Bali Medical Journal (*Bali Med J)* 2019, Volume 8, Number 2: 537-541
P-ISSN.2089-1180, E-ISSN: 2302-2914

Published by DiscoverSys

Cardiorenal syndrome type 1: a literature review

Starry Homenta Rampengan[1*]

ABSTRACT

Kidney injury is one of the most common problems in the first two days of treatment for patients with acute heart failure. Renal dysfunction associated with acute heart failure causes fairly high morbidity and mortality. This literature review seeks a variety of literature that helps to explain the relationship between kidney injury and acute heart failure and the factors that play an important role in both of these pathologies. Completion of rapid and prompt diagnosis and treatment from various disciplines of patients with heart failure is important. The laboratories investigation is very important to get an early diagnosis, also determine the complications that occur in patients with acute heart failure. New markers such as *Kidney-1 Injury Molecule* (KIM-1), *Neutrophil Gelatinase-Associated Lipocalin* (NGAL), *L-type FABP Protein* (L-FABP), and *Cystatin-C* which can be used to detect acute kidney injury (AKI) early in its course hence promote a better clinical outcome and patient prognosis.

Keywords: Acute kidney injury, acute heart failure, cardiorenal syndrome
Cite this Article: Rampengan, S.,H. 2019. Cardiorenal syndrome type 1: a literature review. *Bali Medical Journal* 8(2): 537-541. DOI: 10.15562/bmj.v8i2.1549

[1]Department of Cardiology and Vascular Medicine, Universitas Sam Ratulangi, Manado, Indonesia

*Correspondence to:
Starry Homenta Rampengan
Department of Cardiology and Vascular Medicine, Universitas Sam Ratulangi, Manado, Indonesia.
starry8888@yahoo.com

Received: 2019-07-11
Accepted: 2019-07-13
Published: 2019-08-01

INTRODUCTION

Acute kidney injury is one of the most common complications in the first 48 hours in patients with acute heart failure. It involves complex pathophysiology and requires multidisciplinary treatment. In addition, the incidence of acute kidney injury can only be detected with serum creatinine markers at least 48 hours after treatment, and it is possible that it already caused permanent damage to renal glomerulus.[1] Acute kidney injury related to the occurrence of acute heart failure has fairly high morbidity and mortality. The incidence of acute heart failure accompanied by acute kidney injury is often also referred to as cardiorenal syndrome.[2,3]

Acute heart failure is one of the major causes of death. Patients with acute heart failure often come with complaints of severe dyspnea due to pulmonary congestion. Elimination of the excess fluid is the main target of therapy, and the discharge of the fluid is mainly from the kidneys. However, many patients with acute heart failure also experience deterioration of kidney function during the treatment period because indeed the relationship of the heart to the kidneys affects each other.[2] Decreased kidney function due to low perfusion followed by venous congestion in the kidney is the mechanism that causes cellular damage in acute kidney injury (AKI).[4]

ACUTE KIDNEY INJURY IN ACUTE HEART FAILURE

Acute kidney injury is one of the complications of acute heart failure. The relationship between the two important organs serves to maintain hemodynamic stability, both in regulating blood volume and maintaining vascular tone. If there is a disruption in one, there will be dysfunction or damage to the other organs. The relationship between these two organs is shown as distinct clinical pathophysiology called cardiorenal syndrome (CRS).[5] In patients with acute heart failure, the prevalence of deteriorating kidney function reaches 10-40% of total patients.[6] Of these, mortality in 1 year of patients acute heart failure with complications of acute kidney injury ranges from 30%, which is around 1.5 to 2 times if without acute kidney injury.[7] It can be stated that kidney damage is an independent predictor of mortality in patients with heart failure.[8]

According to the 2013 Acute Dialysis Quality Initiative workgroup (ADQI), AKI is divided into five classifications based on the main organ that is dysfunctional, the heart or kidney, or other processes that affect both organs as well as the onset of events (acute or chronic) (Table 1). If the main problem is the heart, and it causes impaired kidney function, then it categorized as type 1 and 2 cardiorenal syndromes, if the main problem is the kidney, then it categorized as type 3 and 4

Table 1. Classification and definition of the cardiorenal syndrome from the Consensus Conference of the Acute Dialysis Quality Initiative

