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Under-recognized post-stroke acute kidney injury: risk factors and relevance for stroke outcome of a frequent comorbidity

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Abstract

Background Acute kidney injury (AKI) is emerging as a predictor of poor stroke outcome, however, it is often not recognized. The aim of our study was to evaluate post-stroke AKI burden, AKI risk factors and their influence in post-stroke outcome.

Methods From 2013 to 2016, 440 individuals with stroke diagnosis admitted in Stroke Unit, Foundation IRCCS Policlinico San Matteo (Pavia, Italy), were retrospectively enrolled. AKI cases identified by KDIGO criteria through the electronic database and hospital chart review were compared with the ones reported in discharge letters or in administrative hospital data base. Mortality data were provided by Agenzia Tutela della Salute of Pavia.

Results We included 430 patients in the analysis. Median follow-up was 19.2 months. We identified 79 AKI cases (18% of the enrolled patients, 92% classified as AKI stage 1), a fivefold higher number of cases than the ones reported at discharge. 37 patients had AKI at the admission in the hospital, while 42 developed AKI during the hospitalization. Cardioembolic ($p=0.01$) and hemorrhagic ($p=0.01$) stroke types were associated with higher AKI risk. Admission National Institutes of Health Stroke Scale (NIHSS, $p<0.05$) and Charlson Comorbidity Index ($p<0.01$) were independently associated with overall AKI, while admission NIHSS ($p<0.05$) and eGFR ($p<0.005$) were independently associated with AKI developed during the hospitalization. AKI was associated to longer in-hospital stay ($p=0.01$), worse Rankin Neurologic Disability Score at discharge ($p<0.0001$) and discharge disposition other than home ($p=0.03$). AKI was also independently associated to higher in-hospital mortality (OR 3.9 95% CI 1.2–12.9 $p=0.023$) but not with long-term survival.

Conclusions Post-stroke AKI diagnosis needs to be improved by strictly monitoring individuals with cardioembolic or hemorrhagic stroke, reduced kidney function, higher Charlson Comorbidity Index and worse NIHSS at presentation.

Keywords Acute renal failure · Cerebrovascular accident · Disability

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Background

Acute kidney injury (AKI) is characterized by high mortality and morbidity independent of the underlying cause [1]. AKI might be under-recognized [2], because it occurs often with mild reduction of kidney function. Acute stroke is one of the major causes of death in Western Countries [3] and despite the emerging role of AKI in post-stroke outcome, there are very limited number of studies exploring post-stoke AKI [4–8].

The aim of our retrospective study was to compare the number of post-stroke AKI cases defined by the most recent KDIQO criteria [9] and identified through health record analysis and hospital chart review with the ones reported in administrative health database at discharge. The secondary

aim was to identify post-stroke AKI risk factors and to evaluate AKI influence in post-discharge disposition, in-hospital and long-term mortality in individuals with stroke diagnosis admitted in our Stroke Unit.

Methods

Study population

We conducted a retrospective monocentric cohort study enrolling 440 cases with a CT-confirmed stroke diagnosis hospitalized between 1 January 2013 and 31 December 2016 in the Stroke Unit, Foundation IRCCS Policlinico San Matteo (Pavia, Italy).

Data collection and follow-up

Demographic details, comorbidities, laboratory data, outcome and discharge disposition were retrieved from the electronic hospital database. Charlson Comorbidity Index [10] was calculated for each individual by chart review. Rankin Neurologic Disability Score [11], a clinician-reported measure of global disability characterized by six grades of stroke severity and aimed to categorize the functional recovery of cerebrovascular disease at the time of discharge, was assessed in all patients by Stroke Unit protocol. Mortality data were provided by Agenzia Tutela della Salute (ATS), the local National Health Service office of Pavia. Median follow-up for mortality end point was 19.2 months.

