Acute Kidney Injury in Critically Ill Patients

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Abstract

Introduction: The assumption that critically ill patient is well defined, promptly recognized and immediately transported into the Intensive Care Unit (ICU), leads to wrong estimations and erroneous viewpoints of critically ill patient’s epidemiology. The ‘critically ill’ definition neither presupposes his admission into ICU nor precludes his hospitalization in the hospital ward. The purpose of the present study was to evaluate the incidence and risk factors of AKI taking into account the totality of critically ill patients of a given time period.

Methods: This is a retrospective study conducted in the general ICU of the University hospital “Attikon”. Participants were adult patients in which an intensivist’s consultation was effectuated by the ICU staff, during a period of 2.5 months. The estimated baseline creatinine was calculated using the MDRD formula, assuming a lower limit of normal baseline glomerular filtration ratio (GFR) of 75ml/min/1.73m². The presence of AKI was assessed only within the first consultation and was stratified by the three RIFLE categories of severity (Risk, Injury and Failure). The impact on disease’s incidence of demographic characteristics, medical history, clinical data and severity scores of the participants was evaluated.

Results: A total of 69 critically ill patients were enrolled in the study. The overall incidence of AKI by the time of first consultation was 43% with the women being more frequently and more severely affected. The severity score seemed to be the principal independent risk factor for early AKI occurrence. The adjusted risk of AKI, increased by 14% per unit of increase in the APACHE score (OR 1.12 CI 95% 1.03-1.21 P=0.008).

Conclusion: Severity score is an independent risk factor of AKI in critically ill patients. Identification of high risk patient and early diagnosis is the only available way to prevent the disease and to improve outcomes.

ABBREVIATIONS

AKI: Acute Kidney Injury; ICU: Intensive Care Unit

INTRODUCTION

Acute kidney injury (AKI) represents a common clinical finding in critically ill patients leading to increased length of hospital stay, mortality and healthcare costs [1].

Until recently, due to lack of universally-agreed standard definition of AKI and existence of more than 35 different definitions, a wide range of prevalence (1-70%) and mortality rate of the disease (15-80%), was reported in the critically ill patients [2-4].

In 2004 Acute Dialysis Quality Initiative Group (ADQI), involving a broad consensus of experts in nephrology and critical care, introduced the RIFLE criteria of definition and classification of renal dysfunction [5]. A subsequent modification was proposed by the Acute Kidney Injury Network (AKIN) on 2007 [6] followed by Kidney Disease: Improving Global Outcomes (KDIGO) criteria proposed on 2012 [7].

Therefore, in the last decade, many studies have been published regarding epidemiology, disease severity and outcome in this setting, highlighting its impact to illness severity and risk of death. The concept of acute renal failure (ARF) was re-evaluated and the term was replaced by the term acute renal injury (AKI) highlighting that even small changes in serum creatinine levels influences outcome [8]. In addition, Cross-link between injured kidney and remote organs has been already demonstrated by a series of clinical, translational and experimental studies [4,9,10] contributing in the new perception of AKI which should be no longer considered a single disease or a marker of death process but rather a syndrome that involves many organs and clinical conditions.

According to recent results, the world incidence of AKI was identified to be very high and it was estimated that 1 in 5 adults experience AKI during a hospital episode of care. The incidence of the disease differed depending on geographical region and on the definition criteria used, however the higher rate was reported in critical care settings (31.7% in ICU) [1].

The accurate evaluation of AKI epidemiology in critical illness is very important within appropriate decisions, clinical practice and management of the patients. However, in most of the studies...
that has been completed in this direction, the ICU registries were the principal source of information supply [11-14].

Nevertheless, it is possible that a grade of misinterpretation regarding epidemiologic estimations may take place in cases of delayed ICU admission which seems to be associated with increased mortality. The impact of the suboptimal quality of care prior to ICU admission is of crucial importance regarding the potential reversibility of patient's condition and the increased morbidity and mortality of the delayed ICU-admitted patients may be wrongly correlated to various factors or diseases [15,16]. The frequency of all causes-delayed admission in ICU, vary between the counties as even by the definition of "delayed admission" used. Studies in England [17], Brazil [18] and Denmark [19] report the admission to be "delayed" in the 39, 69 and 52% respectively.

