

Original Article

Incidence of CKD and Death among Reproductive Age Women with Dialysis Requiring Acute Kidney Injury in Ethiopia: The Role of Obstetric Risk Factors

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Abstract

Background: Obstetric risk factors are major preventable causes of Acute Kidney Injury (AKI) in reproductive-age women. Obstetric-related AKI (ORAKI) significantly increases AKI burden in resource-constrained settings, leading to poor maternal and perinatal outcomes. Hence, understanding the impact of these factors on AKI progression is crucial. This study sought to determine the incidence of chronic kidney disease (CKD) and death, and obstetric risk factors' effect on these outcomes among reproductive-age women with dialysis-requiring AKI at Ethiopia's national renal transplant center.

Methods: A retrospective cohort study was conducted on 127 AKI cases (57 ORAKI and 70 non-ORAKI) who were on dialysis at the center from January 2018 to June 2020. Data characterization and comparison was made using frequencies with percentages, median with interquartile range, chi-square test/ Fischer's exact test and Mann-Whitney U test. Incidence rate (IR) was measured using person day (PD) observation. A Robust Poisson regression model was used to identify factors that affect AKI progression to CKD and death, with adjusted relative risk (ARR), 95% CIs for ARR, and P-values reported for result interpretation.

Results: The overall IR of CKD was 5.4 per 1000 PD (ORAKI group=0 and non-ORAKI group= 9.7 per 1000 PD) and the overall IR of death was 7.8 per 1000 PD (ORAKI group=5.5 per 1000 PD and non-ORAKI group= 9.7 per 1000 PD). Participants with ORAKI had a 22% lower risk of progression to CKD or death than those with non-ORAKI (ARR=0.78, 95% CI=0.67-0.90, p=0.001).

Conclusions: Although having obstetric related risk factors has been associated with an increased risk of developing AKI, once it occurs, those with ORAKI have a significantly better prognosis than those with non-ORAKI. Continued efforts to prevent AKI in pregnant women and to slow its progression once it has developed are critical for a better maternal and fetal outcome.

Key words: Obstetric related Acute Kidney Injury, Progression to Chronic Kidney Disease, Retrospective cohort, Robust Poisson regression, Ethiopia

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Introduction

Acute kidney injury (AKI) refers to an abrupt (within hours) decrease in kidney function, resulting in the retention of urea and other nitrogenous waste products (1, 2). AKI is a frequent complication encountered in both community (3, 4) and hospital (5-7) settings. In hospitalized patients, several factors can

contribute to AKI including high-risk characteristics like older age (8, 9), critical illness or major surgery requiring intensive care unit admission (10-12), trauma (13), complications from sepsis (14), exposure to certain antibiotics such as vancomycin (15,16), underlying chronic kidney disease (17), pre-existing cardiovascular risk factors (18, 19),

and obstetric risk factors (19-21). Depending on the severity of the underlying condition and the timing of initiation of treatment, the outcome of AKI can range from full recovery with no long-term sequelae (5, 22-24) to progression to chronic kidney disease (21, 24), and death (14, 17, 25, 26).

Obstetric risk factors are among the leading preventable causes of AKI in hospitalized reproductive age women. Obstetric related AKI (ORAKI) has been reported to contribute significantly to the overall burden of AKI in resource-limited settings, resulting in poor maternal and fetal outcomes (21,25,27). Given that the majority of obstetric-related maternal deaths occur in developing countries, particularly Sub-Saharan Africa, understanding the major causes, such as AKI, is critical because these are conditions that can be avoided and treated with a good prognosis for both the mother and fetus if detected early (27).

Pre-eclampsia and eclampsia were found to be the most common causes of ORAKI in any setting, accounting for up to three-quarters of cases. In developing countries, this is followed by puerperal sepsis and shock, both of which account for a sizable proportion (28-32). According to reports, the prognosis for ORAKI is good, with a large proportion of these cases, 50 to 80 percent, recovering from AKI. In the remaining one-fifth to one-quarter, they either progressed to end-stage renal disease (ESRD) or died (28,29,33).

