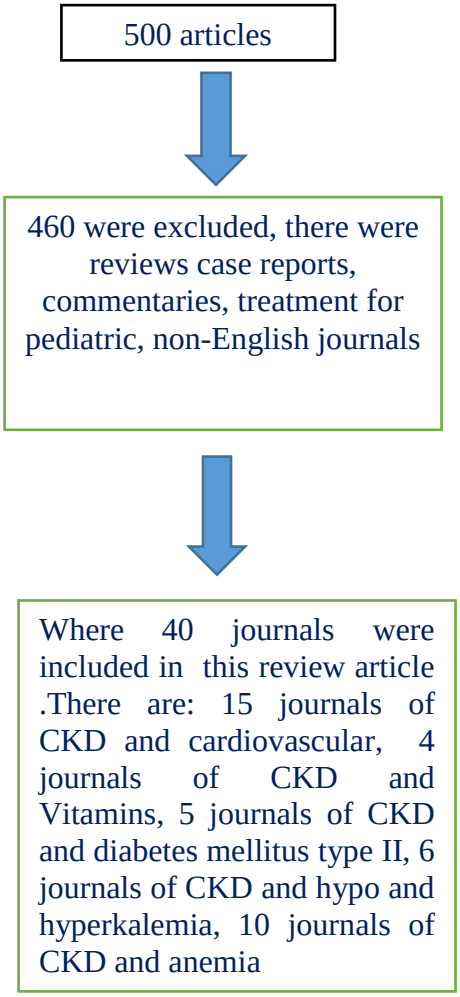
INTRODUCTION:

Chronic kidney disease (CKD) is a common disease throughout the world and a major risk factor for end-stage stage renal disease (ESRD) [1,2,3]. Complication of chronic kidney disease or end-stage renal disease is a cardiovascular disease (CVD) such as chronic heart failure, arrhythmias or ischemia of heart [3,4]. The good treatment will avoid complication of chronic kidney disease or end-stage renal disease.

Cardiovascular disease (CVD) is an increase in the high level of renal failure (Chronic kidney disease stage V or end-stage renal failure) [5]. A recent study showed more than 200,000 patients start dialysis therapy. Despite improvements in dialysis therapy,



Forty journals are found. There are 15 journals of CKD and cardiovascular, 4 journals of CKD and Vitamins, 5 journals of CKD and diabetes mellitus type II, 6 journals of-of CKD and hypo and hyperkalemia and 10 journals of CKD and anemia.

the mortality rate or death rate has also been increased in patients going the process of hemodialysis [6].

MATERIALS AND METHODS:

Searching the articles associated with chronic kidney disease or end-stage renal disease, hemodialysis (risk factors, comorbidity, survival, clinical outcome and mortality).Inclusion criteria were all of the related studies and exclusion criteria were pediatric journals and non-English Journals. Studies were included in the meta-analysis if they match all criteria have been defined.

Kidney and cardiovascular disease

Chronic kidney disease (CKD) is associated with increased risk factor of mortality whereas in this case glomerular filtration rate (GFR) decreases below 60 ml / min per 1.73 (m^2) [7]. This condition will produce high blood pressure and definitely it is a major risk factor for coronary heart disease, arrhythmias, heart failure, cerebrovascular disease, and peripheral artery disease and kidney failure [8]. If this condition is not handled properly, it will give harmful effect on the organs of the body [9].

Chronic kidney disease (CKD) levels are assessed by estimating of glomerular filtration rate (GFR). The level of glomerular filtration rate will be a predictor of mortality in adult patients with heart failure entire left ventricle spectrum systolic function [10,11] . Chronic kidney disease will gradually lead to permanent loss of kidney function [12]. The final stage of chronic kidney disease (CKD) is end-stage renal disease (ESRD) Stage V is the final stage of it and characterized by kidney failure and requires dialysis. Patients with stage 5 of CKD have abnormal blood mineral levels and high level of parathyroid hormone, a condition known as secondary hyperparathyroidism (SHPT) [12]. Atherosclerosis is increased in CKD patients. It is known from Zahran, M. et.al study [13]. In that study, they did research about risk factor of atherosclerosis by measuring of carotid intima-media thickness (CIMT) for all subjects [13]. There had 50 renal patients which divided into two groups of equal size (25 patients with ESRD on regular hemodialysis and 25 chronic renal disease patients on conservative treatment [13]. If treatment of atherosclerosis is not well so it can be heart failure. Cardiac resynchronization therapy (CRT) is a new treatment option that can improve cardiac performance in patients with severe heart failure [14,15]. Besides that, the recent research found that CKD was to be associated with the outcome of CRT [14,15].

