Research Article

Community-Acquired Acute Kidney Injury as a Risk Factor of de novo Heart Failure Hospitalization

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Keywords

Community-acquired acute kidney injury · Heart failure · Hospitalization · Risk factor · Cardiorenal syndrome

Abstract

Objectives: Because patients with hospital-acquired acute kidney injury (AKI) are at risk for subsequent development of heart failure (HF) and little is known about the relation between community-acquired AKI (CA-AKI) and HF, we sought to determine if CA-AKI is a risk factor for incident HF hospitalization. **Methods:** We utilized Baylor Scott & White Health databases at the primary care and inpatient hospitalization levels to identify adults without a prior history of HF who had 2 or more serum creatinine measurements within 13 months in the primary care setting. We defined CA-AKI as a serum creatinine increase ≥ 0.3 mg/dL or ≥ 1.5 times the baseline for consecutive values within a 13-month period. We created a flag for de novo HF hospitalization at 90, 180, and 365 days following CA-AKI evaluation. **Results:** In the analyses, 210,895 unique adults were included, of whom 5,358 (2.5%) had CA-AKI. Those with CA-AKI had higher rates of comorbidities, higher rate of males (48 vs. 42%, $p < 0.001$), and were older (61.5 [50.3, 73.1] vs. 54.1 [42.8, 64.7] years, $p < 0.001$) than those who did not have CA-AKI. In total, 607 (0.3%), 833 (0.4%), and 1,089 (0.5%) individuals had an incident HF hospitalization in the 90, 180, and 365 days following the CA-AKI evaluation, respectively. After adjusting for demographic and clinical characteristics, patients with CA-AKI had >2 times the risk of de novo HF hospitalization compared with patients who did not have CA-AKI (90 days: 2.35 [1.83–3.02], $p < 0.001$; 180 days: 2.52 [2.04–3.13], $p < 0.001$; 365 days: 2.16 [1.77–2.64],

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$p < 0.001$). These multivariable models yielded strong predictive abilities, with the areas under the receiver-operating characteristic curve >0.90 . **Conclusion:** After controlling for baseline and clinical characteristics, patients with CA-AKI were at approximately twofold the risk of de novo HF hospitalization (within 90, 180, and 365 days) compared with those who did not have CA-AKI. Hence, detecting CA-AKI may provide an opportunity for early intervention at the primary care level to possibly delay HF development.

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Introduction

While there has been considerable attention to hospital-acquired (HA) acute kidney injury (AKI), far fewer studies exist regarding community-acquired AKI (CA-AKI), i.e., AKI occurring outside of the hospital. Further, the generalizability of what is known about CA-AKI is somewhat limited, as there is no universally accepted definition, and several detection methods have been utilized. For example, in addition to having 3 methods to identify it (International Classification of Diseases [ICD] codes, Kidney Disease: Improving Global Outcomes [KDIGO] guidelines, and Risk, Injury, Failure, Loss of Kidney Function, and End-Stage Kidney Disease [RIFLE] classifications), CA-AKI may be detected in 2 distinct locations: in the hospital or in the primary care/outpatient setting, yielding a range in estimated prevalence from 0.7 to 17.2% [1–3]. Regardless of the identification method, CA-AKI has been associated with a poor clinical course, progression to chronic kidney disease (CKD), and death, in a similar fashion as the well-studied HA-AKI [4].

Deterioration in renal function is commonly observed in patients with heart failure (HF) and likewise, the risk of HF increases with deterioration of renal function [5]. For that reason, HA-AKI and its effects on short- and long-term cardiac outcomes have been extensively studied [6, 7]. With regard to HF, specifically, Bansal et al. [8] determined that patients who developed HA-AKI had a 23% increased risk for HF development within 2 years, as defined by ≥ 1 hospitalization or ≥ 2 outpatient visits with a diagnosis of HF. This is particularly concerning, as some studies suggest that CA-AKI may be >3 times as common as HA-AKI, and >5.7 million adults in America have HF, with an incidence nearing 1 per 100 over 65 years of age [9–11]. Hence, we aimed to study the impact of CA-AKI on HF development, as defined by de novo inpatient HF hospitalization.

