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Recent Pattern of Acute Kidney Injury in Bosnia and Herzegovina

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ABSTRACT

Introduction: Acute kidney injury (AKI) is one of the major public health issues with constantly increasing incidence, with epidemiology and outcomes that vary substantially across the world. **Aim:** Aim of our study was to determine epidemiological characteristics and causes of AKI and to provide a comparison of our findings with data from other low and middle income countries. **Methods:** This retrospective observational study conducted during an 18-month period included 84 patients. Data were collected from hospital information system and patients' medical records. All data were analyzed using descriptive statistics. **Results:** More than two-thirds of patients were older than 56 years. Most cases of AKI (54,76%) were hospital-acquired and predominantly developed in intensive care units (32,14%). Dominant risk factor was underlying chronic kidney disease (48,81%) and chronic heart failure (45,24. In majority of patients (73,81%) were identified multiple factors that may have contributed to AKI: infection (90,48%), prerenal factors (77,38%), nephrotoxic agents (69,05%), and sepsis (28,57%). Multiple organ failure was identified in 94,05% of patients: cardiovascular (64,56%), respiratory (58,23%) and hematological (56,96%) system. Half of all patients were alive at last observation day. Leading cause of death was infection/sepsis (21,43%), followed by cancer (16,67%) and shock (14,28%). **Conclusion**: Data on AKI show great variation, but general picture of AKI resembles more that from high income countries. The need for dialysis and overall mortality remains high. This highlights the importance of early recognition of AKI, timely referral to nephrologist and need for national guidelines and standardized protocols for AKI.
Keywords: acute kidney injury, chronic kidney disease, outcome.

1. INTRODUCTION

Acute kidney injury (AKI) is one of the major public health issues, occurring in about 13 million people per year and claiming at least 1,7 million lives a year (1). The incidence of AKI worldwide is constantly increasing (1-4). According to a meta-analysis involving more than 77 million individuals over a period of 10 years, the pooled incidence of AKI in low-and middle-income countries (LMICs) is found progressively closer to that of high-income countries (HICs) (1). This result may be due to improved and systematized collection of patients health informations, increased public and professional attention to AKI, better healthcare access and improved diagnostics including use of uniform diagnostic criteria (Kidney Disease: Improving Global Outcomes - KDIGO, or KDIGO - equivalent) (1, 2, 4).

The epidemiology, aetiology, pathophysiology, management and outcomes of AKI vary substantially across the world (1). In HICs, AKI is more often hospital-acquired and associated with major surgeries, patients are older and have multiple comorbidities, and leading causes of AKI are sepsis, volume depletion, nephrotoxic drugs and ischemia (1, 2, 5-9). In LMICs, AKI develops mainly in the community setting due to public health issues such as contaminated water, poor sanitation and hygiene, and limited availability of health-care facilities (1, 2, 5-9).

It has been estimated that 20-25% of patients with AKI require acute renal replacement therapy (RRT), with major clinical practice variation (10). Recent trends show increasing incidence of dialysis-requiring AKI (4) including increasing availability, earlier and more liberal initiation of dialysis (4) and increase in the number of older hospitalized patients with high comorbidity burden (4).

AKI is an independent risk factor associated with negative outcomes, including death (2). According to the previously mentioned meta-analysis of global epidemiology of AKI, the

overall mortality of patients with AKI was 21%, probably because majority of patients included in the study were with the mild stages of AKI (1). As expected, patients with the more severe AKI (KDIGO stage 3) or those in need of dialysis had a higher mortality rates (42% and 46%) (1). Studies vary substantially in differences in mortality between LMICs and HICs, which is probably reflective of high population-selection variations, etiologic heterogeneity, and different socioeconomic conditions across and within countries (1, 2, 8). Patients who experience AKI face greater risk for recurrent AKI, developing CKD, mortality and elevated risk of cardiovascular disease events (11). Guidelines recommend follow-up within 3 months after AKI, in other to identify patients with CKD (11).

Most LMICs, including Bosnia and Herzegovina (upper middle-income country), don't have data on trends in AKI. According to our literature search and review, there are only few articles on treatment and outcomes of AKI in tertiary hospitals in Bosnia and Herzegovina (12-16).