Type	Description	Clinical Example
CRS type 1 (acute CRS)	Acute heart failure cause acute kidney injury	Acute cardiogenic event that causes cardiogenic shock and acute kidney injury
CRS type 2 (Chronic CRS)	Chronic heart failure cause chronic kidney disease	Chronic heart failure
CRS type 3 (Acute renocardiac syndrome)	Acute kidney injury causes acute heart failure	Acute kidney damage (decreased cardiac contractility due to uremia, cardiac arrhythmia due to hyperkalemia, lung edema due to fluid overload)
CRS type 4 (chronic renocardiac syndrome)	Chronic kidney disease causes chronic heart failure	Chronic kidney disease caused left ventricle hypertrophy, coronary heart disease, and diastolic dysfunction
CRS type 5 (Secondary CRS)	Presence of systemic comorbid that cause acute or chronic cardiac and renal dysfunction	amyloidosis, sepsis, diabetes mellitus, vasculitis, non-cardiogenic shock

cardiorenal syndromes or also called renocardiac syndrome. Whereas the last type, also called secondary cardiorenal syndrome, is a cardiorenal syndrome due to triggers are originated other than the heart or kidney, but from comorbid factors that cause disturbances both the heart and kidney.[9]

CARDIORENAL SYNDROME TYPE 1

Cardiorenal syndrome (CRS) type 1 is most commonly found in patients with acute heart failure, especially acute decompensated heart failure (ADHF), ischemic events (myocardial infarction and cardiac surgery) and also non-ischemic events (valve disorders, aortic dissection, pulmonary embolism, cardiac tamponade).[10] CRS occurs in approximately 40-60% of patients with ADHF based on the current criteria of AKI.[11] In a Study of Left Ventricular Dysfunction (SOLVD) study by Ahmad et al., it was shown that a low glomerular filtration rate increased mortality in heart failure patients with left ventricular dysfunction.[12]

There are several variants of CRS type 1 which is divided into 4 subgroups, namely 1) Acute heart failure (de novo) which results in acute kidney injury, 2) Acute heart failure (de novo) which results in acute on chronic kidney injury, 3) acute on chronic decompensated heart failure which causes acute kidney injury (de novo), 4) acute on chronic decompensated heart failure resulting in acute on chronic kidney injury. Nevertheless, CRS type 1 is a condition when an acute heart failure that causes acute kidney injury, both in ADHF patients, acute myocardial infarction with symptoms of heart failure or who have decreased ejection of the left ventricular fraction.

The basic mechanism of CRS type 1 is due to a decrease in cardiac output, neurohormonal activation, and the release of vasoactive substances, all of which cause a decrease in perfusion to the kidneys and this causes renal ischemia. Also, high central venous pressure will increase intra-abdominal pressure which ultimately causes venous congestion, sympathetic nerve activation, activation of the renin-angiotensin-aldosterone system and the release of vasoactive substances such as endothelin, anemia and immune system disorders which play a role in the occurrence of AKI.[13–17]

The mechanism of hemodynamics plays a major role in the occurrence of CRS type 1. Reduced renal artery flow due to decreased cardiac output causes a decrease in the glomerular filtration rate (GFR). If hemodynamics state returned to normal in the early stages, the heart and kidney parameters would also return to normal. Hemodynamic in "cold" conditions are a sign of a decrease in the amount of effective circulating fluid, so that there is a possible decrease in blood flow to the kidneys and activation of the renin-angiotensin-aldosterone system which causes vasoconstriction in renal afferents and decreased effective glomerular perfusion pressure. When there is an increase in central venous pressure (CVP), a "wet" condition will be found in the patient. This condition is also characterized by increased pulmonary and systemic congestion. When CVP increases, interstitial pressure also increases, and kidney tubules collapse so that the glomerular filtration rate also decreases (Figure 1).[14–19]

The non-hemodynamic mechanisms also play certain roles in the pathogenesis of CRS type 1. The non-hemodynamic mechanisms are the action of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system, chronic inflammation, and an imbalance between the production of reactive oxygen species (ROS)/nitric oxide (NO) which ultimately contribute to ischemic damage to the renal tubules (Figure 1).[14,15,20]

