Original Article

Impact of Early Nephrology Referral on the Outcomes of Patients with Acute Kidney Injury

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Abstract

Background: Acute kidney injury (AKI) is associated with an increase in patient mortality and high rates of renal/non-renal complications. Late detection of the disease has been associated with worse prognosis, but no such study has been conducted from Saudi Arabia.

Objectives: To assess the impact of early nephrology referral on the outcomes of patients with AKI.

Methods: This retrospective record review included all adult patients (≥18 years) with AKI who were referred to the Nephrology Department at King Abdulaziz University Hospital, Jeddah, Saudi Arabia, between May 2019 and July 2020. AKI was defined according to the Kidney Disease Improving Global Outcomes criteria. AKI patients evaluated by nephrologists were stratified into early referral group (i.e., referral in <48 h from the first detection of AKI) and late referral group (referral ≥48 h after the first detection of AKI).

Results: A total of 400 patients met the inclusion criteria, of which 264 (66%) were early referrals. A significant association was found between delayed referral and mortality rates and length of hospital stay (for both, $P = 0.001$). Late referral was also significantly associated with increased likeliness of the need for renal replacement therapy ($P = 0.037$) and sepsis ($P = 0.005$).

Conclusions: The outcomes were worse for patients with AKI receiving late referrals to nephrologists. Raising the awareness of AKI among non-nephrologists would likely increase the proportion of earlier referrals.

Keywords: Acute kidney injury, late referral, length of stay, mortality, renal replacement therapy, Saudi Arabia

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INTRODUCTION

Acute kidney injury (AKI) is an abrupt reduction in kidney function that results in the retention of metabolic waste products and fluids, electrolytes, and acid-base homeostasis dysregulations.[1] AKI is associated with serious morbidity and mortality, and also plays an essential role in the development of chronic kidney disease (CKD), progression of end-stage renal disease (ESRD), and in causing long-term non-renal morbidity.[2-4]

The global prevalence of AKI has been found to vary from >1% to 66%. Such huge differences in the reported prevalence is not only because of differences in country-wise populations and income level but also because

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of differences in the AKI classification criteria used.[5] Currently, the most commonly used classification is the Kidney Disease: Improving Global Outcomes (KDIGO) classification, which has evolved mainly from the Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) classification and its subsequently modified Acute kidney injury network classification.[6]

The care of patients with AKI is often suboptimal and not well-standardized.[7] There are many reasons for this phenomenon, but the two most important are delays in referring these patients to nephrologists and the challenges in managing the complexity of the condition.[8] In terms of delays in referrals, a study from a Brazilian teaching hospital found that nephrology consultations were delayed in 62.3% of the patients with AKI, which in turn contributed to an increase in the mortality rate.[9] Similarly, a recent study found that a 4-day delay in referring AKI patients to nephrologist was associated with an increased likelihood of mortality compared to those receiving referral within 4 days (74.5% vs. 50.0%, respectively).[10] A similar finding was also reported in a study from Italy,[11] while in a study from Canada, better survival rates were reported in patients who had early nephrologist consultations and were subsequently started on short-term dialysis.[12]

A considerable amount of literature has been published on the effect of nephrology referral time, and based on these findings, it has been hypothesized that late referral leads to poorer outcomes, longer hospital stays, and increased mortality rates. However, to the best of the author's knowledge, no such study has been conducted in a Saudi cohort. Accordingly, this study was conducted with the objective of demonstrating the impact of early nephrology referral on the outcomes of patients with AKI at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia.

METHODS

Study setting and participants

This retrospective chart review included all adult patients (≥18 years) with AKI who were referred to the Nephrology Department at KAUH between May 1, 2019 to July 31, 2020. KAUH which is the main teaching hospital in the Western region of Saudi Arabia and a tertiary care hospital that provides multinational healthcare to a mixed socio-economic population. This study was approved by the Institutional Review Board (IRB) at KAUH.

