Hospital-Acquired Acute Kidney Injury in Israel

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ABSTRACT: **Background:** Acute kidney injury remains a common significant clinical problem. Yet there are scant data in Israel on the incidence of hospital-acquired AKI and on diagnosis validity.

Objectives: To describe the epidemiology of AKI among hospitalized patients in the Western Galilee Hospital, Nahariya, compare discharge summaries to laboratory diagnosis, and investigate the impact of AKI on mortality and length of stay.

Methods: Computerized medical and laboratory data of 34,802 hospitalized subjects were collected. AKI was diagnosed according to three different definitions. We calculated the sensitivity and specificity of AKI based on ICD-9 diagnosis compared to patient's laboratory data as the gold standard.

Results: The overall AKI annual incidence rate was 1–5.1%, depending on the AKI definition used. The incidence of AKI based on ICD-9 diagnosis was significantly lower compared to the laboratory-based diagnosis. Average in-hospital length of stay was 2.4 times longer among patients with AKI compared to subjects without this condition. Furthermore, the in-hospital death rate among AKI patients was 14 times higher than among non-AKI hospitalized subjects, with a positive association between AKI severity and risk of death.

Conclusions: Using AKI laboratory diagnosis as the gold standard revealed ICD-9 diagnosis to be 9.1% sensitive and 99.4% specific. Hospital-acquired AKI is a major contributor to prolonged length of stay and high mortality rates; therefore, interventions to reduce in-hospital disease incidence are required.

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KEY WORDS: acute kidney injury, hospitalized patients, incidence rate, length of stay, mortality

Acute kidney injury is characterized by an abrupt decline in renal function resulting in inability of the kidney to excrete metabolic wastes and maintain proper fluid and electrolyte balance [1-5]. Although there is no universal laboratory definition of AKI, many studies define AKI as an increase in serum creatinine level of at least 0.5 mg/dl or 1.0 mg/dl compared to baseline level [2,6-8]. Recently, the ADQI (Acute Dialysis Quality Initiative) published a consensus definition of AKI using a set of criteria based on the severity of kidney damage, called the RIFLE criteria (**r**isk, **i**njury, **f**ailure, **l**oss, **e**nd stage) [9]. Studies have shown that the severity of renal function, as described by the RIFLE criteria, correlates with negative clinical outcomes, such as death [10-13].

AKI has been reported among 2–7% of hospitalized patients (reports from single centers) [2,6]. These rates are increasing [14], due not only to the aggressive treatment of an aging population but also to the impact of newer nephrotoxic medications and diagnostic procedures [2,13]. Despite advances in understanding the pathophysiology of AKI and improvement in medical techniques during the past several decades, patient mortality remains high [14]. Overall, 20% death rates were reported; 40–50% among patients with previous renal insufficiency and in those requiring renal replacement therapy [2].

There is abundant literature on the epidemiology of AKI, although most studies exploring downstream effects of AKI have either considered AKI requiring dialysis or dealt with selective homogenous populations, such as patients exposed to radio-contrast agents or undergoing cardiothoracic surgery [6], none of which focused on the epidemiology of AKI in Israel. The present study was undertaken for determining the incidence and outcome of AKI in a heterogeneous population in a public hospital in the north of Israel.

PATIENTS AND METHODS

We conducted a retrospective cohort study at the Western Galilee Hospital in Nahariya, Israel. The study population consisted of all adults and adolescents (aged 17 and above) admitted during the year 2006 (1 January to 31 December 2006). Exclusion criteria were: age < 17 years; pregnant women treated at the high risk pregnancy department/delivery room; patients with chronic kidney disease undergoing dialysis during hospital stay and/or patients with basal SCr level ≥ 6 mg/dl; and subjects referred to the emergency room during the study period and discharged on the same day.

A total of 34,802 eligible hospital admissions were identi-

AKI = acute kidney injury

SCr = serum creatinine

fied from a review of computerized hospital discharge medical records. SCr data were available for 30,484 patients from reviewing computerized laboratory records.