2. AIM

The aim of our study was to determine epidemiological characteristics and causes of AKI in Tuzla Canton, the most populated canton in Bosnia and Herzegovina, and University Clinical Center Tuzla that is recognized as tertiary referral center with highest patient inflow in this area and to provide a comparison of our findings with other data from low and middle income countries.

3. METHODS

This retrospective observational study was conducted during an 18-month period (from July 2017 to December 2018) and included 84 patients treated in University Clinical Center Tuzla. Data were collected from hospital information system and patients' medical records. AKI definition was based on modified KDIGO criteria: an increase in serum creatinine of greater than 0.3 mg/dl (> 25 micromol/L), an increase in serum creatinine greater than or equal to 50% from baseline, and/or documented oliguria (< 200 ml for 6 hours or more). The exclusion criteria were patients on chronic dialysis in the past 3 months or presently on dialytic therapy, or patients with a functioning kidney graft. The data were collected through questionnaire from AKI Global Snapshot, a web-based global cohort study carried out under the International Society of Nephrology (ISN) 0by25 Initiative to eliminate avoidable deaths from AKI by 2025 (17). The data collected were as follows: demographic factors, comorbidities, risk factors for AKI (age > 75, diabetes, chronic liver and/or kidney disease, and chronic heart failure), clinical presentation, location where patient was seen and where AKI was developed (community or hospital), factors that may have contributed to patient's AKI, known sites of infection, other organ failure (defined according to American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference as follows: Presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention), non-dialytic (fluid therapy, diuretics, vasopressors, antibiotics, urinary diversion) and dialytic treatment (indications, modality, number of treatments) received by the patient, laboratory data (on AKI confirmation day and at last observation), urinalysis, kidney ultrasound and/or biopsy, length of hospital stay, and kidney recovery status. Recovery was defined as follows: no recovery (still worsening, unchanged renal function or requiring dialysis), complete (creatinine equal or lower than baseline) or partial recovery (creatinine lower than at diagnosis not on dialysis) or unknown (17). Available follow-up data were also analyzed. All data were entered into Excel worksheet and analyzed using descriptive statistics.

4. RESULTS

A total of 84 patients with AKI hospitalized at University Clinical Centre during an 18-month period was analyzed. Patients whose medical records were incomplete were excluded from the study. More than two-thirds of patients were older than 56 years (mean age 65.69 ± 15.07, median 68, mode 60, range 20 - 93 years) and most of them were male (57.14%) (Table 1). Most cases of AKI (54.76%) were hospital-acquired and predominantly developed in intensive care unit (ICU) (32.14%), internal

Sociodemographic characteristic	Variables	Frequency	Percent	Median years	Mode years
Gender	Male	48	57.14		
	Female	36	42.85		
Age (years)	18 – 35	4	4.76		
	36 – 55	14	16.67	68	60
	≥ 56	66	78.57		
Location of AKI development	Hospital	46	54.76		
	Community	38	45.24		

Table 1. Sociodemographic characteristic of patients with AKI* *AKI – acute kidney injury

Department	Frequency	Percent
Intensive care units	27	32.14
Internal medicine	22	26.19
Surgery	17	20.24
Infectious Diseases	10	11.90
Oncology and Hematology	4	4.76
Obstetrics and Gynecology	2	2.38
Neurology	2	2.38

Table 2. Distribution of patients with AKI* in different departments of UKC Tuzla. *AKI – acute kidney injury, ** UKC – University Clinical Center**

Risk factor	Frequency	Percent**
Chronic kidney disease	41	48.81
Chronic heart failure	38	42.24
Age > 75 years	31	36.91
Diabetes	29	34.52
Chronic liver disease	7	8.33
Balkan endemic nephropathy	4	4.76

Table 3. Analysis of risk factors for AKI*. *AKI – acute kidney injury, **Some patients had more than one risk factor for AKI, so total sum is more than 84 (100%)

Factor that may have contributed to AKI*	Frequency	Percent**
Infection	76	90.40
Dehydration	65	77.38
Nephrotoxic agents	58	69.05
Cardiac	44	52.38
Hypotension and shock	43	51.19
Systemic diseases	29	34.52
Urinary tract obstruction	18	21.43
Liver disease	15	17.86
Trauma	10	11.90
Rhabdomyolysis	8	9.52
Acute kidney disease	7	8.33
Poisoning	1	1.19
Kidney tumor	1	1.19
Pregnancy and delivery related	1	1.19

