CASE STUDY

Evaluation of Few Immunological Parameters in Patients with Chronic Renal Failure in Najaf

Buthaina Abd E. Naser*, Zainab S. Mahdi

Department of Biology, College of Education for Girls, Kufa University, Iraq

Received: 07th March, 2023; Revised: 16th June, 2023; Accepted: 20th August, 2023; Available Online: 25th September, 2023

ABSTRACT

Kidney failure is a chronic disease currently spreading worldwide, and one of its most important complications. Many indicators can be used to detect kidney disease early, which, if not treated, will eventually lead to failure. Kidney disease often leads to death. The study aimed to find a relationship between chronic renal failure and some immunological parameters and its relationship to the mechanism of dialysis, if it was hemorrhagic or peritoneal This study was conducted at the Kidney Center in Al-Sadr Teaching Hospital, Al-Najaf, and lasted from September 2022 to May 2023, including 57 males with chronic renal failure and 33 males. Listening male subjects who were considered as a control group. It was divided into age groups from 20 to 70, the duration of infection from 1 to 4 years, 5 to 7 and 8 to 15 years, and the body mass index included normal, excess, and obesity for patients with hemodialysis, peritoneal dialysis, and patients who did not reach the stage hemodialysis. The study concluded significant differences in the immunological indicators MCP-1 NTN-1, IL-1, α-TNF in the renal failure serum compared with healthy subjects. There was a positive relationship in the MCP-1, NTNT-1,IL-1, α TNF level. The results showed that there are significant differences $p < 0.05$ in age groups and body mass index in patients with renal failure compared with healthy subjects. There are no significant differences $p > 0.05$ with the duration of infection in patients with chronic renal failure compared with healthy controls. The presence of significant differences predicted kidney failure, $p < 0.05$, in the MCP-1 immunological indicators NTN-1, IL-1, α-TNF –TNF, The approved ROC table in patients with renal failure showed that the highest area of the biomarker NTN-1 and the lowest area is the biomarker α- TNF and immunological indicators are considered as predictors of early diagnosis of chronic renal failure.

Keywords: Kidney failure, Immunological indicators, NTN-1, IL-1, α-TNF.

International Journal of Drug Delivery Technology (2023); DOI: 10.25258/ijddt.13.3.51

How to cite this article: Naser BAE, Mahdi ZS. Evaluation of Few Immunological Parameters in Patients with Chronic Renal Failure in Najaf. International Journal of Drug Delivery Technology. 2023;13(3):1100-1106.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Renal failure in the whole disease, in the case of renal failure in the removal and repair of metabolic end products of renal disease. Blood, fluid regulation, electrolytes, and the pH balance of extracellular fluids. The underlying cause may be renal disease, the treatment of which is of non-renal origin.[1] Renal failure can present as an acute or chronic disorder.[2]

Compare acute renal failure with different causes in different hematological functions.[3] The most common indicator of acute renal failure is azotemia, which is the accumulation of nitrogenous waste products in the blood.[4]

Chronic renal failure (CRF) resolves gradually and has irreversible circuits.[5] It appears that the leading cause of death is from kidney disease. It can result from a number of conditions that cause permanent kidney loss, including chronic pyelonephritis, glomerulonephritis, hypertensive cardiomyopathy, obstructive uropathy, polycystic kidneys, and drugs and toxins.[6] Manifestations of chronic renal failure include accumulation of nitrogenous wastes, changes in water, electrolyte, and acid-base balance regulation, anemia, hypertension and changes in cardiovascular function, gastrointestinal disorders, neurological complications, and immunological disorders. Disturbing skin changes such as itching.[7]

The impact of kidney failure varies according to gender, age, race, geographical environment, dietary habits, level of medical care, and health and social awareness of the patient.