Methods

We combined information from 2 clinical databases within our health care system using a single unique identifier. One database contained information obtained by the electronic health record for all patients treated at Baylor Scott & White Healthcare in the primary care setting. We collected demographics, patient history, and laboratory values from that system. The other database contained inpatient hospitalization records based on billing codes, from which we collected diagnosis codes and admission dates for our outcome of interest. To assemble the analytic data set, we identified adult individuals who had 2 or more serum creatinine (sCr) laboratory values recorded in the primary care setting within 13 months (Fig. 1), a time period chosen to capture individuals who typically visit a clinic only for an annual examination during the time period from January 2007 to December 2013. Those with a prior history of HF, solid organ transplant, and/or cancer were excluded from the study. We created a flag for CA-AKI when consecutive sCr values (within 13 months) increased by ≥ 0.3 mg/dL or ≥ 1.5 times the baseline. This was based on KDIGO guidelines (stage 1 or higher), with adaptation to the time frame [12]. Next, we linked inpatient HF hospitalization records to those meeting the aforementioned study criteria. To do so, we scanned the patients' confirmed primary diagnosis during the inpatient hospitalization record for the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of 428.XX and a description of All Patients Refined Diagnosis

Color version available online

Fig. 1. Consort diagram; CA-AKI, community-acquired acute kidney injury.

Related Groups (APR DRG) containing the text string of “heart f” [13]. We identified the first HF hospitalization records for individuals and created a flag for this outcome at 90, 180, and 365 days.

Continuous variables are reported as medians (quartile 1, quartile 3), and categorical variables are reported as frequencies (%). Differences in sample characteristics between patients who developed CA-AKI and patients who did not develop CA-AKI were assessed by Wilcoxon rank sum tests and χ^2 tests, as appropriate. We constructed unadjusted and adjusted logistic regression models to assess the effect of CA-AKI on incident HF hospitalization within 90, 180, and 365 days of CA-AKI evaluation. The fully adjusted models controlled for age, weight, hypertension, anemia, diabetes, coronary artery disease (CAD), and chronic obstructive pulmonary disease. These variables were used in the models because they had previously been identified as risk factors for HF [14–16]. There were no concerning findings regarding model fit, influential observations, or multicollinearity. Analyses were performed in SAS 9.4 (Cary, NC, USA).

Results

There were 210,895 adults meeting criteria for analyses, 5,358 (2.5%) of whom had CA-AKI. Those who developed CA-AKI had higher rates of comorbidities (diabetes, CAD, hypertension, etc.), higher rate of males (48 vs. 42%, $p < 0.001$), and were older (61.5 [50.3, 73.1] vs. 54.1 [42.8, 64.7] years, $p < 0.001$) than those who did not develop CA-AKI (Table 1). Those who had CA-AKI had a median time between sCr laboratory draws of 126 (64, 222) days, compared to 182 (93, 304) days among those who did not have CA-AKI ($p < 0.001$).

In total, 607, 833, and 1,089 individuals had an incident HF hospitalization in the 90, 180, and 365 days following the CA-AKI evaluation, respectively. Those who developed CA-AKI were at increased risk of having an incident HF hospitalization at all times examined (Fig. 2); the odds ratios (ORs) and areas under the curve (AUCs) are provided in Table 2. In unadjusted models, i.e., using only CA-AKI, the odds of HF hospitalization increased between 5- and 6-fold for those who had CA-AKI compared to those who did not. Even after adjusting for demographic and clinical characteristics, the effect of CA-AKI remained clear, those who had CA-AKI were at significantly higher risk of de novo HF hospitalization than those who did not have CA-AKI (Table 2). Additionally, the fully adjusted models (adjusted for age, weight, hypertension, anemia, diabetes, CAD, and chronic obstructive pulmonary disease) exhibited strong predictive ability, with all AUCs > 0.90 (Fig. 3).