Table 4. Analysis of factors that may have contributed to AKI*. *AKI – acute kidney injury, **Some patients had more than one risk factor for AKI, so total sum is more than 84 (100%)

Treatment	Frequency	Percent*
Fluid therapy	43	100.00
Diuretics	77	91.67
Antibiotics	80	95.24
Vasopresors	32	38.09
Urine diversion	4	4.76
Dialysis	45	53.57

Table 5. Applied treatment analysis. *Patients were treated with more than one treatment modality, so total sum is more than 84 (100%)

Indication	Frequency	Percent*
Solute control**	43	95.55
Fluid overload	33	73.33
Electrolytes or acid/base disturbances	25	55.55

Table 6. Analysis of indications for starting dialysis. *Most patients had more than one indications for dialysis, so total sum is more than 45 (100%). **Elevated creatinine, BUN or symptomatic uremia

medicine (26.19%) and surgical (20.24%) patients (Table 2).

Dominant risk factor in our study population was underlying CKD (48.81%), followed by chronic heart failure (45.24%), age of 75 or more (36.91%) and diabetes (34,52%). Table 3 summarizes all identified risk factors in our study population.

In majority of patients (73.81%) were identified multiple factors that may have contributed to AKI, in order as follows: infection (90.48%), prerenal factors (77.38%), nephrotoxic agents (69.05%), and sepsis (28.57%) (Table 4). Most common sites of infection were lungs (61.84%), urinary (51.31%) and gastrointestinal (40.79%) tract. Twenty four (28.57%) patients had sepsis, in some cases with absent positive blood culture, but with clear clinical and other laboratory criteria indicating septic state. Nephrotoxic agents were defined according to 0by25 Global Snapshot, as follows: transplant medication, non-prescription and other prescription drugs, chemotherapy, IV drug abuse, aminoglycosides, antibiotics other than aminoglycosides, non steroidal anti-inflammatory drugs (NSAIDs), contrast, IV hemolysis (hgb, uric acid injury) and rhabdomyolysis. Multiple organ failure was identified in 94.05% of patients. Organ systems most commonly involved were: cardiovascular (64.56%), respiratory (58.23%) and hematological (56.96%) system.

Cause of death	Frequency	Percent
Infection/sepsis	9	21.43
Cancer	7	16.67
Shock	6	14.28
Cardiovascular	3	7.14
Trauma	3	7.14
Pulmonary condition	3	7.14
Neurological condition	3	7.14
Vasculitis	2	4.76
Other systemic diseases	2	4.76
Hemorrhage	1	2.38
Liver failure	1	2.38
Hepatorenal syndrome	1	2.38
Lactic acidosis	1	2.38
Total	42	100.00

Table 7. Analysis of death causes in the patients with AKI*. *AKI – acute kidney injury

Analyzing modified KDIGO criteria for AKI from 0by25 Global Snapshot in our patients, we found that 45.24% of patients had an increase in serum creatinine > 25 micromol/L, and/or an increase in serum creatinine greater than or equal to 50% from baseline. About one-third of patients (35.71%) were oliguric. On AKI confirmation day, urine output was known for 69.05% of patients (mean 1011, range 0 – 3500 ml), and almost half of the patients (48.27%) were with the urine output more than 1000 ml, mostly forced by diuretics and fluid.

Urinalysis was performed in 64.28%, and kidney ultrasound in 46.43% of patients**.** Biopsy was performed in only one patient. Baseline serum creatinine level was unknown in 42.86% of patients, and in the rest of the patients (57.14%) was 136.10 ± 92.09 micromol/L. On AKI confirmation day, the mean value of serum creatinine was 512.69 ± 318.74 micromol/L, and 340.12 ± 233.42 micromol/L on last observation day.

All patients received fluid therapy, and nearly all of the patients (91.67%) received diuretics. More than a third of patients (38.09%) were treated with vasopressors. Antibiotic were used in 95.24% of patients. More than a half of the patients (53.57%) required dialysis. Intermittent hemodialysis (IHD) was performed in most of the cases, but often combined with other modalities, such as prolonged intermittent renal replacement therapy (PIRRT). The most common indication for dialysis (95,55%) was solute control (elevated creatinine, BUN or symptomatic uremia). Fluid overload was found in 73.33%, and disorder of electrolytes and/or acid base balance in 55.55% patients. Most of the patients that required dialysis had all indications for dialysis initiation (44.44%) (Table 6). Among patients who were not dialyzed (46.43%), absence of indications was the most common reason for not commencing dialysis, and in three patients treat-

ment was considered futile. Mean number of dialytic treatments that patients received was 5,8 (range 1 - 21).