Inclusion criteria, stroke and acute kidney injury definition

All patients included in the study were older than 18 years and had their stroke confirmed by a CT scan. Transient ischaemic attacks (TIA) were excluded. Stroke type (haemorrhagic or ischemic) was defined by neuroimaging (CT in all cases and MRI when required), while ischemic stroke subtypes were defined by TOAST criteria [12]. If contrast imaging was deemed necessary, an iso-osmolar radiocontrast media was used for the CT scan. Severity of neurologic impairment was evaluated by National Institutes of Health Stroke Scale (NIHSS) [13]. We considered for the analysis only the individuals for whom it was possible to identify or exclude acute kidney injury. Patient baseline creatinine was considered the first value recorded at admission (in Emergency Department or in the ward). AKI was defined and classified based on 2012 KDIGO criteria (increase in serum creatinine by 0.3 mg/dl within 48 h; or increase in serum creatinine to 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume less than 0.5 ml/kg/h for 6 h) [9]. Because the limited number of hourly urinary output data recorded, AKI diagnosis was mainly based on serum creatinine values. Estimated glomerular filtration rate (eGFR) was calculated by CKD-EPI creatinine-based equation [14].

Statistics

Descriptive statistics were produced for demographic characteristics of the patients in this study. The Shapiro–Wilk test was used to test the normal distribution of quantitative variables. When quantitative variables were normally distributed, the results were expressed as the mean value and standard deviation (SD), otherwise median and interquartile range (IQR; 25th–75th percentile) were reported. Qualitative variables were summarized as counts and percentages. Associations between the AKI development and continuous variables were performed through *t* test or non-parametric Mann–Whitney test, while Chi square test was used for qualitative variables.

Univariate and multivariate (including factors significantly associated with AKI development at univariate analysis) logistic regression models were fitted to identify risk factors for AKI and in-hospital mortality. Results are expressed as odds ratio (OR) and reported with 95% confidence interval (95% CI).

Overall survival (OS) was described through a Kaplan–Meier curve. Univariate and multivariate (including factors significantly associated with survival at univariate analysis) Cox models were fitted to study long-term mortality. Results are expressed as hazard ratio (HR) and reported with 95% CI.

$p < 0.05$ was considered statistically significant. All tests were two-sided. The data analysis was performed with the STATA statistical package (release 14.0, 2015, Stata Corporation, College Station, Texas, USA).

Results

Baseline demographic

We enrolled 440 patients with stroke diagnosis in the study. Creatinine data were insufficient (less than two measurements) in ten patients that were excluded. Mean age was 75 ± 12 years, 51% were males, 74% of them had hypertension history and 24% were affected by type 2 diabetes, 27% had atrial fibrillation history, while 22% had previous stroke and 13% had chronic kidney disease history ($n = 7$ CKD stage 2; $n = 35$ CKD stage 3; $n = 12$ CKD stage 4; $n = 3$ stage not specified). The median NIHSS score was 7 [IQR 3–16.5], while the median Charlson Comorbidity Index was 3 [IQR 1–4]. The eGFR at admission in the clinic was 71 ± 26 ml/min/1.73 m [2]; only 8% had hemorrhagic stroke,

while 92% subjects sustained an ischemic stroke; within the ischemic stroke cardioembolism was the most prominent subtype (32%). All the patients' baseline characteristics are summarized in Table 1.

AKI incidence

Laboratory data allowing AKI diagnosis or exclusion were available for 430 patients. AKI diagnosis was reported in discharge letters or identifiable by ICD-9 codes recorded in administrative data base in 14 (3%) subjects with stroke: 10 (72%) were classified as AKI stage 1, 2 patients (14%) as stage 2 and 2 subjects (14%) as stage 3. However, accurate revision of the clinical and laboratory data records allowed identification of 79 AKI cases (a fivefold higher number of the 14 cases above equal to 18% of total population enrolled). 37 patients on 79 cases had AKI at the admission into the hospital, while in 42 patients, AKI onset was during the hospitalization.

Among the 79 subjects identified with AKI, 73 subjects (92%) were classified as stage 1, four (5%) as stage 2 and 2 patients (3%) as stage 3, based on KDIGO AKI criteria. AKI recovered within 72 h in 48 out of 79 individuals (61%).

