Risk factors for the progression of chronic kidney disease after acute kidney injury

Fatores de risco para a progressão da doença renal crônica após a lesão renal aguda

Authors

Benedito Jorge Pereira [1,2,3]

Silvana Barreto [1]

Thais Gentil [2]

Larissa S. Assis [2]

Emília MD Soeiro [1]

Isac de Castro [4]

Sandra M. Laranja [2]

[1] Universidade Nove de Julho.
[2] Hospital do Servidor Público Estadual de São Paulo.
[3] HCFMUSP.
[4] Universidade de São Paulo.

Submitted on: 11/6/2016.
Approved on: 12/5/2016.

Correspondence to:
Benedito Jorge Pereira.
Instituto de Assistência ao Servidor Público Estadual (IAMSPE).
Av. Ibirapuera, nº 981, Vila Clementino, São Paulo, SP, Brazil.
CEP: 04038-034
E-mail: beneditopereira@iamspe.sp.gov.br

DOI: 10.5935/0101-2800.20170041

Abstract

Introduction: The incidence of chronic kidney disease (CKD) is increasing with the increasing age of the population and the increasing number of elderly survivors of acute kidney injury (AKI). The risk factors for the progression of CKD after AKI are unclear. **Objective:** To investigate the association between AKI and its progression to CKD and the risk factors involved. **Methods:** An observational, retrospective study of AKI patients followed from 2009 to 2012 was carried out. We evaluated the etiology of AKI, the use of vasoactive drugs and mechanical ventilation, the need for dialysis, the presence of comorbidities, the glomerular filtration rate (GFR), the length of stay and the progression of CKD. Statistical analyses, including the Chi-square test and Pearson's correlation, were performed using SPSS. **Results:** The 207 patients analyzed had a mean age of 70.1 ± 13.1, and 84.6% of the male patients exhibited decreased renal function and CKD (*vs.* 60.4% of the female patients). The progression of AKI to CKD was more frequent in patients admitted to wards (63.8%), cancer patients (74.19%), patients with sepsis (67.18%) and patients with obstruction (91.66%). Dialyses were performed in 16.4% of the patients, but this was not correlated with the progression of CKD. **Conclusions:** Being an elderly male patient with AKI due to sepsis and obstruction was correlated with progression to CKD following discharge.

Keywords: acute kidney injury; kidney diseases; kidney failure, chronic; renal dialysis; dialysis.

Resumo

Introdução: A incidência da doença renal crônica (DRC) está aumentando com o aumento da idade da população e o número crescente de idosos sobreviventes da lesão renal aguda (LRA). Os fatores de risco para a progressão da DRC após a lesão renal aguda (LRA) não são claros. **Objetivos:** Investigar a associação entre a LRA e sua progressão para a DRC e os fatores de risco envolvidos. **Métodos:** Foi realizado estudo observacional, retrospectivo de pacientes com LRA acompanhados de 2009 a 2012. Foram avaliados a etiologia da LRA, o uso de drogas vasoativas, ventilação mecânica, necessidade de diálise, presença de morbidades associadas, ritmo de filtração glomerular estimado (eGFR), duração da internação e a progressão da DRC. As análises estatísticas incluíram o teste Qui-quadrado e a correlação de Pearson utilizando o programa do SPSS. **Resultados:** Os 207 pacientes analisados apresentaram idade de 70,1 ± 13,1 anos, 84,6% eram do sexo masculino e que apresentaram redução da função renal e DRC (*vs.* 60,4% dos pacientes do sexo feminino). A progressão da LRA para DRC foi mais frequente em pacientes internados em enfermarias (63,8%), pacientes com câncer (74,19%), com sepse (67,18%) e com obstrução do trato urinário (91,66%). As dialises foram realizadas em 16,4% dos pacientes, mas isso não foi correlacionado com a progressão da DRC. **Conclusões:** Pacientes idosos com LRA devido à sepse e obstrução do trato urinário foram correlacionados com a progressão para DRC após a alta.

Palavras-chave: Lesão renal aguda; nefropatias; falência renal crônica; diálise renal; diálise.

Introduction

Acute kidney injury (AKI) is one of the most significant complications in critically ill patients, contributes to more than half of mortalities,[1-5] increases patients' length of stay (LOS) at the hospital and the risk of death and is associated with the need for renal replacement therapy (RRT).[1,2,6-11]

Individuals who survive one episode of AKI are at risk for the development chronic kidney disease (CKD) and can progress into more advanced stages of CKD.[2,3,6-9,12-15] A meta-analysis published by Coca *et al.*[14] showed that AKI is an independent risk factor for the development of end-stage renal disease (ESRD) morbidity and mortality by cardiovascular disease.