People with kidney failure are characterized by a severe deficiency in systemic immunity, and the infection is responsible for about 20 to 30% of deaths in these patients who are still on hemodialysis.[8] Another predictive sign of the progression of renal disease is increased levels of monocyte attractant protein MPC-1, which is one of the main chemokines belonging to small molecular weight cytokines and has

*Author for Correspondence: nidhal.albdairi@uokufa.edu.iq

a role in selective stimulation of monocytes, neutrophils and lymphocytes. Leukocyte infiltration is one of the most important hallmarks of surveillance. The immune system the inflammatory response, and neutrophils are the first to infiltrate, followed by monocytes and lymphocytes,[9] where the MPC-1 attractant protein is associated with inflammation and increases the risk of coronary artery disease, and the resulting inflammation contributes to the emergence of hardened areas in the arteries. It leads to their rupture, platelet aggregation, Blood clots, and clot formation.[10] Studies have shown that increased levels of MPC-1 lead to inflammation in the renal tissue, hyperglycemia, and increased complications of morbidity in patients with type 2 diabetes.[11]

Most of these factors may specifically weaken the systemic immunity of patients with chronic renal failure, and from this, we found it necessary to search and investigate some immunological criteria for people with chronic renal failure in Al-Najaf Governorate at the present time due to the difference in some environmental and physiological criteria for people with failure renal each according to its nature. The available studies on immunological variables for patients with renal failure in Iraq are few and do not cover many important variables. It is not commensurate with the seriousness of the disease and its rapid spread in recent years. The current study attempted to achieve the following objectives: The study aimed to find a relationship between renal failure and some immunological parameters and its relationship to the mechanism of action of dialysis, whether hematologic or peritoneal, through the following axes.

Objectives of the Study

Study of some immunological parameters for patients with chronic renal failure: it includes.

- Measuring the concentration of monocyte chemoattractant protein (MCP-1)
- Measurement of IL-1 concentration
- Measurement of α-TNF concentration.

MATERIALS AND METHODS

Subject and Study Place

This study included a follow-up of 90 samples divided into two groups: the first consisted of 33 healthy males only as a control group, and the second consisted of 57 male patients with chronic renal failure who also visited the Kidney Center in Al-Sadr Teaching Hospital, Al-Najaf Al-Ashraf, and the average age of the two groups was (Healthy and injured) between 20 and >70 years old, in equal proportions. The study began in September 2022 and continued until May 2023. The patients and healthy people were divided according to the age group into three groups, as it included the first group from (20–50) years, while the second group was from (51–70) years. The last group 70<, In addition to this division, patients' groups were divided into three subgroups based on body mass index, namely: Normal (18.5–25) kg/m^2, overweight (25–30) kg/m^2, and obese (30–40) kg/m^2. The body mass index was calculated using the formula:

BMI = body weight (kg)/height (m^2) (Han *et al*., 2006), and patients were divided according to the duration of infection into three groups: (1–4) years and the second (5–7) years, while the third and last group It included (8–15) years.

As for the information that was collected, it included (name, age, height, weight, and duration of injury), chronic diseases (such as pressure and diabetes), those who do not do dialysis, and the type of dialysis for patients only (hemodialysis and peritoneal dialysis). Smokers and those with thyroid and cancer diseases were excluded.

Collection of Blood Samples

In 5 mL of venous blood was drawn for men only (healthy people and those with renal failure) at the time between 10:00 to 12:00 am for peritoneal dialysis patients, and for hemodialysis patients and chronic renal failure patients who did not reach the stage of dialysis. In 5 mL of venous blood was drawn for men only at the time between 9:00 to 10:00. Then 4 mL of blood was transferred into tubes containing an anticoagulant gel tube to measure the concentration of albumine, creatinine and urea in the blood, and 1-mL of blood was placed in gel tubes of serum were left at room temperature for about 30 minutes. They were centrifuged at a speed of 4000 rpm for 10 minutes to separate the serum from the other components, and then about 1-mL of the serum samples (healthy and sick) were kept at a temperature of -20°C to the time of performing the immunological blood tests represented by examining the concentration of MCP-1, IL-1, NTN-1 and α-TNF by ELISA method.

Collection of Urine Samples

The men's urine samples were collected only immediately after blood was drawn and placed in a sterile plastic container to estimate the urine's albumin to creatinine ratio (ACR).

RESULTS AND DISCUSSION

Effect of Age and Duration of Infection in Patients with Chronic Renal Failure

The current study found significant differences in the age groups and duration of infection in people with chronic renal failure compared with healthy subjects.[12] They explained,[13] that the important risk factors that have a major role in the development of chronic renal failure are (the person's advanced age, blood sugar level, glomerular hyperfiltration, sex), where a significant correlation was observed as the person progressed age with abnormally increased urinary albumin secretion (Figure 1 and Table 1).