Table 1 Baseline characteristics, $n = 440$

Mean age (SD)	75 (12)
Gender (% male)	51
Active smoker (%)	15
History of	
Type 2 diabetes (%)	24
Hypertension (%)	74
Atrial fibrillation (%)	27
Obesity (%)	21
Chronic ischemic heart disease (%)	18
Chronic heart failure (%)	9
Stroke (%)	22
Chronic kidney disease (%)	13
Charlson CI, median [IQR]	3 [1–4]
SBP, mmHg; mean (SD)	151 (25)
DBP, mmHg; mean (SD)	81 (15)
TCHOL, mg/dl; mean (SD)	178 (47)
TGL, mg/dl; mean (SD)	115 (56)
WBC, $\times 10^3$/μl; mean (SD)	8.7 (3)
HTC, %; mean (SD)	40. (6)
TNI, ng/ml; median [IQR]	0.02 [0.01–0.06]
CRP, mg/dl; median [IQR]	1.9 [0.6–5.5]
eGFR (ml/min/1.73 m^2, mean (SD)	71 (26)
NIHSS, median [IQR]	7 [3–16]
Stroke cause, %	
Cardioembolism	31
Large artery atherosclerosis	13
Haemorrhagic	8
Small vessel disease	17
Arterial dissection and rare causes	2
Undetermined	29

IQR interquantile range, *DM* diabetes mellitus, *HTN* history of systemic hypertension, *CKD* history of chronic kidney disease, *AF* history of atrial fibrillation, *Charlson CI* Charlson Comorbidity Index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *TCHOL* total cholesterol, *TGL* triglycerides, *WBC* white blood cells count, *HTC* haematocrit, *TNI* troponin I, *CRP* c-reactive protein, *eGFR* estimated glomerular filtration rate, *NIHSS* NIH Stroke Scale/Score

AKI risk factors

Patients with AKI were significantly older and suffered more often from atrial fibrillation, systemic hypertension history and chronic kidney disease history; they had also a higher Charlson Comorbidity Index. Admission blood pressure, total cholesterol and haematocrit levels were lower, while baseline eGFR, urinary protein to creatinine ratio (UPCR), TNI and CRP were higher in patients with AKI was significantly lower in the overall population with AKI. AKI was associated with neurologic damage severity (measured as admission NIHSS). AKI was also associated with hemorrhagic stroke and cardioembolic stroke (Table 2) in comparison to small vessel disease stroke. Indeed, taking as a reference small vessel disease strokes, cardioembolic (OR 3.7, 95% CI 1.3–12.3; $p = 0.01$) and hemorrhagic strokes (OR 3.5, 95% CI 1.03–10.2; $p = 0.01$) were also independently associated with AKI, after adjusting for admission NIHSS. Antibiotics were more often administrated during the hospitalization in patients with AKI (58%, vs 44%, AKI vs non-AKI; $p = 0.04$) as well as diuretics (47% vs 26%, AKI vs non-AKI; $p = 0.01$). Patients with AKI at the admission in the hospital were older than the ones who developed AKI during the hospitalization (82 ± 1 years vs 77 ± 1 years, $p < 0.005$), while they had a similar type of stroke, history of diabetes, history of hypertension, history of obesity, history of atrial fibrillation, history of chronic kidney disease and admission blood pressure (data not shown). We thus built two multivariable models to evaluate AKI risk factors in patients with stroke. We compared patients without AKI with the overall population with AKI ($n = 79$, model #1, Table 3) or with patients who developed AKI during the hospitalization ($n = 42$, model #2, Table 4). In model #1, we tested age, baseline UPCR, baseline total cholesterol and baseline haematocrit, baseline NIHSS and Charlson Comorbidity Index. In model #2, we tested the same variables as model #1 and baseline eGFR. Baseline NIHSS (OR 1.05, 95% CI 1.00–1.09; $p = 0.027$) and Charlson Comorbidity Index (OR 1.23, 95% CI 1.06–1.42; $p = 0.006$) were independently associated with AKI in model #1, while baseline NIHSS (OR 1.05, 95% CI 1.00–1.10; $p = 0.043$) and baseline

