Etiological factors, prognostic assessment, and outcomes of patients with acute kidney injury and multiple organ dysfunction syndrome

Z. Gao[1], D.W. Mu[2], L. Guo[3], X.M. Li[1] and L.D. Lun[1]

[1]Department of Nephrology, Air Force General Hospital, Beijing, China
[2]Department of Urology, Air Force General Hospital, Beijing, China
[3]Department of Ultrasound, Air Force General Hospital, Beijing, China

Corresponding author: L.D. Lun
E-mail: lideluncn@126.com

ABSTRACT. This clinical study assessed the etiological factors implicated in acute kidney injury (AKI). AKI has a complicated etiology with many serious complications. Understanding the interactions among these factors will help physicians treat patients with AKI. This retrospective study analyzed the etiological factors and assessed the incidence and outcome of 123 patients with AKI and multiple organ dysfunction syndrome. The general conditions, original disease, number of organ dysfunctions, type of organ dysfunction, complications, score, time, dose of renal replacement therapy, and outcomes were recorded. The etiologies of the manifested diseases were complicated. The number of injured organs was directly associated with prognosis. Cardiovascular dysfunction and cataphora were independently associated with a risk of mortality ($P < 0.05$; odds ratios: 12.44 and 2.16, respectively). Meanwhile, cardiovascular dysfunction and choloplania were independently associated with a risk of irreparable

renal function (P < 0.05; odds ratios: 23.64 and 11.59, respectively). In summary, the etiologies of the manifested diseases are complex. In addition, cardiovascular dysfunction is significantly associated with prognosis including survival and the recovery rate of renal function.

Key words: Acute kidney injury; MODS; Etiological factors; Prognostic assessment

INTRODUCTION

Acute kidney injury (AKI), which clinically manifests as rapid deterioration of renal function, is caused by many factors. Oliguria, edema, electrolyte disturbances, and acid/base disturbance can occur in serious cases. In China, the incidence of AKI exceeds 5% each year. AKI mainly occurs in people aged >60 years. Common causes of AKI include acute and chronic nephrosis, psychosocial factors, injury, blood loss, urinary tract stones, prostatic hypertrophy, and tumors. Iatrogenic renal injury is also being given increasing importance. During the diagnosis and treatment of kidney disease, the rate at which AKI develops as a result of contrast agent nephrosis is reportedly 8.5% (Okumura et al., 2012). The 2011 KDOQI Guide reports that the cause of the disease should be determined first followed by the classification of the risk degree and deciding the next therapeutic schedule on the basis of the established cause and risk degree (AKI guideline for AKI, 2011). The mortality rate of AKI can be decreased if the disease is diagnosed early and treated in a timely manner, and replacement therapy is administered at the right time (Sesso et al., 2004; Bagshaw et al., 2006; Basile, 2008; Bentley, 2011; Kim et al., 2013).

Multiple organ dysfunction syndrome (MODS) is defined as a group syndrome of ≥2 organ dysfunctions, with failure occurring simultaneously or in sequence after a serious injury such as serious disease, trauma, infection, and shock. MODS is a serious emergency that is difficult to clinically treat and has high mortality. Once MODS occurs, synchronization treatment targeting multiple organs often needs to be administered simultaneously. The kidneys are important organs for metabolism and discharging toxins. Thus, drug administration is directly limited by the damaged function of the kidneys, which affects the treatment effectiveness of MODS.

Moreover, multiple organ failure plays a role in MODS. The mortality of MODS complicated with AKI is high, ranging from 50 to 80% (Metnitz et al., 2002; Bagshaw et al., 2005; Huijuan et al., 2007; Friedericksen et al., 2009). AKI is also an independent risk factor inducing MODS (Tonelli et al., 2002). Thus, clinical thinking, analyzing the causes of the disease, and adopting intervention methods at an early stage are critical for AKI patients with MODS and high-risk factors, and can improve overall prognosis.

Accordingly, this study summarized the characteristics of 123 patients with AKI and MODS and analyzed the causes of disease, therapeutic effects, and relevant prognostic factors.

