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Acute kidney injury in neurocritical patients: a retrospective cohort study

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Abstract

Background /Objective Acute kidney injury (AKI) is a significant complication in critical care units (CCU). Non-neurological complications such as AKI are an independent predictor of poor clinical outcomes, with an increase in morbidity and mortality, financial costs, and worse functional recovery. This work aims to estimate the incidence of AKI and evaluate the risk factors and complications of AKI in neurocritical patients hospitalized in the CCU.

Methods A retrospective cohort study was conducted. Patients admitted to the neurocritical care unit between 2016 and 2018 with a stay longer than 48 h were retrospectively analyzed in regard to the incidence, risk factors, and outcomes of AKI.

Results The study population comprised 213 neurocritical patients. The incidence of AKI was 23.5%, with 58% KDIGO 1 and 2% requiring renal replacement therapy. AKI was an independent predictor of prolonged use of mechanical ventilation, cerebral edema, and mortality. Cerebral edema [OR 4.40 (95% CI 1.98–9.75) $p < 0.001$] and a change in chloride levels greater than 4 mmol/L at 48 h (OR 2.44 (95% CI 1.10–5.37) $p = 0.027$) were risk factors for developing AKI in the first 14 days of hospitalization.

Conclusion There is a high incidence of AKI in neurocritical patients; it is associated with worse clinical outcomes regardless of the CCU admission etiology or AKI severity.

Keywords Acute kidney injury · Critical care · Traumatic brain injury · Subarachnoid hemorrhage · Cerebral hemorrhage · Stroke

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Introduction

Acute kidney injury (AKI) has traditionally been defined as a rapid deterioration (in hours to weeks) in glomerular filtration rate which is usually reversible [1]. AKI is a complex clinical syndrome rather than a single disease and is an important complication in patients hospitalized in critical care units (CCU), where its prevalence exceeds 50% [2, 3].

Intensive care in neurocritical units has advanced substantially in recent decades, allowing for meeting the more complex needs of neurocritical patients, who require multidisciplinary management to achieve better clinical outcomes [4]. However, AKI has not been widely described in this scenario. Its importance lies in the fact that non-neurological complications are an independent predictor of poor clinical outcomes, with an increase in morbidity and mortality, financial costs, and worse functional recovery [2–5]. In this context, AKI stands out for its frequency, with an incidence

that ranges from 8 to 43% according to the definitions used and the type of neurocritical disease [4]. Survivors of neurological diseases with AKI are at greater risk of developing chronic kidney disease (CKD) and progression to the terminal stage [6, 7].

The pathophysiology of AKI in neurocritical patients is complex and multifactorial, involving preoperative, intraoperative, and postoperative factors such as: abnormalities in the brain–kidney connection with renal sympathetic hyperstimulation and an imbalance between parasympathetic–sympathetic pathways; activation of the renin–angiotensin–aldosterone system; abnormalities in the renal tubular epithelium with apoptosis secondary to the systemic inflammatory reaction in severe brain injury; hypernatremia and hyperchloremia; AKI induced by contrast media and the microembolization of endovascular procedures; ischemic AKI due to an intense reduction in systolic pressure; use of mannitol; and deregulation of brain–kidney blood flow [4].

The early recognition of patients at high risk of developing AKI allows for developing strategies targeted at a careful management of fluids, appropriate hemodynamic support, and adjustment of pharmacological treatment to eliminate or reduce nephrotoxicity. Nevertheless, there are few tools for predicting AKI in neurocritical patients.

This work aims to describe the epidemiological profile of these patients, estimate the incidence of AKI, identify the risk factors of patients with neurocritical diagnoses who develop AKI, and determine its clinical impact on mortality and length of hospital stay.

Methods

A retrospective cohort study was conducted on patients over 18 years of age who were admitted to the CCU of the Carlos Van Buren Hospital of Valparaíso, Chile, from October 29, 2016 to November 5, 2018 with admitting neurological diagnoses of subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), cerebral infarction, intracerebral hemorrhage, cerebral venous sinus thrombosis, and brain tumors with a requirement for postoperative monitoring in the CCU.

Patients were excluded if they had any stage of AKI at the time of admission to the CCU regardless of the cause, those with a diagnosis of CKD in chronic renal replacement therapy (RRT), admission with a diagnosis of brain death, stays of less than 48 h in the CCU, dead within 72 h of admission in the CCU, and/or those missing information on their medical record.

AKI was defined according to KDIGO guidelines as any of the following criteria occurring in the 14 days after admission: (1) increase in serum creatinine levels greater than or equal to 0.3 mg/dL in a 48-h period; (2) increase in serum creatinine levels greater than or equal to 1.5 times the baseline value in a period of 7 days; (3) diuresis less than or equal to 0.5 mL/kg/h in a period of 6 h. The severity of AKI was classified according to the 2012 KDIGO recommendations as stage 1, 2, or 3 [8]. The baseline serum creatinine value was the result obtained on tests prior to admission.