Table 2 AKI risk factors

	AKI				
	Yes (79)	No (351)	OR	95% CI	*p* value
Mean age (SD), per years	79 (9)	74 (12)	1.05	1.02–107	< 0.001
Male gender, %	49	49	1.0	0.6–1.6	0.990
DM, %	25	22	1.01	0.6–1.9	0.795
HTN, %	71	85	2.2	1.2–4.6	0.15
CKD, %	30	9	4.5	2.4–8.2	< 0.001
AF, %	40	25	2.0	1.2–3.3	0.010
Obesity, %	23	21	1.1	0.6–2.0	0.716
Charlson CI, median [IQR], per one point	4 [3–5]	3 [1–4]	1.2	1.01–1.3	0.002
SBP, mmHg; mean (SD, per 10 mmHg	145 (25)	153 (24)	0.87	0.78–0.98	0.021
DBP, mmHg; mean (SD), per 10 mmHg	77 (18)	82 (14)	0.80	0.68–0.99	0.040
HR, bpm; mean (SD)	79 (20)	80 (19)	1.0	0.99–1.01	0.805
TCHOL, mg/dl; mean (SD), per 10 mg/dl	163 (41)	182 (47)	0.91	0.85–0.97	0.004
TGL, mg/dl; mean (SD), per 10 mg/dl	121 (48)	114 (57)	1.01	0.97–1.06	0.575
WBC, $\times 10^3$/µl; mean (SD)	8.7 (2.9)	8.7 (3.0)	1.03	0.95–1.11	0.461
HTC, %; mean (SD)	38 (6)	41 (6)	0.93	0.89–0.97	< 0.001
TNI, ng/ml; median [IQR]	0.03 [0.02–0.07]	0.02 [0.01–0.06]	0.96	0.83–1.11	0.602
CRP, mg/dl; median [IQR]	3.1 [1.3–7.9]	1.6 [0.5–5.0]			0.018
eGFR, ml/min/1.73 m^2; mean (SD)	45 (23)	77 (24)	0.94	0.93–0.96	< 0.001
UPCR, mg/g; %					
> 100 ≤ 150	24	45	Ref		
> 150 ≤ 300	28	25	2.0	0.9–4.3	0.079
> 300 ≤ 500	21	13	2.8	1.2–6.7	0.016
> 500	28	16	3.1	14–6.9	0.005
NIHSS, median [IQR] per one point	9 [4–20]	6 [3–15]	1.05	1.02–1.08	0.002
Stroke cause, %					
Small vessel disease	6.3	19.4	Ref		
Cardioembolism	44.3	29.3	4.6	1.7–12.4	0.002
Large artery atherosclerosis	13.9	12.8	3.3	1.1–10.2	0.036
Haemorrhagic	10.1	6.8	4.5	1.3–15.2	0.014
Arterial dissection and rare cause	1.3	1.7	2.3	0.2–22.7	0.486
Undetermined	24.0	29.9	2.5	0.9–6.9	0.087

Univariate logistic regression analysis

IQR interquantile range, *DM* diabetes mellitus, *HTN* history of systemic hypertension, *CKD* history of chronic kidney disease, *AF* history of atrial fibrillation, *Charlson CI* Charlson Comorbidity Index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *TCHOL* total cholesterol, *TGL* triglycerides, *WBC* white blood cells count, *HTC* haematocrit, *TNI* troponin I, *CRP* c-reactive protein, *eGFR* estimated glomerular filtration rate, *UPCR* urinary protein to creatinine ratio, *NIHSS* NIH Stroke Scale/Score

eGFR (OR 0.97, 95% CI 0.95–0.99; $p = 0.002$) were independently associated with AKI in model #2.

Hospitalization length, disability and post-stroke discharge disposition

Length of stay in hospital was longer in patient with AKI [12 days (IQ 8–15) vs 10 days [8–13], AKI vs non-AKI; $p = 0.01$]. Patients with AKI had worse Rankin Neurologic Disability Score at discharge [mean 4 (SD 1.9) vs 3 (SD 1.7), $p < 0.0001$], and were more frequently discharged to inpatient rehabilitation facility (58% vs 55%, AKI vs non-AKI) or long-term care facility (8% vs 5%, AKI vs non-AKI) rather than home (16% vs 30%, AKI vs non-AKI) ($p = 0.03$).