Factors of age and duration of chronic renal failure in infected patients increase the risk of albuminuria, as it was found that more than 45% of people with chronic renal failure were of the older age group and had a diagnosis of glomerular filtration rate (GFR) twice as high when compared to healthy people of the same age group who also have a normal body mass index.[14] In the study, Chen (2014),[15] also confirmed that elderly individuals with chronic kidney disease were treated below the required standard, as they may develop more complications when the necessary care is not taken, including

Table 1: Distribution of clinical features in patients with (ACR) in men

Variables	*Patients n=57*	*Control n=33*	*p-value*
Age (year)	52.18 ± 2.22	39.18 ± 2.51	0.0001*
=<40 year > 41 year	13 (22.8%) 44 (77.2%)	17 (51.5%) 16 (48.5%)	X2= 7.705 0.005 *
BMI (kg/m^2)	24.75 ± 0.51	26.5 ± 0.65	0.039 *
Normal weight Overweight Obesity	32 (56.1%) 19 (33.3%) 6 (10.5%)	15 (45.5%) 12 (36.4%) 6 (18.2%)	X2= 1.431 0.489 ns
MCP-1	24.52 ± 1.35	15.93 ± 0.49	0.0001*
IL-1	11.05 ± 0.32	5.94 ± 0.38	0.0001*
α- TNF	7.27 ± 0.23	6.08 ± 0.21	0.001*
NTN-1	8.6 ± 0.24	3.36 ± 0.23	0.0001*

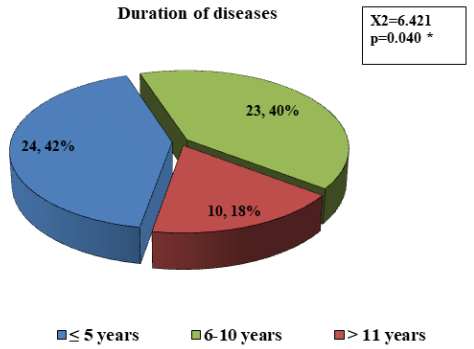

Figure 1: Diagram of renal failure patients' distribution according to the disease period

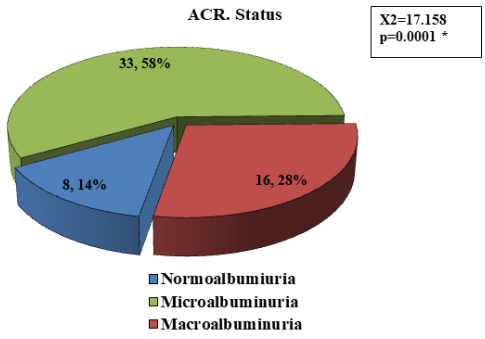

Figure 2: Distribution of chronic renal failure patients according to ACR status

Table 2: Comparison of demographic parameters and renal function in chronic kidney patients according to ACR status

Variables	*Normoal buminuria*	*Microal buminuria*	*Macroal buminuria*	*p-value*
Age (year)	41.25 ± 3.93	53.18 ± 3.08	55.56 ± 3.9	0.123 ns
BMI (kg/m^2)	24.44 ± 1.22	24.61 ± 0.66	25.21 ± 1.08	0.854 ns
Duration (year)	6.63 ± 1.5	7.3 ± 0.84	7.88 ± 0.92	0.804 ns
MCP-1	15.45 ± 1.15	21.24 ± 1.26	35.84 ± 2.0	0.0001*
IL-1	9.92 ± 0.84	10.86 ± 0.34	12.01 ± 0.76	0.107 ns
α- TNF	6.23 ± 0.32	7.09 ± 0.25	8.15 ± 0.55	0.021*
NTN-1	7.23 ± 0.48	8.39 ± 0.31	9.71 ± 0.41	0.003*

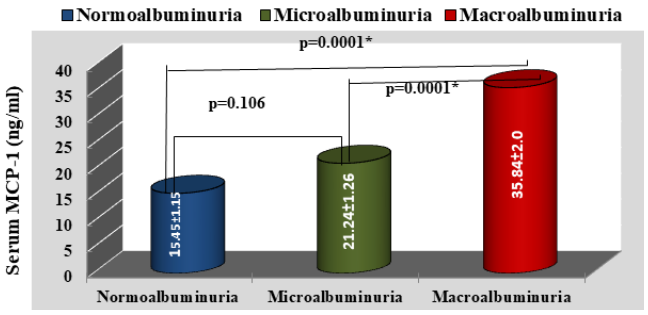

Figure 3: Comparison of MCP-1 in serum of patients with renal failure matched with ACR status