Relevant risk factors for the progression of AKI to CKD include the need for RRT, AKI severity, old age and diabetes.[16-22] However, the mechanism by which AKI leads to progressive CDK is not fully understood, pre-clinical studies point to possible mechanisms, such as acute endothelial injury, nephron loss and the degree of tubulointerstitial fibrosis is the best predictor of ESRD.[1,7,17,23]

Clinical studies conducted to obtain better information about the progression of AKI to CKD represent a significant contribution to the understanding the relationship between AKI and CKD.[7,21,22] In this paper, our objective was to investigate the association between AKI and CKD and the risk factors involved in CKD development.

Case series and methods

AKI patients followed by the Nephrology Division of the Hospital do Servidor Público Estadual (HSPE) of São Paulo, Brazil from 2009 to 2012 were retrospectively assessed. A total of 1,200 patients were evaluated based on the records referral forms; patients who died during the follow-up period and patients with stage 5 CKD were excluded. The following data were evaluated: etiology of AKI, use of vasoactive drugs, mechanical ventilation for more than 48 hours, need for RRT and the presence of comorbidities.

The glomerular filtration rates (GFRs) were estimated using the Chronic Kidney Disease-Epidemiology Collaboration Equation (CKD-EPI) in patients who had basal creatinine levels taken at admission, discharge and as outpatients; the need for dialysis, the duration of AKI and LOS were also recorded. The assessed outcomes were death and progression to CKD. In the patients with GFR < 60 ml/min, the CKD stage was classified according to the Kidney Disease | Improving Global Outcomes (KDIGO) criteria[24] and the progression to later stages of CKD was assessed following discharge from the hospital.

This study was approved by the Research Ethics Committee.

For the statistical analyses, the qualitative variables were summarized as absolute (n) and relative (%) frequencies and the quantitative variables as the means, standard deviations (SD), medians and minimum and maximum values. The associations between clinical outcomes (discharge or death) and the variables of interest were investigated using Pearson's Chi-square Test or the Likelihood Ratio. The significance level was set to 0.05 for all of the tests; the analyses were performed using SPSS version 15.0 for Windows (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA.)

Results

A total of 1,200 follow-up forms from 2009 to 2012 that were available at the Nephrology Division of the HSPE were assessed; 993 cases were excluded because they met the exclusion criteria. A total of 207 patients were included in the analysis. The average age was 70.1 ± 13.1 years, and 53.6% of the patients were male. The median duration of AKI was 10 days; the average LOS at the hospital was 21 days; the time until a follow-up by a nephrologist was 6 days; and the length of survival after discharge was 103 days. These data are described in Table 1.

The serum creatinine (SCr) level before follow-up by the Nephrology Division was 1.27 ± 0.41 mg/dl (GFR = 56.3 ± 4.7 ml/min). The SCr levels at admission (2.89 ± 2.68 mg/dl), at discharge (1.66 ± 0.85 mg/dl) and after discharge (1.84 ± 1.25 mg/dl) are presented in Table 2.

Table 1 Clinical characteristic of patients with AKI during hospitalization (n = 207)

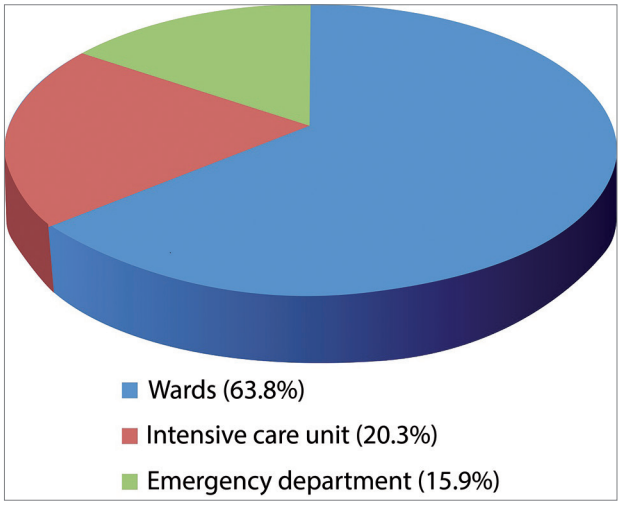
Age (years)	70.15 ± 13.15
Male (n = 111)	53.6%
AKI duration (days)	10 (1-219)
Length of stay (days)	21 (1-369)
Follow-up by nephrologist (days)	6 (1-93)
Survival after discharge (days)	103 (7-1416)