In-hospital and long-term mortality

Mortality data were available only for 403 individuals (94%). Of the 79 AKI patients, 10 subjects (13%) died in the hospital vs 5% non-AKI patients ($p < 0.001$). In univariate analysis of the hospital, mortality was associated with AKI (OR 3.1, 95% CI 1.3–7.4), NIHSS at admission (OR 1.2

Table 3 AKI risk factors

AKI	OR	95% CI	*p* value
Age	1.03	1.00–1.07	0.064
Charlson CI	1.22	1.06–1.42	0.006
NIHSS	1.05	1.00–1.09	0.027
UPCR, mg/dl			
> 100 ≤ 150	1.22	0.49–3.02	0.668
> 150 ≤ 300	1.45	0.54–3.88	0.455
> 300 ≤ 500	2.02	0.81–5.02	0.130
TCHOL	0.99	0.99–1.00	0.136
HTC	0.95	0.90–1.00	0.080

Multivariable model # 1

Charlson CI Charlson Comorbidity Index, *TCHOL* total cholesterol, *HTC* haematocrit, *UPCR* urinary protein to creatinine ratio, *NIHSS* NIH Stroke Scale/Score

Table 4 AKI risk factors

AKI	OR	95% CI	*p* value
Age	0.97	0.93–1.02	0.252
Charlson CI	1.12	0.92–1.37	0.235
NIHSS	1.05	1.00–1.10	0.043
UPCR, mg/dl			
> 100 ≤ 150	1.60	0.39–6.50	0.510
> 150 ≤ 300	2.78	0.66–11.68	0.160
> 300 ≤ 500	4.04	0.95–15.65	0.053
TCHOL	0.99	0.99–1.00	0.681
HTC	0.95	0.89–1.02	0.192
eGFR	0.97	0.95–0.98	0.002

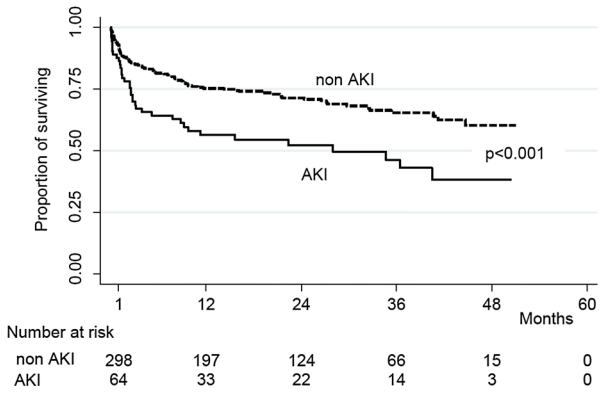
Multivariable model # 2

Charlson CI Charlson Comorbidity Index, *TCHOL* total cholesterol, *HTC* haematocrit, *eGFR* estimated glomerular filtration rate, *UPCR* urinary protein to creatinine ratio, *NIHSS* NIH Stroke Scale/Score

95% CI 1.1–1.3, $p < 0.001$), age (OR 1.5, 95% CI 1.1–2.4 for 10-year increase $p = 0.047$), eGFR at admission (HR 0.99, 95% IC 0.98–0.99, $p < 0.001$). In a multivariate model, in-hospital mortality was associated only with AKI (OR 3.9, 95% CI 1.2–12.9, $p = 0.023$), NIHSS at admission (OR 1.2, 95% CI 1.1–1.3, $p < 0.001$) but not with age and eGFR at admission.

On the contrary, in univariate analysis, long-term mortality was associated with AKI (HR 2.0, 95% CI 1.3–2.9, $p < 0.001$) as shown by the Kaplan–Meier curve (Fig. 1), age (HR 1.07, 95% CI, 1.05–1.09, $p < 0.001$), Charlson Comorbidity Index (HR 1.14, 95% CI 1.05–1.22, $p < 0.001$), male gender (HR 1.9, 95% CI 1.3–2.9, $p = 0.002$) and NIHSS (HR 1.11, 95% CI 1.09–1.14, $p < 0.001$).