AKI was defined according to the KDIGO guidelines as any of the following: an increase in serum creatinine (SCr) to ≥0.3 mg/dl within 48 h, an increase in SCr to ×1.5 baseline values, which is known or presumed to have occurred within the past 7 days, or urine volume <0.5 ml/kg/h for 6 hours.[13] AKI patients evaluated by nephrologists were stratified into two groups: the early and late referral groups (comprising those referred <48 h and ≥48 h from the first detection, respectively). Patients aged <18 years, with end-stage renal disease on regular hemodialysis, kidney transplantation, and/or with no data regarding the time of nephrologist referral were excluded.

Outcomes

The primary outcome was to explore the association between referral time and mortality. Clinical and laboratory characteristics, comorbid conditions, length of hospital stay, and need for renal replacement therapy (RRT) were also recorded.

Data collection

The following data were extracted from the medical records of the hospital's electronic system (Phoenix): medical record number, age, gender, nationality, requesting service, comorbid conditions (diabetes mellitus, hypertension, ischemic heart disease, chronic heart failure, malignancy, cerebrovascular disease, thyroid disease, chronic liver disease, peripheral vascular disease, respiratory disease, and CKD), precipitating factors of AKI (hypotension, obstructive uropathy, sepsis, contrast-induced nephropathy, urinary tract infection and dehydration), need for RRT, time of referral, and length of hospitalization. Several clinical laboratory tests were used to evaluate kidney function, including SCr, potassium, sodium, and blood urea nitrogen levels at admission. The SCr level were documented on the day of referral and days 1, 2, and 7 after referral; only the maximum level was recorded for this study. Before the discharge or death, the latest SCr levels were also measured to estimate disease improvement or progression. SCr levels were determined using the Jaffe method.

Statistical analysis

Microsoft Excel 2016 was used for data entry, and statistical analysis was performed using the SPSS version 25. Qualitative data were expressed as numbers and percentages, and the Chi-squared test was used to assess the relationship between variables. Quantitative data were expressed as mean and standard deviation (±SD). Data normality was assessed using the one-sample Kolmogorov–Smirnov test, where the Mann–Whitney test was used for non-parametric variables. Variables with significant univariate associations were used in multivariable analysis. Multivariable logistic regression analysis was performed using backward variable selection to adjust for confounding and selection bias for

factors associated with increase mortality. Variables not selected by the automated procedure were added back into models individually to evaluate for residual confounding. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 400 patients met the inclusion criteria, of which the majority were male (58%). When stratified by referral, most patients were referred early (66%). The median age at diagnosis was 61.5 years and 67 years for the early and late referral groups, respectively.

The differences between the early and late referral groups based on patient characteristics, comorbidities, RRT, and length of hospitalization are presented in Table 1. The late referral group had a higher mortality rate than the early referral group (56.7% vs. 43.3%, $P = 0.001$), and longer length of hospitalization (21.4 ± 21.0 days vs. 14.8 ± 16.1 days; $P = 0.001$). The proportion of patients who needed RRT and who had sepsis were lower in the early referral group than in the late referral group (28% [74/264] vs. 38.2% [52/136]; $P = 0.037$) and 26.1% [69/264] vs. 39.7% [54/136], $P = 0.005$, respectively) [Table 1]. Table 2 shows that the two groups did not differ significantly in terms of SCr, sodium, potassium, and blood urea nitrogen levels. As shown in Table 3, patients who died were significantly older and referred late ($P = 0.001$). Also, a higher proportion of these patients had diabetes mellitus ($P = 0.007$), sepsis ($P = 0.001$), chronic liver diseases and hypotension ($P = 0.001$). Additionally, these patients had a higher mean SCr level on day 7 after referral ($P = 0.026$), and their most recent SCr reading before death and blood urea nitrogen were increased ($P = 0.001$). On the other hand, a non-significant relationship was found between mortality and gender, other chronic diseases, SCr level on the day of referral, maximum SCr level during admission, serum potassium, or serum sodium. The multivariate logistic regression analysis identified multiple independent predictors of mortality among the patients including older age [odds ratio (OR) = 0.96; 95% confidence interval (CI): 0.95-0.98; $P = 0.001$], ischemic heart diseases (OR = 1.92; 95% CI: 1.05-3.51; $P = 0.032$), autoimmune diseases (OR = 5.54; 95% CI: 1.06-28.89; $P = 0.042$), chronic liver diseases (OR = 4.69; 95% CI: 1.76-12.48; $P = 0.002$), hypotension (OR = 2.76; 95% CI: 1.2-6.35; $P = 0.016$), obstructive uropathy (OR = 0.34; 95% CI: 0.1-1.08; $P = 0.09$), sepsis (OR = 2.77; 95% CI: 1.58-4.58; $P < 0.001$), high level of blood urea nitrogen (OR = 0.96; 95% CI: 0.95-0.98; $P < 0.001$), and time of referral (OR = 0.15; 95% CI: 0.08-0.28; $P < 0.001$) [Table 4].