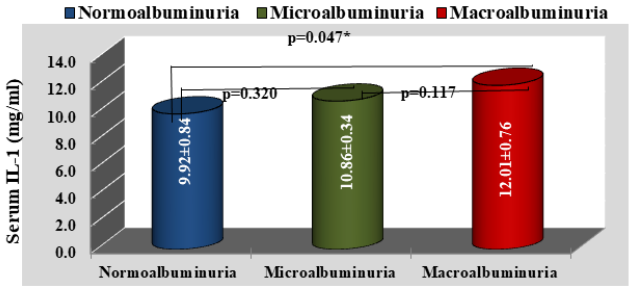

Figure 4: Comparison of serum IL-1 of chronic renal failure patients according to ACR status

Table 3: Distribution of characteristics in patients with renal failure of pressure and diabetes

Variables	*Non*	*Hyper.*	*Hyper. + DM*	*p-value*
Age (year)	44.31 ± 5.49	51.6 ± 3.21	56.92 ± 3.22	0.088
BMI (kg/m^2)	22.74 ± 1.12	24.39 ± 0.7	26.14 ± 0.79	0.030*
Duration (year)	5.46 ± 1	7.25 ± 1	8.5 ± 0.92	0.131
MCP-1	21.63 ± 2.38	27.07 ± 2.51	23.97 ± 2.02	0.310
IL-1	10.59 ± 0.41	11.59 ± 0.56	10.85 ± 0.57	0.452
α- TNF	6.62 ± 0.37	6.76 ± 0.29	8.05 ± 0.4	0.012*
NTN-1	8.34 ± 0.6	8.66 ± 0.31	8.69 ± 0.42	0.848

(heart disease, eye disease, and peripheral blood vessels), as well as many elderly people. People with diabetes suffer from a significant deficiency in their immunity and are at high risk of developing many of the known aging syndromes, such as (depression, enuresis, cognitive impairment, persistent pain), and the reason for this may be that most of the patients included in this study are likely to have been exposed to for severe fatigue and stress, and this reason is due to not following a balanced diet and not performing any useful exercises, and the reason may also be due to the lack of good control of blood sugar levels, which in turn stimulates and induces the super oxidation of fats, which produces an increase in the rate of free radicals and these radicals It attacks vital molecules (carbohydrates, proteins, fats) and may attack nitrogenous bases such as DNA, which results in a depletion of enzymatic and non-enzymatic antioxidants, especially the glutathione molecule, as these molecules reduce free radicals and prevent the damage they cause to the body (Figure 2 and Table 2).[16]

Table 4: Correlation between all variables in chronic kidney disease

Variables	*emotional connection factor*	*Age (year)*	*BMI (kg/m^2)*	*MCP-1*	*NO*	*NTN1*	*IL-1*
BMI (kg/m^2)	r	0.212	1				
	p-value	0.113					
MCP-1	r	.292*	-0.015	1			
NTN-1	r	0.517**	-0.030	0.476**	-0.146	1	
	p-value	0.000	0.825	0.000	0.279		
IL-1	r	0.219	-0.037	0.561**	-0.250	0.299*	1
	p-value	0.101	0.784	0.000	0.061	0.024	
TNF-∝	r	-0.016	0.032	0.353**	-0.280*	0.110	0.190
	p-value	0.906	0.811	0.007	0.035	0.414	0.157

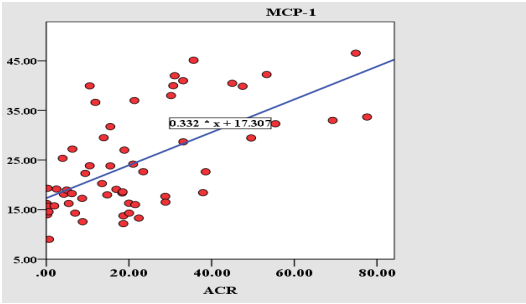

Figure 5: Positive relationship between MCP-1 level and ACR in male patients with chronic renal failure