Patient information was gathered from the medical records of the CCU of the Carlos Van Buren Hospital. The variables analyzed included demographic characteristics (age, sex, comorbidities); medical history relevant to the hospitalization and procedures performed (Sequential Organ Failure Assessment (SOFA) score, Glasgow Coma Scale, vasograde (a grading system to predict the development of delayed cerebral ischemia in SAH, combining World Federation of Neurosurgical Societies and modified Fisher scales), hemoglobin, diagnostic and therapeutic angiography, decompressive craniectomy, implantation of an intracranial pressure monitoring devices and/or tissue oxygen tension monitoring devices, aneurysm clips); and relevant data up to 14 days postoperative (serum creatinine, sodium, chloride, and glucose values; diuresis; fluid balance; development of AKI; requirement for RRT; use of angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin-2 receptor blockers (ARBs), nonsteroidal anti-inflammatory drugs (NSAIDs), contrast media, blood products, or balanced or colloidal solutions; presence of vasospasm in patients with SAH; and cerebral edema diagnosed with computed tomography). The length of stay in the CCU and mortality during hospitalization and in the first 30 days post-discharge were also recorded.

The use of ACE inhibitors/ARBs, NSAIDs, antibiotics associated with direct tubular injury (vancomycin, aminoglycosides, and piperacillin–tazobactam), and the use of contrast media were considered to be nephrotoxic.

The data obtained were shown as means and standard deviation for quantitative variables. The Chi-square test was used to compare categorical variables and Student's *t* test for independent samples for continuous variables. Simple and multivariate logistic regression models were calculated for possible predictive variables of AKI. The variables included were age, sex, changes in chloride levels greater than 4 mmol/L, use of vasoactive drugs (VAD) at doses greater than 0.3 µg/kg/min, use of antibiotics associated with direct tubular injury or blood products, or cerebral edema. A value of $p < 0.05$ was defined as statistically significant. All analyses were conducted using the STATA 14 program.

This study was approved by the San Antonio Valparaíso Health Service Ethics Committee. Informed consent was not required given that the data were obtained from anonymized CCU medical records.

Results

A total of 303 patients were admitted with neurocritical diagnoses to the Carlos Van Buren Hospital of Valparaíso, Chile between October 2016 and November 2018. Ninety patients were excluded for meeting an exclusion criterion: 59 who had incomplete information on their medical records, 1 with CKD with a requirement for RRT, 2 with an admitting diagnosis of brain death, 25 with a hospital stay less than 48 h, and 3 who died within 72 h of admission. Therefore, a total of 213 patients were analyzed.

Patients' demographic and clinical characteristics are shown in Table 1. The mean age was 55.7 ± 17.3 years and 43.7% were women. The body mass index mean was 27.9 ± 5.0, and 29.6% had a history of active smoking. A total of 57.3% had hypertension, 17.4% had DM2, 2.3% had CKD with a GFR less than 60 mL/min/1.73 m^2, 7.5% had ischemic cerebrovascular disease, and 5.6% had coronary disease.

Upon admission to the CCU, the mean SOFA score was 5 ± 2.9 points. A total of 40.4% had an admitting diagnosis of SAH (32.6% VASOGRADE-Red), 38.9% of TBI (73.7% with a Glasgow Coma Scale score less than or equal to 8), and 11.7% of intracerebral hemorrhage. In regard to those who underwent surgical procedures, 34.7% had aneurysm clipping, 13.6% had a decompressive craniectomy, 36.6% had a hematoma evacuation, 7.6% had an external