Kidney disease and vitamin D deficiency

Traditionally, vitamin D is considered as a vitamin essential for the regulation of calcium metabolism [16]. Vitamin D is not only important for bone and mineral metabolism but also, it can inhibit the proliferation and differentiation of many cells where it is so important for the immune system [16]. Besides, vitamin D can affect insulin secretion and inhibits renin secretion [16]. Low levels of serum vitamin D is associated with a number of non-skeletal disorders including cancer, heart disease, high blood pressure, diabetes, Parkinson's disease, multiple sclerosis and skin diseases [16]. Chronic kidney disease (CKD) changes the metabolism of vitamin D which is one of the most important factors in the pathogenesis of secondary hyperparathyroidism and chronic kidney disease - mineral bone disorder (CKD - MBD) [16]. Vitamin D can be taken orally or can be used as endogenous skin after exposure to sunlight or the light changes the metabolism of vitamin D UVB [16]. Changing in vitamin D metabolism in CKD with hyperphosphatemia and hypocalcemia leads to secondary hyperparathyroidism [16].

Vitamin D is the hormonal system which involved in the regulation of calcium homeostasis and bone metabolism [17]. Vitamin D deficiency is a significant risk factor for many chronic diseases[17]. Calcidiol and Calcitriol deficiency is common in patients with CKD [17]. Vitamin D is essential for maintaining the homeostasis of calcium and phosphate[18].

End-stage renal disease in patients with renal replacement therapy with diabetes mellitus has a higher death rate and prevalence lack of vitamin D compared to those without diabetes [18]. This is still debated if vitamin D deficiency is a risk factor for mortality in patients with chronic kidney disease [19].

Kidney disease and diabetes mellitus type 2

Diabetic patients with CKD are more likely to have a higher prevalence than the CKD diagnosis without complications [20].In the hospital, mortality remained unchanged in diabetic patients with complications of CKD, while CKD patients without diabetes mellitus (DM) (20.2% dying in 1999, and 11.3% died in 2009) [20]. Diabetes Mellitus (DM) in CKD patients continue to be very high levels of mortality in hospital [20].

The prevalence of type 2 diabetes is increasing rapidly worldwide, with a prevalence of more than 170 million people [21] . Cox regression analysis was performed to explore the relationship between the development of neuropathy and pro12Ala polymorphisms after adjusting for potential factors (age, duration of diabetes, glucose control,) HbA1c, basic UAER and eGFR, blood pressure, and blockers of the renin system angiotensin [22].

Generally, in a large cohort study of type 2 diabetes condition and retinopathy affects 47% of renal condition patients [23]. Diabetic patients with retinopathy will sooner affect the kidneys of patients compared with diabetic patients without retinopathy where eGFR is becoming lower and increased proteinuria[23]. The occurrence of microvascular complications will increase the disruption of the renal function [23]. It is known that the risk of chronic kidney disease (CKD) is increased in patients with diabetes mellitus but it is not clear whether the increase because of impaired glucose tolerance [24].

The overall prevalence of CKD varies from 94.9% for proteinuria, during 10 years of follow-up, 34.7% for end-stage renal disease during 5 years of follow-up and 18.4% of the deaths of nephropathy during 20 years of follow-up [25]. Diabetes, blood pressure, age, and obesity are also determinant factors of renal disease [25].