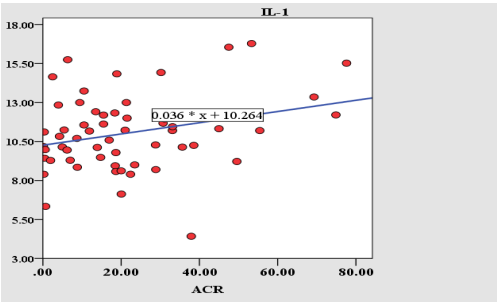

Figure 6: Positive relationship between IL-1 level and ACR in male patients with chronic renal failure

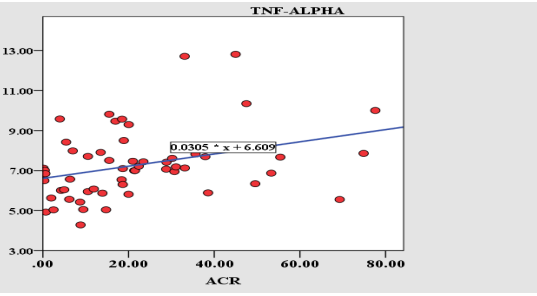

Figure 7: Positive relationship between∝- TNF level and ACR in male patients with chronic renal failure

As for the duration of infection, we have found in our current study that there is a significant difference between the duration of infection for patients with chronic renal failure. (2014) that there were no significant differences in the duration of chronic renal failure, and this study differed with the study.[17]

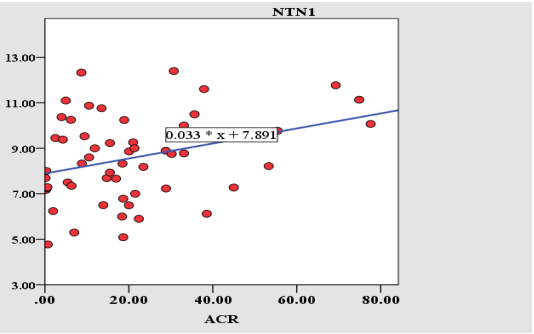

Figure 8: Positive relationship between NTN-1 level and ACR in male patients with chronic renal failure

Table 5: Prediction depending on variables in chronic kidney disease

Independent variables	*Unstandardized Coefficients*		*T*	*p-value*
	B	*Std. Error*		
MCP-1	1.160	0.198	5.875	0.0001*
NTN-1	3.492	1.313	2.659	0.010*
IL-1	2.215	1.011	2.190	0.033*
α- TNF	3.690	1.399	2.637	0.011*

Immunological study

Comparison of immunological parameters in the two groups of control and patients with chronic renal failure.

- *Comparison of MCP-1 levels of monocyte attractant protein between healthy groups and patients with chronic renal failure, demographic criteria and some indicators*

The current study showed a significant increase in the level of the MCP-1 attractant protein for monocytes in men with chronic renal failure than in healthy subjects (Figure 3). The attraction of macrophages from the blood to the kidneys at sites of inflammation through interaction with the MCP-1 receptor activates macrophages and releases ROS and proinflammatory cytokines that stimulate the occurrence of the fibrotic response in glomerular cells and the accumulation of myofibroblasts and phagocytes around the renal tubules. This causes tubular injury and renal fibrosis in patients with chronic renal failure, as a study indicates (Lestarini *et al.*, 2020). The study showed a rise in the level of MCP-1 attractant protein for monocytes

Table 6: Estimation of AUC, the main indicator adopted in renal failure

Test Result Variable(s)	*Area*	*Std. Error*	*p-value*	*95% Confidence Interval*	
				Lower Bound	*Upper Bound*
MCP-1	0.780	0.048	0.0001	0.687	0.873
IL-1	0.939	0.025	0.0001	0.890	0.988
α- TNF	0.698	0.055	0.002	0.591	0.805
NTN-1	0.990	0.007	0.001	0.976	1.000

with advancing age. Still, it did not rise to a significant level in patients with chronic renal failure. The result agreed with the study,[18] which is attributed to kidney damage, one of the main factors that Lead to infections resulting from immunodeficiency in the elderly. These infections lead to changes in the structural structure and functional performance of the kidneys and increase the processes of catabolism and stabilization of growth processes.[19] This may be attributed to the fact that increased production of MCP-1 indicates poor renal performance due to glomerular changes such as increased basement membrane thickness and mesenteric expansion that affect the filtration rate and lead to hardening of the glomeruli due to the high level of sugar in the blood, which leads to an increase in the excretion of proteins in the urine.[20]