Table 1 Demographic data and clinical characteristics of patients

	All patients	AKI	NO AKI	*p* value
(a) Sociodemographic				
Age, *x* ± SD	55.7 ± 17.3	59.8 ± 17.5	54.4 ± 17	0.054
Gender, *n* (%)				
Male	120 (56.3)	35 (29.2)	85 (70.8)	0.026*
Female	93 (43.7)	15 (16.1)	78 (83.9)	
(b) Clinical variables				
BMI, *x* ± SD	27.9 ± 5.0	28.6 ± 4.7	27.6 ± 5.1	0.230
Smoking, *n* (%)	63 (29.6)	10 (20.4)	53 (32.7)	0.219
Comorbidity *n* (%)				
Hypertension	122 (57.3)	33 (66)	89 (54.6)	0.154
Diabetes mellitus	37 (17.4)	12 (24)	25 (15.3)	0.157
CKD (GFR < 60)	5 (2.3)	4 (8)	1(0.6)	0.003*
HF	9 (4.2)	4 (8)	5 (3.1)	0.129
Peripheral vascular disease	1 (0.5)	0 (0)	1(0.6)	0.579
Cirrhosis	6 (2.8)	0 (0)	6 (3.7)	0.169
Cerebrovascular diseases	16 (7.5)	7 (14)	9 (5.5)	0.047*
CAD	12 (5.6)	3 (6)	9 (5.5)	0.898
SOFA, *x* ± SD	5 ± 2.9	6.3 ± 3.3	4.7 ± 2.7	0.001**
(c) Diagnosis				
Subarachnoid hemorrhage, *n* (%)	86 (40.4)	16(32)	70 (42.9)	0.168
Red vasograde, *n* (%)	28 (32.6)	6 (42.9)	22 (78.6)	0.408
Traumatic brain injury, *n* (%)	83 (38.9)	19 (38)	64 (39.3)	0.873
Severe, n(%)	62 (74.7)	18 (69.2)	44 (53)	0.145
Intracerebral hemorrhage, *n* (%)	25 (11.7)	8(16)	17(10.4)	0.284
Stroke, *n* (%)	16 (7.5)	6(12)	10 (6.1)	0.169
Others, *n* (%)	3 (1.4)	1 (2)	2 (1.2)	0.685
(d) Surgical procedures				
Aneurysm clipping, *n* (%)	74 (34.7)	12 (24)	62 (38)	0.068
Decompressive craniectomy, *n* (%)	29 (13.6)	9 (18)	20 (12.3)	0.301
Hematoma evacuation, *n* (%)	78 (36.6)	14 (28)	64 (39.3)	0.148
EVS, *n* (%)	29 (7.6)	13 (26)	16 (9.8)	0.004**
Therapeutic angiography, *n* (%)	27 (12.7)	6 (12)	21 (12.9)	0.870

AKI, acute kidney injury; BMI, body mass index; HF, heart failure; GFR, glomerular filtration rate; CKD, chronic kidney disease; CAD, coronary artery disease; EVS, external ventricular shunt

*$p \leq 0.05$; **$p \leq 0.01$

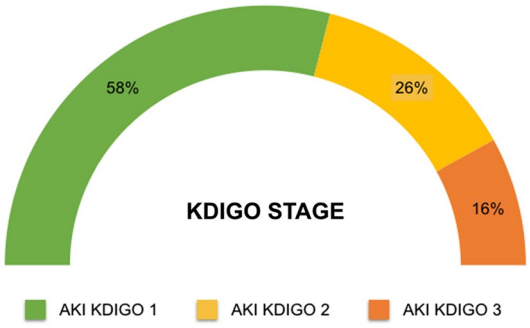

Fig. 1 Percentage of AKI KDIGO groups

ventricular shunt, and 12.7% had therapeutic angiography (including a thrombectomy and coiling).

The incidence of AKI in neurocritical patients was 23.5%. In regard to severity of AKI, 58% had AKI KDIGO 1, 26% had AKI KDIGO 2, and 16% had AKI KDIGO 3 (Fig. 1). Of all patients with AKI, 3.3% presented with oliguric AKI with creatinine elevation and the 96.7% of patients as non-oliguric AKI. Only 2% required RRT. A mortality rate of 14.5% was reported in the total group and 40% in the group that developed AKI ($p < 0.001$).

The development of AKI was associated with male sex, a medical history of CKD with a GFR less than 60 mL/min/1.73 m^2 ($p = 0.003$), and a history of cerebrovascular disease ($p = 0.047$). The SOFA score upon admission was higher among patients who developed AKI (6.3 ± 3.3 vs 4.7 ± 2.7, $p = 0.001$), and 73.3% of patients with SOFA score greater than or equal to 10 required VAD at high doses in contrast to 27.7% of patients with SOFA less than or equal to 10, who required high-dose VAD ($p < 0.001$). A medical history of type 2 diabetes mellitus was not more common among patients with AKI. Patients with AKI had more hyperchloremia and hypernatremia during the first 14 days of hospitalization (Fig. 2).

Regarding the surgical and endovascular procedures performed, no association was reported between AKI and aneurysm clipping, decompressive craniectomy, hematoma evacuation, or therapeutic angiography, though there was an association in patients who required implantation of external ventricular drainage systems (26% vs 9.8%, $p = 0.004$).

Patients who developed AKI had a greater duration of mechanical ventilation (12.6 ± 10.8 vs 8.7 ± 9.3 days, $p = 0.017$), a greater requirement of VAD at doses greater than 0.3 µg/kg/min, a greater presence of brain edema, and higher mortality. The development of AKI was not associated with a longer stay in the CCU (15.7 ± 10.3 days vs 12.7 ± 7.9 days, $p = 0.059$) (Table 2). The group of patients who required VAD at high doses was higher in patients who developed vasospasm (32.3% vs 13.2%, $p = 0.001$).