In essence, three main processes promote the occurrence of cardiorenal syndrome type 1. The first is the presence of hemodynamic changes or hemodynamic disorders. Second is the presence of neurohormonal disorders. The third is the existence of other mechanisms related to cardiovascular

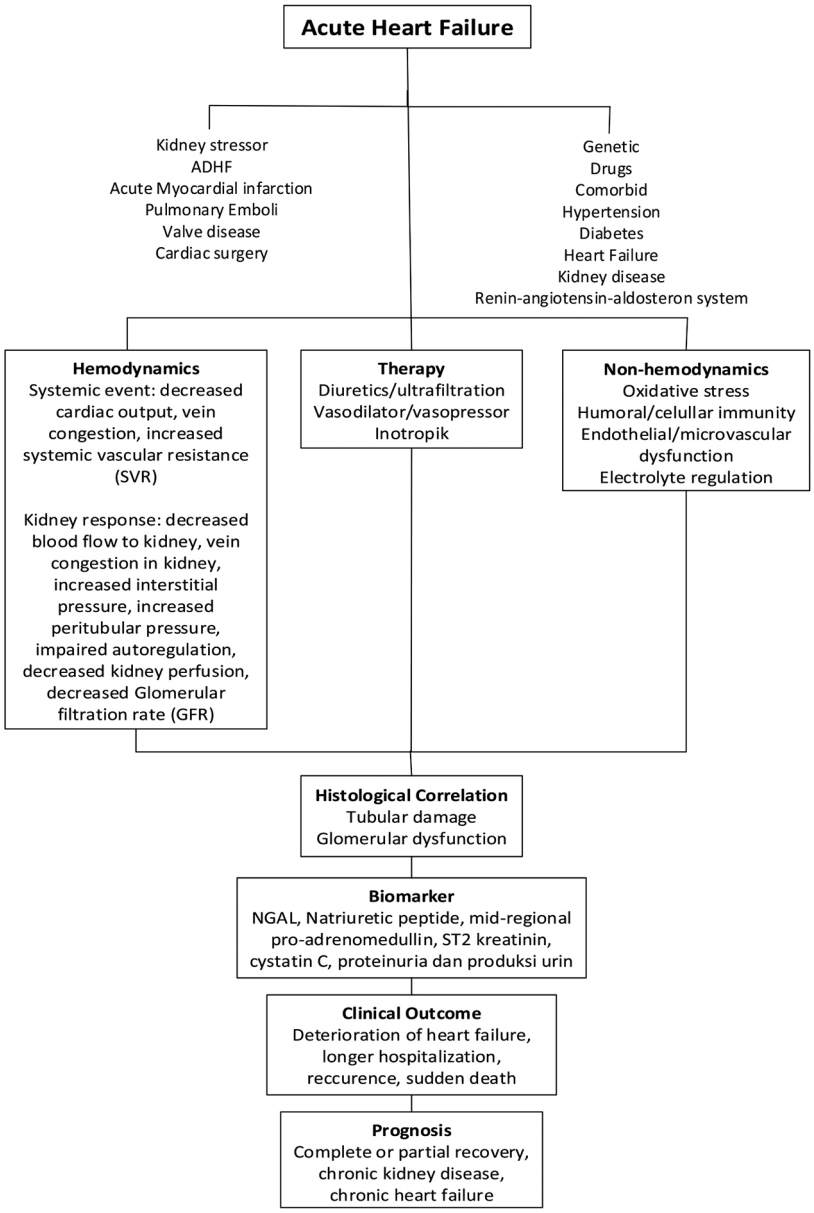

Figure 1. The mechanism, histological correlation, biomarkers, and clinical output of CRS type 1 in acute heart failure.

diseases such as atherosclerosis, diabetes mellitus, hypertension, cachexia, chronic anemia which directly or indirectly contribute to worsening of the heart and kidneys through hemodynamics and non-hemodynamics pathway.[21]

Diagnosis of CRS type 1 is based on the presence of impaired kidney function that is indicated by an increase in kidney-related markers or reduced urine production. Although only a slight decrease in kidney function was associated with a poor prognosis. Acute kidney injury has the potential to recover hence early detection of AKI is important to improve patient outcome.[8]