- *Comparison of interleukin-1 levels between healthy groups and patients with renal failure, demographic criteria and some biochemical indicators*

The results of the current study showed that there was a significant increase in interleukin-1 levels in patients with renal failure compared to healthy men, and this result agreed with many studies (Suri *et al.*, 2021). The study showed an increase in the level of interleukin-1 with age, but it is not significant, and this is attributed to the diseases associated with the elderly, such as atherosclerosis and diabetes, and the stimulation of inflammatory pathways that are more common with age and affect the levels of IL-1, as indicated by it (Figure 4).[21]

It was also noted from the statistical analysis a significant increase in the levels of interleukin-1 in the serum with the progression of the stages of renal impairment and the GFR. The kidneys are due to a high blood glucose level, especially in the end stages of chronic renal failure, as indicated by some studies.[22]

- *Comparison of α-TNF levels between the two groups of healthy subjects and patients with renal failure, demographic criteria and some biochemical indicators.*

The current study found a significant increase in the level of α-TNF in patients with renal failure compared with healthy subjects, and this is consistent with Mehaffey and Majid (2017)[23] (Table 2) as they found that an increase in stimulation of the formation of α-TNF level as a result of kidney injury and an increase in blood pressure with an increase in the level of angiotensin 11 and stress factors oxidative stress. A decrease in GFR, constriction of blood vessels in the kidneys, and an increase in free radical and ROS interactions all lead to an increase in the level of α-TNF.[24] α- TNF is directly related to kidney disease, as it mediates blood flow changes in the kidneys› blood vessels, the excretory process, and the regulation of blood circulation Within the kidneys, it promotes the anti-natraemic response and the regulation of blood pressure by TNFR-2, which response to inflammation and kidney injury.[25]

- *Comparison of Netrin-1 levels between the two groups of healthy subjects and patients with renal failure, demographic criteria and some biochemical indicators.*

There are significant differences in the level of netrin-1 compared with healthy subjects, and it was consistent with many studies Emre *et al.* (2016)[26] indicated that netrin-1 is a recently identified diagnostic biomarker for chronic renal failure through animal experiments, where the level of NTN-1 is significantly increased in the management of acute kidney damage.

The researchers noted that NTN-1 in the serum of diabetic nephropathy patients increased significantly in microalbuminuric compared with normoalbuminuric and healthy subjects. There were no significant differences with normoalbuminuric and healthy subjects. Netrin-1 is significantly associated with albumin and GFR. Therefore, the researchers concluded that netrin-1 is significantly increased when glomeruli are damaged in diabetic nephropathy and is not dependent on age or gender.

Ramesh *et al.* (2010)[27] found that the level of netrin-1 in serum as a biomarker of acute renal failure and as an initiator protein important for the formation of nerves and blood vessels.[28] Five types were diagnosed in mammals (1,3,4, G1 and G2). All of these types, including the laminin-like protein, netrin-1, are associated with elevated protein secretion after induced acute and chronic kidney injury and their secretion in the urine in a mouse and human study.[29]
Punithavathi *et al.* (2013)[30] noted that netrin-1 plays a role in regulating the production of prostaglandin metabolites from neutrophil egg cells in and out of vivo after disease events, when severe injury to the kidneys of mice was induced, which led to a significant increase in neutrophil egg cell infiltration and leucocyte and netrin-1 suppression in animals led to decreased prostaglandin and thromboxane B production and filtration of neutrophil leukocytes into the kidneys, and was associated with decreased apoptosis and inflammation and improved renal function, and maybe a treatment for many inflammatory immune disorders.

Some studies indicate that when administering netrin-1 to mice, it causes inhibition of white blood cell migration through the UNC5B receptor, which leads to an increase in the level of adenosine monophosphate, inhibition of chemotaxis, and

suppression of filtration and inflammation in many diseases, bacteremia, acute kidney infection, and pneumonia. Acute, hypoxic peritonitis by suppressing the function of immune cells (Figures 5-8).[31,32]

The urine level is considered a sensitive indicator for patients within sufficiency. Mohammad *et al.* (2017)[33] indicated acute kidney failure 6 hours after cardiac surgery instead of serum creatinine level that rises only 24 hours after cardiac surgery in patients with heart disease associated with acute renal failure (Tables 3-6).