So far, studies on ORAKI have focused on characterizing patients and determining its effect on the development of AKI, demonstrating that it is a significant factor and that the risk is further determined by other personal and medical conditions (32,34). However, there has been little research done to assess the effect of obstetric risk factors on the progression of AKI, once it occurred, and its outcome, particularly in developing countries. Hence, the objective of this study was to determine the incidence of CKD and death,

and the effect of obstetric risk factors on these outcomes among reproductive age women with dialysis requiring AKI at the national renal transplant center in Ethiopia.

Methods

Study Design, Population and Sample Size

An institution-based retrospective cohort study was conducted from October to November 2020 at St Paul's Hospital Millennium Medical College (SPHMMC), a tertiary teaching hospital under the Federal Ministry of Health in Addis Ababa, Ethiopia. SPHMMC is the country's second largest government hospital, as well as the first government hospital to provide both acute and chronic hemodialysis services in collaboration with the Egyptian government, and thus serves as the primary government-owned referral center for AKI patients. The hospital currently has around forty hemodialysis machines for ESRD and six hemodialysis machines for AKI.

The cohort included the following exposure groups:

- Women of reproductive age (15-49 years) with AKI 2° to obstetric risk factors/ ORAKI (**Exposed group**): These are cases who were admitted to the center for dialysis between January 2018 to June 2020 for AKI following obstetric related risk factors.
- Women of reproductive age (15-49 years) with AKI 2° to none obstetric risk factors/ non-ORAKI (**Non-exposed group**): These are cases who were admitted to the center for dialysis between January 2018 to June 2020 for AKI due to causes other than obstetric related risk factors.

During the observation period, a total of 143 women were managed at the center. Of which, 127 were in the reproductive age group and were included in the study. Among the 127 cases, 57 were women with AKI 2° to obstetric risk factors and 70 were women with AKI 2° to none obstetric risk factors. (**Figure 1**)

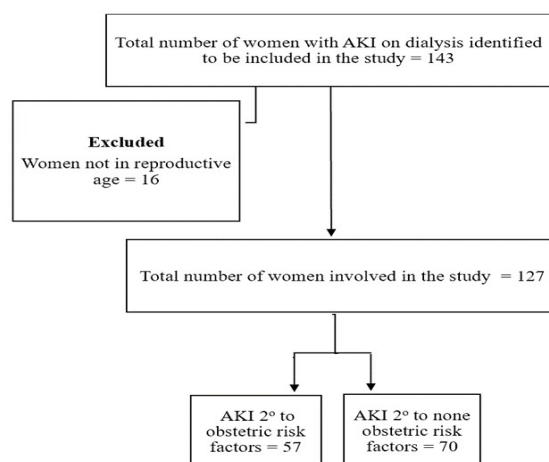


Figure 1: Flow chart showing the disposition of study participants in the final analysis

To assess the adequacy of the final sample size, the power of the study was calculated using G*Power 3.19.4 using a two-tailed z-test for difference between two independent proportions with the following statistical parameters; 5% level of significance, prevalence and sample size in the non-ORAKI group of 41.3% and 63, respectively; and prevalence and sample size in the ORAKI group of 12.0% and 50, respectively. Finally, the power of the study was estimated to be 94.5%.

Operational Definition

Progression to chronic kidney disease: It is diagnosed when a patient who is initially admitted with an assessment of AKI and kept on hemodialysis failed to show clinical or biochemical improvement and later diagnosed to have CKD.

Data collection and Quality assurance

A pretested data abstraction tool was used to extract data from patients' charts. The tool included questions on socio-demographics, medical illness history, obstetric and surgical history, exposure to nephrotoxic drugs, pre-renal causes, and AKI outcome. Two trained General Practitioners extracted the data. To ensure data quality, it was cleaned by checking for inconsistencies, numerical errors, and missing parameters, and appropriate measures were taken. In the event of a discrepancy in patient information, data was double-checked by referring to the main record and cross-referencing with another database whenever possible. SPSS version 25.0 software was used for data management and analysis.

Statistical analysis

To characterize the study population, descriptive analysis using frequencies with percentages and median with interquartile range (after testing the assumption of normality) was run. To measure the outcome, incidence density with 95% CI was run and reported using person day (PD) observation.