DATA COLLECTION

Selective data were electronically extracted from the following hospital computerized medical databases: a) discharge summary records, providing data on dates of patient's admission and discharge, name of relevant departments (admission and discharge), patient's ID and hospital admission number, patient's birth date, gender and status at discharge (alive or dead); b) diagnosis records, providing date of discharge that was collected for each patient diagnosed with at least one of the following medical conditions (ICD-9 coded): chronic kidney disease, heart failure, diabetes mellitus, hypertension, sepsis, ischemic heart disease, and cancer; c) laboratory records, providing patient's SCr level.

In order to merge all the above-mentioned data into a uniform platform, and enabling the creation of the necessary new variables needed for data analysis, new computerized programs were written, using visual basic application.

DEFINITIONS OF AKI

The presence of AKI was determined using three different definitions:

- *CD-9 diagnosis* – a patient was diagnosed with AKI if one of the following ICD-9 codes was noted in the hospital discharge records: 584 (acute renal failure), 584.5 (with lesion of tubular necrosis), 584.6 (with lesion of renal cortical necrosis), 584.7 (with lesion of renal medullary [papillary] necrosis), 584.8 (with other specified pathological lesion in kidney), and 584.9 (acute renal failure, unspecified).
- *Laboratory diagnosis* – the difference between peak and baseline SCr levels was calculated. A patient was diagnosed with AKI if laboratory records confirmed an increase in SCr level of at least 0.5 mg/dl during the patient's hospitalization. For individuals with only two determinations, the second, when higher than the first, was considered the peak. We assumed that individuals with no further monitoring or change in SCr level did not experience AKI. For individuals with more than two SCr measurements, we considered the minimum level as the baseline and the maximum, if measured after baseline, as the peak level. In case of a decrease in SCr level during hospitalization, not followed by increasing SCr results, the patient was considered not to have AKI.
- *RIFLE diagnosis* – a patient was diagnosed with AKI if data of SCr levels in laboratory records met with the RIFLE classification [9]. The differences between the peak and the baseline SCr levels were calculated similarly to that described above, except for the use of relative increase values (at least 1.5-fold) rather than a change in the absolute values. The severity of AKI was determined using the first three categories of the RIFLE classification (injury, risk and failure) and excluding the other two (loss of kidney function and end-stage kidney disease) due to absence of data regarding renal function for the long-term period (4 weeks and more than 3 months).

Data analysis of ICD-9 diagnosis (the first definition) refers to all eligible hospital admissions (34,802). Data analysis for the other definitions (laboratory and RIFLE diagnosis) refers only to admissions with SCr measurements (30,484).

DATA ANALYSIS

Data analysis was performed using SPSS software. Dichotomous variables were described as frequencies. Means and standard deviations were calculated for continuous variables. The demographic (age and gender) and clinical (co-morbidity) characteristics of subjects developing AKI during hospital stay were compared to characteristics of patients who did not develop AKI, using chi-square tests (for dichotomous variables), and *t*-tests (for continuous variables). Comparison of outcome variables was also performed using measures such as length of stay and mortality. Associations between AKI occurrence and hospital length of stay were examined using linear regression analysis. Length of stay was log-transformed to accommodate for data that were expectedly right-skewed. The associations between laboratory-defined AKI and mortality were tested using logistic regression models. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test.

RESULTS

A total of 34,802 patients were admitted to our hospital during the study period, including 30,484 (87.6%) admissions with one or more SCr measurements and 23,527 (67.6%) with two or more results. The demographic and clinical characteristics of the total population and of patients with known SCr levels are presented in Table 1.

A comparison between hospitalized patients who had at least one SCr reading and hospitalized patients without SCr results (regardless to AKI occurrence) revealed the former to be older (average age 58.9 vs. 41.6 years, $P < 0.001$), to have longer average length of stay (5.9 vs. 2.8 days, $P < 0.001$) and higher mortality rates (2.8% vs. 0.2%, $P < 0.001$).