Fig. 2. A comparison of de novo heart failure (HF) hospitalization rates over time between those with and without community-acquired acute kidney injury (CA-AKI).

Table 1. Patient characteristics

Variable	Acute kidney injury (<i>n</i> = 5,358)	No acute kidney injury (<i>n</i> = 205,537)	<i>p</i> value
Gender (male)	2,569 (48.0%)	86,588 (42.1%)	<0.001
Age, years	61.5 [50.3, 73.1]	54.1 [42.8, 64.7]	<0.001
Weight, lbs	190 [165.7, 214.0]	183.3 [161.8, 207.6]	<0.001
Diabetes	1,428 (26.7%)	31,784 (15.5%)	<0.001
Coronary artery disease	102 (1.9%)	2,133 (1.04%)	<0.001
Chronic obstructive pulmonary disease	521 (9.7%)	10,294 (5.0%)	<0.001
Anemia	467 (8.7%)	8,172 (4.0%)	<0.001
Hypertension	3,103 (57.9%)	85,355 (41.5%)	<0.001
Smoker	441 (8.2%)	16,875 (8.2%)	0.92
Race			<0.001
African American	728 (13.6%)	19,363 (9.4%)	
Asian	91 (1.7%)	6,142 (3.0%)	
Caucasian	3,282 (61.3%)	135,460 (65.9%)	
Other/unknown	1,257 (23.5%)	44,572 (21.7%)	

Discussion

In this cohort of 210,895 adults without a history of HF, few (2.5%) had CA-AKI, as identified by ≥ 0.3 mg/dL or ≥ 1.5 times the baseline sCr in the primary care setting, and a total of 1,089 (0.5%) were admitted for an incident HF hospitalization within 1 year of CA-AKI evaluation. Further, even after controlling for confounding baseline characteristics, CA-AKI was associated with a twofold increase in the risk of de novo HF hospitalization, providing evidence of its utility as a risk factor. Further, multivariable prediction models including CA-AKI, age,

Fig. 3. Receiver-operating characteristic curve for the outcome of 1-year heart failure hospitalization. Adjusted odds ratio: 2.16 (1.77–2.64), $p < 0.001$; area under the curve (AUC): 0.91 (0.91–0.92), $p < 0.001$; change in AUC due to community-acquired acute kidney injury (CA-AKI): 0.002 (0.001–0.004), $p < 0.001$. Covariates include CA-AKI, age, weight, hypertension, anemia, diabetes, coronary artery disease, and chronic obstructive pulmonary disease injury.

Table 2. Odds ratio (OR) of community-acquired acute kidney injury (CA-AKI) versus no CA-AKI for the outcome of incident heart failure hospitalization

Model	Outcome time frame	Events	OR (95% CI)	p value (OR)	AUC (95% CI)	Change in AUC due to CA-AKI ¹	p value (change in AUC)
Unadjusted	90 days	607	5.73 (4.51–7.27)	<0.001	0.55 (0.54–0.57)	0.052 (0.038–0.065)	<0.001
	6 months	833	6.01 (4.91–7.35)	<0.001	0.55 (0.54–0.57)	0.054 (0.043–0.066)	<0.001
	1 year	1,089	5.11 (4.24–6.17)	<0.001	0.54 (0.54–0.56)	0.045 (0.036–0.055)	<0.001
Age adjusted	90 days	607	3.27 (2.57–4.18)	<0.001	0.86 (0.85–0.87)	0.008 (0.004–0.012)	<0.001
	6 months	833	3.48 (2.83–4.28)	<0.001	0.86 (0.85–0.87)	0.009 (0.005–0.013)	<0.001
	1 year	1,089	2.98 (2.46–3.61)	<0.001	0.85 (0.84–0.86)	0.007 (0.005–0.013)	<0.001
Adjusted ²	90 days	607	2.35 (1.83–3.02)	<0.001	0.92 (0.91–0.93)	0.003 (0.001–0.004)	0.002
	6 months	833	2.52 (2.04–3.13)	<0.001	0.92 (0.91–0.92)	0.003 (0.001–0.004)	<0.001
	1 year	1,089	2.16 (1.77–2.64)	<0.001	0.91 (0.91–0.92)	0.002 (0.001–0.004)	<0.001