REFERENCES

1. Kasper DL, Braunwald E, Fauci AS. Harisson's principles of internal medicine. 16th Edition, McGraw-Hill Companies. Inc., Boston. 2005; 2104-2126
2. Albright Jr RC. Acute renal failure: a practical update. InMayo Clinic Proceedings 2001 Jan 1;76(1): 67-74). Elsevier.
3. Singri N, Ahya SN, Levin ML. Acute renal failure. J. A. M. A. 2003;289(6): 747–751
4. Hilton R. Acute Renal Failure . B.M.J. 2006; 333:786-790
5. Kasacka I, Sawicki B, Ostrowska H. Pulmonary neuroendocrine cells in chronic renal failure. Roczniki Akademii Medycznej w Bialymstoku (1995). 2004 Jan 1;49:149-51.
6. Bethesda MD. United States Renal Data System. Kidney disease of diabetes. 2007; USRDS Annual Data Report: National Institute of Diabetes& Digestive and Kidney Disease. available on line at www.catalog.niddk.nih.gov
7. Henry TY. Progression of chronic renal failure. Archives of internal medicine. 2003 Jun 23;163(12):1417-29.
8. Wynne K, Giannitsopoulou K, Small CJ, Patterson M, Frost G, Ghatei MA, Brown EA, Bloom SR, Choi P. Subcutaneous ghrelin enhances acute food intake in malnourished patients who receive maintenance peritoneal dialysis: a randomized, placebo-controlled trial. JOURNAL-AMERICAN SOCIETY OF NEPHROLOGY. 2005 Jul 1;16(7):2111.
9. Yoshimura T. The production of monocyte chemoattractant protein-1 (MCP-1)/CCL2 in tumor microenvironments. Cytokine. 2017 Oct 1;98:71-8.
10. Blanco-Colio LM, Méndez-Barbero N, Pello Lázaro AM, Aceña Á, Tarín N, Cristóbal C, Martínez-Milla J, González-Lorenzo Ó, Martín-Ventura JL, Huelmos A, Gutiérrez-Landaluce C. MCP-1 predicts recurrent cardiovascular events in patients with persistent inflammation. Journal of Clinical Medicine. 2021 Mar 9;10(5):1137.
11. Xu L, Sharkey D, Cantley LG. Tubular GM-CSF promotes late MCP-1/CCR2-mediated fibrosis and inflammation after ischemia/reperfusion injury. Journal of the American Society of Nephrology: JASN. 2019 Oct;30(10):1825.
12. Omozee EB, Okaka EI, Edo AE, Obika LF. Urinary N-acetyl-beta-d-glucosaminidase levels in diabetic adults. Journal of laboratory physicians. 2019 Jan;11(01):001-4.
13. Rohilla A, Tiwari SK, Rohilla S, Kushnoor A. Diabetic Nephropathy: Pathogenesis , Prevention and Treatment . Pelagia Research Library, Europ. J. of Exp. Bio. 2011;1(4):72-80
14. Cheng YW, Malik U, Chang SL. The risk factors of diabetic nephropathy in Taiwan, including old age, hypertension and aspirin therapy. International Journal of Diabetes in Developing Countries. 2013 Jun;33(2):128-.
15. Chen J. Diabetic nephropathy: scope of the problem. Diabetes and kidney disease. 2014 Apr 17:9-14.
16. Ackermann RT, Cheng YJ, Williamson DF, Gregg EW. Identifying adults at high risk for diabetes and cardiovascular disease using hemoglobin A1c: National Health and Nutrition Examination Survey 2005–2006. American journal of preventive medicine. 2011 Jan 1;40(1):11-7.
17. Vujičić B, Turk T, Crnčević-Orlić, Ž, Đorđević, G and Rački S. Diabetic Nephropathy. Licensee InTech.http://creativecommons.org/licenses/by/3.0, 2012:71-96
18. Mahmoud R. Gaballa, Farag YMK. Predictors of diabetic nephropathy. Cent. Europ. J. Med. 2021; 8(3): 287-296.
19. Chi M, Tian Zi, Ma K, Li Y, Wang L, Nasser MI, and Liu C. Diseased kidneys: aging and immune aging. Immunity and Aging. 2022; 19(1): 1-12