Patients with two or more SCr results were more likely to have higher co-morbidity rates (hypertension, cancer, chronic kidney disease, ischemic heart disease, diabetes, heart failure, or sepsis), to have longer length of stay, higher mortality rates, and to be older [Table 1].

Cumulative incidence of AKI in the total population ranged from 1% to 5.1%, depending on the AKI definition

Table 1. Demographic and clinical characteristics of study populations

		Total population (N=34,802)		Available SCr level (N= 30,484)		One SCr result (N= 6957) (1)		Two or more SCr results (N= 23,527) (2)		*P* value (1) vs. (2)
	Category	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Gender	Male	16582	47.6	14966	49.1	3356	48.2	11610	49.3	< 0.001
	Female	18220	52.4	15518	50.9	3601	51.8	11917	50.7	
	Total	**34,802**	**100.0**	**30484**	**100.0**	**6957**	**100.0**	**23527**	**100.0**	
Age (yrs)	17–24	3389	9.7	2390	7.8	1143	16.4	1247	5.3	< 0.001
	25–44	7421	21.3	5681	18.6	2460	35.4	3221	13.7	
	4—64	9027	25.9	8188	26.9	1823	26.2	6365	27.1	
	65-74	5754	16.5	5405	17.7	763	11.0	4642	19.7	
	75+	9211	26.5	8820	28.9	768	11.0	8052	34.2	
	Total	**34,802**	**100.0**	**30484**	**100.0**	**6957**	**100.0**	**23527**	**100.0**	
Age, mean (SD)	Male	56.6 (20.5)		57.8 (20.2)		47.6 (19.8)		60.8 (19.3)		< 0.001
	Female	56.9 (22.2)		59.9 (21.4)		44.5 (19.8)		64.7 (19.6)		< 0.001
	Total	**56.8 (21.4)**		**58.9 (20.8)**		**45.9 (19.9)**		**62.7 (19.5)**		**< 0.001**
Co-morbidity	HTN	4043	11.6	3801	12.5	503	7.2	3298	14.0	< 0.001
	IHD	2600	7.5	2512	8.2	201	2.9	2311	9.8	< 0.001
	DM	2250	6.5	2139	7.0	278	4.0	1861	7.9	< 0.001
	CKD	1418	4.1	1372	4.5	107	1.5	1265	5.4	< 0.001
	Cancer	1256	3.6	1161	3.8	226	3.2	935	4.0	0.005
	HF	959	2.8	950	3.1	37	0.5	913	3.9	< 0.001
	Sepsis	271	0.8	270	0.9	12	0.2	258	1.1	< 0.001
Exposure	Contrast media	2227	6.4	2187	7.2	457	6.6	1729	7.3	0.027
	Surgery	8221	23.6	5540	18.2	2163	31.1	3377	14.4	< 0.001
Outcomes	Mortality	856	2.5	847	2.8	84	1.2	763	3.2	< 0.001
	LOS days (SD)	5.5 (5.8)		5.9 (6.0)		3.8 (2.5)		6.6 (6.0)		< 0.001

HTN = hypertension, IHD = ischemic heart disease, DM = diabetes mellitus, CKD = chronic kidney disease, HF = heart failure, LOS = length of stay.

used [Table 2]. The ICD-9 diagnosis displayed the lowest incidence. Using AKI laboratory diagnosis as the gold standard revealed ICD-9 diagnosis to be 9.1% sensitive, 99.4% specific, and to have a positive predictive value of 48.5% and a negative predictive value of 94.5%. Overall accuracy was 94.0 %.