A chi-square test/ Fischer's exact test and Mann-Whitney U test were used to identify the presence of a statistically significant difference between the ORAKI and non-ORAKI groups in terms of their underlying characteristics. A statistically significant difference was detected for variables with a p-value of ≤ 0.05 .

To identify the effect of obstetric related risk factors on outcome of AKI, Robust Poisson regression model was used. Univariate analysis at 25% level of significance was run to identify exposures to be controlled for in the final analysis. On the final multivariable analysis, at 5% level of significance, adjusted relative risk (ARR) with 95% CI, and P-value were used to test significance and interpret results. Variables with p-value ≤ 0.05 were considered as significant predictors of AKI outcomes.

Results

Baseline characteristics of participants

Of the 127 participants, majority resided in two regions; 52 (40.9%) in Oromia and 24 (18.9%) in Addis Ababa,

and were between the ages of 25 and 34 (38.6%). One or more underlying acute and/or chronic medical illnesses were present in 96 (75.6%) participants. Hypertension and cardiovascular disease were the most common chronic illnesses, accounting for 33 (26.0%) and 15 (11.8%) of all cases, respectively. The most common acute conditions were sepsis in 52 (40.9%) and shock in 36 (28.3%), which constituted septic shock (18/36), hypovolemic shock (17/36), and cardiogenic shock (1/36). AKI due to obstetric complications was diagnosed in 57 (44.9%). From these, 50 had preeclampsia and/or HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), 14 had peripartum hemorrhage, and eight had puerperal sepsis, with the majority having more than one complication, particularly preeclampsia/HELLP syndrome with the other two. The vast majority (94.5%) had a history of exposure to at least one nephrotoxic drug. Proton Pump Inhibitors (PPI) (110/120), vancomycin (67/120), and ceftriaxone (44/120) were the most commonly used medications. Glomerular disease was diagnosed in 91 (71.7%) of the participants. Acute Tubular Necrosis (ATN) was the most common type (56/91), with 26/56 being ischemic ATN and the remaining 30/56 being septic ATN. Acute Glomerulonephritis (AGN) (18/91), Rapidly Progressive Glomerulonephritis (RPGN) (18/91), and Post-infectious Glomerulonephritis (PIGN) (11/91) were also diagnosed in the majority of cases. Only two (1.8%) cases had a post-renal cause, both of which were due to ureteric stone. Major surgery was performed on 23 (18.1%) of the participants for obstetric or other reasons. Twenty-three (18.1%) of the participants required Intensive Care Unit (ICU) admission, with 14 (24.6%) having a pregnancy-related risk factor and nine (2.9%) having no such risk.

The comparison of the underlying characteristics of participants between groups with ORAKI and non-ORAKI revealed that a statistically significant difference in age, exposure to vancomycin, Angiotensin-Converting Enzyme Inhibitors/ Angiotensin II Receptor Antagonists (ACEIs/ARBs), and PPI, diagnosis of AGN and RPGN, and history of major surgery. Accordingly, a significantly higher proportion of participants with ORAKI were younger, mainly 25-34 years (50.9%), than those with non-ORAKI who were between 35 and 49 years of age (41.4%) ($p=0.007$). In terms of drug exposure, vancomycin was taken by a greater proportion of participants with ORAKI (66.7% vs 41.4%, $p=0.005$). On the other hand, a higher proportion of participants with non-ORAKI were exposed to PPI (77.2% vs 94.3%). Furthermore, seven (10%) participants with non-ORAKI took ACEIs/ARBs, with a p-value of 0.016, indicating a significant difference between the two groups. AGN (5.3% vs 21.4%, $p=0.009$) and RPGN (5.3% vs 21.4%,

p=0.009) were diagnosed at a significantly lower proportion in the group with ORAKI. Finally, a significantly higher proportion of participants with ORAKI (28.1%

vs 10.0%, p=0.009) underwent major surgery. (Table 1)

Table 1: Baseline characteristics of participants and comparison based on exposure status (n=127)