Table 2 Creatinine levels and eGFR during the follow-up of patients with AKI (n = 207)

	SCr (mg/dl)	CKD-EPI (ml/min)
Basal	1.27 ± 0.41	56.3 ± 4.7
Admission	2.89 ± 2.68	23.2 ± 5.3
Discharge	1.66 ± 0.85	44.2 ± 16.1
After discharge	1.84 ± 1.25	46.5 ± 10.1

Progression to CKD of AKI patients after discharge occurred, in order of decreasing frequency, in patients admitted to hospital wards (63.8%), patients admitted to the ICU (20.3%) and patients admitted to the emergency department (15.9%) (Figure 1).

Figure 1. Progression to CKD of AKI patients after discharge and the hospitalization setting of AKI patients.



During their hospital stay, 34 patients (16.4%) required dialysis. The mortality after discharge was 53%, 63% and 70.58% in patients who needed RRT, patients with mechanical ventilation and patients with septic shock, respectively. There was a significant correlation between mortality and more than one episode of AKI upon hospital admission (Table 3).

Table 3 Correlation between clinical complications of AKI patients during their hospital stay and mortality after discharge

Complications	N	%	*p*
Dialysis	18	(53.00)	0.92
Vasoactive drugs	25	(62.50)	0.14
Ventilation for more than 48 hours	19	(63.33)	0.18
Septic shock	24	(70.58)	0.19
More than one AKI episode upon adimission	2	(20.00)	0.037

The use of vasoactive drugs, the need for mechanical ventilation for more than 48 hours, septic shock and the need for dialysis had no correlation with the progression of CKD in these patients (Table 4).

Table 4 Correlation between clinical complications during hospital stay and progression to CKD based on the last estimated GFR

Complications	Total n = 2017 (%)	CKD-EPI (ml/min) n = 152 (%)	*p*
Vasoactive drugs	40 (19.00)	26 (65.00)	0.066
Ventilation for more than 48 hours	30 (14.50)	20 (66.67)	0.36
Septic shock	34 (16.42)	23 (67.64)	0.45
Need for dialysis	34 (16.42)	26 (76.47)	0.28

The progression of AKI to CKD was more frequent in 84.68% male patients, admitted to wards (63.8%), cancer patients (74.19%), patients with sepsis (67.18%) and patients with obstruction (91.66%) (Table 5).

Death occurred in 55.3% of the patients admitted to wards (p = 0.06) and 57.35% of patients whose AKI was caused by sepsis (p = 0.06). Vascular disease (70.58%), cancer (70.96%) and nephrolithiasis (8.33%) were factors that were significantly associated with this outcome (p = 0.01, p = 0.02 and p = 0.02, respectively) (Table 6).

Among the 142 patients whose AKI progressed to CKD, changes between CKD stages during the hospital stay were assessed at discharge based on the last recorded SCr. The results showed that CKD advanced by two stages and one stage in 11.3% and 19% of the patients, respectively. The disease status did not change, regressed by one stage and regressed by two stages in 23.2%, 10.6% and 4.9% of the patients, respectively (Figure 2).

Shifts in the CKD stage that occurred after discharge from the hospital, based on the last SCr recorded before death, showed that the disease advanced by two stages, advanced by one stage, did not change in status, regressed by one stage and regressed by two stages in 14.1%, 14.1%, 18.3%, 19.7% and 2.8% of the patients, respectively (Figure 3).