Kidney disease with hyperkalemia or hypokalemia

Severe hypokalemia causes significant morbidity and mortality in CKD patients[26]. Increasing of serum potassium concentration will worsen renal function[26]. Research Je Sung Yoo, et al showed that the point of care potassium (POC-K +)will increase the serum K + with no significant difference compared with the reference test, regardless of the patient's renal function[26]. Screening using the POC carried out for a quick evaluation of the patient's condition and treatment of hyperkalemia [26]. Point of care potassium ($-K^{+)}$ results correlate well with value-value obtained from laboratory tests which in this case, there was no change in serum [26].

Abnormal serum potassium is associated with higher mortality in CKD patients, but the impact on the result of chronic kidney disease (CKD) is less clear [27]. In research Jhon Hayes, et al, Glomerular filtration rate (GFR) is associated with serum potassium in 1227 for male patients with CKD [27]. Hypokalemia and hyperkalemia associated with overall mortality in 933 white patients and 294 black patients [27]. Hypokalemia is associated with loss of I mEq kidney function independent of race [27].

Hypo and hyperkalemia are associated with higher mortality in patients with CKD [27]. Black patients have better potassium level than white patients [27]. Both hypokalemia and hyperkalemia are associated with an increased risk of CKD in the use of diuretics, a decreased risk of CKD in the use of renin-angiotensin system (RAS) blockade, malnutrition and the use of addictive substances[28].

In elderly patients with CKD have a risk of anemia, hyperkalemia, acidosis, and hyperphosphatemia[29].

Age does not change the relationship of GFR and development of metabolic complications [29]. In the elderly patients with low GFR should be rapidly monitored of declining in the kidney function and, in this case, the further studies are needed to make clear the differences observed in clinical [30].

Kidney disease and anemia

Hematuria is traditionally regarded as a hallmark of several diseases. Hematuria can reduce kidney function [31]. Hematuria is closely associated with a rapid decline in kidney function in CKD patients, especially in younger CKD patients with proteinuria higher level[31]. Hematuria can worsen anemia condition in CKD patients. Therefore, high-risk patients should get treatment, supervision, and medical treatment intensive [31].

Anemia is a situation where patient with chronic kidney disease (CKD) cannot produce Erythropoietin Stimulating Agent (ESA) like a normal patient [32]. Therefore, for some cases of CKD require erythropoietin from outside the body [32]. Erythropoietin has a long half-life for granted every month [33]. Monthly dose treatment with erythropoietin is safe and effective. Erythropoietin doses 75-100 mg / month are enough to maintain the stability of hemoglobin levels[33]. However, in these patients should be monitored to prevent an increase in the causes of death [34,35].

The disease varies based on the value of GFR in CKD patients[36]. The lower level of GFR will worsen CKD patient's condition and definitely, it will give impact to anemia condition. Some causes of CKD in men and women are age, the habit of alcohol consuming, smoking, hypertension, diabetes, and body mass index were extensive[36]. Observational studies have shown a relationship between the results of anemia with chronic kidney disease (CKD) [37]. However, randomized trials failed to identify the benefits of a higher hemoglobin concentration [37]. The study conducted a prospective cohort of 326 patients with stage 3 to 5 of CKD to see the effect on the fluid status of the patient's hemoglobin concentration cardiovascular and renal [37].

In the study Shu-Chun Hung, et al demonstrated that hypertension (HT) and renal anemia (RA) is a marker of the risk of fluid status in which the measurement of the level of overhydrating (OH) by bioimpedance, negatively correlated with hemoglobin concentration at baseline (r =? 0.438, P <0.001) [38]. In the multivariate regression analysis, OH remained an independent predictor of hemoglobin and glomerular filtration rate[38]. Patients were classified into 3 groups: anemia (n = 105), correct anemia (n = 82), and anemia with excess OH (n = 139) (OH relative level ≥7%, the 90th percentile of a healthy population)[38]. Fluid retention associated with the severity of anemia and cardiovascular adverse in patients with CKD [38]. Further research is needed to classify whether the correction fluid retention, instead of increasing erythropoiesis but improve the outcome of CKD-related anemia[38]. Cardiovascular disease will also appear in patients with chronic kidney disease (CKD)[38]. CKD will bring stimulus for left ventricular hypertrophy (LVH), which significantly participated in heart complications in uremic patients (patients with renal impairment)[38]. Hypertension is very common after kidney transplantation (KTX) and it has been observed in up to 75% of patients [39].