MATERIAL AND METHODS

General data

From December 2008 to September 2011, adult patients were given a definitive diagnosis of AKI with MODS at our hospital. The inclusion criteria were as follows: diagnosis of

AKI; AKI complicated with MODS; and kidney replacement therapy administered at bedside for >3 days (the AKI patient may have already presented MODS at the start of kidney replacement therapy, or MODS may have developed with the progression of AKI). Meanwhile, the exclusion criteria were as follows: chronic kidney insufficiency complicated with simultaneous organ dysfunctions and multiple organ dysfunctions but without AKI, thus not requiring kidney replacement therapy.

The diagnostic criteria for MODS were in accordance with the criteria of Marshall et al. (1995). The diagnostic criteria for AKI were based on the diagnostic criteria of the Acute Dialysis Quality Initiative (Molitoris et al., 2007) and were as follows: elevated serum creatinine level at 0.3 mg/dL (25 mM) within 48 h; a 50% increase compared with the previous level; and/or hypercrinia <0.5 mL·kg^{-1}·h^{-1} at >6 h with obstructive nephropathy and dehydrated state ruled out. Patient prognosis was classified as death or survival. Kidney turnover was classified as recovery of kidney function (i.e., survival does not depend on dialysis) and non-recovery of kidney function (i.e., survival depends on dialysis). The observation endpoint was 30 days after termination of kidney replacement therapy.

This study adhered to the Principles of the Declaration of Helsinki, and the hospital's Ethics Committee approved the study protocol.

Research method

The following data were recorded: general conditions, results of chemical examination (i.e., temperature, breathing, heart rate, mean arterial pressure, pO_2, serum HCO^{3-} level, serum potassium level, serum sodium level, serum creatinine level, packed cell volume, and total white blood cell count); diagnosis of primary disease; number, type, and degree of complications in injured organs; dose of kidney replacement therapy and time of maintenance therapy; acute physiology and chronic health status (APACHE) II score before and after treatment; and prognostic conditions.

Kidney replacement therapy

For kidney replacement therapy, the filter and main dialyser and pipelines were filled with heparin saline in advance. Patients without hemorrhagic tendency were administered common heparin for anticoagulation; the first dose was 0.3 to 0.5 mg/kg, and the superaddition was at 2-10 mg/h. Patients with hemorrhagic tendency were administered low molecular weight heparin; the first dose was 2000 to 4000 IU, and the superaddition was at 400 to 800 IU/h. Patients with severe hemorrhagic tendency and those who underwent surgery were not administered an anticoagulant but instead periodically received displacement liquid to rinse the filter. A polysulfone membrane was used for dilution and continuous veno-venous hemofiltration (CVVH). According to individual patient's conditions, the duration of bedside treatment was 8 to 12 h per day, and 16 to 24 L bicarbonate displacement liquid was infused. For patients with high catabolism, bedside treatment was administered continuously for 24 h. The displacement liquid was 400 to 2200 mL/h (20 to 32 L/day), and the dialysis dose was increased for patients with severely high catabolism.

Statistical analysis

SPSS version 13.0 was used for statistical analysis. The means of 2 samples were

compared using Student *t*-tests. Data are reported as means ± standard error. Logistic regression analysis was used to analyze the risk factors influencing kidney function recovery, and the Cox proportional hazards model was used to analyzed factors influencing survival. The level of significance was set at $P < 0.05$.

RESULTS

Causes of primary disease and general clinical data

The 123 patients included 77 men and 46 women. The mean age was 59.1 ± 17.9 years. The causes of the primary disease and clinical data are shown in Tables 1 and 2.

Table 1. Causes of primary disease in 123 patients with severe AKI combined with MODS.

Cause of primary disease	N
AKI after major operation	23
Renal parenchyma disease	13
AKI caused by tumor in advanced stage	11
AKI caused by MODS	31
AKI caused by infection and pyemia	18
AKI complicating severe pancreatitis	12
AKI caused by trauma and compression syndrome	6
AKI caused by drugs (including chemotherapeutics)	9

AKI = acute kidney injury; MODS = multiple organ dysfunction syndrome.