There are four criteria for the definition of AKI based on serum creatinine, and evaluation of glomerular filtration rate according to RIFLE[22] (Risk, Injury, Failure, Loss of Kidney Function, and Kidney Disease End-Stage), AKIN[23] (Acute Kidney Injury Network), KDIGO[24] (Kidney Disease, Improving Global Outcome). It is summarized in Table 2. Essentially, all of these criteria based on the presence of WRF (Worsening Renal Function) or deterioration of kidney function indicated by increased creatinine levels, and a decrease in glomerular filtration rate (Table 2).[6]

Acute kidney injury can also be demonstrated by reduced urine production. Mehta et al. used patient urine production to diagnose acute kidney injury. The criteria divide AKI into 3 stages, stage-1 if urine production ≤0.5 mL/kg per hour for more than 6 hours, stage-2 when urine production is less than 0.5 mL/kg per hour for more than 12 hour, and stage-3 which if the urine production is less than 0.3 mL/kg per hour for more than 24 hours or no urine production at all (anuria) for 12 hours.[23]

Recent studies concluded that worsening kidney function occurs in hospitalized patients associated with poor outcome.[16,25,26] Voors et al., assess the deterioration of renal function in 30% of patients with acute heart failure patients associated with decreased systolic blood pressure.[27] According to Akhter et al., elevated creatinine significantly extend the period of treatment and the effect on long-term mortality.[28] According to Chittineni et al., AKI occurs in 21% of patients with congestive heart failure and is associated with increased risk of recurrent.[29] According to Damman et al., worsening renal function in patients with acute heart failure both during hospital care and after hospital discharge, independently associated with poor prognosis.[25] Blair et al. assessed deterioration of kidney function occurred in 13.8% of patients during treatment and 11.9% after outpatient treatment in heart failure with a decrease in left ventricular ejection function of less than 40%.[30] It is somewhat rational to recommend that renal function monitoring is important even after the patients have discharged.

It is important to distinguish kidney deterioration that occurs, whether temporary or permanent, because this affects the long-term prognosis. According to Metra et al., increased serum creatinine caused by artery underfilling and decreased renal perfusion due to the effect of therapeutic diuresis or initiation of therapy or increased doses of angiotensin conversion enzyme blockers or adrenergic receptors (also called vasomotor nephropathy) is usually temporary and is not associated with permanent kidney damage and a poor prognosis.[31]

Table 2. Criteria and definition of acute kidney injury

Parameter	Serum creatinine	Duration
KDIGO	• Stage 1: creatinine ≥1,5 times the initial value or increases ≥0,3 mg / dL • Stage 2: creatinine ≥2 times the initial value • Stage 3: creatinine ≥3 times the initial value or increases in creatinine to ≥ 4.0 mg / dL	The definition of AKI requires a change in creatinine ≥1,5 times of the initial value and occurs in at least 7 days or an increase of 0.3 mg / dL in the first 48 hours.
AKIN	• Stage 1: increased creatinine 0.3 mg / dL (≥26,2 mol / L) or increase in value up to ≥150% -199% (1.5 to 1.9 times) • Stage 2: increased creatinine up to 200% -299% (≥2 up to 2.9 times) of the initial value • Stage 3: elevated creatinine up to 300% (≥3 times) the initial value or initial creatinine ≥ 4 mg / dL (≥354 mol / L) with an acute rise ≥0,5 mg / dL (44µmol / L) or requiring hemodialysis therapy	Acute creatinine changes occur within the first 48 hours for care
RIFLE	• At risk: increased creatinine ≥ 1.5 times the initial value or decrease glomerular filtration rate ≤ 25% • Injuries: increased creatinine ≥ 2.0 times the initial value or decrease glomerular filtration rate ≥ 50% • Failure: increased creatinine ≥ 3.0 times the initial value or decrease glomerular filtration rate ≥ 75% or the absolute value of creatinine ≥ 4 mg / dL (≥354 mol / L) with an acute rise at least 0.5 mg / dL (44 mol/L)	Creatinine changed in 1-7 days, began after 24 hours
WRF	• Increased creatinine ≥ 0.3 mg / dL (26.5 mol / L) of the initial creatinine values	Increased creatinine may occur at any time during treatment