Before kidney transplantation (KTx) 86% of the patients had hypertension (HT), and renal anemia (RA) was confirmed in all patients[39]. Echocardiographic findings were normal owned by 33% of patients and 67% of patients had echocardiography LVH [39]. Before a group of kidney transplantation with left ventricular hypertrophy have higher stats, average values of blood pressure or mean blood pressure (MBP) (p = 0.053) compared with the group with diastolic left ventricular ejection fraction (LVEF) (p = 0.0047) and left ventricular systolic-diastolic dysfunction (LVSD) (p = 0.0046)[39]. These results confirm that the positive echocardiographic left ventricular remodeling after a successful kidney transplant is a complex process that depends on many factors and elimination of risk factors associated uremia- which is a priority[39]. A total of 457 patients (162 anemia and 295 non-anemic) analyzed [40]. Multivariate analysis showed that the probability of developing anemia is greater for patients with stage 5 of CKD (OR 16.76, p <0.001), patients with hematologic disorders (OR 18.61, p <0.001) and patients with breathing disorders (OR 4:54, p = 0.004) [39]. Lower probability of developing anemia for patients with higher hemoglobin concentrations before taking iron supplements (OR 0:32, p <0.001) and in patients who received iron supplements (OR 0:44, p = 0.031) [40]. Gender and race are not found as a significant predictor for anemia[40]. Increased risk of anemia in patients with severe CKD, hematological disorders, respiratory disorders, and patients who did not take iron supplements are found in some research. This research has enhanced our understanding for the subgroup of patients at risk of anemia [40].

CONCLUSION:

From some of the literature found that the cause of death of non-hemodialysis patients with CKD is a complication with cardiovascular disease, vitamin D deficiency, complications with diabetes mellitus type II disease, fluid balance disorders such as hyper or hypokalemia and anemia. In addition, age, gender, race and lifestyle also increases the risk factor for death in patients with CKD non-hemodialysis.

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Conflict of Interest

There is no conflict of interest regarding of this publication.

REFERENCES:

1.Temimovic, R., Rasic, S. & Muslimovic, A. High Prevalence of Early Chronic Kidney Disease in High Risk Outpatients. Mater Sociomed 79–82 (2015). doi:10.5455/msm.2015.27.79-82

2.Kim, A. J. et al. Low-Dose Aspirin for Prevention of Cardiovascular Disease in Patients with Chronic Kidney Disease. PLoS One 9, (2014).

3.Alani, H., Tamimi, A. & Tamimi, N. Cardiovascular co-morbidity in chronic kidney disease: Current knowledge and future research needs. World J. Nephrol. 3, 156–168 (2014).

4.Hamm, L. L. et al. Interrelationship of Multiple Endothelial Dysfunction Biomarkers with Chronic Kidney Disease The Harvard community has made this article openly available . Please share how this access benefits you . Your story matters . Citation Accessed Interrelationshi. PLoS One (2016). doi:10.1371/journal.pone.0132047

5.Beck, H. et al. Heart Failure in a Cohort of Patients with Chronic Kidney Disease : The GCKD Study. PLoS One 1–16 (2015). doi:10.1371/journal.pone.0122552

6.Hill, N. R. et al. Benefits of Aldosterone Receptor Antagonism in Chronic Kidney Disease (BARACK D) trial – a multi-centre , prospective , randomised , open , patients within primary care with stage 3b chronic kidney disease to compare the efficacy of spironolactone 25 mg. Trials 15, 1–14 (2014).

7.CDC. National Chronic Kidney Disease Fact Sheet , 2014. Natl. Cent. Chronic Dis. Prev. Heal. Promot. (2014).