Table 1: Comparison between the early and late referral groups based on clinical and demographic characteristics

Variable	Early referral group	Late referral group	χ^2	*P*
Median age (years)	61.5	67.0	2.81*	0.005
Gender				
Female	119 (70.8)	49 (29.2)	3.01	0.082
Male	145 (62.5)	87 (37.5)		
Nationality				
Non-Saudi	137 (63.1)	80 (36.9)	1.73	0.188
Saudi	127 (69.4)	56 (30.6)		
Death				
Yes	58 (43.3)	76 (56.7)	46.33	0.001
No	206 (77.4)	60 (22.6)		
Diabetes mellitus	174 (67.2)	85 (32.8)	0.45	0.499
Hypertension	185 (67.5)	89 (32.5)	0.89	0.345
Ischemic heart disease	73 (64.6)	40 (35.4)	0.13	0.711
Chronic heart failure	46 (60.5)	30 (39.5)	1.25	0.263
Malignancy	47 (58)	34 (42)	2.87	0.09
Cerebrovascular diseases	37 (64.9)	20 (35.1)	0.03	0.851
Thyroid disorders	16 (64)	9 (36)	0.04	0.827
Chronic liver diseases	18 (66.7)	9 (33.3)	0.006	0.94
Peripheral vascular diseases	10 (71.4)	4 (28.6)	0.19	0.662
Respiratory diseases	43 (67.2)	21 (32.8)	0.04	0.827
Obstructive uropathy	28 (70)	12 (30)	0.31	0.573
Dehydration	38 (62.3)	23 (37.7)	0.44	0.507
Hypotension	22 (56.4)	17 (43.6)	1.77	0.183
Sepsis	69 (26.1)	54 (39.7)	7.76	0.005
Contrast-induced nephropathy	14 (56)	11 (44)	1.18	0.276
Urinary tract infection	33 (68.8)	15 (31.3)	0.18	0.668
CKD	90 (64.3)	50 (35.7)	0.28	0.595
Needed for RRT	74 (28.0)	52 (38.2)	4.33	0.037
Length of hospitalization (days)	14.83±16.05	21.42±21.03	3.23*	0.001

*Mann–Whitney test. RRT – Renal replacement therapy; CKD – Chronic kidney disease

DISCUSSION

The distribution of early and late referral to nephrology in this study (i.e., 66% and 34%, respectively) is in line with the findings from a Brazilian teaching hospital that found 34% of the referrals were late.[14] The high proportion of early referral in the current study is likely due to our hospital being a tertiary care teaching center with a multidisciplinary system that allows immediate referral to a variety of specialties including nephrology. Nonetheless, given that the rate of sepsis and RRT were found to be significantly lower in the early referral group, it is important that future studies determine factors for late referrals in Saudi Arabia. In low income/resource limited countries, the knowledge of non-nephrologist has mostly been found to be modest.[15,16] Surprisingly, a study from the United Kingdom revealed that 37% of junior doctors were not able to name a single indication of AKI for nephrology referral.[17] From Saudi Arabia, variations were reported in the knowledge of risk factors and assessments for AKI among healthcare professionals.[18] Collectively, these findings indicate that lower knowledge of AKI among non-nephrologists may be a major factor contributing to a considerable proportion of referrals being late.