The importance of early treatment is early recognition and diagnosis. Due to certain criteria needed 48 hours before establishing the diagnosis, a novel biomarkers of acute kidney injury in urine and blood are needed as an early marker of renal tubular damage.[1,31] Few candidate markers have been investigated. The various spectrum of the marker has been studied, the functional markers such as plasma and serum creatinine, as well as serum cystatin-c as well as protein markers such as Kidney Injury Molecule-1 (KIM-1), Neutrophil Gelatinase-Associated Lipocalin (NGAL), L-type Fatty Acid Binding Protein (L-FABP), and Interleukin-18 and enzyme markers, namely N-acetyl-β-D-glucosaminidase (NAG) and α-glutathione S-transferase (α-GST). Biomarkers that have shown adequate sensitivity and specificity to renal tubular damage were NGAL, KIM-1, and Cystatin-C.[14,32–34]

CONCLUSION

Acute heart failure is one of the causes of patients being taken to the hospital, which is often encountered with a fairly high mortality rate. An immediate and appropriate diagnosis and treatment is important for a better clinical outcome. Several limitations of the current criteria of acute kidney injury hinder early intervention. Therefore it is hoped that there will be new markers would support early and faster detection of kidney injury, especially in the setting of acute heart failure.

CONFLICT OF INTEREST

Authors declare no conflict of interest regarding the publication of this article

REFERENCES

1. Arifianto H. Furosemide Stress Test Sebagai Penanda Diagnosis Acute Kidney Injury pada Gagal Jantung Akut. [Thesis]. Universitas Sebelas Maret; 2016.
2. Han S.W., Ryu K.H. Renal dysfunction in acute heart failure. *Korean Circ J*. 2011;41(10):565–74.
3. Kim J.Y. Renal Dysfunction in Korean Acute Heart Failure Patients. *Korean Circ J*. 2017;47(5):692–3.
4. Thind G.S., Loehrke M., Wilt J.L. Acute cardiorenal syndrome: Mechanisms and clinical implications. *Cleve Clin J Med*. 2018;85(3):231–9.
5. Ronco C., Haapio M., House A.A., Anavekar N., Bellomo R. Cardiorenal Syndrome. *J Am Coll Cardiol*. 2008;52(19):1527–39.
6. Rangaswami J., Bhalla V., Blair J.E.A., Chang T.I., Costa S., Lentine K.L., et al. Cardiorenal Syndrome: Classification, Pathophysiology, Diagnosis, and Treatment Strategies: A Scientific Statement From the American Heart Association. *Circulation*. 2019;139(16):e840–78.
7. Chen J., Normand S.-L.T., Wang Y., Krumholz H.M. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries, 1998-2008. *JAMA*. 306(15):1669–78.
8. Shamagian L.G., Otero I.G., Lamela A. V, Juanatey J.R. Renal failure is an independent predictor of mortality in hospitalized heart failure patients and is associated with a worse cardiovascular risk profile. *Rev Esp Cardiol*. 2006;59(02):99–108.
9. McCullough P.A., Shaw A.D., Haase M. Diagnosis of acute kidney injury using functional and injury biomarkers: workgroup statements from the tenth Acute Dialysis Quality Initiative Consensus Conference. Vols. 182. 2013. 13–29 p.
10. Bagshaw S.M., Cruz D.N., Aspromonte N. Epidemiology of cardio-renal syndromes: workgroup statements from the 7th Conference: Oxford University Press. 2010.
11. Ronco C., McCullough P.A., Anker S.D. Cardiorenal syndromes: an executive summary from the consensus conference of the Acute Dialysis Quality Initiative (ADQI). Cardiorenal Syndromes in Critical Care. Vols. 165. 2010. 54–67 p.