8.Assi, L. K. et al. The Association between Polyclonal Combined Serum Free Light Chain Concentration and Mortality in Individuals with Early Chronic Kidney Disease. PLoS One 1–15 (2015). doi:10.1371/journal.pone.0129980

9.Drozdz, D. & Kawecka-jaszcz, K. Cardiovascular changes during chronic hypertensive states. Pediatr. Nephrol. 29, 1507–1516 (2014).

10.Smith, D. H. et al. Chronic Kidney Disease and Outcomes in Heart Failure With Preserved Versus Reduced Ejection Fraction. Natl. Institutes Heal. 6, 333–342 (2014).

11.Ohsawa, M. et al. Comparison of Predictability of Future Cardiovascular Events Between Chronic Kidney Disease (CKD) Stage Based on CKD Epidemiology Collaboration Equation and That Based on Modification of Diet in Renal Disease Equation in the Japanese General Population– I. Circ. J. 77, (2013).

12.Davies, E. W. et al. Health state utilities associated with major clinical events in the context of secondary hyperparathyroidism and chronic kidney disease requiring dialysis. Health Qual. Life Outcomes 1–11 (2015). doi:10.1186/s12955-015-0266-9

13.Zahran, M. et al. The Role of Hemostatic Factors in Atherosclerosis in Patients with Chronic Renal Disease. Electron. physician 7, 1270–1276 (2015).

14.Uchikawa, T., Shimano, M., Inden, Y. & Murohara, T. Serum Albumin Levels Predict Clinical Outcomes in chronic kidney disease (CKD) Patients Undergoing Cardiac Resynchronization Therapy. Intern. Med. 555–561 (2013). doi:10.2169/internalmedicine.53.1209

15.Pavlovic, D., Katicic, D., Gulin, T. & Josipovic, J. Vitamin D in the Patients with Chronic Kidney Disease : When , to Whom and in Which Form. Mater Sociomed 3, 122–124 (2015).

16.Mendley, S. R., Spyropoulos, F. & Counts, D. R. Case Report Short Stature in Chronic Kidney Disease Treated with Growth Hormone and an Aromatase Inhibitor. 2015, (2015).

17.Lajdova, I. et al. The Impact of Vitamin D 3 Supplementation on Mechanisms of Cell Calcium Signaling in Chronic Kidney Disease. Biomed Res. Int. 2015, (2015).

18.Kalousova, M. et al. Vitamin D Binding Protein Is Not Involved in Vitamin D Deficiency in Patients with Chronic Kidney Disease. Biomed Res. Int. 2015, (2015).

19.Schiller, A., Gadalean, F., Schiller, O., Timar, R. & Bob, F. Vitamin D Deficiency — Prognostic Marker or Mortality Risk Factor in End Stage Renal Disease Patients with Diabetes Mellitus Treated with Hemodialysis — A Prospective Multicenter Study. PLoS One 1–13 (2015). doi:10.1371/journal.pone.0126586

20.Mcmanus, D. D. et al. Decade-long trends (1999 – 2009) in the characteristics , management , and hospital outcomes of patients hospitalized with acute myocardial infarction with prior diabetes and chronic kidney disease. Int. J. Nephrol. Renovasc. Dis. 41–51 (2015).

21.Yamada, Y., Matsui, K., Takeuchi, I., Oguri, M. & Fujimaki, T. Association of genetic variants of the α - kinase 1 gene with type 2 diabetes mellitus in a longitudinal population - based genetic epidemiological study. Biomed. Reports 1–8 (2015). doi:10.3892/br.2015.439

22.Lapice, E. et al. The PPAR γ 2 Pro12Ala variant is protective against progression of nephropathy in people with type 2 diabetes. J. Transl. Med. 1–6 (2015). doi:10.1186/s12967-015-0448-6