Table 2. Comparison of AKI patients by stage.

Group	N	Age (years ± SD)	Gender ratio (male/female)	Serious complications [N (%)]		
				Coma	Mechanical ventilation	Pressor agent usage
Stage I AKI	7	61.3 ± 20.3	3/4	2 (28.6%)	2 (28.6%)	3 (42.9%)
Stage II AKI	47	58.4 ± 19.4	27/20	15 (31.9%)	16 (34.0%)	16 (34.0%)
Stage III AKI	69	63.7 ± 24.4	36/33	24 (34.8%)	22 (31.9%)	23 (33.3%)

Treatment effectiveness and prognosis analysis

After 1 week of CVVH treatment among AKI patients of different stages, the APACHE II score decreased significantly in patients with stage I and II AKI. However, the score changes were not apparent in patients with stage III AKI (Table 3).

Table 3. Changes in APACHE II scores in severe cases after kidney replacement therapy.

Group	APACHE II score			
	Before treatment	1 day after treatment	3 days after treatment	7 days after treatment
Stage I/II AKI	27.8 ± 4.1	25.3 ± 3.9	22.2 ± 4.4	19.1 ± 4.5
Stage III AKI	26.7 ± 4.8	27.4 ± 5.7	25.7 ± 5.3	25.4 ± 5.8

Data are reported as means ± SD.

Among the 123 patients, 89 died (72.36%) and 34 survived (27.6%). Among patients with stage I and II AKI, 28 died (51.9%) and 15 recovered kidney function (27.7%). A total of

61 patients with stage III AKI died (88.4%), whereas 3 recovered kidney function (4.3%). The fatality rate of patients with stage III AKI was significantly higher than that of patients with stage I and II AKI. In contrast, the recovery rate of kidney function in patients with stage III AKI was significantly lower than that in patients with stage I and II AKI.

The number of organs failing because of complications increased with increasing AKI stage. However, the mortality of patients increased with an increasing number of injured organs. The mortality rate of patients with >4 injured organs was 100%. The recovery rate of kidney function decreased with an increasing number of injured organs. Kidney function did not recover in most patients with >4 injured organs (Table 4).

Table 4. Prognosis of 123 patients with severe AKI combined with MODS.

Number of injured organs	N	Deaths	Recovery of kidney function	Fatality rate (%)	Recovery rate of kidney function (%)
2	26	5	7	19.2	26.9
3	28	19	5	67.9	17.9
4	39	35	4	89.7	10.3
5	24	24	2	100.0	8.3
6	6	6	0	100.0	0.0

Risk factors affecting survival rate

The number of injured organs differed significantly between the patients who survived and those who died. This difference persisted regardless of cardiovascular system failure (in which a pressor agent must be used), the incidence of coma, respiratory failure (in which mechanical ventilation must be used), etc. The results of multivariate regression analysis show that the incidences of cardiovascular system failure and coma were independently associated with a risk of death (Table 5).

Table 5. Factors associated with survival.

	Regression coefficient	Standard error	Wald value	P	OR
Cardiovascular system failure	2.52	0.71	12.55	0.000	12.44
Coma	0.77	0.36	4.36	0.037	2.16

Factors affecting the recovery rate of kidney function

Cardiovascular system failure, oliguric renal failure, and jaundice were significantly associated with the non-recovery of kidney function. The Cox proportional hazards model showed that cardiovascular system failure and jaundice were independently associated with the recovery of kidney function (Table 6).

Table 6. Factors associated with recovery of kidney function.