CI, confidence interval; AUC, area under the (receiver-operating characteristic) curve.

¹ Values obtained by performing contrast on the ROC for the specified model with CA-AKI minus the specified model without CA-AKI.

² Adjusted for age, weight, hypertension, anemia, diabetes, coronary artery disease, and chronic obstructive pulmonary disease.

weight, hypertension, anemia, diabetes, CAD, and chronic obstructive pulmonary disease yielded strong predictive abilities to anticipate a first HF hospitalization.

Our work shows that detecting CA-AKI in the primary care setting is a valuable tool to gauge the risk of poor short- and long-term HF outcomes for individuals without a prior history of HF; however, determining the cause of CA-AKI is critical in order to attempt to reduce its severity/progression and associated risks. Even as a relatively new study concept, several risk factors for CA-AKI have been identified, many of which are reflective of those for

HA-AKI, such as age, diabetes, congestive HF, CKD, human immunodeficiency virus, obstructive uropathy, and volume depletion [1, 9]. Patients with CA-AKI are more likely to have comorbidities than patients with HA-AKI [17]. The most common etiology of CA-AKI is typically prerenal, such as gastrointestinal loss, poor intake, and/or medications such as nonsteroidal anti-inflammatory drugs, diuretics, and/or angiotensin-converting enzyme inhibitors [18]. In patients with HF, adjusting the use of diuretics, changes in blood volume, effective blood flow to the kidneys, venous congestion, and the rates of plasma refill from the extravascular space after diuresis, all play a role in sCr measurements [19]. Further, a study spanning >15 years confirmed the following additional factors corresponding to increased sCr screening: reduced kidney function, albuminuria, male gender, diabetes, and age [20]. As such, we observed the median time between sCr analyses for patients with CA-AKI was 56 days shorter than for those without CA-AKI, an indication that physicians were ordering labs in response to some change(s) in their patient's clinical status and/or medication regimen. Despite the difficulty of understanding sCr in an increasingly complex HF population, our data suggest casual measurements in the ambulatory arena can serve as indicators, and, when elevated, as risk predictors for HF hospitalization.

In our cohort, 2.5% patients developed CA-AKI, as detected in the primary care setting via consecutive sCr values. Our incidence rate is close to that of the previously published rate by Wonnacott et al. [21], who demonstrated an incidence of 4.3%, as detected upon hospital admission. CA-AKI rates are known to vary based on the detection location, i.e., at the hospital or at the primary care clinic [22]. Identification in the hospital is more common and typically more severe than CA-AKI as identified in primary care; however, both have been associated with increased mortality [9]. A Veterans Affairs Center study revealed that 23.6% of patients hospitalized from 2004 to 2005 in Upstate New York had AKI, and approximately 78% of those instances were attributed to CA-AKI, indicating that primary care clinics should regularly screen for AKI before the patient deteriorates and requires hospitalization [9]. Additionally, CA-AKI has been shown to be predictive of a poor clinical course, progression to CKD, and death, with 5-year mortality as high as 64% [4, 23]. Among elderly Medicare beneficiaries (≥ 67 years), Ishani et al. [24] documented that the risk of developing end stage renal disease after AKI was 13 times higher than for those without AKI. This is particularly concerning, as patients with end stage renal disease on dialysis have been shown to have >10 times the risk of cardiovascular mortality than individuals without CKD of the same age and gender [25]. This well-described phenomenon of a paired decline in renal and cardiac function is termed the cardiorenal syndrome [5]. As such, the patients in our cohort who suffered CA-AKI and later developed HF may be classified by this syndrome, specifically type 3 or type 4, in which acute decline (type 3) or chronic abnormalities (type 4) of renal function cause cardiac dysfunction [26].