Discussion

There are few data on the long-term progression of CKD in hospitalized patients who survived an episode

Table 5 Correlation between clinical characteristics and progression to CKD of AKI patients, according to last recorded CKD-EPI

	All patients		CKD-EPI < 60 ml/min		*p*
	N = 207	%	N = 152	%	
Gender					
Female	96	(46.37)	58	(60.41)	
Male	111	(53.63)	94	(84.68)	0.01*
Comorbidities					
Hypertension	132	(64.10)	97	(73.48)	0.57
Diabetes	57	(27.70)	47	(82.45)	0.06
Vascular disease	34	(16.40)	22	(64.70)	0.17
Heart failure	37	(17.90)	28	(75.67)	0.20
Cancer	31	(15.00)	23	(74.19)	0.01*
Cirrhosis	15	(7.20)	13	(86.66)	0.06
Nephrolithiasis	12	(5.80)	10	(83.33)	0.28
Other causes	18	(8.70)	15	(83.33)	0.32
Hospital settings					
Wards	132	(63.80)	105	(79.54)	< 0.04*
ICU	41	(20.30)	25	(59.52)	
Emergency department	33	(15.90)	22	(66.55)	
Cause of acute kidney injury					
Nephrotoxicity	23	(11.10)	18	(78.26)	0.54
Pre-renal	88	(42.51)	66	(75.00)	0.49
Obstructive	24	(11.60)	22	(91.66)	0.3*
Sepsis	68	(32.85)	43	(67.18)	0.01*
Urinary tract infection	25	(12.10)	19	(76.00)	0.35
Acute interstitial nephritis	7	(3.50)	4	(57.14)	0.30
Ischemia	5	(2.40)	3	(60.00)	0.16
Other causes	23	(11.10)	18	(78.26)	0.40

*$p < 0.05$.

of AKI and did not undergo acute dialysis.[18] Several studies included patients admitted to the ICU, whereas other studies only included patients with severe AKI or individuals requiring RRT.[25]

The average age of the population analyzed in the present study was 70.15 ± 13.15 years, which is similar to ages reported by other authors.[18,25-28] In addition, elderly patients have a poorer quality of life and reduced their functional status following AKI, which are factors that contribute to adverse outcomes.[29,30] AKI was due to obstruction in 11.6% of patients in the present study and was associated with progression to CKD in 91.66% of patients.[31]

In our study, the median duration of AKI was 10 days, and it varied between 1 and 219 days. These findings agree with other reports in the literature, which also describe longer durations because the condition occurs in elderly patients with several comorbidities and clinical complications during the course of AKI.[32-35]

Among the AKI survivors, the median length of time to a follow-up by nephrologists was 6 days; this value might be considered low compared with the LOS (21 days), but it is in agreement with the average duration of AKI (10 days). These findings suggest that AKI did not occur early during hospitalization. The follow-up after discharge by nephrologists has a significant impact on the duration of AKI and on patient mortality.[25]

Evidence from epidemiological studies suggests that old age increases the odds that basal renal function will not recover after an episode of AKI at the time of discharge.[22] In our study, we found that the SCr was elevated before discharge compared with the SCr before admission, in accordance with several authors that have observed that aging reduces the capacity for kidney recovery after AKI.[30,36-38]

Table 6 Correlation between clinical characteristics and mortality in AKI patients (n = 207)

	All patients		Deaths		*p*
	N = 207	%	N = 108	%	
Gender					
Female	96	(46.37)	58	(47.20)	
Male	111	(53.63)	57	(52.80)	0.76
Comorbidities					
Hypertension	132	(64.10)	66	(50.00)	0.45
Diabetes	57	(27.70)	28	(49.12)	0.61
Vascular disease	34	(16.40)	24	(70.58)	0.01*
Heart failure	37	(17.90)	21	(56.75)	0.53
Cancer	31	(15.00)	22	(70.96)	0.02*
Cirrhosis	15	(7.20)	10	(66.67)	0.24
Nephrolithiasis	12	(5.80)	1	(8.33)	0.02*
Other causes	18	(8.70)	8	(50.00)	0.84
Hospital settings					
Wards	132	(63.80)	73	(55.30)	0.06
ICU	41	(20.30)	26	(63.41)	
Emergency department	33	(15.90)	9	(0.27)	
Cause of acute kidney injury					
Nephrotoxicity	23	(11.10)	10	(43.48)	0.65
Pre-renal	88	(42.51)	45	(51.00)	0.79
Obstructive	24	(11.60)	15	(62.50)	0.28
Sepsis	68	(32.85)	39	(57.35)	0.06
Urinary tract infection	25	(12.10)	11	(44.00)	0.38
Acute interstitial nephritis	7	(3.50)	3	(42.85)	0.61
Ischemia	5	(2.40)	3	(20.00)	0.14
Other causes	23	(11.10)	11	(47.80)	0.65

*$p < 0.05$.

Figure 2. Shifts between CKD stages of AKI patients at discharge (n = 142).