As a matter of fact, in different counties of the world (as in Greece) a non-immediately available bed in ICU is a very common problem. A prospective cohort study performed with critically ill patients in Brazil reports a 45% of delayed (with waiting period of 3 days) admissions and 23% of patient's death while waiting for an ICU bed [20]. Studies ICU-registries restricted, does not take into account the patients that will die while awaiting transfer or available ICU-bed, those that will be admitted in different units or those thaw will be transferred in a private or regional ICU. Furthermore, because of the limited number of ICU beds, a longer waiting time is observed in critically ill non-incubated patients and the majority of them may not be admitted (so neither counted) unless they get incubated within deterioration of their clinical condition. Taking into account the low percentage of critically ill patients admitted in ICU and the increased risk for death for each hour of delay of admission [18] it is clear how much generalizable might be the results of the ICU-registers restricted studies.

In the present study, for the reasons outlined above, the participants were represented by the totality of the critically ill patients instead of admitted patients only.

MATERIALS AND METHODS

This is a single-center retrospective study conducted in a general ICU of the University hospital "Attikon", an acute care tertiary hospital that provides comprehensive care, with the exception of transplant surgery and burn care.

Intensivists' consultations during a period of 2.5 months were considered. A total of 133 consultations, regarding 85 patients, took place in this period of time. Each patient participated only with the data available by the time of the first consultation while the cases of re-consultations were ignored. A total of 69 patients were included in the study after the exclusion of patients <18 years old (1), on chronic dialysis (n=7) and those with chronic renal failure (n=8). Chronic renal disease was defined as an estimated GFR <60 ml/min/1.73m² using MDRD equation (for the cases with known baseline serum creatinine level)

Data

Demographic data of the patients included age, sex, cause of attendance and source of consultation requested. The severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE II) and Sequential Organ Failure Assessment Score (SOFA). Physiologic data of the patients included: vital signs, Glasgow Coma Scale (GCS), hematocrit, white blood cells, sodium, potassium, glucose, bilirubin, gas-analysis, PO₂/FiO₂ ratio, A-a gradient. Clinical data included: the clinical diagnosis at time of referral, the need of vasoactive agents and pre-existing comorbidities. The triage priority 3 (SCCM) was also completed.

Identification of AKI

The presence of AKI was assessed only within the first consultation and was stratified by the three RIFLE categories of severity (Risk, Injury and Failure). Generally, all RIFLE categories are defined on basis of change in serum creatinine level and/or urine output. The last two letters of the acronym, L and E that represent two outcome criteria, according to the duration of loss of kidney function (Loss and End stage renal disease), they haven’t been evaluated in this study (Figure 1).

Because of the lack of information regarding the baseline creatinine of the patients the renal function was evaluated, as has been successfully adapted in other studies [21,22], with the Modification of Diet in Renal Disease (MDRD) formula, assuming a lower limit of normal baseline glomerular filtration ratio (GFR) of 75mI/min/1.73m². With this method, the baseline creatinine of a patient is calculated (in mg/dl or μmol/l) taking into account the patient's age, race and gender.

Statistical analysis

Statistical analysis was performed using the 16th version of Statistical Package for Social Sciences (SPSS) software. Normality was tested using Kolmogorov-Smirnov test. Normally distributed continuous variables are presented as mean and standard deviation (± SD) while the non-normally distributed are presented as median and interquartile range (IQR). Categorical and ordinal variables are presented as absolute and relative frequencies. Data were statistically tested using Chi square test, Students’ “t” test and the Mann Whitney test when appropriate. Logistic regression was performed in order to calculate the Odds ratio of independent risk factors of AKI.

Figure 1 RIFLE criteria.
RESULTS

The sample of the study consisted of 69 patients from 20 to 93 years old (med=72 IQR: 59-81). No difference regarding the age of the subjects was observed between man and women (P=0.26) (Table 1).

