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Original Article

Time to recovery and predictors among acute kidney injury patients on hemodialysis at the national renal transplant center in Ethiopia

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Abstract

Background: *Acute kidney injury (AKI) is defined as a sudden decline in kidney function in 48 hours. Unless diagnosed and managed early, AKI causes significant morbidity and mortality due to the associated increased risk of renal damage with every delay in recovery. There is a paucity of information on the pattern of recovery time from AKI and its contributing factors. Hence, this study aimed to estimate the median time to recovery and identify predictors among AKI patients on dialysis at the national renal transplant center in Ethiopia.*

Methods: *A retrospective chart review study was conducted among 232 AKI patients on dialysis who were managed at the center from January 2018 to June 2020. Data was summarized and compared using frequency tables, median survival times, KM survival plots and Log-rank tests. To identify predictors of time to recovery from AKI, a Cox Proportional Hazard (PH) survival model was used, where Adjusted Hazard ratio (AHR), 95% CIs for AHR, and P-values were used for interpretation of results. Data management and analysis was done using SPSS software V. 25.0.*

Results: *From the 232 AKI patients on dialysis, 127 (54.7%, 95% CI=48.7%-61.3%) achieved recovery and the median time to recovery was 25.0 days (95% CI=22.1, 27.9). On the Cox PH model, having cardiovascular disease (AHR=0.51, 95% CI=0.28,0.93, p=0.028), sepsis (AHR=0.59, 95% CI=0.37, 0.95, p=0.031) and acute glomerulonephritis (AGN) (AHR=0.31, 95% CI=0.14,0.71, p=0.005) were found to be significant predictors of time to recovery from AKI.*

Conclusions: *The median time to recovery from AKI is optimal given the high-risk nature of the studied population. However, this duration may be associated with an increased risk of both short and long-term complications from continued renal damage. Having cardiovascular disease, sepsis and AGN were found to be associated with delayed recovery from AKI. Therefore, strict monitoring of AKI patients in general, and the high-risk groups in particular, is essential for rapid recovery.*

Keywords*: Acute Kidney Injury, time to recovery, survival analysis, Cox PH model, Ethiopia*
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Introduction

Acute kidney injury (AKI) is defined as a sudden decline in kidney function in 48 hours as manifested by an increase in serum creatinine of more than 0.3 mg/dl, an increase in serum creatinine of more than 50%, or the development of oliguria (1). AKI can be caused by a variety of factors in both the community and hospital setting. Pre-renal causes account for 30-40% of these causes, which include medical illnesses (both acute and chronic) and exposure to nephrotoxic drugs. Renal causes from various glomerular diseases, as well as post-renal causes, account for a significant proportion too (2-17). Given that all of these factors are common in hospitalized patients, AKI diagnosis is a common occurrence in

hospitalized patients.
Unless diagnosed and managed early, AKI causes significant morbidity and mortality and costs the healthcare system. This indicates the significance of time in the management of AKI. Delay in recovery from AKI is associated with an increased risk of renal damage, which can result in permanent loss of function and even death (1,2) . As a result, the epidemiological understanding of AKI should not only focus on its outcomes per se, but also on the time it takes to recover. The current body of literature has primarily focused on the first one, understanding the outcome of AKI, and it has been reported that AKI is associated with a poor prognosis, particularly in developing countries where early identification and management of cases is difficult due to low healthcare seeking behavior and an underdeveloped healthcare system (3,4,18-26). This indirectly implies that most patients are subjected to a continuing renal insult, which facilitates the poor prognosis in addition to the severity of the underlying cause of the AKI. As a result, understanding the pattern of recovery time and its contributors is crucial for planning evidence-based interventions for favorable short and long-term patient outcomes. Therefore, the aim of this study was to estimate the median time to recovery and identify predictors among AKI patients on dialysis at the national renal transplant center in Ethiopia.