	Regression coefficient	Standard error	Wald value	P	OR
Cardiovascular system failure	7.13	2.99	5.66	0.017	23.64
Jaundice	4.06	2.05	3.91	0.048	11.59

DISCUSSION

AKI is a critical condition encountered in internal medicine with a high mortality rate if combined with MODS (Kierdorf and Seeliger, 1997; Rodríguez et al., 1998). The mortality rate of MODS patients with 2 and ≥4 dysfunctional organs is 50 to 60% and nearly 100%, respectively (de Mendonça et al., 2000; Sirvent et al., 2010). Thus, the fatality rate of AKI increases and kidney function is more difficult to restore with an increasing number of dysfunctional organs. The fatality and recovery rates of kidney function in the present study are concordant with internal and published data (Vincent et al., 2004; Abosaif et al., 2005; Okusa, 2010).

In this study, patients were classified into stage I to III AKI (on the basis of kidney injury risk, kidney injury, and kidney failure stages) according to the new AKI criteria. The prognosis and treatment effectiveness of kidney replacement therapy in patients in different stages were analyzed. The fatality rate increased and the recovery rate of kidney function decreased with increasing AKI stage. In addition, the treatment effectiveness of continuous blood purification also differed to some extent with respect to AKI stage. The scores regarding the severity of cases during treatment showed that treatment was most obviously effective in patients with stage I and II AKI. Thus, early diagnosis and active continuous kidney replacement treatment have significant implications for patients with stage I and II AKI. Early diagnosis and treatment can improve the general state of the patient, survival, kidney recovery, and prognosis. The different AKI stages, which are based on diagnostic criteria, have direct implications on early diagnosis and prognostic judgment for AKI. Prompt kidney replacement therapy can effectively prevent and delay the progression of AKI.

Many studies have analyzed the prognostic factors for AKI patients with MODS; however, given the complicated etiology of AKI and its many associated complications, severe disease and serious complications are important prognostic factors (Uchino, 2006; Faubel, 2009). Uchino et al. (2005) speculate that unfavorable prognosis can be estimated on the basis of age, the use of mechanical ventilation, the use of pressor agents to maintain blood pressure, poor basic function, and other factors. Similar to the results of Uchino et al., all unfavorable prognostic factors in the present study are related to kidney hypoperfusion. Thus, heart dysfunction and low circulation pressure can cause kidney hypoperfusion and AKI. In addition, regression analysis indicated that circulatory failure is a common critical factor that results in death and kidney injury, which further corroborates the importance of blood flow perfusion in the maintenance of kidney function. In this study, the incidence of coma was also a risk factor for death in AKI patients, indicating that coma is closely associated with death. Thus, common conditions must be considered when clinically treating patients with severe AKI. Jaundice is another unfavorable prognostic factor for kidney function. Given that bilirubin clearance is related to kidney function, bilirubin level can be regarded as an evaluative index of kidney function. For example, when the bilirubin level increases to that indicative of jaundice, kidney function replacement therapy should be adopted eventually. For AKI patients with severe injury in other organs, cardiovascular system function should be maintained, and steady blood pressure and effective organ perfusion should be ensured. Most previous studies of AKI patients focused on indexes of kidney function and observing changes. In addition, analyses of etiology are concentrated in previous nephropathic studies. The present study analyzed AKI patients with MODS; we retrospectively analyzed the causes of the severe conditions of the patients and obtained objective results through regression analysis. The results indicate that circulatory disorders are important causes of death and non-recovery of kidney function in patients with severe AKI.

In summary, for AKI patients with MODS, the cause of the primary disease should be actively treated, the degree of pathogenicity should be evaluated accurately, and kidney replacement therapy should be administered in a timely manner. For effective kidney replacement therapy, cardiovascular system function should be maintained and enabling factors that cause continuous congestive heart failure and low blood pressure should be minimized. Furthermore, bilirubin should be cleared to prevent and treat other injured organs besides the kidneys.

REFERENCES

Abosaif NY, Tolba YA, Heap M, Russell J, et al. (2005). The outcome of acute renal failure in the intensive care unit according to RIFLE: model application, sensitivity, and predictability. *Am. J. Kidney Dis.* 46: 1038-1048.

AKI guideline for AKI (2011). UK Renal Association Final. Version 08.03.