Variable		ORAKI (n=57)	Non-ORAKI (n=70)	Total (%)	p-value
Age category (in years)	15-24	18 (31.6)	21 (30.0)	39 (30.7)	0.007*
	25-34	29 (50.9)	20 (28.6)	49 (38.6)	
	35-49	10 (17.5)	29 (41.4)	39 (30.7)	
Hypertension	Yes	14 (24.6)	19 (27.1)	33 (26.0)	0.741
	No	43 (75.4)	51 (72.9)	94 (74.0)	
Cardiovascular illness	Yes	4 (7.0)	11 (15.7)	15 (11.8)	0.131
	No	53 (93.0)	59 (84.3)	112 (88.2)	
Diabetes mellitus	Yes	0	4 (5.7)	4 (3.1)	0.127
	No	57 (100.0)	66 (94.3)	123 (96.9)	
HIV	Yes	2 (3.5)	5 (7.1)	7 (5.5)	0.458
	No	55 (96.5)	65 (92.9)	120 (94.5)	
Sepsis	Yes	24 (42.1)	28 (40.0)	52 (40.9)	0.810
	No	33 (57.9)	42 (60.0)	75 (59.1)	
Shock	Yes	16 (28.1)	20 (28.6)	36 (28.6)	0.950
	No	41 (71.9)	50 (71.4)	91 (71.7)	
Vancomycin	Yes	38 (66.7)	29 (41.4)	67 (52.8)	0.005*
	No	19 (33.3)	41 (58.6)	60 (47.2)	
Ceftriaxone	Yes	19 (33.3)	25 (35.7)	44 (34.6)	0.779
	No	38 (66.7)	45 (64.3)	83 (65.4)	
ACEIs/ARBs	Yes	0	7 (10.0)	7 (5.5)	0.016*
	No	57 (100.0)	63 (90.0)	120 (94.5)	
NSAIDs	Yes	0	3 (4.3)	3 (2.4)	0.252
	No	57 (100.0)	67 (95.7)	123 (97.6)	
PPI	Yes	44 (77.2)	66 (94.3)	110 (86.6)	0.005*
	No	13 (22.8)	4 (5.7)	17 (13.4)	
AGN	Yes	3 (5.3)	15 (21.4)	18 (14.2)	0.009*
	No	54 (94.7)	55 (78.6)	109 (85.8)	
RPGN	Yes	3 (5.3)	15 (21.4)	18 (14.2)	0.009*
	No	54 (94.7)	55 (78.6)	109 (85.8)	
PIGN	Yes	6 (16.2)	5 (7.1)	11 (10.3)	0.184
	No	31 (83.8)	65 (92.9)	96 (89.7)	
ATN	Yes	27 (47.4)	29 (41.4)	56 (44.1)	0.502
	No	30 (52.6)	41 (58.6)	71 (55.0)	
Ureteric stone	Yes	1 (1.8)	1 (1.4)	2 (1.6)	1.000
	No	56 (98.2)	69 (98.6)	125 (98.4)	
Major surgery	Yes	16 (28.1)	7 (10.0)	23 (18.1)	0.009*
	No	41 (71.9)	63 (90.0)	104 (81.9)	
ICU admission	Yes	14 (24.6)	9 (12.9)	23 (18.1)	0.088
	No	43 (75.4)	61 (87.1)	104 (81.9)	

N.B: ORAKI: obstetric related acute kidney injury, HIV: Human Immunodeficiency Virus, ACEIs: Angiotensin-Converting Enzyme Inhibitors, ARBs: Angiotensin II Receptor Blockers, NSAIDs: Nonsteroidal Anti-inflammatory Drugs, PPI: Proton Pump Inhibitor, AGN: Acute Glomerulonephritis, RPGN: Rapidly Progressive Glomerulonephritis, PIGN: Post-infectious Glomerulonephritis, ATN: Acute Tubular Necrosis, ICU: Intensive Care Unit.

Total and Sub-group Incidence Density of CKD and Death

Among the 127 patients, outcome data was not recorded for 14 participants who were transferred to another facility for reasons other than medical indications. A statisti-

cal comparison of the underlying characteristics of the 14 transferred patients and the remaining 113 patients was performed to determine the presence of significant differences in their exposure to important factors that could have made them more

inclined to be at high risk of developing one group of outcomes, potentially biasing the overall result of the study findings. However, no significant difference was found in any of the comparisons (p-values for chi-square/Fischer's exact tests and Mann-Whitney U-tests were greater than 0.05).