Materials and methods

Study Design and Setting

A retrospective chart review study, with an observation period from January 2018 to June 2020, was conducted 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 governmental hospital, as well as the first governmental 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 approximately forty hemodialysis machines for end-stage renal disease and approximately six hemodialysis machines for acute kidney injury (27).

Population, Eligibility and Sample size

During the two years and half observation period, from January 2018 to June 2020, a total of 290 AKI patients received dialysis service at the center. Hence due to the small number of the source population, we included all eligible cases. Finally, 232 eligible patients, who did not have CKD at the time of admission, and had data on major exposures and outcomes, were included in the final analysis.

Operational Definition

Recovery from AKI: Recovery is declared when a patient who is diagnosed to have AKI and kept on hemodialysis achieves clinical improvement and not further requiring dialysis.

Event: Recovery from AKI
Censoring: Includes patients who were lost to follow-up, transferred out, died or completed the follow -up period before recovery from AKI.
Time to event or censoring: time between admission to the center up to recovery or censoring (in days).

Data Collection and Quality Assurance

Data was collected from medical charts of the patients using a pretested data abstraction tool that contains questions on socio-demographics, medical illness history, obstetric and surgical history, exposure to nephrotoxic drugs, pre-renal causes, and AKI outcome. To improve data quality, training on the basics of the questionnaire and data collection tool was given for two data collectors (General practitioners) for two days. In addition, double data entry, and data cleaning through checking for inconsistencies, numerical errors and missing parameters was done. Where discrepancies are observed, data entered was verified with the primary data source. Where possible, data was validated by comparing a certain percentage of data in our database with that of another database. Data consistency and completeness was checked before an attempt was made to enter the code and analyze the data. Once data cleaning was complete, the data was exported to SPSS version 25.0 software for data management and analysis.

Statistical Analysis

Data was summarized using proportions with frequency tables, Kaplan Meier (KM) plots and median survival times. Survival experience of different groups was compared using KM survival curves and Log-rank test was used to assess the statistical significance of any observed difference between the groups.
A chi-square test was used to compare the underlying characteristics of the transferred patients and the remaining patients in order to identify the presence of a statistically significant difference in their exposure to important factors that could have made them more prone to develop one group of outcome has and in turn could have biased the overall result of the study findings.
To identify predictors of time to recovery from AKI, Cox proportional hazard (PH) survival model was used. Univariate analysis at 25% level of significance was performed to calculate crude hazard ratio (CHR)

and to screen out potentially independent variables. The selected variables were included into the final multivariable Cox PH survival model at 5% level of significance where adjusted hazard ratio (AHR), 95% CI for AHR and p-value were used to interpret the results. The basic assumption of Cox Proportional Hazard model, the proportional hazards assumption, was tested using log minus log function and the plot shows a reasonable fit to the assumption with parallel lines between groups indicating proportionality. (**Supplementary file 1**)

Results

Socio-demographic and clinical characteristics

Among the 232 AKI patients on dialysis, the majority were between the age of 30 and 49 years (40.9%) followed by those 16 to 29 years (38.4%) and 122 (52.6%) were females.

The majority (85.3%) of the patients had one or more medical illnesses upon admission. From which, chronic medical illnesses, mainly hypertension (40.9%), cardiovascular disease (15.9%), and diabetes mellitus (8.6%), constituted a larger proportion. Acute medical conditions, mainly sepsis, shock and LRTI were diagnosed in 86 (37.1%), 63 (27.2%) and 63 (27.2%), respectively. Forty-two patients (18.1%) underwent major surgery.

Exposure to nephrotoxic drugs was identified in 225 (97.0%) of the patients. Among these, the majority were on PPI (89.2%), followed by vancomycin (50.9%) and ceftriaxone (35.8%). Only 22 patients were taking ACE2 expression inhibiting drugs, particularly ACEIs/ARBs by 11 (4.7%) and NSAIDs by 11 (4.7%).

Three-fourth of all patients (77.6%) were diagnosed with a glomerular disease. From which the majority had ATN (46.1%), followed by RPGN (19.4%), AGN (11.2%), and PIGN (10.3%).