The average length of hospitalization was 21.5 days (range 2 - 145 days). More than half of patients (57.78%) who were started on dialysis died during hospital stay. At last observation day, eight patients (17.78%) no longer received any form of dialytic therapy, six patients (13.33%) remained dialysis dependent, and data is not available for four patients (8.89%). One patient was discharged home with no need for further dialytic therapy, but died later from cardiovascular cause. At last observation day, 46.43% of all patients in the study did not recover renal function. Complete renal recovery was found in 20.24%, and partial renal recovery in 29.76% of patients. There were no available data on three patients. Half of all patients in the study were alive at last observation day. Leading cause of death was infection/sepsis (21.43%), followed by cancer (16.67%) and shock (14.28%) (Table 7).

Only eight patients (18.60%) were seen by a nephrologist after hospital discharge. Data were not available on seven (16.28%) patients.

5. DISCUSSION

This retrospective observational study was conducted to shed light on trends in epidemiology, aetiology and outcome of AKI in Tuzla canton, the most populated canton in Bosnia and Herzegovina, and University Clinical Center Tuzla that is recognized as tertiary referral center with highest patient inflow in this area. There are no data on epidemiology, characteristics and outcomes of patients with AKI within health system in Bosnia and Herzegovina and there are no guidelines or standardized protocols for diagnostics, treatment and dialysis initiation. There is no consensus strategy for prevention from AKI, not even in the ICUs, which are considered as high-risk settings for AKI. These unfortunate facts lead to the conclusion that studies like this are necessary to improve prevention, early recognition and adequate treatment of AKI, as well as to ensure adequate spending of already limited resources in Bosnia and Herzegovina and other LMICs.

The majority of our study patients were older, which can be explained by increasing number of elderly in overall population of Bosnia and Herzegovina (18). In addition to that, older patients are susceptible to the prerenal causes, infections and nephrotoxic agents, which are recognized as leading causes of AKI in our study. Prerenal AKI is reversible condition, but if not timely recognized and treated, progresses to acute tubular necrosis (19). Further on, the elderly patients take at least twice as many medications compared with younger population, including nephrotoxic drugs, and are vulnerable to drug toxicity due to pharmacokinetics and pharmacodynamic changes, which is why drug dosing adjustment is necessary but often neglected in these patients (20). We conclude that it is necessary to raise awarenesses of nephrotoxic effects of commonly prescribed drugs in elderly population, listed as follows: NSAIDs, angiotensin-converting-enzyme inhibitors (ACEi), angiotensin II receptor blockers (ARB), diuretics, aminoglycosides, beta lactam and cephalosporins drugs (21).

In our study population AKI was predominantly hospital acquired, especially during the ICU stay, which is not surprising considering that patients on an ICU are critically ill, often with multi organ failure and undergoing invasive diagnostic and therapeutic procedures. In the last 20 years, AKI has been recognized as multi system disease rather than a single organ phenomenon (22), which is consistent with our study results that show AKI as a part of multi organ failure in 94,05% of patients.

Analysis of factors that may have contributed to AKI drew our attention to surprisingly small number of patients diagnosed with sepsis (28,57%). According to the literature data, sepsis is one of the leading causes of AKI and multi organ failure, with evident rise in incidence rates, but sources for these data are mainly from HICs (2, 4, 6, 7, 9, 22-25). Data from LMICs are missing, incomplete or showing significantly lower incidence compared to HICs (6, 7, 9, 26). Possible explanations for this is late or lack of recognition and/or underreporting sepsis, especially as independent risk factor for AKI. Hence, it is necessary to raise awareness of sepsis, in order to ensure early recognition, confirmation, and adequate treatment, which is of vital importance.

Encouraging is the fact that pregnancy and delivery related causes of AKI were found in only one patient in our study. This result indicates good antenatal care, prevention and adequate treatment of obstetric complications in our country, which is contrary to data from other LMICs, where obstetric factors are major causes of AKI.