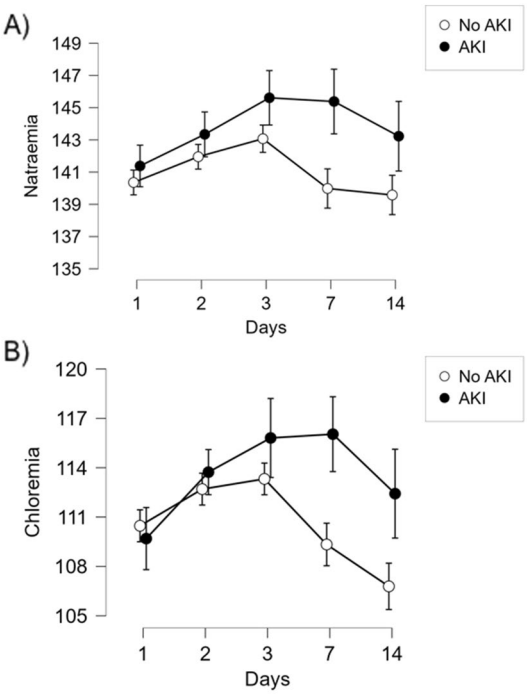

Fig. 2 Plasma natraemia and chloremia. Shown are the mean change in natraemia (**A**) and chloremia (**B**) in each group during the first 14 days from admission to critical care unit. During the first 14 days, all the values presented a significant difference between both groups

In regard to the use of nephrotoxins, 16.9% of patients received ACE inhibitors or ARBs during their CCU stay and 60.6% received NSAIDs as an analgesic following surgery and/or during their CCU stay. A total of 62.4% required having a study with contrast performed during the CCU stay and 26.3% required the administration of 10% hypertonic saline solution as management for elevated intracranial pressure. There were no significant differences between the groups except in the use of blood products.

Among the possible risk factors associated with the development of AKI, it was observed that older age, male gender, a change in chloride levels greater than 4 mmol/L at 48 h of admission (OR 2.44; CI 1.10–5.37), use of VAD at high doses (OR 2.41; CI 1.02–5.71), and presence of cerebral edema (OR 4.40; CI 1.98–9.75) may be linked to a greater incidence of AKI. The univariate and multivariate analyses are shown in Table 3.

Table 2 Clinical and laboratory characteristics of patients

	All patients	AKI	NO AKI	*p* value
Intensive care				
Days of length in ICU, $x \pm$ SD	13.4 ± 8.6	15.7 ± 10.3	12.7 ± 7.9	0.059
Mechanical ventilation requirement, *n* (%)	177 (83.1)	49 (98)	128 (78.5)	0.001**
Days of MV, $x \pm$ SD	9.6 ± 9.8	12.6 ± 10.8	8.7 ± 9.3	0.017*
High-dose vasoactive drugs, *n* (%)	62 (29.1)	23 (46)	39 (23.9)	0.003**
Brain edema, *n* (%)	65 (30.5)	29 (58)	36 (22.1)	< 0.001**
Mortality, *n* (%)	31 (14.5)	20 (40)	11 (6.7)	< 0.001*
Nephrotoxic agents				
Anti-infectives, *n* (%)	110 (51.6)	33 (66)	77 (47.2)	0.020*
Contrast agents, *n* (%)	133 (62.4)	30 (60)	103 (63.2)	0.684
Manitol, *n* (%)	17 (8.0)	3 (6)	14 (8.6)	0.555
Nephrotoxic medication, *n* (%)	135 (63.3)	33 (66)	102(62.6)	0.660
Blood product transfusions, *n* (%)	32 (15)	14 (28)	18 (11)	0.003**
10% HS, *n* (%)	56 (26.3)	15 (30)	41 (25.2)	0.496
Laboratory				
Chloremia mmol/L, $x \pm$ SD				
Delta chloride 48 h	2.9 ± 4.9	4.52 ± 5.3	2.3 ± 4.6	< 0.001**
Day 2	113.2 ± 5.8	115.1 ± 7.6	112 ± 5	0.029*
Day 3	113.6 ± 7.3	117.5 ± 9.4	112.4 ± 6	0.001**
Day 7	110.6 ± 7.9	116.2 ± 9	108.8 ± 6.6	< 0.001**
Natraemia mmol/L, $x \pm$ SD				
Day 2	142.6 ± 4.6	144.2 ± 5.6	142 ± 4.1	0.017*
Day 3	143.5 ± 5.7	146.4 ± 6.8	142.6 ± 5	0.001**
Day 7	141.4 ± 6.2	145.7 ± 6.7	139.9 ± 5.4	< 0.001**
Glycemia mg/dL, $x \pm$ SD				
Day 2	142.4 ± 55.5	156.8 ± 76.3	138.6 ± 48	0.090
Day 3	136.2 ± 55.5	140.9 ± 55.4	134.5 ± 55.8	0.593
Day 7	167.5 ± 53.7	169.9 ± 62.6	166.4 ± 49.8	0.802
Admission hemoglobin gm/dL, $x \pm$ SD	12.1 ± 1.9	12.1 ± 2.3	12 ± 1.8	0.839
Cumulative fluid balance, mL, $x \pm$ SD				
Day 2	1134.1 ± 2339.1	1927.8 ± 2406.6	899.5 ± 2273.7	0.008**
Day 3	1187.8 ± 2874	2354.6 ± 3032.3	836.2 ± 2738.5	0.001**
Day 7	1442.3 ± 4012.9	2744.3 ± 4128.2	1042.5 ± 3906.7	0.020*
> 10% fluid overload, *n* (%)	38 (17.8)	13 (26)	25 (15.3)	0.085