In a multivariate model, long-term mortality was associated with age (HR 1.1, 95% CI 1.02–1.11, $p = 0.001$), NIHSS



AKI, acute kidney injury

Fig. 1 Kaplan–Meier curve of long-term survival in patients with or without AKI in univariate analysis

(HR 1.12, 95% CI 1.07–1.16, $p < 0.001$) and male gender (HR 2.03, 95% CI 1.08–3.83, $p = 0.027$) but not with AKI (HR 1.3, 95% CI 0.8–2.1, $p = 0.23$).

Discussion

Our study shows that AKI burden after stroke is significantly underestimated in "real clinical life". The differences between AKI cases reported in discharge records and the ones identified after the careful review of the clinical data available could be mainly explained by the mild renal impairment characterizing the unrecognized cases of AKI and by the prompt recovery of kidney function in most of the cases. Nevertheless, we do not have enough data allowing us to determine accurately the cause of AKI being under-reported.

AKI cases were identified by serum creatinine variation, unfortunately serum cystatin-c was not dosed and urinary volume was available only for few patients. The mean age of the subjects enrolled was 75 years (SD 12 years). The most appropriate method to estimate kidney function in elderly people is still a matter of debate, however, the CKD-EPI creatinine-based equation employed in our study provides satisfactory results in this population as reported in literature [15]. Despite these limits, the overall post-stroke AKI incidence that we observed is comparable to the one described by the only two retrospective studies available, evaluating AKI in both ischemic and hemorrhagic strokes [6, 7]. On the contrary, a higher AKI incidence was found by Tsagalis et al. [4] in their prospective cohort likely because of the different study designs.

Several works have shown that most severe neurologic impairment quantified by NIHSS is associated with increased infection rate (mainly chest and urinary) and

need for intravenous fluid administration because of poor oral intake [16–18]. Infections, dehydration and fluid overload are well-known causes of acute kidney injury [1]. In our study, we have observed that NIHSS score is independently associated with post-stroke AKI. While we were not able to determine acute injury causes due to the retrospective design, we observed that antibiotics and diuretics were administered in hospital more often in subjects that experienced post-stroke AKI.

We found that patients who developed AKI during the hospitalization had lower admission eGFR compared to the individuals who did not. Furthermore, the overall population with AKI was older. On one hand, decrease in the glomerular filtration rate could be considered part of the aging physiological processes [20], and on the other, reduced kidney function is an established AKI risk factor [19] and it has been demonstrated that elderly individuals are at a higher risk of AKI, because renal functional reserve is impaired with aging [21].

Several evidences show that AKI is associated with chronic kidney disease progression [22, 23]. Unfortunately, because of the retrospective design of our study, we were not able to evaluate kidney function after hospital discharge. Therefore, it appears relevant to assess the influence of AKI on CKD progression in elderly individuals with stroke in future prospective studies.

We report a higher prevalence of impaired eGFR at the admission compared to the low number of known CKD history (70% of individuals with admission eGFR < 90 ml/min/1.73 m^2 vs < 15% with CKD history). This observation could be partly explained by the influence of age on GFR estimate calculation employing CKD-EPI creatinine-based equation. Patients without known history of CKD having admission eGFR < 90 ml/min/1.73 m^2 (66 ± 16 ml/min/1.73 m^2) and no AKI at the admission ($n = 229$), because the old age (77 ± 10 years) they showed a mild elevation of admission creatinine values (1.02 ± 0.27 mg/dl). These minor serum creatinine alterations might have been considered not significant before the hospitalization.

However, we cannot rule out that the lack of kidney function screening, that occurs also in high-risk populations such as subjects with systemic hypertension and type 2 diabetes as described by previous studies [24], might have contributed to this discrepancy. Of note, hypertension and type 2 diabetes are also major stroke risk factors [25].

Proteinuria is considered a predictor of decline in kidney function and stroke risk factor [26, 27]. However, our results show that reduced kidney function rather than proteinuria is associated with AKI risk after stroke, because a higher concentration of proteinuria is associated with AKI in univariate analysis, but not when baseline kidney function was introduced in the multivariate model.