A quarter of all patients (11.2%) were diagnosed with post-renal causes of AKI, mainly ureteric stone in 19 (8.2%) patients. Thirty-four (14.7%) of patients needed an Intensive Care Unit (ICU) admission. **(Table 1)**

Censoring status and median time to recovery from AKI

From the 232 AKI patients on dialysis, 127 (54.7%, 95% CI=48.7%-61.3%) achieved recovery and the rest 105 (45.5%, 95% CI=38.7%-51.3%) were censored. Among the 105 censored observations, 33 (31.4%) developed CKD, 38 (36.2%) died and the remaining 34 (32.4%) were transferred to another hospital either for convenience of family visit or seeking private hospital care. A statistical comparison of the underlying characteristics of the 34 transferred patients and the remaining 198 patients were made to identify the presence of significant difference in their exposure to important factors that could have made them more inclined to be at high risk of recovering or not and hence has biased the overall result of the study findings. Accordingly, all comparisons showed no significant difference (p-value of all -square tests were >0.05).

The overall median time to recovery was 25.0 days (95% CI=22.1, 27.9). The comparison of the median time to recovery between groups showed that there is a statistically significant difference in the time based on cardiovascular disease and sepsis. Accordingly, a significantly delayed recovery from AKI was observed among patients with cardiovascular disease (38 Vs 22 days) and those with sepsis (28 Vs 21 days) as compared with those with no such medical illnesses. **(Table 1)**

Predictors of time to recovery from AKI

To identify predictors of time to recovery from AKI, Cox proportional hazard (PH) survival model was used. Crude analysis of each independent variable with the time to recovery was run at 25% level of significance. From univariate analysis; age group, gender, hypertension, cardiovascular disease, diabetes mellitus, sepsis, shock, LRTI, major surgery, vancomycin, PPI, ACEIs/ARBs, NSAIDs, RPGN, PIGN, AGN, and ureteric stone were found to be significant and were fed into the final multivariable regression model.

In the final model, at a 5% level of significance, cardiovascular disease, sepsis and AGN were found to be significantly associated with time to recovery from AKI.

Accordingly, after adjusting for other covariates, the rate of achieving recovery among patients with cardiovascular disease was 49% lower than patients with no cardiovascular disease (**AHR=0.51, 95% CI=0.28,0.93, p=0.028**). In addition, being in sepsis was associated with a 41.0% lower rate of achieving recovery as compared to those with no sepsis (**AHR=0.59, 95% CI=0.37, 0.95, p=0.031**). Furthermore, the rate of achieving recovery among patients with AGN was 69.0% lower than those with no AGN (**AHR=0.31, 95% CI=0.14,0.71, p=0.005**). (**Table 2**)

Table 1: Participant characteristics, censoring status, and comparison of median time to recovery between groups among AKI patients on dialysis from January 2018 to June 2020, Ethiopia (n=232)