AKI, acute kidney injury; ICU, intensive care unit; MV, mechanical ventilation; 10%HS, hypertonic saline

*$p \leq 0.05$; **$p \leq 0.01$

Discussion

AKI is a frequent complication in neurocritical patients that involves various pathophysiological pathways depending on the neurological etiology at admission. It is associated with more complications during the hospital stay [4].

In this single-center retrospective study analyzing 213 unselected neurocritical patients, AKI occurred in 23.5% of patients, with most classified as AKI KDIGO 1. The incidence of AKI in this study was in line with other international reports, including in terms of the severity of AKI [9–11]. Nevertheless, as described in the literature, this complication was associated with mortality in diseases such as TBI [12], stroke [13], and subarachnoid hemorrhage regardless of the severity of AKI [14]. In regard to AKI with a requirement for RRT, a lower incidence of 2% was found, which is similar to what has been reported in other studies [10].

In our cohort, AKI was significantly associated with a greater need for and prolongation of mechanical ventilation and a tendency toward a longer CCU stay. AKI does not occur in isolation; it is a systemic disease and its main risk to mortality arises from extrarenal complications. These complications are usually related to dysfunction in other organs

Table 3 Univariate and multivariate analysis of risk factor significantly associated with AKI

Parameter	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% IC)	*p* value
Age	1.01 (0.99–1.03)	0.056	1.04 (1.01–1.07)	0.002*
Male gender	2.14 (1.08–4.22)	0.028*	2.55 (1.01–6.43)	0.046*
Hypertension	1.6 (0.83–3.13)	0.156		
Diabetes mellitus	1.7 (0.80–3.79)	0.161		
Chronic kidney diseases	14.1 (1.54–129.1)	0.019*		
Stroke	2.08 (0.71–6.05)	0.176		
Severe TBI	1.38 (0.47–4.13)	0.555		
Subarachnoid hemorraghe (red vasograde)	1.45 (0.46–4.59)	0.523		
Therapeutic angiography	0.92 (0.35–2.43)	0.870		
> 10% fluid ovearload	1.9 (0.90–4.16)	0.088		
Delta chloride > 4 (48 h)	2.48 (1.25–4.89)	0.009*	2.44 (1.10–5.37)	0.027*
Norepinephrine > 0.3 µg/kg/min	2.7 (1.40–5.25)	0.003*	2.41 (1.02–5.71)	0.044*
ACEi/ARA2	1.83 (0.84–3.99)	0.129		
Antibiotics	2.17 (1.12–4.20)	0.022*	1.84 (0.79–4.25)	0.151
NSAIDs	1.08 (0.56–2.08)	0.812		
Contrast media	0.87 (0.46–1.67)	0.684		
10% HS	1.28 (0.63–2.57)	0.496		
Manitol	0.68 (0.19–2.47)	0.557		
Vasospasm	0.78 (0.33–1.82)	0.566		
Blood product transfusions	3.13 (1.43–6.89)	0.005*	1.67 (0.61–4.53)	0.314
Brain edema	4.87 (2.49–9.55)	< 0.001*	4.40 (1.98–9.75)	< 0.001*

All *p* values reported are two sided, and all confidence intervals are 95% intervals. Statistical significance was defined as $p \leq 0.05$

Model: age, male gender, delta chloride > 4 (48 h), norepinephrine > 0.3 µg/kg/min, antibiotics, blood product transfusions, brain edema

TBI, traumatic brain injury; ACEi, angiotensin-converting enzyme inhibitors; ARA2, angiotensin-II receptor antagonists; 10% HS, hypertonic saline

*$p \leq 0.05$; ** $p \leq 0.01$

involving various inflammatory cascades activated in AKI that generate expression of cell adhesion molecules and cytokines–chemokines, leukocyte infiltrates, deregulation of apoptosis, and oxidative stress in various organs, translating into a complex crosstalk mechanism between the injured kidney and various organs such as the lung, liver, heart, and brain [15]. In this context, AKI has been associated with greater lung complications, translating into a higher rate of mechanical ventilation [10].