Our work extends from what is known about the relation between HA-AKI and HF to the lesser known CA-AKI risk for de novo HF hospitalization. This is a significant finding, as it provides an opportunity for earlier intervention. Appropriate upstream disease detection and management strategies should be devised with the aim of reducing the global burden of both AKI and HF hospitalization. With advances in the electronic medical record systems, there are options for e-alerts pertaining to CA-AKI [4]. In the hospital setting, e-alerts have been associated with a lower risk of overlooked HA-AKI, severe HA-AKI, improved odds of nephrologist referral, and improved HA-AKI recovery [27]. Similarly, a 3-month descriptive observational study demonstrated the ability to use CA-AKI alerts at the hospital, whether or not patients were actually admitted to the hospital [28]. Similar alerts could be implemented at the primary care level, before the patient requires observation at the hospital, to encourage physicians to provide appropriate education to patients with CA-AKI, to refer patients to nephrologists and/or to discuss the implementation of a cardiorenal protective diet [29, 30].

Limitations

These results are from a single center experience. Additionally, the data were collected via retrospective chart review and have possibility for misclassification. However, we conducted an in-depth medical history review for a random sample and determined the rate of diabetes misclassification was <4%, which provides evidence in support of high data quality. Additionally, we are not aware of the etiologies of CA-AKI or patients' medications, which could have been associated with CA-AKI and HF hospitalization. We considered only sCr for the detection of CA-AKI; however, other biomarkers, such as neutrophil gelatinase-associated lipocalin, serum cystatin C, and brain natriuretic peptide exist for the detection of renal and cardiac injury [31–33]. Additionally, we did not distinguish between HF with preserved or reduced ejection fraction, and we elected to use only the ICD-9-CM code of 428.XX to identify HF cases. We acknowledge that using only 1 code may have missed some cases; however, this code has been proven as the most sensitive, and adding other codes does not significantly change the detection rate [13]. Additionally, we considered the relationships between hypertension and CAD with HF hospitalization, but we acknowledge that other cardiovascular diseases play a role in HF hospitalization. Finally, we could not adequately calculate body mass index due to the lack of standardization in height data, so we adjusted the models using weight instead of body mass index.

Conclusions

Our large clinical review of adults without a prior history of HF revealed that few (2.5%) patients developed CA-AKI, as detected in the primary care setting. Additionally, after controlling for clinical characteristics, those who developed CA-AKI had an approximately twofold risk of de novo HF hospitalization (within 90, 180, and 365 days of CA-AKI evaluation) than those who did not develop CA-AKI. Hence, detecting CA-AKI may provide an opportunity for early intervention at the primary care level in an attempt to delay and/or prevent HF development.

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Statement of Ethics

We received institutional review board approval from the Baylor Scott & White Research Institute prior to conducting research-related activities, and informed consent was waived for this retrospective study. Data from this study will not be made publicly available.

Disclosure Statement

The authors have nothing to disclose.