Referring to the total population, the cumulative incidence of AKI was similar between genders (5.8% in males vs. 6.1% in females, $P = 0.4$), but was positively associated with patient's age: for patients aged 17–24, 25–44, 45–64, 65–74 and 75+, the incidence rates were 0.8%, 1.2%, 4.1%, 8.2% and 10.7% respectively ($P < 0.001$). The average age of AKI patients (72.3 years, SD 14.32) was higher than that of patients who did not develop AKI (58.1 years, SD 20.91, $P < 0.001$); this phenomenon was demonstrated for both genders: for males (N=14,966), the average age of AKI patients was 70.7 years (SD 14.8) vs. 57.0 years (SD 20.2) for patients who did not develop AKI ($P < 0.001$); for females, the average age of AKI patients was 73.9 years (SD 13.6) vs. 59.1 years (SD 21.5) for patients who did not develop AKI ($P < 0.001$).

AKI was more prevalent among patients who had co-morbidities, such as sepsis, chronic kidney disease, heart failure, cancer, ischemic heart disease, diabetes and hypertension [Table 3]. Intensive care units (general and respiratory) were the wards with the highest incidence of AKI (cumulative incidence: 54.4%, incidence rate 67.2/1000 person days).

CLINICAL OUTCOMES

Length of stay: Total population average in-hospital LOS was 5.5 days (SD 5.8). Among patients with AKI, the average LOS was 2.4 times longer compared to subjects without this condition [13.2 days (SD 12.52) vs. 5.5 days (SD 5.08) respectively, $P < 0.001$]. A positive association was noticed between AKI severity (as reflected by the RIFLE classification) and average LOS: compared to an average of 5.4 hospitalization days in subjects without AKI, the average number of hospitalization days for patients with AKI was 13.3 days for cases in the RIFLE "risk" category, 18.6 for cases in the "injury" category and 21.0 days for cases in the "failure" category ($P < 0.001$). The linear regression model explained approximately 21% of the variance in LOS and was well fit (P value for statistic $F < 0.001$). Other factors affecting LOS, in decreasing importance, were age, undergoing surgical procedure, exposure to contrast media, and presence of heart failure, chronic kidney disease, cancer, sepsis, diabetes and ischemic heart disease.

Mortality: Mortality rates among 1809 patients with laboratory diagnosis AKI was 13.6 times higher compared to patients without AKI (21.8% vs. 1.6% respectively, $P < 0.001$). Using a logistic regression model to control for potential confounders – characteristics that were significantly associated with mortality in the univariate analysis (chronic kidney disease, heart failure, malignancy, sepsis, age and gender) – revealed a risk of mortality almost 10 times (odds ratio = 9.8) higher among patients who developed AKI as compared to those who did not. Higher odds ratios for in-hospital mortality were also noticed with increasing severity of AKI based on the RIFLE classification [Table 4].

LOS = length of stay

Table 2. Incidence of AKI (%) by diagnostic criteria

Diagnostic criteria	Total population (N=34,802)		Patients with SCr level (N=30,484)	
	N	%	N	%
ICD-9 diagnosis	342	1.0	338	1.1
RIFLE diagnosis*	1331	3.8	1331	4.4
Laboratory diagnosis**	1809	5.1	1809	5.9

* Ref. [9]

** An increase in SCr level of at least 0.5 mg/dl compared to baseline level

Table 3. Prevalence ratios and odds ratios for laboratory acute kidney injury by selected medical conditions (N=30,484)

		Total (N=30,484)		AKI (N=1809)		PR	OR (95% CI)	*P* value
		N	%	N	%			
Sepsis	Yes	270	100.0	140	51.9	9.40	18.4	< 0.001
	No	30214	100.0	1669	5.5		(14.43-23.50)	
Chronic kidney disease	Yes	1372	100.0	293	21.4	4.11	4.9	< 0.001
	No	29112	100.0	1516	5.2		(5.68–4.30)	
Heart failure	Yes	950	100.0	155	16.3	2.90	3.2	< 0.001
	No	29534	100.0	1654	5.6		(3.91–2.74)	
Cancer	Yes	1161	100.0	120	10.3	1.77	1.9	< 0.001
	No	29323	100.0	1689	5.8		(2.29–1.55)	
Ischemic heart disease	Yes	2512	100.0	212	8.4	1.47	1.5	< 0.001
	No	27972	100.0	1597	5.7		(1.76–1.31)	
Diabetes mellitus	Yes	2139	100.0	170	7.9	1.36	1.4	< 0.001
	No	28345	100.0	1639	5.8		(1.65–1.19)	
Hypertension	Yes	3801	100.0	256	6.7	1.16	1.2	0.02
	No	26683	100.0	1553	5.8		(1.34–1.02)	