23.Bello, N. A., Pfeffer, M. A. & Mcgill, J. B. Retinopathy and clinical outcomes in patients with type 2 diabetes mellitus , chronic kidney disease , and anemia. BMJ Open Diabetes Res. Care (2014).
24.Jadhakhan, F., Marshall, T. & Gill, P. A systematic review investigating the cumulative incidence of chronic kidney disease in young adults with impaired glucose tolerance. Biomed Cent. 1–6 (2015). doi:10.1186/s13643-015-0059-6
25.Noubiap, J. J. N. et al. Diabetic nephropathy in Africa : A systematic review. World J. Diabetes 6, 759–773 (2015).
26.You, J. S. et al. Evaluating the Utility of Rapid Point-of-Care Potassium Testing for the Early Identification of Hyperkalemia in Patients with Chronic Kidney Disease in the Emergency Department. Yonsei Med J 55, 1348–1353 (2014).
27.Anderson, J. E. & Kovesdy, P. Association of Hypo- and Hyperkalemia with Disease Progression and Mortality in Males with Chronic Kidney Disease : The Role of Race. nephron Clin Pr. (2012). doi:10.1159/000329511
28.Wang, H. et al. Hypokalemia , Its Contributing Factors and Renal Outcomes in Patients with Chronic Kidney Disease. PLoS One 8, (2013).
29.Paul E, Drawz, Denise C, Babineau, R. M. Metabolic Complications are Common in Elderly Patients with Chronic Kidney Disease. Natl. Institutes Heal. 60, 310–315 (2013).
30.Yamaguti, P. M. et al. Identification of the first large deletion in the CLDN16 gene in a patient with FHHNC and late-onset of chronic kidney disease : case report. BMC Nephrol. 1–6 (2015). doi:10.1186/s12882-015-0079-4
31.Yuste, C., Rubio-navarro, A., Barraca, D. & Aragoncillo, I. Haematuria Increases Progression of Advanced Proteinuric Kidney Disease. PLoS One 4, 1–12 (2015).
32.Vega, A. et al. Dose equivalence between continuous erythropoietin receptor activator (CERA), Darbepoetin and Epoetin in patients with advanced chronic kidney disease. Hipokratia 315–318 (2014).
33.Mcdonald, H. I., Nitsch, D., Millett, E. R. C., Sinclair, A. & Thomas, S. L. Original Article Are pre-existing markers of chronic kidney disease associated with short-term mortality following acute community-acquired pneumonia and sepsis ? A cohort study among older people with diabetes using electronic health records. Nephrol. Dial. Transplant. 1–8 (2015). doi:10.1093/ndt/gfu401
34.Rognant, N. et al. Impact of prior CKD management in a renal care network on early outcomes in incident dialysis patients : a prospective observational study. BMC Nephrol. 14, (2013).
35.Matsha, T. E., Kengne, A. P., Masconi, K. L., Yako, Y. Y. & Erasmus, R. T. APOL1 genetic variants , chronic kidney diseases and hypertension in mixed ancestry South Africans. BMC Genet. 1–9 (2015). doi:10.1186/s12863-015-0228-6
36.Kent, S. et al. What is the impact of chronic kidney disease stage and cardiovascular disease on the annual cost of hospital care in moderate-to-severe kidney disease ? BMC Nephrol. 1–8 (2015). doi:10.1186/s12882-015-0054-0
37.Wang, W., Bhole, V. M. & Krishnan, E. Chronic kidney disease as a risk factor for incident gout among men and women : retrospective cohort study using data from the Framingham Heart Study. BMJ Open Access (2015). doi:10.1136/bmjopen-2014-006843
38.Hung, S., Lai, Y., Kuo, K. & Tarng, D. Volume Overload and Adverse Outcomes in Chronic Kidney Disease : Am. Hear. Assoc. 1–12 (2015). doi:10.1161/JAHA.115.001918
39.Dzemidzic, J., Rasic, S., Rebic, D. & Uncanin, S. Role of Hypertension and Anaemia in Left Ventricular Remodelling in Patient with Renal Allograft in the First Post-transplant Year. Mater Sociomed 27, 104–107 (2015).
40.Chang, B. et al. Predictors of anemia in a multi ethnic chronic kidney disease population : a case – control study. Springerplus (2015). doi:10.1186/s40064-015-1001-z