References

- 1 Schissler MM, Zaidi S, Kumar H, Deo D, Brier ME, McLeish KR. Characteristics and outcomes in community-acquired versus hospital-acquired acute kidney injury. *Nephrology (Carlton)*. 2013 Mar;18(3):183–7.
- 2 Mesropian PD, Othersen J, Mason D, Wang J, Asif A, Mathew RO. Community-acquired acute kidney injury: A challenge and opportunity for primary care in kidney health. *Nephrology (Carlton)*. 2016 Sep;21(9):729–35.
- 3 Evans RD, Hemmilä U, Craik A, Mtekatika M, Hamilton F, Kawale Z, et al. Incidence, aetiology and outcome of community-acquired acute kidney injury in medical admissions in Malawi. *BMC Nephrol*. 2017 Jan;18(1):21.
- 4 Talabani B, Zouwail S, Pyart RD, Meran S, Riley SG, Phillips AO. Epidemiology and outcome of community-acquired acute kidney injury. *Nephrology (Carlton)*. 2014 May;19(5):282–7.
- 5 McCullough PA, Ahmad A. Cardiorenal syndromes. *World J Cardiol*. 2011 Jan;3(1):1–9.
- 6 Odutayo A, Wong CX, Farkouh M, Altman DG, Hopewell S, Emdin CA, et al. AKI and Long-Term Risk for Cardiovascular Events and Mortality. *J Am Soc Nephrol*. 2017 Jan;28(1):377–87.
- 7 Tecson KM, Brown D, Choi JW, Feghali G, Gonzalez-Stawinski GV, Hamman BL, et al. Major Adverse Renal and Cardiac Events After Coronary Angiography and Cardiac Surgery. *Ann Thorac Surg*. 2018 Jun;105(6):1724–1730.
- 8 Bansal N, Matheny ME, Greevy RA Jr, Eden SK, Perkins AM, Parr SK, et al. Acute Kidney Injury and Risk of Incident Heart Failure Among US Veterans. *Am J Kidney Dis*. 2018 Feb;71(2):236–45.
- 9 Der Mesropian PJ, Kalamaras JS, Eisele G, Phelps KR, Asif A, Mathew RO. Long-term outcomes of community-acquired versus hospital-acquired acute kidney injury: a retrospective analysis. *Clin Nephrol*. 2014 Mar;81(3):174–84.
- 10 Levey AS, James MT. Acute Kidney Injury. *Ann Intern Med*. 2018 Jun 5;168(11):837.
- 11 Writing Group Members. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al; American Heart Association Statistics Committee; Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. *Circulation*. 2016 Jan;133(4):e38–360. Erratum in: *Circulation*. 2016 Apr;133(15):e599.
- 12 Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl*. 2012;2:1–138.
- 13 Saczynski JS, Andrade SE, Harrold LR, Tjia J, Cutrona SL, Dodd KS, et al. A systematic review of validated methods for identifying heart failure using administrative data. *Pharmacoepidemiol Drug Saf*. 2012 Jan;21 Suppl 1:129–40.
- 14 Dunlay SM, Weston SA, Jacobsen SJ, Roger VL. Risk factors for heart failure: a population-based case-control study. *Am J Med*. 2009 Nov;122(11):1023–8.
- 15 Caramelo C, Justo S, Gil P. [Anemia in heart failure: pathophysiology, pathogenesis, treatment, and incognitae]. *Rev Esp Cardiol*. 2007 Aug;60(8):848–60. Spanish.
- 16 Onishi K. Total management of chronic obstructive pulmonary disease (COPD) as an independent risk factor for cardiovascular disease. *J Cardiol*. 2017 Aug;70(2):128–134.
- 17 Hsu CN, Lee CT, Su CH, Wang YC, Chen HL, Chuang JH, et al. Incidence, Outcomes, and Risk Factors of Community-Acquired and Hospital-Acquired Acute Kidney Injury: A Retrospective Cohort Study. *Medicine (Baltimore)*. 2016;95(19):e3674.
- 18 Dreischulte T, Morales DR, Bell S, Guthrie B. Combined use of nonsteroidal anti-inflammatory drugs with diuretics and/or renin-angiotensin system inhibitors in the community increases the risk of acute kidney injury. *Kidney Int*. 2015 Aug;88(2):396–403.
- 19 De Vecchis R, Ciccarelli A, Ariano C, Cioppa C, Giasi A, Pucciarelli A, et al. In chronic heart failure with marked fluid retention, the i.v. high doses of loop diuretic are a predictor of aggravated renal dysfunction, especially in the set of heart failure with normal or only mildly impaired left ventricular systolic function. *Minerva Cardioangiol*. 2011 Dec;59(6):543–54.
- 20 Oke J, Shine B, McFadden E, Stevens R, Lasserson D, Perera R. Trends in serum creatinine testing in Oxfordshire, UK, 1993–2013: a population-based cohort study. *BMJ Open*. 2015 Dec;5(12):e009459.
- 21 Wonnacott A, Meran S, Amphlett B, Talabani B, Phillips A. Epidemiology and outcomes in community-acquired versus hospital-acquired AKI. *Clin J Am Soc Nephrol*. 2014 Jun;9(6):1007–14.
- 22 Emmett L, Tollitt J, McCorkindale S, Sinha S, Poulikakos D. The Evidence of Acute Kidney Injury in the Community and for Primary Care Interventions. *Nephron*. 2017;136(3):202–10.
- 23 Sawhney S, Fluck N, Fraser SD, Marks A, Prescott GJ, Roderick PJ, et al. KDIGO-based acute kidney injury criteria operate differently in hospitals and the community-findings from a large population cohort. *Nephrol Dial Transplant*. 2016 Jun;31(6):922–9.
- 24 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 Jan;20(1):223–8.
- 25 Segall L, Nistor I, Covic A. Heart failure in patients with chronic kidney disease: a systematic integrative review. *Biomed Res Int*. 2014;2014:937398.
- 26 Scabbia EV, Scabbia L. The Cardio-renal Syndrome (CRS). *IJC Metab Endocr*. 2015 Dec;9:1–4.
- 27 Park S, Baek SH, Ahn S, Lee KH, Hwang H, Ryu J, et al. Impact of Electronic Acute Kidney Injury (AKI) Alerts With Automated Nephrologist Consultation on Detection and Severity of AKI: A Quality Improvement Study. *Am J Kidney Dis*. 2018 Jan;71(1):9–19.