The department of requested consultation was the department of emergency (ED) in 29% of the cases while in the remaining 71% the source was the medical (46%) and surgical ward (recovery room included). The majority of the patients were incubated (87%) by the time of the first consultation. Less than a half of the patients (40%) were admitted to the ICU while a 12% was admitted in the Coronary Care Unit (CCI). A totality of 10 patients (15%) was transported in other regional or private ICU while the remaining 33% of the patients (n=23) died after a variable recovery time in the ward.

Diuresis was not recorded in 12 patients (17.5%) while in the rest of the cases a normal or diminished diuresis was assigned. Since no more specific data (as hourly output or recording time) was reported, such information was considered of a restricted value for the scope of the study. However, it is worth noting that in 56.5% of the cases an unaffected urine output (UO) was reported while in the 26% of the patients a grade of acute kidney injury (AKI) was detected (Table 2).

The estimated-creatinine baseline was calculated for each patient using the MDRD equation, assuming a lower limit of normal baseline GFR of 75ml/min/1.73m². By the time of first consultation a total of 30 patients (43%) presented a grade of renal dysfunction (Figure 2).

The patients were assigned, according to the Serum Creatinine Criteria only, to three RIFLE categories of severity (Risk, Injury and Failure).

Compared to the estimated-creatinine, an increase of more than 25% to 50% was observed in 20% of the cases (category R), an increase of 50% to 70% was observed in 10% of the subjects (category I) while a 13% of the patients presented a remarkable increase of 70% or more (category F).

The patients with AKI were more likely to be older. The prevalence of the disease was significantly lower in men (29%vs 59% x² 6.4 p<0.05). Logistic regression and chi square test with post hoc analysis were used to assess the association of AKI and of each RIFLE category with age and gender. Females were more likely to be more severely affected and the prevalence of the disease remained significantly higher compared to men at any group of age (Figure 3,4).

Patients with AKI were more frequently women (67%) and in 80% of the cases there was a positive medical history for chronic disease. One in two patients was hypertensive (53%) while medical history of cancer was the less representative of the chronic diseases that was taken in exam (20%). Infection was the initial diagnosis in the 50% and 36% of the patients with AKI and no-AKI patients respectively (P=0.24) and there were no difference in the developing AKI among medical and surgical patients (P=0.3).

Urea as well as creatinine blood levels were significantly

Table 1: Demographic characteristics, consultation’s source, clinical data, and incidence of AKI in the total of the participants.

| Age (years) | 72 (59-81) |
| Male sex % (N) | 51 (35) |
| consultation’s source (medical) % (N) | 65 (45) |
| Comorbidity (yes) % (N) | 75 (52) |
| Mechanical ventilation (yes) % (N) | 87 (60) |
| Vasoactive drug need (yes) % (N) | 64 (44) |
| APACHE II mean ± SD | 24 (±10) |
| SOFA mean ± SD | 8 (±3) |
| AKI % (N) | 43 (30) |

According to their distribution, continuous variables are presented either as mean and standard deviation (SD) or as median and Q1-Q3 interquartile range (IQR). APACHE II (Acute Physiology and Chronic Health Disease Classification System II, ranges from 0 to 71) and SOFA (Sequential Organ Failure Assessment, ranges from 0 to 24) are severity scores systems based on a number of laboratory values and patient signs.

Table 2: Demographic characteristics, medical history, clinical data and severity scores of the participants stratified by the presence of AKI.