Variable		AKI outcome		Total (%)	Median time to recovery (in days)	P-value
		Recovered (%)	Censored (%)			
Age category (in years)	16-29	48 (53.9)	41 (46.1)	89 (38.4)	25.0	0.249
	30-49	60 (63.2)	35 (36.8)	95 (40.9)	24.0	
	≥ 50	19 (39.6)	29 (60.4)	48 (20.7)	30.0	
Gender	Male	54 (49.1)	56 (50.9)	110 (47.4)	27.0	0.623
	Female	73 (59.8)	49 (40.2)	122 (52.6)	25.0	
Hypertension	No	77 (56.2)	60 (43.8)	137 (59.1)	25.0	0.535
	Yes	50 (52.6)	45 (47.4)	95 (40.9)	26.0	
Cardiovascular illness	No	113 (57.9)	82 (42.1)	195 (84.1)	22.0	**0.02***
	Yes	14 (37.8)	23 (62.2)	37 (15.9)	38.0	
Diabetes mellitus	No	118 (55.7)	94 (44.3)	212 (91.4)	25.0	0.517
	Yes	9 (45.0)	11 (55.0)	20 (8.6)	28.0	
Liver disease	No	120 (55.3)	97 (44.7)	217 (93.5)	25.0	0.570
	Yes	7 (46.5)	8 (53.5)	15 (6.5)	20.0	
Sepsis	No	89 (61.0)	57 (39.0)	146 (62.9)	21.0	**0.03***
	Yes	38 (44.2)	48 (55.8)	86 (37.1)	28.0	
Shock	No	94 (55.6)	75 (44.4)	169 (72.8)	23.0	0.102
	Yes	33 (52.4)	30 (47.6)	63 (27.2)	28.0	
LRTI	No	95 (56.2)	74 (43.8)	169 (72.8)	25.0	0.536
	Yes	32 (50.8)	31 (49.2)	63 (27.2)	24.0	
Gastroenteritis	No	121 (56.3)	94 (43.7)	215 (92.7)	25.0	0.886
	Yes	6 (35.3)	11 (64.7)	17 (7.3)	26.0	
Major surgery	No	98 (51.6)	92 (48.4)	190 (81.9)	25.0	0.520
	Yes	29 (69.0)	13 (31.0)	42 (18.1)	26.0	
Vancomycin	No	66 (57.9)	48 (42.1)	114 (49.1)	22.0	0.054
	Yes	61 (51.7)	57 (48.3)	118 (50.9)	27.0	
Ceftriaxone	No	78 (52.3)	71 (47.7)	149 (64.2)	20.0	0.063
	Yes	49 (59.0)	34 (41.0)	83 (35.8)	21.0	
ACEIs/ARBs	No	122 (55.2)	99 (44.8)	221 (95.3)	25.0	0.866
	Yes	5 (45.5)	6 (54.5)	11 (4.7)	23.0	
NSAIDs	No	121 (54.8)	100 (45.2)	221 (95.3)	25.0	0.792
	Yes	6 (54.5)	5 (45.5)	11 (4.7)	25.0	
PPI	No	12 (48.0)	13 (52.0)	25 (10.8)	26.0	0.633
	Yes	115 (55.6)	92 (44.4)	207 (89.2)	25.0	
ATN	No	59 (47.2)	66 (52.8)	125 (53.9)	26.0	0.163
	Yes	68 (63.6)	39 (36.4)	107 (46.1)	22.0	
RPGN	No	101 (54.0)	86 (46.0)	187 (80.6)	25.0	0.587
	Yes	26 (57.8)	19 (42.2)	45 (19.4)	25.0	
PIGN	No	115 (55.3)	93 (44.7)	208 (89.7)	25.0	0.683
	Yes	12 (50.0)	12 (50.0)	24 (10.3)	25.0	
AGN	No	117 (56.8)	89 (43.2)	206 (88.8)	25.0	0.074
	Yes	10 (38.5)	16 (61.5)	26 (11.2)	27.0	
Ureteric stone	No	115 (54.0)	98 (46.0)	213 (91.8)	25.0	0.536
	Yes	12 (63.2)	7 (36.8)	19 (8.2)	26.0	
ICU admission	No	112 (56.6)	86 (43.4)	198 (85.3)	24.0	0.089
	Yes	15 (44.1)	19 (55.9)	34 (14.7)	30.0	

***Note:** *statistically significant*

Kaplan Meir (KM) survival function graphs of these two groups also showed that those with cardiovascular disease and sepsis had a prolonged time to clinical recovery throughout the time as compared to those with no such medical illnesses. (**Figure 2**)