AKI cases were 25% in individuals with hemorrhagic stroke and 19% in individuals with ischemic stroke ($p = $ n.s.) similar to Khatri et al.'s report [6]. Among stroke subtypes, hemorrhagic and cardioembolic stroke were associated with higher AKI risk independently of the neurologic impairment. We also observed that CRP was higher in AKI individuals. Systemic release of proinflammatory cytokines and peripheral immune system activation often occur after brain injury [28–31] and may contribute to poor outcome especially after hemorrhagic stroke [32–35]. Because inflammation plays a pivotal role in AKI [36–38], future studies are needed to evaluate if increased systemic inflammatory response could enhance post-stroke AKI risk. Atrial fibrillation history, which is the main cause of cardioembolic stroke, was associated with post-stroke AKI in our population. Interestingly, it has been shown that atrial fibrillation-associated haemodynamic alterations might impair endothelial function and enhance profibrotic/inflammatory kidney gene expression. Furthermore, the use of anticoagulant drugs employed in individuals with atrial fibrillation has been found to be related to AKI [39–43].

According to the literature, we found that a lower concentration of haematocrit was associated with increased post-stroke AKI risk [4, 44–46]. Anemia can be caused by erythropoietin deficiency in chronic kidney disease, however, we found no correlation between haematocrit levels and kidney function. Unfortunately in our study, we were not able, due to insufficient laboratory data, to correlate the admission haematocrit levels with common causes of anemia such as iron or vitamin B12/folate deficiencies. Lower haematocrit levels in AKI individuals might be in part associated to the greater number of comorbidities in vascular neurologic patients. Given the correlation between higher CRP and worse Charlson Comorbidity Index with AKI risk, we can speculate that chronic inflammatory status characterizing polypathological individuals could have contributed to the lower levels of haematocrit.

The greater use of lipid-lowering drugs by polypathological and polymedicated individuals might explain the association found between lower cholesterol levels and AKI in our study.

Of note, Charlson Comorbidity Index was independently associated with AKI in the multivariable model including the overall AKI population, however, it failed to predict AKI risk when admission eGFR was tested in the model including patients who developed AKI during hospitalization.

Iodine contrast media administration can cause contrast-induced nephropathy (CIN) especially in high-risk AKI patients (i.e., individuals with reduced kidney function or affected by type II diabetes) [47]. However, we observed a significantly lower incidence of AKI in individuals undergoing iso-osmolar contrast media CT scan (11.4% vs 28.3%, AKI vs non-AKI $p = 0.001$). Such apparent discrepancy

might be explained by the selection of patients undergoing contrast media CT scan among subjects with lower risk for CIN, namely the ones with greater admission kidney function.

AKI was independently associated with increased in-hospital mortality as previously shown by others [6, 7]. AKI was also associated with worse long-term survival in the univariate analysis but not when the analysis was adjusted for other relevant variables such as age, Charlson Comorbidity Index, NIHSS and gender, probably because our follow-up was relatively short compared to other studies [4].

We recognize that the observational and retrospective design represents one of the limits of our study. Furthermore, serum creatinine was not dosed daily and only patients with at least two creatinine measurements were included in the analysis, therefore a selection bias might have occurred.

Finally we report for the first time that AKI negatively influences short-term post-stroke outcome, being associated with worse Rankin Neurologic Disability Score at discharge and increased need for admission in specialized facilities after discharge [48]. Approximatively 50% of discharged patients were admitted in rehabilitation facilities. Because we show that AKI was associated with prolonged hospitalization, as reported by others previously [49], and AKI is emerging as a risk factor for long-term risk of increased frailty [50], it would be important to assess AKI impact on rehabilitation process of stroke patients in future studies.

Conclusions

Prompt recognition of AKI high-risk patients is mandatory for AKI prevention and treatment strategies in patients with stroke. Based on our findings, we suggest that kidney function should be strictly monitored in individuals with new onset of stroke, admitted in hospital. Subjects presenting reduced kidney function at admission, higher stroke severity, several comorbidities, cardioembolic or hemorrhagic stroke are at a higher risk to develop post-stroke AKI.

Our study also shows that physicians need to be further encouraged to improve AKI diagnosis and record in the health care database. Correct identification and report of AKI cases appear to be pivotal for long-term health care system strategies planning [51] given the influence of AKI on short-term stroke outcome and post-discharge disposition.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This retrospective study was approved by our Institutional Ethic Committee (protocol number 5344/2016) and all the procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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