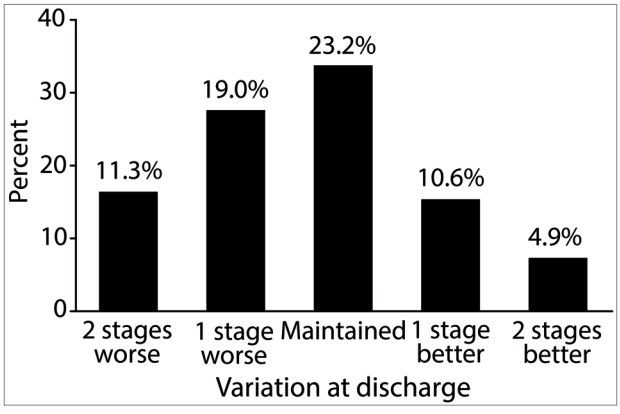
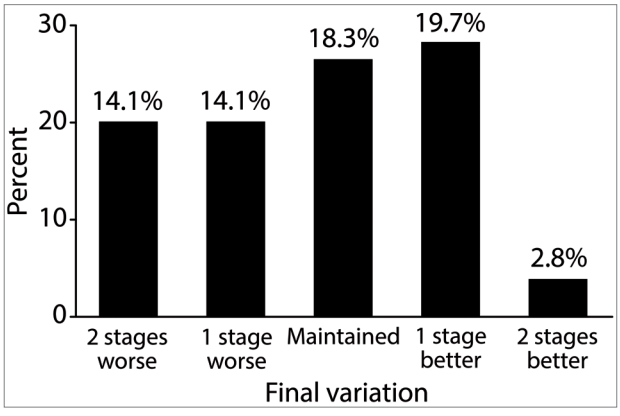


Figure 3. Shifts between CKD stages of AKI patients after discharge (n = 142).



Because our study assessed AKI survivors, the population admitted to hospital wards was the most representative and was significantly associated with CKD progression ($p < 0.04$); this population also tended to have a higher mortality after discharge ($p = 0.06$). Most of the patients analyzed were not severely ill, and few patients required admission to the ICU. The lack of illness severity could be why these patients were discharged and therefore developed CKD or exhibited worsening kidney function, as reported in other studies that followed up critical AKI patients.[39-41]

Post-renal AKI caused by obstruction of the urinary tract is generally observed in elderly patients.[27] In our study, obstructive AKI was significantly associated with CKD progression, in accordance with urinary tract obstruction being a significant cause of AKI. When the obstruction is complete, kidney injury occurs within 12 to 24 hours; however, the repercussions of the permanent damage and recovery of kidney function depend on the duration and degree of obstruction, the previous kidney function status and the presence of comorbidities or infection.[27,42] This data is also compatible as described in models of renal fibrosis after ureteral obstruction.[43,44]

Sepsis-induced AKI is a common occurrence in the ICU and in our study, the incidence of sepsis was 32.85% and was associated with 57.35% of mortality after discharge (p = 0.06) and with progression to CKD in 67.18% of the cases (p = 0.01).[45,46]

Despite the relatively large number of individuals monitored after discharge, our study had several limitations. This was a retrospective observational study conducted at a single center. In addition, it only included patients with available records of SCr who had survived an episode of AKI without considering its degree of severity.

Conclusions

The occurrence of AKI was associated with the development of CKD or progression to more advanced stages of renal disease among patients with GFR < 60 ml/min before AKI, patients with cancer, with sepsis-induced or obstructive AKI and patients who had been admitted to hospital wards. Patients with neoplasms or vascular disease exhibited the lowest survival rates after discharge. Prospective randomized clinical trials are needed to more thoroughly investigate the impacts of single or multiple interventions before and after AKI on the need for chronic dialysis and mortality.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