The brain–kidney connection is critical in this group of patients given the anatomical, functional, and biochemical changes that AKI can generate in the brain, which are mainly mediated by changes in concentrations of neurotransmitters, cytokines, acid–base homeostasis, and drug metabolism; these can generate direct and indirect injuries. Concomitantly, efferent impulses from the CNS can increase renal sympathetic activity causing renin secretion, an increase in tubular sodium absorption, and a decrease in renal blood flow [4]. High inflammatory cytokine levels in the brain and cellular inflammation in astrocytes and microglia together with anatomical and functional abnormalities derived from the diagnoses upon admission to the CCU increase the permeability of the blood–brain barrier and cause direct damage to the CNS [4, 16]. Our group found a correlation between the development of AKI and the presence of cerebral edema, which is relevant to explaining the relationship between AKI and the worse neurological outcomes at 3 months reported by the Fandler-Hofler group, who reported a KDIGO 1 prevalence of 89.4% [9, 17]. This further emphasizes how careful clinicians must be in regard to volume management and RRT to avoid exacerbating secondary lesions. Small amounts of fluid extravasated to the brain extravascular intestitium may have an impact on brain compliance in a patient when the BBB is disrupted and promote cerebral edema. Therefore, when serum tonocity is key, it is safer to use the isotonicity of normal saline than hypotonic solutions such as lactated ringer or 5% albumin and achieve euvolemia [18, 19].

Knowing the risk of AKI is relevant. One study demonstrated how interventions targeted at preventing AKI in patients undergoing cardiac and noncardiac surgery guided

by KDIGO recommendations were able to decrease the incidence of AKI through optimization of hemodynamic management, metabolic control, and discontinuation of nephrotoxic agents, among other measures, thus limiting tubular damage in these patients [20, 21].

In regard to the use of contrast media and the development of AKI, despite the frequent use in this cohort (62.4%) for both diagnostic and therapeutic techniques (CT scans and angiography), a greater incidence of AKI was not found among these patients. This is in line with several studies that have shown a very low incidence of contrast medium-induced AKI in various groups of patients, including those with SAH and stroke (4% and 3%, respectively), and even without demonstration of structural damage by not increasing biomarkers. Therefore, it has been concluded that studies with contrast media can be performed in this group without waiting for renal function test results [22–24].

In relation to the use of ACE inhibitors/ARB as "nephrotoxic" and the concern that their use leads to the precipitation of structural AKI (which is poorly documented), our group found no statistical differences. Although the use of ACE inhibitors/ARB generates efferent arteriolar vasodilation and may indeed cause a further fall in GFR during hypotension, this also maintains blood flow to the kidney tubules and together with its anti-inflammatory properties, theoretically they could protect them from hypoxemia and a structural AKI. However, this is still a controversial issue that must be evaluated in randomized, controlled trials [25].

Our study confirms that patients with presence of risk factors such as CKD and CVA-type risk factors such as stroke present with a greater incidence of AKI, results that are in agreement with other series [13].

It is necessary to consider exposure to nephrotoxins in our group (NSAIDs), use of antibiotics associated with direct tubular injury, and use of blood products. This, together with older age and high chloride and sodium values in the first days in the CCU, could be related to the higher rate of development of AKI in our study group, unlike in other series. Furthermore, the incidence found in this work could also be explained by the inclusion of KDIGO 1 patients in the analysis of results [10]. In relation to requirement for VAD at high doses as a risk of AKI, this result reflects a group of more severe patients documented with higher SOFA score, possibly with hemodynamic instability that could contribute to the development of acute tubular injury, and also a group of patients with high MAP goals to optimize PPC and/or DCI management (our patients with vasospasm required higher doses of VAD). A group reported an association between clinical vasospasm and AKI, explained among other elements, vasopressor management; however, this needs to be confirmed in prospective studies [26]. The use of mannitol has been shown to be nephrotoxic; however, our group did not find a relationship, possibly due to the low use of mannitol, prioritizing the use of hypertonic saline.