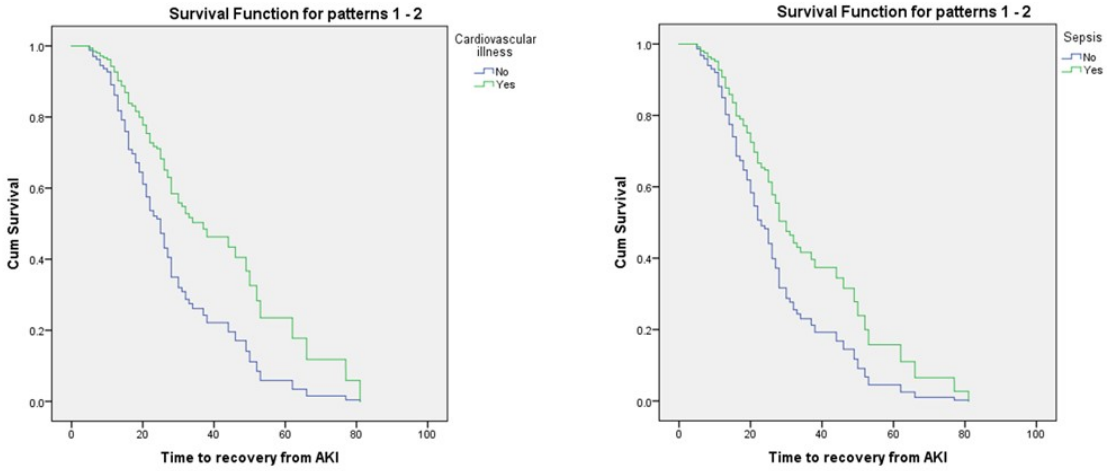

Fig 2: Kaplan-Meier survival graph of recovery time from AKI stratified by cardiovascular disease and sepsis

Table 2: Predictors of time to recovery among AKI patients on dialysis from January 2018 to June 2020, Ethiopia (n=232)

Variable	CHR (95% CI)	AHR (95% CI)	P-value
Age category (R=16-29 years)			
30-49	0.95 (0.65, 1.39)	0.94 (0.63, 1.40)	0.771
≥ 50	0.65 (0.38, 1.11)	0.65 (0.36, 1.19)	0.160
Gender (Male Vs Female)	1.09 (0.77,1.56)	1.05 (0.70,1.57)	0.823
Hypertension (Yes)	0.89 (0.63, 1.28)	0.99 (0.66, 1.48)	0.963
Cardiovascular disease (Yes)	0.53 (0.30, 0.92)	**0.51 (0.28, 0.93)**	**0.028***
Diabetes Mellitus (Yes)	0.80 (0.41, 1.58)	0.80 (0.39, 1.68)	0.559
Sepsis (Yes)	0.66 (0.45, 0.97)	**0.59 (0.37, 0.95)**	**0.031***
Shock (Yes)	0.72 (0.48, 1.08)	0.68 (0.41, 1.13)	0.137
LRTI (Yes)	1.14 (0.76, 1.71)	1.24 (0.77, 1.99)	0.384
Major surgery (Yes)	1.14 (0.75, 1.73)	1.14 (0.67, 1.96)	0.625
Vancomycin (Yes)	0.71 (0.49, 1.01)	0.85 (0.57, 1.26)	0.405
PPI (Yes)	0.87 (0.48, 1.58)	0.92 (0.48, 1.76)	0.800
ACEIs/ARBs (Yes)	1.08 (0.44, 2.65)	0.91 (0.36, 2.31)	0.836
NSAIDs (Yes)	1.12 (0.49, 2.54)	1.33 (0.56, 3.19)	0.516
RPGN (Yes)	0.89 (0.58, 1.37)	0.62 (0.38, 1.02)	0.062
PIGN (Yes)	1.13 (0.62, 2.06)	0.86 (0.43, 1.71)	0.659
AGN (Yes)	0.52 (0.25, 1.09)	**0.31 (0.14, 0.71)**	**0.005***
Ureteric stone (Yes)	1.20 (0.66, 2.19)	0.91 (0.42, 1.97)	0.814

Note: CHR, Crude Hazard ratio; AHR, Adjusted Hazard ratio; CI, Confidence interval; *statistically sig-

Discussion

The study aimed to estimate the median time to recovery and identify predictors among AKI patients on dialysis who were on follow at the national renal transplant center in Ethiopia from January 2018 to June 2020.