References

1. Lo LJ, Go AS, Chertow GM, McCulloch CE, Fan D, Ordoñez JD, et al. Dialysis-requiring acute renal failure increases the risk of progressive chronic kidney disease. Kidney Int 2009;76:893-9. PMID: 19641480 DOI: http://dx.doi.org/10.1038/ki.2009.289
2. Wald R, Quinn RR, Luo J, Li P, Scales DC, Mamdani MM, et al.; University of Toronto Acute Kidney Injury Research Group. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. JAMA 2009;302:1179-85. PMID: 19755696 DOI: http://dx.doi.org/10.1001/jama.2009.1322
3. Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. Kidney Int 2012;82:516-24. DOI: http://dx.doi.org/10.1038/ki.2012.208
4. Pannu N, James M, Hemmelgarn BR, Dong J, Tonelli M, Klarenbach S; Alberta Kidney Disease Network. Modification of outcomes after acute kidney injury by the presence of CKD. Am J Kidney Dis 2011;58:206-13. DOI: http://dx.doi.org/10.1053/j.ajkd.2011.01.028
5. Peters E, Heemskerk S, Masereeuw R, Pickkers P. Alkaline phosphatase: a possible treatment for sepsis-associated acute kidney injury in critically ill patients. Am J Kidney Dis 2014;63:1038-48. DOI: http://dx.doi.org/10.1053/j.ajkd.2013.11.027
6. Livingston MJ, Dong Z. Autophagy in acute kidney injury. Semin Nephrol 2014;34:17-26. DOI: http://dx.doi.org/10.1016/j.semnephrol.2013.11.004
7. Chawla LS, Amdur RL, Amodeo S, Kimmel PL, Palant CE. The severity of acute kidney injury predicts progression to chronic kidney disease. Kidney Int 2011;79:1361-9. DOI: http://dx.doi.org/10.1038/ki.2011.42
8. Lafrance JP, Miller DR. Acute kidney injury associates with increased long-term mortality. J Am Soc Nephrol 2010;21:345-52. DOI: http://dx.doi.org/10.1681/ASN.2009060636
9. Jones J, Holmen J, De Graauw J, Jovanovich A, Thornton S, Chonchol M. Association of complete recovery from acute kidney injury with incident CKD stage 3 and all-cause mortality. Am J Kidney Dis 2012;60:402-8. DOI: http://dx.doi.org/10.1053/j.ajkd.2012.03.014
10. Bucaloiu ID, Kirchner HL, Norfolk ER, Hartle JE 2nd, Perkins RM. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. Kidney Int 2012;81:477-85. DOI: http://dx.doi.org/10.1038/ki.2011.405
11. Vesconi S, Cruz DN, Fumagalli R, Kindgen-Milles D, Monti G, Marinho A, et al.; DOse REsponse Multicentre International collaborative Initiative (DO-RE-MI Study Group). Delivered dose of renal replacement therapy and mortality in critically ill patients with acute kidney injury. Crit Care 2009;13:R57.
12. Bonventre JV, Yang L. Cellular pathophysiology of ischemic acute kidney injury. J Clin Invest 2011;121:4210-21.
13. Abdel-Kader K, Palevsky PM. Acute kidney injury in the elderly. Clin Geriatr Med 2009;25:331-58.
14. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int 2012;81:442-8. DOI: http://dx.doi.org/10.1053/j.ajkd.2008.11.034
15. Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis 2009;53:961-73.
16. Palevsky PM. Chronic-on-acute kidney injury. Kidney Int 2012;81:430-1.
17. Garg AX, Parikh CR. Yin and yang: acute kidney injury and chronic kidney disease. J Am Soc Nephrol 2009;20:8-10.
18. Wald R, Quinn RR, Adhikari NK, Burns KE, Friedrich JO, Garg AX, et al.; University of Toronto Acute Kidney Injury Research Group. Risk of chronic dialysis and death following acute kidney injury. Am J Med 2012;125:585-93. PMID: 22516564
19. Ishani A, Nelson D, Clothier B, Schult T, Nugent S, Greer N, et al. The magnitude of acute serum creatinine increase after cardiac surgery and the risk of chronic kidney disease, progression of kidney disease, and death. Arch Intern Med 2011;171:226-33.
20. Lo L, Liu KD, Hsu C. Long-term outcomes after acute kidney injury: where we stand and how we can move forward. Am J Kidney Dis 2009;53:928-31.