The logistic regression analysis showed that age, a change in chloride levels greater than 4 mmol/L in the first 48 h of hospitalization, a requirement for VAD at high doses, and the presence of cerebral edema were clinical factors that increased the risk of AKI on the multivariate analysis. Among these variables, the change in chloride levels is a factor that can be modified to attempt to decrease the incidence of AKI. Nevertheless, expert recommendations and our usual practice in neurocritical patients is to favor the use of crystalloids as preferred maintenance fluids when necessary, knowing this effect on chlorine, but avoiding generating secondary brain injury [19, 27]. A small group required the use of 10% hypertonic solution to manage ICP elevation. We believe that given the small number of cases, we have not been able to find differences between the risk of 10% hypertonic solution and the development of AKI. Nevertheless, the greater use of saline solution, demonstrated by higher positive fluid balances in the AKI group, suggests that this could be the explanation for the greater development of hyperchloremia and hypernatremia in this group. The foregoing, based on recommendations to avoid negative balances and restrictive fluid management in neurocritical patients, make it difficult to avoid these hydrosaline outcomes, which must be monitored as a safety objective [19]. Studies in critical patients have suggested that hyperchloremia can trigger or worsen AKI and increase the risk of RRT. Therefore, diagnosing and managing it is key to preventing renal complications [27, 28].

Regarding the diagnosis of AKI, despite obtaining a incidence of 23.5%, when determining the diagnosis according to KDIGO criteria, it is possible that this group of patients, in general, required a greater fluid load to avoid volume contraction and augmented renal clearance [29], leading to lower levels of AKI diagnoses when only determined by elevated creatinine levels. This was demonstrated in a study of patients with TBI, which found an increase in urinary levels of low-molecular-weight proteins and plasma NGAL, which are associated with apoptosis of tubular epithelial cells, though serum creatinine levels were normal. Therefore, the incidence of AKI may be even higher when incorporating biomarkers in the diagnosis in this group in particular, in which the main cause of admission was TBI.

The main limitation of this study is related to its retrospective design. However, the availability of a medical record database in the unit allowed for collecting data according to the procedure performed, which minimized potential biases. These data obtained are from a single center; in contrast, different local management protocols may lead to variations in the outcomes. We believe that not using biomarkers as an additional parameter for defining presence of AKI could have led to an underestimation of AKI incidence. Nevertheless, standardized

AKI diagnostic criteria indicated in the international KDIGO guidelines, including diuresis, were used.

Conclusion

This study confirms that AKI is a frequent complication in neurocritical patients and its presence is correlated with more prolonged use of mechanical ventilation in critical care, greater risk of cerebral edema, and greater mortality. Patients who were older, those who had a medical history of CKD with a GFR lower than 60 mL/min/1.73 m^2, those with a change in chloride levels greater than 4 mmol/L at 48 h of admission, and the use of VAD at high doses are factors associated with a greater incidence of AKI.

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Availability of data and materials All data generated or analyzed during this study are included in this published article.

Declarations

Conflict of interest GRG has received funding for lectures for Baxter. CR has received funding for lectures, been consultant or advisory board member for Asahi, Astute, B. Braun, Baxter, bioM´erieux, Bioporto, CytoSorbents, Estor, Fresenius Medical Care, General Electric (GE), Jafron, Medtronic, Toray. None of the other authors declare any competing interests.

Ethics approval and consent to participate Biochemical and clinical parameters were collected under the approval of the scientific ethics committee of the health service of Valparaiso—San Antonio.

Statement of ethics Waiver of informed consent was authorized by the local ethics committee due to the retrospective nature of the study and anonymization of the data.