The remaining 113 participants were followed for a median of 21.0 days (IQR, 13.0-25.0), and there was no significant difference in follow-up duration between the

two groups ($p=0.938$). The overall incidence rate (IR) of CKD was 5.4 per 1000 PD (95% CI=3.1 - 9.3). The overall death rate was 7.8 per 1000 PD (95% CI= 5.0 - 12.3). According to the subgroup analysis, none of the cases with ORAKI progressed to CKD, and six died, resulting in a death rate of 5.5 per 1000 PD (95% CI= 2.5-12.3). Among those with non-ORAKI, 13 developed CKD (IR=9.7 per 1000 PD, 95% CI=5.7-16.8) and 13 died (IR=9.7 per 1000 PD, 95% CI=5.7-16.8). (Table 2).

Table 2: Comparison of AKI outcomes and length of stay based on exposure status (n=113)

Variable	ORAKI (n=50)	Non-ORAKI (n=63)	Total (%)
Disease outcome (n, %)			
Progression to CKD	0	9.7 per 1000 PD	5.4 per 1000 PD
Death	5.5 per 1000 PD	9.7 per 1000 PD	7.8 per 1000 PD
Length of stay in days (Median, IQR)	21.0 (14.8-21.5)	20.0 (13.0-26.0)	21.0 (13.0-25.5)

Effect of obstetric related risk factor on AKI outcome

To assess the effect of obstetric related risk factor on AKI outcome, a multivariable Robust Poisson Regression model was run after adjusting for age category, pregnancy related risk factor, cardiovascular disease, vancomycin, ceftriaxone, PPI, AGN, PIGN, RPGN, ATN and surgery which were found to be significantly associated with AKI outcomes on the univariate analysis.

Accordingly, the risk of progression to CKD or death among participants with ORAKI was 22% lower than those with non-ORAKI (ARR=0.78, 95%CI=0.67-0.90, $p=0.001$). Moreover, having cardiovascular disease and taking vancomycin were associated with an increased risk of progression to CKD and death by 18% (ARR=1.18, 95%CI=1.01,1.39, $p=0.044$) and 19% (ARR=1.19, 95%CI=1.05,1.34, $p=0.006$) as compared to those with no cardiovascular disease and did not take vancomycin, respectively. (Table 3)

Discussion

Among the 127 participants, ORAKI was diagnosed in 57 (44.9%). From which, 50/57 had preeclampsia/HELLP syndrome, 14/57 had peripartum hemorrhage and 8/57 had puerperal sepsis. This pattern corresponds to the most common cause of obstetric-related AKI in both developed and developing countries (28-32).

The incidence of CKD and death among the groups demonstrated that the majority of ORAKI cases recovered when compared to those with non-ORAKI. Such favorable outcome is also reported in other studies conducted in Ethiopia, Tanzania and Iran, where a higher proportion of cases with obstetric-related causes recovered and a lower proportion progressed to CKD and died

(28,29,30). Further regression analysis to determine the effect of obstetric factors on AKI outcome revealed that cases with ORAKI had a 22% lower risk of progressing to CKD or dying, indicating that cases with ORAKI have a much better prognosis than cases with non-ORAKI. This could be because most ORAKI cases are otherwise healthy, with few underlying medical conditions that could lead to complication, as in our study where a significantly higher proportion had clinically favorable factors such as younger age, less frequent underlying glomerular disease, particularly AGN and RPGN, and lack of exposure to specific nephrotoxic drugs such as ACEIs/ARBs. Moreover, because ORAKI occurs following pregnancy, labor and delivery while the woman is under strict medical care, timely diagnosis of AKI and initiation of management is highly likely, contributing to the favorable outcome.

Furthermore, cardiovascular disease and vancomycin exposure were linked to an 18% and 19% increased risk of CKD progression and death, respectively. These factors have also been shown to be significant predictors in a number of other studies, owing to their underlying pathophysiologic mechanisms that damage the kidney and their prevalence/exposure in the majority of cases (16,24,25).