21. Schrier RW. Early intervention in acute kidney injury. Nat Rev Nephrol 2010;6:56-9.
22. Coca SG, Cho KC, Hsu CY. Acute kidney injury in the elderly: predisposition to chronic kidney disease and vice versa. Nephron Clin Pract 2011;119:c19-24.
23. Sinha R, Nandi M, Tullus K, Marks SD, Taraphder A. Ten-year follow-up of children after acute renal failure from a developing country. Nephrol Dial Transplant 2009;24:829-33.
24. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Inter Suppl 2013;3:1-150.
25. Ali T, Khan I, Simpson W, Prescott G, Townend J, Smith W, et al. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. J Am Soc Nephrol 2007;18:1292-8.
26. Chao CT, Lin YF, Tsai HB, Wu VC, Ko WJ. Acute kidney injury network staging in geriatric postoperative acute kidney injury patients: shortcomings and improvements. J Am Coll Surg 2013;217:240-50.
27. AlZahrani A, Sinnert R, Gernsheimer J. Acute kidney injury, sodium disorders, and hypercalcemia in the aging kidney: diagnostic and therapeutic management strategies in emergency medicine. Clin Geriatr Med 2013;29:275-319.
28. Anderson S, Eldadah B, Halter JB, Hazzard WR, Himmelfarb J, Horne FM, et al. Acute kidney injury in older adults. J Am Soc Nephrol 2011;22:28-38.
29. Chao CT, Tsai HB, Lin YF, Ko WJ. Acute kidney injury in the elderly: Only the tip of the iceberg. J Clin Gerontol Geriatr 2014;5:7-12.
30. Schmitt R, Coca S, Kanbay M, Tinetti ME, Cantley LG, Parikh CR. Recovery of kidney function after acute kidney injury in the elderly: a systematic review and meta-analysis. Am J Kidney Dis 2008;52:262-71.
31. Coca SG, King JT Jr, Rosenthal RA, Perkal MF, Parikh CR. The duration of postoperative acute kidney injury is an additional parameter predicting long-term survival in diabetic veterans. Kidney Int 2010;78:926-33. DOI: http://dx.doi.org/10.1038/ki.2010.259
32. Brown JR, Kramer RS, Coca SG, Parikh CR. Duration of acute kidney injury impacts long-term survival after cardiac surgery. Ann Thorac Surg 2010;90:1142-8.
33. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 2005;16:3365-70.
34. Gong Y, Zhang F, Ding F, Gu Y. Elderly patients with acute kidney injury (AKI): clinical features and risk factors for mortality. Arch Gerontol Geriatr 2012;54:e47-51.
35. Lai CF, Wu VC, Huang TM, Yeh YC, Wang KC, Han YY, et al.; National Taiwan University Hospital Study Group on Acute Renal Failure (NSARF). Kidney function decline after a non-dialysis-requiring acute kidney injury is associated with higher long-term mortality in critically ill survivors. Crit Care 2012;16:R123.
36. Amdur RL, Chawla LS, Amodeo S, Kimmel PL, Palant CE. Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis. Kidney Int 2009;76:1089-97.
37. Lameire NH, Bagga A, Cruz D, De Maeseneer J, Endre Z, Kellum JA, et al. Acute kidney injury: an increasing global concern. Lancet 2013;382:170-9.
38. Boling B. Renal issues in older adults in critical care. Crit Care Nurs Clin North Am 2014;26:99-104.
39. Goldberg R, Dennen P. Long-term outcomes of acute kidney injury. Adv Chronic Kidney Dis 2008;15:297-307.
40. Thakar CV, Christianson A, Himmelfarb J, Leonard AC. Acute kidney injury episodes and chronic kidney disease risk in *diabetes mellitus*. Clin J Am Soc Nephrol 2011;6:2567-72.
41. Campbell GA, Hu D, Okusa MD. Acute kidney injury in the cancer patient. Adv Chronic Kidney Dis 2014;21:64-71.
42. Del Giudice A, Piemontese M, Valente G, Prencipe M, Di Giorgio C, Aucella F. Acute kidney injury in the elderly: epidemiology, risk factors and outcomes. J Nephrol Therapeut 2012;2:129.
43. Klahr S, Morrissey J. Obstructive nephropathy and renal fibrosis. Am J Physiol Renal Physiol 2002;283:F861-75.
44. Nakagawa S, Nishihara K, Miyata H, Shinke H, Tomita E, Kajiwara M, et al. Molecular Markers of Tubulointerstitial Fibrosis and Tubular Cell Damage in Patients with Chronic Kidney Disease. PLoS One 2015;28:e0136994.
45. Ostermann M, Chang RW. Impact of different types of organ failure on outcome in intensive care unit patients with acute kidney injury. J Crit Care 2011;26:635.e1-635.e10.
46. Ishani A, Xue JL, Himmelfarb J, Eggers PW, Kimmel PL, Molitoris BA, et al. Acute kidney injury increases risk of ESRD among elderly. J Am Soc Nephrol 2009;20:223-8.