| Age (years) | AKI (N=30) | NO AKI (N=39) | P-value |
| Male sex % (N) | 73 (63-81) | 72 (51-82) | 0.56 |
| Comorbidity (yes) % | 33 (10) | 64 (25) | 0.011* |
| medical history of: | | | |
| CVD % (N) | 33 (10) | 28 (11) | 0.6 |
| DM % (N) | 37 (11) | 21 (8) | 0.13 |
| CRD % (N) | 23 (7) | 23 (9) | 0.9 |
| MALIGN % (N) | 20 (6) | 28 (11) | 0.4 |
| HTN % (N) | 53 (16) | 38 (15) | 0.2 |
| MAP mmHg | 80 (±20) | 80 (±12) | 0.9 |
| HRR/min | 96 (±25) | 97 (±22) | 0.9 |
| A-a gradient mmHg | 478 (256-560) | 455 (220-560) | 0.7 |
| PO₂/FIO₂ mmHg | 117 (82-242) | 121 (71-300) | 0.9 |
| PCO₂ mmHg | 48 (35-74) | 45 (35-61) | 0.8 |
| HCO₃ mmol/l | 24 (16-30) | 23 (20-31) | 0.6 |
| PH | 7.23 (7.09-7.36) | 7.34 (7.25-7.44) | 0.009* |
| Hct % | 34 (±7) | 35 (±7) | 0.3 |
| WBC* 10⁹/µl | 15032 (±7100) | 13700 (±11100) | 0.5 |
| PLT* 10⁹/µl | 242 (202-286) | 240 (159-302) | 0.8 |
| K* mmol/l | 4.4 (3.9-5.3) | 3.9 (3.4-4.4) | 0.01* |
| Na* mmol/l | 137 (±8) | 139 (±7) | 0.4 |
| Ca mg/dl | 8.2 (±1) | 8.3 (±0.9) | 0.7 |
| Glu mg/dl | 148 (115-180) | 142 (115-183) | 0.8 |
| LAC mmol/l | 4.5 (1.7-11.3) | 2.3 (1.5-5.7) | 0.05 |
| Bil mg/dl | 0.6 (0.4-0.7) | 0.5 (0.3-0.8) | 0.9 |
| Alb g/dl | 2.9 (±0.7) | 3.3 (±0.6) | 0.1 |
| Urea mg/dl | 103 (69-131) | 44 (35-65) | <0.001* |
Creatinine mg/dl 1.75 (1.4—2.7) 0.9 (0.7-1.1) <0.001*
APACHE II 29 (±10) 21 (±7) <0.001*
SOFA 10 (±4) 8 (±3) 0.004*

**Abbreviations:** CVD: Cardiovascular Disease; DM: Diabetes Mellitus; CRD: Chronic Respiratory Disease; MALIGN: Malignancy; HTN: Hypertension; MAP: Mean Arterial Pressure; HR b/min: Heart Rate beats/minute; A-a gradient: Pa arterial - Pa alveolar O2 (measure of oxygenation--a normal A-a gradient for a young adult non-smoker breathing air, is between 5–10 mmHg); Glu: Glucose; LAC: Lactic Acid; Bil: Bilirubin; alb: Albumin

**APACHE II** (Acute Physiology and Chronic Health Disease Classification System II, ranges from 0 to 71) and **SOFA** (Sequential Organ Failure Assessment, ranges from 0 to 24) are severity scores systems based on a number of laboratory values and patient signs.

*p<0.05

**DISCUSSION**

Studies regarding critically ill patients usually are based on ICU-registries excluding in many cases a quiet important group of patients that are not be taken into account either because of their transfer in a private/regional ICU.

Besides, “delayed admissions” for reasons other than unavailability of ICU bed have been reported to be very common, and are associated with increased morbidity and mortality rates [23]. In these cases the potential opportunity of clinical-reversibility may get lost and the mortality may be wrongfully correlated to various factors or diseases [15].

In the present study, in order to evaluate the incidence and risk factors correlated to acute kidney injury we decided to include the totality of the critically ill patients instead of admitted patients only.

An increase in serum creatinine (SC) and/or a decrease in urine output (UO) are criteria for AKI detection and are both included in RIFLE, AKIN and KDIGO classification systems that define and stratify the severity of AKI. Common practical problems of all classification systems are the required accurate
Table 3: Odds ratio of independent risk factors of AKI (binary logistic regression).

<table>
<thead>
<tr>
<th>B</th>
<th>Adjusted OR</th>
<th>95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>-1.39</td>
<td>0.25</td>
<td>0.076-0.8</td>
</tr>
<tr>
<td>PH</td>
<td>-2.4</td>
<td>0.087</td>
<td>0.02-4.8</td>
</tr>
<tr>
<td>APACHE II</td>
<td>0.11</td>
<td>1.12</td>
<td>1.03-1.2</td>
</tr>
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Hosmer and Lameshow test P=0.73 and area under the curve (ROC) = 0.83 in the logistic regression model *p<0.05

hourly measurement of UO for at least six consecutive hours and the need of baseline creatinine level to be known. Taking into account the practical difficulties and the multifactorial influence on UO (hypotension, fluid balance, use of diuretics) AKI detection is often restricted on serum creatinine level. Besides, using MDRD formula (assuming a lower limit of normal baseline GFR of 75ml/min/1.73m²), changes in creatinine levels may be detected even in cases where the baseline creatinine is unknown. This way a very early detection of AKI in critically ill patients is allowed even in prior-ICU settings.