The study's finding is valuable addition to the existing literature, as it addressed a less studied research question and was conducted in the largest national referral dialysis Centre. Furthermore, despite its relatively small size, the sample achieved a post-hoc power of 94.5%, indicating that the obtained results were sufficiently powered to answer

Table 3: Predictors of AKI outcome among patients on dialysis (n=113)

Variable	Outcome		CRR (95% CI)	ARR (95% CI)	P-value
	Recovery	CKD/ Death			
Age category (in years)					
15-24	23	12	1	1	
25-34	35	9	0.89 (0.77, 1.05)	0.92 (0.80, 1.06)	0.267
35-49	23	11	0.98 (0.83, 1.17)	0.99 (0.84, 1.16)	0.913
Pregnancy related risk factor					
No	37	26	1	1	
Yes	44	6	0.79 (0.71, .089)	0.78 (0.67, 0.90)	0.001*
Cardiovascular disease					
No	76	25	1	1	
Yes	5	7	1.27 (1.05, 1.53)	1.18 (1.01, 1.39)	0.044*
Vancomycin					
No	40	13	1	1	
Yes	41	19	1.06 (0.93, 1.20)	1.19 (1.05, 1.34)	0.006*
Ceftriaxone					
No	50	21	1	1	
Yes	31	11	0.97 (0.85, 1.11)	0.98 (0.86, 1.13)	0.834
PPI					
No	11	4	1	1	
Yes	70	28	1.02 (0.84, 1.23)	0.89 (0.75, 1.08)	0.253
AGN					
No	74	25	1	1	
Yes	7	7	1.19 (0.99, 1.45)	1.09 (0.89, 1.33)	0.305
PIGN					
No	75	28	1	1	
Yes	6	4	1.10 (0.88, 1.38)	1.09 (0.89, 1.33)	0.368
RPGN					
No	70	27	1	1	
Yes	11	5	1.03 (0.86, 1.24)	0.92 (0.76, 1.09)	0.341
ATN					
No	40	20	1	1	
Yes	41	12	0.92 (0.81, 1.05)	0.97 (0.86, 1.10)	0.643
Surgery					
No	62	29	1	1	
Yes	19	3	0.86 (0.75, 0.99)	0.92 (0.78, 1.08)	0.315

N.B: CRR: Crude relative risk, CI: Confidence Interval, ARR: Adjusted relative risk, CKD: Chronic Kidney Disease, PPI: Proton Pump Inhibitor, AGN: Acute Glomerulonephritis, PIGN: Post-infectious Glomerulonephritis, RPGN: Rapidly Progressive Glomerulonephritis, ATN: Acute Tubular Necrosis, *statistically significant

the research question. However, due to the study's retrospective nature and insufficient chart recording with limited information on additional exposures, further relevant confounders could not be controlled for.

Conclusions

Although having obstetric related risk factors has been reported to be associated with an increased risk of developing AKI, once it occurs, the prognosis for those with ORAKI with standard management is

significantly better than those with non-ORAKI. Continued efforts to prevent the development of AKI in pregnant women and minimize its progression once it has occurred are essential for a better maternal and fetal outcome. In addition, stringent monitoring of those with cardiovascular disease and those taking vancomycin is crucial to mitigate risk of progression. To generate additional evidence, a large-scale cohort study with a thorough assessment of all exposures is required.

Declaration

Ethics approval

The study was conducted after securing ethical clearance from St. Paul's Hospital Millennium Medical College institutional review board (SPHMMC-IRB) (Reference no: PM.23/724). The study was carried out in accordance with relevant guidelines and regulations. Medical record number was used for the data collection and personal identifiers of the patient were not used in the research report. Access to the collected information was limited to the research team and confidentiality was maintained throughout the project.

Consent to participate: Not applicable

Availability of data and materials: All relevant data are available upon reasonable request from the corresponding author.

Competing interests: The authors declare that they have no known competing interests

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Author's Contribution: ATL and TWL conceived and designed the study. TAL, SKO, MBA, and DBM contributed to the conception and design of the study. ATL supervised the data collection. TWL performed statistical analysis, and drafted the initial manuscript. TAL, SKO, and MBA contributed to statistical analysis. DBM revised the draft manuscript. All authors approved the final version of the manuscript.

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