12. McCullough P.A. Cardiorenal syndromes: pathophysiology to prevention. *Int J Nephrol*. 2010;2011:762590.
13. Haase M., Mueller C., Damman K. Pathogenesis of cardiorenal syndrome type 1 in acute decompensated heart failure: workgroup statements from the eleventh consensus conference of the Acute Dialysis Quality Initiative (ADQI). on and Cardiorenal Syndromes. Vols. 182. 2013. 99–116 p.
14. Damman K., Testani J.M. The kidney in heart failure: an update. *Eur Heart J*. 36(23):1437–44.
15. Metra M., Cotter G., Gheorghiade M., Dei Cas L., Voors A.A. The role of the kidney in heart failure. *Eur Heart J*. 33(17):2135–42.
16. Metra M., Nodari S., Parrinello G., Bordonali T., Bugatti S., Danesi R., et al. Worsening renal function in patients hospitalised for acute heart failure: clinical implications and prognostic significance. *Eur J Heart Fail*. 10(2):188–95.
17. Bock J.S., Gottlieb S.S. Cardiorenal syndrome: new perspectives. *Circulation*. 121(23):2592–600.
18. Uthoff H., Breidthardt T., Klima T., Aschwanden M., Arenja N., Socrates T., et al. Central venous pressure and impaired renal function in patients with acute heart failure. *Eur J Heart Fail*. 13(4):432–9.
19. Ghori I., Ahmed I., Bukhari F., Tohid H. Cardiac output and renal function: an association. *Sci Ther 2*. 2016;7(252).
20. Di Lullo L., Bellasi A., Barbera V., Russo D., Russo L., Di Iorio B., et al. Pathophysiology of the cardio-renal syndromes types 1-5: An update. *Indian Heart J*. 69(2):255–65.
21. Schefold J.C., Filippatos G., Hasenfuss G., Anker S.D., von Haehling S. Heart failure and kidney dysfunction: epidemiology, mechanisms and management. *Nat Rev Nephrol*. 12(10):610–23.
22. Bellomo R., Ronco C., Kellum J.A., Mehta R.L., Palevsky P., Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care*. 8(4):R204-12.
23. Mehta R.L., Kellum J.A., Shah S. V, Molitoris B.A., Ronco C., Warnock D.G., et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11(2):R31.
24. KDIGO. KDIGO clinical practice guidelines for the prevention, diagnosis, evaluation, and treatment of hepatitis C in chronic kidney disease. *Kidney Int Suppl S1*. 2008(109).
25. Damman K., Jaarsma T., Voors A.A., Navis G., Hillege H.L., van Veldhuisen D.J., et al. Both in- and out-hospital worsening of renal function predict outcome in patients with heart failure: results from the Coordinating Study Evaluating Outcome of Advising and Counseling in Heart Failure (COACH). *Eur J Heart Fail*. 11(9):847–54.
26. Forman D.E., Butler J., Wang Y., Abraham W.T., O'Connor C.M., Gottlieb S.S., et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol*. 43(1):61–7.
27. Voors A.A., Davison B.A., Felker G.M., Ponikowski P., Unemori E., Cotter G., et al. Early drop in systolic blood pressure and worsening renal function in acute heart failure: renal results of Pre-RELAX-AHF. *Eur J Heart Fail*. 13(9):961–7.
28. Akhter M.W., Aronson D., Bitar F., Khan S., Singh H., Singh R.P., et al. Effect of elevated admission serum creatinine and its worsening on outcome in hospitalized patients with decompensated heart failure. *Am J Cardiol*. 94(7):957–60.
29. Chittineni H., Miyawaki N., Gulipelli S., Fishbane S. Risk for acute renal failure in patients hospitalized for decompensated congestive heart failure. *Am J Nephrol*. 2007;27(1):55–62.
30. Blair J.E.A., Pang P.S., Schrier R.W., Metra M., Traver B., Cook T., et al. Changes in renal function during hospitalization and soon after discharge in patients admitted for worsening heart failure in the placebo group of the EVEREST trial. *Eur Heart J*. 32(20):2563–72.
31. Metra M., Davison B., Bettari L., Sun H., Edwards C., Lazzarini V., et al. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. *Circ Heart Fail*. 5(1):54–62.
32. Ronco C., Cicoira M., McCullough P.A. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. *J Am Coll Cardiol*. 60(12):1031–42.
33. Alvelos M., Pimentel R., Pinho E., Gomes A., Lourenço P., Teles M.J., et al. Neutrophil gelatinase-associated lipocalin in the diagnosis of type 1 cardio-renal syndrome in the general ward. *Clin J Am Soc Nephrol*. 6(3):476–81.
34. Waikar S.S., Bonventre J. V. Biomarkers for the diagnosis of acute kidney injury. *Nephron Clin Pract*. 2008;109(4):c192-7.