The incidence of AKI of critically ill patient that were admitted in ICU, was 35.7% but when even the non-admitted patients were included, the overall incidence of AKI was 43%.

Studies that evaluate the incidence of AKI in critically ill patients usually use ICU-registries and the collection of data starts after the patient’s admission in ICU. In situations where the percentage of the non-admitted patients is quite high (as in this study) or in cases where the admissions in ICU are much delayed (as very often is reported), the registries-based studies are not epidemiologically, representative of critically ill patients.

In this study, according to RIFLE-Serum Creatinine Criteria, a grade of kidney dysfunction was observed in the 43% of the patients by the time of the first consultation and in the 30% of them a severe disease was observed (“failure” category). Nevertheless, the majority of the patients (87%) were already incubated by the time of the first ICU-consultation and this could be a warning of misconception or low awareness of critically ill patients leading to delayed consultations.

Acidosis, higher levels of lactic acid and potassium as well as and female gender seemed to contribute significantly with AKI incidence. Nevertheless, the severity of illness represented the major independent risk factor of the disease. The adjusted risk of AKI, increased by 12% per unit of increase of the APACHE II score. Female gender is considered to be one of the risk factors for AKI and is included in several predictive scores. Because of the study’s design any correlation of this gender dimorphism (that still remains of unclear cause) with any potential reason was not feasible. Our results are in line with the increased risk of AKI carried by female gender and by patients with greater illness severity, documented by large observational studies [7,24,25].

As a matter of fact, no significant correlation was found for many well established risk factors as sepsis, need for mechanical ventilation or shock that represent leading precipitant of AKI in critically ill patients [24,26]. This is not surprising, since in the present study were included only data of the first consultation (which in 30% of the cases took place in the emergency department) and no follow up was revised.

There are notable limitations to our study. MDRD equation was used for the identification of AKI due to lack of baseline creatinine information. With this method, AKI’s incidence may be overestimated since in some cases might referred to patients with chronic Kidney disease. However this is in part counterbalance by: 1) the fact that urine-output criteria, that could have identify cases that were not identified with serum creatinine criteria [12,14], was not used and 2) in most of the cases there wasn’t overcome the appropriate or necessary length of time for the AKI to be established or to be detected.

We were not able (for obvious reasons) to evaluate “early AKI in critically ill patients” which commonly presuppose an over 24h admiss mission in ICU, but our aim was to highlight the importance of alertness in diagnosis of AKI and identification of high risk patient

The age, has been reported to be an important risk factor for AKI occurrence. The effect of age varies by the cause of AKI and in some cases is non-apparent. The inability of the present study to point a statistical significant correlation could be attributable to the cause/mechanism of the disease and/or to the limited number of the participants.

No comparison may be done between the incidence of AKI reported in this study with the incidence reported in other studies, where AKI is described during ICU-stay and at any time point.

Many factors such as drugs, metabolic state or nutrition alter urea and creatinine production and tubular adsorption or secretion capacity. This way, the reverse correlation between GFR and creatinine of the steady stage is lost during illness. Besides urine output is very often used as a guide to fluid or diuretics administration influencing both creatinine and urine-output criteria proposed. It is absolutely important the research to identify more accurate and specific markers of kidney injury but till then, the use of traditional markers seems a one-way street.

A large multicenter center analysis, with participation of institutions that share similar characteristics, need to be performed in order to evaluate the suspicious that severity of illness is by far the most important independent risk factor, surpassing the effect of other non-modifiable risk factors as age, gender or medical history.

It is our duty to contribute to the awareness of medical community in order to meliorate the prior-ICU medical care of critically ill patients that is many cases is the cornerstone of patient’s rescue.

REFERENCES

1. Susantitaphong P, Cruz DN, Cerda J, Abulfaraj M, Alqahtani F,