From the 232 AKI patients on dialysis, 127 achieved recovery and the overall median time to recovery was 25.0 days. According to studies, recovery from AKI can take a few days to weeks or even months, depending on the underlying cause of the AKI and the patients' personal risk factors. It is reported that on

average, half of AKI patients recover in 30 days, while the other half may require up to 90 days (28, 29). As a result, a median duration of 25.0 days can be considered an average duration, especially given that the majority of the studied population has an underlying risk factor that, despite their young age, could lead to additional renal damage and delayed recovery. Even if this duration can be considered optimal, it is still a long time given the increased risk of renal and systemic complications with each delay in renal recovery.

On the KM survival plot and log- rank test, a less favorable recovery experience was observed among patients with cardiovascular disease and sepsis. This was further confirmed on the final regression analysis, where having cardiovascular disease and being in sepsis were found to be associated with a 49% and 41% lower rate of achieving recovery, respectively, as compared to those with no such medical illnesses. Studies conducted in both developing and developed countries also indicated that patients with cardiovascular disease and sepsis are at high risk of complications from AKI and leading to progression to AKI and/or death implying that recovery in these groups of patients is delayed when it happens (30-32).

In addition, it was found that the rate of achieving recovery among patients with AGN was 69.0% lower than those with no AGN. As a glomerular disease, AGN causes renal injury through physical damage to the glomeruli. Since most of the time diagnosis can be delayed due to lack of symptoms among these patients, by the time AKI is developed most parts of glomeruli could be damaged. This will in turn result in delay in recovery despite provision of best care (33).

The following are the strengths and limitations of the study which should be considered when interpreting the findings. The first strength of the study is that it addressed an outcome that has received little attention, particularly in Ethiopia. The second strength is that it was conducted in a national center and included all eligible patients during the observation period, and hence it is conducted on a fairly representative sample of the population with AKI. Its limitations are, although several potential exposure variables are controlled in the study, other important exposures such as laboratory, radiologic and behavioral factors are not included due to inconsistent recording of this parameters on the charts. Furthermore, the relatively smaller sample size may have resulted in in lower study power, which may have resulted in a lower detection of other potentially significant relationships.

Conclusions

Given the high-risk nature of the studied population, the median time to recovery from AKI is optimal; however, this duration may very well be associated with an increased risk of both short and long-term complications from continued renal damage. Having cardiovascular disease, sepsis and AGN were found to be associated with delayed recovery from AKI.

As a result, strict monitoring of AKI patients in general, and the high-risk groups in particular, is pivotal for further rapid recovery. A large prospective study that takes into account all potential factors is required to reach a better conclusion.

List of Abbreviations

ACEIs/ARBs … Angiotensin-Converting Enzyme Inhibitors/ Angiotensin II Receptor Antagonists
AKI … Acute kidney injury
ATN … Acute Tubular Necrosis
AGN … Acute Glomerulonephritis
BUN … Blood Urea Nitrogen
CI …. Confidence interval
Cr … Creatinine
GFR … Glomerular filtration rate
IRB … Institutional review board
ICU … Intensive Care Unit
LRTI … Lower respiratory tract infection
NSAIDs … Non-steroidal anti-inflammatory drugs
OR …. Odds ratio
PIGN … Post-infectious Glomerulonephritis
PPI … Proton Pump Inhibitors
RPGN … Rapidly Progressive Glomerulonephritis

Declaration

Ethical Considerations

The study was conducted after securing ethical clearance from SPHMMC institutional review board (IRB) (letter no: PM.23/724). Since the study used secondary data, waiver of consent was obtained from the department of Internal medicine on behalf of the patients to be included in the study. 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.

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. LHJ and TGG contributed to the conception, design of the study and interpretation of findings. ATL and TWL performed statistical analysis, and drafted the initial manuscript. All authors approved the final version of the manuscript.

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Availability of data and materials: All relevant data are available upon reasonable request.

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