References

1. Lameire N, Van Biesen W, Vanholder R (2005) Acute renal failure. Lancet 365(9457):417–430
2. Hoste EA, Bagshaw SM, Bellomo R et al (2015) Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 41:1411–1423
3. Ronco C, Bellomo R, Kellum JA (2019) Acute kidney injury. Lancet 394(10212):1949–1964
4. Ramírez-Guerrero G, Baghetti-Hernandez R, Ronco C (2022) Acute kidney injury at the neurocritical care unit. Neurocrit Care 36(2):640–649
5. Zygun D (2005) Non-neurological organ dysfunction in neurocritical care: impact on outcome and etiological considerations. Curr Opin Crit Care 11(2):139–143
6. Srivastava V, D'Silva C, Tang A et al (2012) The impact of major perioperative renal insult on long-term renal function and survival after cardiac surgery. Interact Cardiovasc Thorac Surg 15:14–17
7. Heung M, Steffick D, Zivin K, Gillespie B, Banerjee T, Hsu C et al (2016) Acute kidney injury recovery pattern and subsequent risk of chronic kidney disease: an analysis of veterans administration data. Am J Kidney Dis 67(5):742–752
8. Kellum JA, Lameire N, Aspelin P, Barsoum R, Burdmann EA, Goldstein SL et al (2012) Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int 2:1–138
9. Saeed F, Adil MM, Khursheed F, Daimee UA, Branch LA Jr, Vidal GA, Qureshi AI (2014) Acute renal failure is associated with higher death and disability in patients with acute ischemic stroke: analysis of nationwide inpatient sample. Stroke 45(5):1478–1480
10. Büttner S, Stadler A, Mayer C, Patyna S, Betz C, Senft C, Geiger H, Jung O, Finkelmeier F (2020) Incidence, risk factors, and outcome of acute kidney injury in neurocritical care. J Intensive Care Med 35(4):338–346
11. Robba C, Banzato E, Rebora P, Iaquaniello C, Huang CY, Wiegers EJA, Meyfroidt G, Citerio G, Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) ICU Participants and Investigators (2021) Acute kidney injury in traumatic brain injury patients: results from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury Study. Crit Care Med 49(1):112–126
12. Corral L, Javierre CF, Ventura JL, Marcos P, Herrero JI, Mañez R (2012) Impact of non-neurological complications in severe traumatic brain injury outcome. Crit Care 16(2):R44
13. Covic A, Schiller A, Mardare NG et al (2008) The impact of acute kidney injury on short-term survival in an Eastern European population with stroke. Nephrol Dial Transplant 23(7):2228–2234
14. Zacharia BE, Ducruet AF, Hickman ZL et al (2009) Renal dysfunction as an independent predictor of outcome after aneurysmal subarachnoid hemorrhage: a single-center cohort study. Stroke 40(7):2375–2381
15. Li X, Hassoun H, Santora R, Rabb H (2009) Organ crosstalk: the role of the kidney. Curr Opin Crit Care 15(6):481–487
16. Liu M, Liang Y, Chigurupati S et al (2008) Acute kidney injury leads to inflammation and functional changes in the brain. J Am Soc Nephrol 19(7):1360–1370
17. Fandler-Hofler S, Odler B, Kneihsl M, Wunsch G, Haudegger M, Poltrum B et al (2021) Acute and chronic kidney dysfunction and outcome after stroke thrombectomy. Transl Stroke Res 12(5):791–798
18. Chen CH, Toung TJ, Sapirstein A, Bhardwaj A (2006) Effect of duration of osmotherapy on blood-brain barrier disruption and regional cerebral edema after experimental stroke. J Cereb Blood Flow Metab 26(7):951–958
19. Oddo M, Poole D, Helbok R, Meyfroidt G, Stocchetti N, Bouzat P et al (2018) Fluid therapy in neurointensive care patients: ESICM consensus and clinical practice recommendations. Intensive Care Med 44(4):449–463
20. Göcze I, Jauch D, Götz M, Kennedy P, Jung B, Zeman F, Gnewuch C, Graf BM, Gnann W, Banas B, Bein T, Schlitt HJ, Bergler T (2018) Biomarker-guided intervention to prevent acute kidney injury after major surgery: the prospective randomized BigpAK study. Ann Surg 267(6):1013–1020
21. Meersch M, Schmidt C, Hoffmeier A, Van Aken H, Wempe C, Gerss J, Zarbock A (2017) Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. Intensive Care Med 43(11):1551–1561

22. Rouve E, Lakhal K, Gandonniere CS, Jouan Y, Bodet-Contentin L, Ehrmann S (2018) Lack of impact of iodinated contrast media on kidney cell-cycle arrest biomarkers in critically ill patients. BMC Nephrol 19(1):308
23. Ray B, Rickert KL, Welch BG et al (2013) Development of contrast-induced nephropathy in subarachnoid hemorrhage: a single center perspective. Neurocrit Care 19(2):150–156
24. Krol AL, Dzialowski I, Roy J et al (2007) Incidence of radiocontrast nephropathy in patients undergoing acute stroke computed tomography angiography. Stroke 38(8):2364–2366
25. Tomson C, Tomlinson L (2019) Stopping RAS inhibitors to minimize AKI: more harm than good? Clin J Am Nephrol 14(4):617–619
26. Tujjar O, Belloni I, Hougardy JM, Scolleta S, Vincent JL, Creteur J et al (2017) Acute kidney injury after subarachnoid hemorrhage. J Neurosurg Anesthesiol 29(2):140–149
27. Sadan O, Singbartl K, Kraft J, Plancher JM, Greven ACM, Kandiah P, Pimentel C, Hall CL, Papangelou A, Asbury WH, Hanfelt JJ, Samuels O (2020) Low-chloride- versus high-chloride-containing hypertonic solution for the treatment of subarachnoid hemorrhage-related complications: the ACETatE (A low ChloriE hyperTonic solution for brain Edema) randomized trial. J Intensive Care 4(8):32
28. Suetrong B, Pisitsak C, Boyd JH, Russell JA, Walley KR (2016) Hyperchloremia and moderate increase in serum chloride are associated with acute kidney injury in severe sepsis and septic shock patients. Crit Care 20(1):315
29. Cook AM, Hatton-Kolpek J (2019) Augmented renal clearance. Pharmacotherapy 39(3):346–354