PR = prevalence ratio, OR = odds ratio, CI = confidence interval

Table 4. Logistic regression model to predict in-hospital mortality by RIFLE classification (N=30,484)

RIFLE	% deceased	OR*	95%CI	*P*
No AKI	1.7	1.0		
Risk	18.6	7.9	(6.3, 9.8)	< 0.001
Injury	37.7	17.2	(12.9, 22.7)	< 0.001
Failure	43.3	28.2	(18.4, 43.0)	< 0.001

* Adjusted for chronic kidney disease, heart failure, cancer, sepsis age and gender.

DISCUSSION

To the best of our knowledge, only one study has examined the epidemiology of AKI in Israel, and that was published three decades ago [15]. According to that study the mean annual incidence of AKI was 4.8/1,000,000. During recent years we have observed more aggressive treatment of an aging population and newer nephrotoxic medications and diagnostic procedures [2,13]. These could be responsible for a change in the epidemiology of AKI. Our study is the only updated study focusing on the epidemiology of AKI in Israel. The incidence of AKI among study participants ranged from 1 to 5.1%, depending on the definition used. The higher incidence rates of AKI based on the laboratory diagnosis, as compared to the ICD-9 diagnosis, suggest that physicians tend to underestimate "mild cases" of AKI. The similarity between our incidence results (3.9–5.1%) based on laboratory diagnosis to other published reports [2,6,14] supports the validity of our laboratory-defined find-

ings. As shown, the ICD-9 diagnosis was most effective in identifying patients without AKI (negative predictive value 94.5%). However, approximately 90% of patients with laboratory criteria for AKI were falsely diagnosed as not having AKI. Similar findings were described by Liangos et al. [16] and Waikar et al. [18].

Our finding of a higher in-hospital death rate among AKI patients is consistent with previous studies [2,14,17,19-22]. The higher mortality and longer LOS were probably due to patients' severe sickness [14], although other studies have indicated that co-morbid conditions only partly account for the mortality difference noted between patients with and without AKI [14,19]. Furthermore, in our multivariate logistic regression models (including other mortality-related variables), AKI was still a significant independent predictor of death.

AKI was strongly associated with older age. This is consistent with several studies that reported older individuals to be at a higher risk for AKI [14,16,17,21]. This is not a surprising finding, especially since kidney function in known to decline in the elderly. Moreover, arguments such as the decrease in patients' ability to accommodate oxidant injury and the increase in vascular stiffness with age are thought to contribute to the increased risk of AKI among older patients [23,24]. As noted in other studies [16,25], we also found that AKI was associated with co-morbid conditions, such as diabetes, hypertension, heart failure, ischemic heart disease, sepsis and cancer.