Bagshaw SM, Mortis G, Godinez-Luna T, Doig CJ, et al. (2006). Renal recovery after severe acute renal failure. *Int. J. Artif. Organs* 29: 1023-1030.

Bagshaw SM, Laupland KB, Doig CJ, Mortis G, et al. (2005). Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. *Crit. Care* 9: R700-R709.

Basile C (2008). The long-term prognosis of acute kidney injury: acute renal failure as a cause of chronic kidney disease. *J. Nephrol.* 21: 657-662.

Bentley W (2011). Towards evidence-based emergency medicine: Best BETs from the Manchester Royal Infirmary. BET 3: RIFLE criteria versus Acute Kidney Injury Network (AKIN) criteria for prognosis of acute renal failure. *Emerg. Med. J.* 28: 900-901.

de Mendonça A, Vincent JL, Suter PM, Moreno R, et al. (2000). Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. *Intensive Care Med.* 26: 915-921.

Faubel S (2009). Acute kidney injury and multiple organ dysfunction syndrome. *Minerva Urol. Nefrol.* 61: 171-188.

Friedericksen DV, Van der Merwe L, Hattingh TL, Nel DG, et al. (2009). Acute renal failure in the medical ICU still predictive of high mortality. *S. Afr. Med. J.* 99: 873-875.

Huijuan M, Xiaoyun W, Xumin Y, Hengjin W, et al. (2007). Effect of continuous bioartificial kidney therapy on porcine multiple organ dysfunction syndrome with acute renal failure. *ASAIO J.* 53: 329-334.

Kierdorf HP and Seeliger S (1997). Acute renal failure in multiple-organ dysfunction syndrome. *Kidney Blood Press. Res.* 20: 164-166.

Kim JC, Cruz D, Garzotto F, Kaushik M, et al. (2013). Effects of dialysate flow configurations in continuous renal replacement therapy on solute removal: computational modeling. *Blood Purif.* 35: 106-111.

Marshall JC, Cook DJ, Christou NV, Bernard GR, et al. (1995). Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit. Care Med.* 23: 1638-1652.

Metnitz PG, Krenn CG, Steltzer H, Lang T, et al. (2002). Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. *Crit. Care Med.* 30: 2051-2058.

Molitoris BA, Levin A, Warnock DG, Joannidis M, et al. (2007). Improving outcomes of acute kidney injury: report of an initiative. *Nat. Clin. Pract. Nephrol.* 3: 439-442.

Okumura N, Hayashi M, Imai E, Ishii H, et al. (2012). Effects of carperitide on contrast-induced acute kidney injury with a minimum volume of contrast in chronic kidney disease patients. *Nephron Extra* 2: 303-310.

Okusa MD (2010). The changing pattern of acute kidney injury: from one to multiple organ failure. *Contrib. Nephrol.* 165: 153-158.

Rodríguez MI, Vallès M, Sirvent JM, Maté G, et al. (1998). Mortality and risk factors in patients with acute renal failure and multiple organ dysfunction. *Med. Clin.* 111: 247-250.

Sesso R, Roque A, Vicioso B and Stella S (2004). Prognosis of ARF in hospitalized elderly patients. *Am. J. Kidney Dis.* 44: 410-419.

Sirvent JM, Valles M, Navas E, Calabia J, et al. (2010). Outcome of critically ill patients with acute renal failure and multiple organ failure treated with continuous venovenous haemodiafiltration. *Med. Intensiva* 34: 95-101.

Tonelli M, Manns B and Feller-Kopman D (2002). Acute renal failure in the intensive care unit: a systematic review of the impact of dialytic modality on mortality and renal recovery. *Am. J. Kidney Dis.* 40: 875-885.

Uchino S (2006). The epidemiology of acute renal failure in the world. *Curr. Opin. Crit. Care* 12: 538-543.

Uchino S, Kellum JA, Bellomo R, Doig GS, et al. (2005). Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA* 294: 813-818.

Vincent JL, Bota DP and De Backer D (2004). Epidemiology and outcome in renal failure. *Int. J. Artif. Organs* 27: 1013-