- 28 Hazara AM, Elgaali M, Naudeer S, Holding S, Bhandari S. The Use of Automated Electronic Alerts in Studying Short-Term Outcomes Associated with Community-Acquired Acute Kidney Injury. *Nephron*. 2017;135(3):181–8.
- 29 Goraya N, Simoni J, Jo C, Wesson DE. Dietary acid reduction with fruits and vegetables or bicarbonate attenuates kidney injury in patients with a moderately reduced glomerular filtration rate due to hypertensive nephropathy. *Kidney Int*. 2012 Jan;81(1):86–93.
- 30 Saneei P, Salehi-Abargouei A, Esmailzadeh A, Azadbakht L. Influence of Dietary Approaches to Stop Hypertension (DASH) diet on blood pressure: a systematic review and meta-analysis on randomized controlled trials. *Nutr Metab Cardiovasc Dis*. 2014 Dec;24(12):1253–61.
- 31 Tecson KM, Erhardtson E, Eriksen PM, Gaber AO, Germain M, Golestaneh L, et al. Optimal cut points of plasma and urine neutrophil gelatinase-associated lipocalin for the prediction of acute kidney injury among critically ill adults: retrospective determination and clinical validation of a prospective multicentre study. *BMJ Open*. 2017 Jul;7(7):e016028.
- 32 Soto K, Campos P, Pinto I, Rodrigues B, Frade F, Papoila AL, et al. The risk of chronic kidney disease and mortality are increased after community-acquired acute kidney injury. *Kidney Int*. 2016 Nov;90(5):1090–9.
- 33 Shrestha K, Borowski AG, Troughton RW, Thomas JD, Klein AL, Tang WH. Renal dysfunction is a stronger determinant of systemic neutrophil gelatinase-associated lipocalin levels than myocardial dysfunction in systolic heart failure. *J Card Fail*. 2011 Jun;17(6):472–8.