Only one third of our patients were oliguric, and almost half of patients had urine output more than 1000 ml on AKI confirmation day, probably a result of receiving proper fluid therapy and diuretics. It is truly disappointing that urinalysis was done in only 64,28%, and kidney ultrasound in only 46,43% of patients. These diagnostic procedures are inexpensive, non-invasive, easy available and of great significance in clinical nephrology. Therefore, it is necessary to find a way to incorporate these, often overlooked approaches, into routine clinical practice in LMICs where use of other biomarkers and/or more sophisticated diagnostic approaches is limited and hardly available. Another discouraging finding is that basal serum creatinine (SCr) level was unknown in 42,86% of patients. It is well established that basal SCr is a good marker of premorbid renal function. Although multiple factors affect the SCr level (age, gender, body mass, nutrition, drugs, decrease in its production in acute illness, dilution in hypervolemia), it can provide useful clinical information through measuring its increase with respect to its basal level and it is important for follow-up of renal function recovery after AKI. Therefore, we need to direct more efforts toward thorough analysis of patient medical history and history of SCr levels.

More than half of our patients required dialytic therapy. We performed analysis of literature data, including PubMed search, and our findings suggested that there is a great variation in number of patients with AKI requiring dialysis. For example, analysis of patients with AKI

hospitalized at one university hospital in Croatia during the five-year period, showed that 12.5 - 21% of patients required dialysis (28). According to results of one prospective observational study that included elderly patients from one center in Macedonia during 8-month period, dialysis was necessary in 58.6% of patients (26). One systematic review of AKI, focusing in sub-Saharan Africa area, showed that 66% of children and 70% of adult met the criteria for dialysis (6). Data from HICs also show great variation: from 30.3% of patients that required dialysis of all ICU patients with AKI in northeastern Italy included in one multi center prospective observational study (23), to 50% of patients according to the multi center prospective observational study conducted in ICUs in Hungary (24). Possible reasons for high number of patients with AKI that required dialysis in our study are late referral to nephrologist who better understands and handle fluid management, old age and a lot of comorbid diagnoses among our study population, with CKD being predominant risk factor (48.81%). In addition to that, majority of our patients had multi organ failure and required critical medical care in an ICUs. Another possible explanation is that in our country, unlike many other LMICs (6, 9), dialytic treatment is available to all patients in need. However, choice of dialysis modality and dose is substantially affected by limited infrastructure in our dialysis centers. Confirmation of the above is our study result that show that majority of patients requiring dialysis were treated with IHD, and continuous renal replacement therapy (CRRT) was mostly unavailable due to stuff and machine shortage. However, we frequently used PIRRT as an alternative for CRRT. PIRRT is considered as hybrid treatment that provides advantages of both IHD and CRRT, and according to numerous studies there are no significant differences in mortality and renal function recovery between PIRRT and CRRT. Therefore, PIRRT seems to be good alternative for CRRT, especially for hemodynamically unstable patients, when CRRT is not available, which is the case in most LMICs (10, 29).

The mortality rate in our study was 50%, which is probably a reflection of previously stated factors (old age, numerous comorbidities, multi organ failure, need for ICU), but also a biased sample due to unrecognized and/or underreported mild stages of AKI, resulting in study population consisting mainly of patients with severe AKI. This highlights the importance of early recognition and timely referral to a nephrologist, in order to prevent further deterioration of renal function, and to increase survival and renal recovery in patients with AKI.

Only 18.6% of all patients with AKI in our study were seen by a nephrologist after hospital discharge, which indicates the need for raising awareness of long-term consequences of AKI in medical community, especially among family medicine physicians. Similar problem is recognized in USA and UK where only 10-15% of patients are seen by a nephrologist within 1 year post AKI (1).

6. CONCLUSION

Data on AKI from our country are scarce, and with this paper we hope to shed some additional light on the topic. Data on AKI show great variation, but general picture of AKI resembles more that from high income countries. The need for dialysis and overall mortality remains high. This highlights the importance of early recognition of AKI, timely referral to a nephrologist and need for national guidelines and standardized protocols for AKI.

We need to arise awareness of this important issue not only among nephrologist, but among physicians working at the ICUs, and doctors in general. Primary care doctors, as well as their patients, most importantly those with CKD or risk factors for it, should be informed on prevention of AKI and importance of followup by nephrologist after the episode of one.

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