Table 2: Comparison between the early and late referral groups based on selected laboratory parameters

Variable	Early referral group	Late referral group	Mann–Whitney test	*P*
SCr level on day of referral (μmol/L)	380.7±320.2	327.0±229.4	0.77	0.436
SCr level on day 1 after referral (μmol/L)	371.5±296.3	316.3±217.6	0.95	0.342
SCr level on day 2 after referral (μmol/L)	337.4±286.7	335±216.8	1.14	0.254
SCr level on day 7 after referral (μmol/L)	309.4±258.3	295.1±202	0.47	0.632
Maximum SCr level during admission (μmol/L)	460.9±376.8	429±259	0.41	0.682
Latest SCr level before discharge (μmol/L)	297.6±234.2	301.2±206.5	0.75	0.45
Blood urea nitrogen (mmol/L)	23.2±15.7	24.5±16.0	0.89	0.372
Serum potassium (mmol/L)	4.3±8.7	4.29±8.6	0.1	0.915
Serum sodium (mmol/L)	136.62±9.7	136.95±7.7	0.98	0.325

SCr – Serum creatinine

Table 3: Relationship between mortality and patient characteristics, comorbidities, length of hospitalization, serum creatinine, sodium, potassium, and blood urea nitrogen levels

Variable	Mortality		χ^2	*P*
	Yes, *n* (%)	No, *n* (%)		
Age	66±15.5	59.3±16.6	3.85*	0.001
Referral				
Early	58 (22)	206 (78)	46.33	0.001
Late	76 (55.9)	60 (44.1)		
Gender				
Female	62 (36.9)	106 (63.1)	1.5	0.22
Male	72 (31)	160 (69)		
Needed for RRT	58 (46)	68 (54)	12.69	<0.001
Diabetes mellitus	99 (88.2)	160 (61.8)	7.36	0.007
Hypertension	99 (36.1)	175 (63.9)	2.7	0.1
Ischemic heart disease	52 (46)	61 (54)	11.07	0.001
Congestive heart failure	28 (36.8)	48 (63.2)	0.47	0.493
Cerebrovascular diseases	27 (47.4)	30 (52.6)	5.73	0.017
Chronic liver disease	17 (63)	10 (37)	11.28	0.001
Malignancy	29 (35.8)	52 (64.2)	0.24	0.623
Obstructive uropathy	6 (15)	34 (85)	6.82	0.009
Sepsis	63 (51.2)	60 (48.8)	25.03	0.001
CKD	37 (26.4)	103 (73.6)	4.83	0.028
Length of hospitalization (days)	22.5±21.1	14.4±15.9	3.7	<0.001
SCr level on the day of referral (μmol/L)	332±208.3	377.5±327.4	0.21	0.827
SCr level on day 7 after referral (μmol/L)	321.1±202.6	295.3±256.1	2.22	0.026
Maximum SCr level during admission (μmol/L)	437.9±211.4	456.1±391.0	1.92	0.054
Latest SCr reading before death (μmol/L)	354.5±191.1	270.5±235.6	5.53	0.001
Blood urea nitrogen (mmol/L)	27.9±15.5	21.5±15.5	4.63	0.001
Serum potassium (mmol/L)	4.3±0.9	4.3±0.8	0.02	0.891
Serum sodium (mmol/L)	138.1±12.5	136.0±6.7	1.81	0.07

RRT – Renal replacement therapy; SCr – Serum creatinine; CKD – Chronic kidney disease

Another possible reason for late referrals is that AKI presentation varies between patients, with some having delays in the rise of SCr levels, thereby affecting physicians' assessment of the condition.[19] Another factor that could have played a role is the change in AKI definition over the last decades, with AKI being redefined multiple times up until the most recent KDIGO classification; yet, although the KDIGO criteria provides a unique basis for epidemiologic and interventional outcome studies, these criteria are not commonly used in clinical settings.[20]

In this study, we found a significant association between referral time and mortality, with patients who were referred late to a nephrologist having significantly higher mortality than those who were referred early ($P = 0.001$). This finding is consistent with that of Silva *et al*.,[14] who found that patients with a late referral had higher mortality rates. The impact of AKI on fluid balance and metabolic product elimination may exacerbate respiratory, cardiac, gastrointestinal, hematologic, central nervous system, and immunological function, which may lead to an increase in mortality.[9] AKI patients are also at a 25% higher risk of developing CKD and even ESRD, which increases the risk of mortality by 50%.[21]