LIMITATIONS

Several methodological limitations should be mentioned. Firstly, we intended to estimate in-hospital occurrence of AKI. In some patients, however, deterioration of renal function may have started in the community. No data regarding last SCr level prior to patients' admission were collected, therefore we could not rule out patients with AKI upon admission. Nevertheless, the similarity of AKI rates to those reported by others [2,6,14] suggests that overestimation of in-hospital AKI, if it exists, is probably minor. Secondly, SCr data were available for 30,484 (87.6%) of all hospitalized patients. The reliance on this selective group, probably characterized by some risk factors for AKI (compared to patients with missing data), might have introduced some overestimation of AKI incidence (selection bias). Sensitivity analysis, assuming that none of the patients with missing SCr level developed AKI vs. all patients with missing SCr level who developed the condition, suggests an AKI incidence range of 5.1–17.6%. Since the first assumption seems more reasonable, the incidence of 5.1% in the total population is reported. Thirdly, the presence of AKI was determined by ICD-9 codes in discharge records. Since no data were available in discharge summaries about nephrologists' involvement in the patient's diagnosis, we do not know what proportion of AKI diagnoses were made by nephrologists. Some inaccuracies may have therefore been introduced. Fourthly, regarding laboratory diagnosis of AKI, we assumed that patients with only one SCr reading did not experience AKI. This may result in underestimation of the proportion of patients who were classified as having AKI. Sensitivity analysis, assuming that none of the patients with one SCr level developed AKI vs. all patients with one SCr reading who developed the condition, suggests an AKI laboratory diagnosis incidence range of 5.9–28.7% respectively. Since the first assumption seems more reasonable, an incidence of 5.9% is reported. Fifthly, the discharge summary records – the source for examining the relationship between AKI and other patient's co-morbidities – had no data on a temporal relationship. Data analysis was therefore treated as cross-sectional, with prevalence ratios and odds ratios calculated. In addition, similar to the underestimation found regarding ICD-9-based AKI occurrence, we might have underestimated the prevalence of co-morbidities as well. Nonetheless, we believe our comparative results are correct since there is no reason to believe that this bias was differently distributed among AKI and non-AKI patients. Finally, the study was conducted in a single general hospital in northern Israel. Although internally valid, it does not necessarily ensure external validity to all Israeli hospitalizations.

STRENGTH OF THE STUDY

The strength of this study stems from the following: first, the study was based on a large cohort (N=34,802) of patients admitted to the hospital during a full calendar year. Hence, it includes a heterogeneous population, admitted at different seasons, to various hospital wards, having both medical and surgical problems and undergoing various procedures. The use of the laboratory definition of AKI (based on SCr level), in addition to the ICD-9-coded medical diagnoses, enabled data analysis for both mild, moderate and severe cases of AKI, thus better estimating incidence and outcome of the condition.

In conclusion, AKI occurred among 5.1% of hospitalized patients, and was associated with significantly increased mortality and LOS. These outcomes were related to AKI severity, using uniform definitions of the RIFLE classification. Based on the present study, ICD-9 diagnosis compared to laboratory diagnosis was found to be only 9.1% sensitive. This markedly low sensitivity emphasizes the necessity to enhance knowledge and awareness among hospital and community clinicians of the definition, diagnosis and clinical outcomes of AKI. We assume that patients who developed mild AKI with an increase in SCr level of 0.5 mg/dl may erroneously have seemed in lesser need of therapy. However, we believe it is of major importance, both from the hospital management and public health points of view, to diagnose them in order

to decrease the high rates of morbidity and mortality. Further inquiry into new prevention strategies and techniques dealing with AKI is required, especially since AKI occurrence is not in decline. Finding new preventive strategies for intervention may reduce the incidence of AKI and probably improve its clinical outcomes. It is necessary to continue collecting and analyzing similar future data in order to identify trends in AKI incidence and outcomes (mortality, LOS), as well as to assess the impact of relevant interventions. Future studies investigating new markers, reflecting early kidney injury, separately from markers used today to detect kidney function, is important for diagnosing AKI in its early stages.

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"Faith" is a fine invention
For gentlemen who see
But microscopes are prudent
In an emergency

Emily Dickinson (1830-1886), U.S. poet. Dickinson was a prolific private poet, though fewer than a dozen of her nearly 18,000 poems were published during her lifetime. Her works are mostly brief intense lyrics on themes of love, death, and nature. She led an introverted and reclusive life and was thought of as an eccentric by the locals; she became known for her penchant for white clothing and her reluctance to greet guests or, later in life, even leave her room. Most of her friendships were therefore carried out by correspondence. Today she is considered a major American poet.