20. Siddiqui K, Joy SS, George TP, Mujammami M, Alfadda AA. Potential role and excretion level of urinary transferrin, KIM-1, RBP, MCP-1 and NGAL markers in diabetic nephropathy. Diabetes, Metabolic Syndrome and Obesity. 2020 Dec 31:5103-11.
21. Qin Z, Li H, Jiao P, Jiang L, Geng J, Yang Q, Liao R, Su B. The value of urinary interleukin-18 in predicting acute kidney injury: a systematic review and meta-analysis. Renal Failure. 2022 Dec 31;44(1):1727-41.
22. Sun J, Evrin C, Samel SA, Fernández-Cid A, Riera A, Kawakami H, Stillman B, Speck C, Li H. Cryo-EM structure of a helicase loading intermediate containing ORC–Cdc6–Cdt1–MCM2-7 bound to DNA. Nature structural & molecular biology. 2013 Aug;20(8):944-51.
23. Mehaffey EP, Castillo A, Navar LG, Majid DS. Intrarenal angiotensinogen production induced by chronic angiotensin II and high salt intake is augmented in tumor necrosis factor-alpha receptor type 1 knockout mice. The FASEB Journal. 2016 Apr;30:1216-3.
24. Shahid SM, Mahboob T. Clinical correlation between frequent risk factors of diabetic nephropathy and serum sialic acid. Int. J. Diabet. Metabol. 2010;14:138-142.
25. Castillo Lopez D, Zhu-Salzman K, Ek-Ramos MJ, Sword GA. The entomopathogenic fungal endophytes Purpureocillium lilacinum (formerly Paecilomyces lilacinus) and Beauveria bassiana negatively affect cotton aphid reproduction under both greenhouse and field conditions. PloS one. 2014 Aug 5;9(8):e103891.
26. Ay E, Marakoğlu K, Kizmaz M, Ünlü A. Evaluation of Netrin-1 levels and albuminuria in patients with diabetes. Journal of clinical laboratory analysis. 2016 Nov;30(6):972-7.
27. Ramesh G, Krawczeski CD, Woo JG, Wang Y, Devarajan P. Urinary netrin-1 is an early predictive biomarker of acute kidney injury after cardiac surgery. Clinical journal of the American Society of Nephrology: CJASN. 2010 Mar;5(3):395.
28. Freitas C, Larrivée B, Eichmann A. Netrins and UNC5 receptors in angiogenesis. Angiogenesis. 2008 Mar;11:23-9.
29. Brian Reeves W, Kwon O, Ramesh G. Netrin-1 and kidney injury. II. Netrin-1 is an early biomarker of acute kidney injury. American Journal of Physiology-Renal Physiology. 2008 Apr;294(4):F731-8
30. Ranganathan PV, Jayakumar C, Mohamed R, Dong Z, Ramesh G. Netrin-1 regulates the inflammatory response of neutrophils and macrophages, and suppresses ischemic acute kidney injury by inhibiting COX-2-mediated PGE2 production. Kidney Int. 2013 Jun;83(6):1087-98. doi: 10.1038/ki.2012.423. Epub 2013 Feb 27. PMID: 23447066; PMCID: PMC3672333.

31. Ly NP, Komatsuzaki K, Fraser IP, Tseng AA, Prodhan P, Moore KJ, Kinane TB. Netrin-1 inhibits leukocyte migration in vitro and in vivo. Proceedings of the National Academy of Sciences. 2005 Oct 11;102(41):14729-34.
32. Wang W, Brian Reeves W, Ramesh G. Netrin-1 and kidney injury. I. Netrin-1 protects against ischemia-reperfusion injury of the kidney. American Journal of Physiology-Renal Physiology. 2008 Apr;294(4):F739-47.
33. Aly MH, Alnahal A, Emad G, Jumaa AA, El Shaarawy MM. Urinary netrin-1 predicts early ischemic acute kidney injury after cardiopulmonary bypass. The Egyptian Journal of Internal Medicine. 2017 Dec;29(4):170-5.