The results of the current study represent an important finding for physicians worldwide, but especially more so in countries with similar socioeconomic and healthcare setting and geographic proximity to Saudi Arabia. This study was conducted in Western Saudi Arabia, which has one the most diverse multi-ethnic citizens and multi-national residents of the country, and thus our findings do raise awareness regarding

Table 4: Multivariate logistic regression analysis of independent predictors (risk factors) of mortality among patients

Variable	*B*	Wald	*P*	OR (95% CI)
Age	0.03	10.69	0.001	0.96 (0.95–0.98)
Gender	0.45	2.54	0.111	1.57 (0.9–2.76)
Diabetes mellitus	0.28	0.62	0.432	1.33 (0.65–2.73)
Hypertension	0.37	1.08	0.297	1.45 (0.71–2.96)
Ischemic heart disease	0.65	4.58	0.032	1.92 (1.05–3.51)
Congestive heart failure	0.21	0.39	0.529	0.8 (0.4–1.58)
Malignancy	0.21	0.31	0.574	1.24 (0.58–2.66)
Cerebrovascular diseases	0.11	0.08	0.768	1.12 (0.51–2.45)
Autoimmune diseases	1.71	4.13	0.042	5.54 (1.06–28.89)
Thyroid disorders	0.01	0.001	0.978	1.01 (0.33–3.04)
Chronic liver diseases	1.54	9.61	0.002	4.69 (1.76–12.48)
Peripheral vascular diseases	0.01	0.001	0.98	0.98 (0.28–3.46)
Respiratory diseases	0.03	0.01	0.919	0.96 (0.46–1.98)
Myocardial infarction	0.41	0.64	0.424	1.51 (0.54–4.2)
Hypotension	1.01	5.78	0.016	2.76 (1.2–6.35)
Obstructive uropathy	1.08	3.31	0.09	0.34 (0.1–1.08)
Dehydration	0.41	1.22	0.268	1.51 (0.72–3.14)
Sepsis	1.02	12.83	<0.001	2.77 (1.58–4.58)
Contrast induced nephropathy	0.1	0.02	0.865	0.9 (0.27–2.59)
Urinary tract infection	0.16	1.79	0.181	0.54 (0.21–1.33)
CKD	0.78	6.63	0.01	0.45 (0.25–0.82)
Serum sodium (mmol/L)	0.02	1.92	0.166	0.98 (0.95–1)
Serum potassium (mmol/L)	0.11	0.45	0.499	0.89 (0.65–1.23)
Blood urea nitrogen (mmol/L)	0.03	14	<0.001	0.96 (0.95–0.98)
Time of referral	1.87	35.82	<0.001	0.15 (0.08–0.28)
Needed for renal replacement therapy	0.54	3.45	0.063	1.71 (0.97–1.07)

OR – Odds ratio; CI – Confidence interval; CKD – Chronic kidney disease

dealing with patients of different sociogenetic backgrounds. Therefore, future studies on the current topic are suggested to establish the sociogenetic factors that may contribute to patients' AKI presentation and physicians' assessments.

Although this is the first such study in a cohort from Saudi Arabia, some limitations of this study should be highlighted. It is a single-center, retrospective study; thus, it has all the limitations inherent to retrospective studies, including the risk of confounding and selection bias, and the presence of residual confounding that cannot be fully excluded due to the observational nature of the study.

CONCLUSION

This study found that the majority of referrals were early; however, late referrals were associated with higher mortality and longer length of hospitalization as well as requirement for RRT and a higher rate of sepsis. The effects of late referrals may be circumvented by providing education to non-nephrologists to better identify the risk factors of AKI.

Ethical consideration

This study was approved by the IRB of KAUH (Ref. no.: 735-19; dated: December 17, 2019). The requirement of informed consent was waived by the IRB due to the retrospective nature of the study. The procedures followed were in accordance with the ethical standards of the responsible committee based on the Good Clinical Practice guidelines and the study adhered to the Declaration of Helsinki, 2013.

Data availability statement

The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Peer review

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Conflicts of interest

There are no conflicts of interest.

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