Addis Ababa University

College of Health Sciences

Department of Internal Medicine

Research title

Worsening Renal Function in Patients Admitted With Acute Decompensated Heart Failure: Incidence and Risk Factors

Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia, 2021: a prospective Study

A manuscript submitted to the Department of Internal Medicine, College of Health Sciences, Addis Ababa University, in partial fulfillment of residency/post graduate study in Internal Medicine.

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Acknowledgment

Foremost, I would like to express my sincere gratitude to my advisors and to the department of internal medicine for giving me the opportunity to conduct this research. My deepest gratitude and appreciation goes to Dr Addisu Melkie (internist and consultant Nephrologist) for his unconditional support and continuous guidance. Above all, I would like to thank almighty God who helped me through all this.

Acronym

Abbreviation	Definition
ACEIs	Angiotensin converting enzyme inhibitors
ACKI	acute-on-chronic kidney injury
ADHF	Acute decompensated heart failure
AHF	acute heart failure
AKI	Acute kidney injury
AKIN	Acute Kidney Injury Network
ARBs	angiotensin receptor blockers
CARESS	Cardiorenal Rescue Study in Acute Decompensated Heart Failure
CCB	Calcium channel blocker
CHD	Congenital heart disease
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration
sCr	serum creatinine
CRS	Cardio renal syndrome
CRVHD	Chronic rheumatic heart disease
D-AKI	Dialysis requiring AKI
DCMP	Dilated cardiomyopathy
ECG	Electrocardiography
EF	ejection fraction
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
HFrEF	heart failure with reduced ejection fraction
HFmrEF	heart failure with mid -range ejection fraction
HFwAKI	heart failure with worsening AKI

HHD	Hypertensive heart disease
HHF	Hospitalized for heart failure
HIV	Human immunodeficiency virus
ICU	Intensive care unit
IHD	Ischemic heart disease
LOS	Length of stay
LVH	Left ventricular hypertrophy
MRAs)	mineralocorticoid receptor antagonists
NICE	National Institute for Health and Care Excellence
RAAS	Rennin angiotensin aldosterone system
RIFLE	Risk, Injury, Failure, Loss, and End-Stage Renal Disease
WRF	worsening renal function
WRFp	persistent WRF worsening renal function
WRFt	transient worsening renal function
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WRFt	transient worsening renal function

Abstract

Title: *Worsening Renal Function in Patients Admitted With Acute Decompensated Heart Failure at TASH: Incidence and Risk Factors*

Background: *acute kidney injury and worsening of renal function is common in patients with acute decompensated heart failure, and development of this entity affects patient's morbidity and mortality.*

Objectives: *The main objective of this study was to assess the prevalence, and associated factors for development of WRF in admitted ADHF patients.*

Methods*: This was a prospective, hospital-based study of cardiac patients admitted to TASH between June, 2021 and October, 2021. A structured questionnaire was used to collect parameters on sociodemographic characteristics, comorbidities and clinical profile of patients. Trained physician data clerks collected the data from the chart, interview and electronic medical records. Data was entered into SPSS version 26 for analysis. Bivariate and multivariate binary logistic regression analyses was done to identify factors associated with AKI and WRF, Statistical significance was considered at the level of significance of 0.05%, and adjusted odds ratio (AOR) with 95% confidence interval (CI) was used to present the estimates of the strength of the association.*

Result*: A total of 104 patients were included in the study. 64(61.5%) were male and 40(38.5) were female. The prevalence of AKI was 21.2% and the prevalence of WRF was 37.5%. The odds of developing AKI in smokers was 3.7 times higher [AOR= 3.7; 95% CI: (0.86, 13.18)].*

Conclusion: *This study demonstrated that WRF is frequent finding complicating management of ADHF patients.*

Contents

1. Introduction

1.1 Background

Acute decompensated heart failure (ADHF) is a growing public health problem and a frequent cause of hospital admission which is associated with an increased risk of worsening renal function (WRF). [1] The interaction between HF and AKI is complex, bidirectional, and interdependent; however, the exact mechanism remains unknown.[2]

Renal dysfunction is often associated with heart failure and it carries adverse outcomes. Identifying heart failure patients at risk of renal dysfunction is important in preventing progression to chronic kidney disease or worsening renal function, informing adjustment to medication management and potentially preventing adverse events since most of the medications also carry risk of WRF.[3] There is a conflict between renal function and heart failure therapy.

Generally cardiorenal syndrome (CRS) type 1 is the development of acute kidney injury in patients with acute decompensated heart failure. The "cardiorenal syndrome" terminology has been used more frequently in the last decade to define this interdependency of the kidney and the heart. [4]

The development WRF occurs in approximately 25-40% of patients hospitalized for ADHF. Several studies have demonstrated that WRF in ADHF patients is associated with increased mortality, length of stay (LOS), heart failure (HF)-associated hospital readmissions, and cost.[5] WRF is an independent risk factor for adverse outcomes in ADHF, WRF can occur as a consequence of new onset kidney injury (AKI) or acute deterioration of pre-existed chronic kidney disease (CKD) (acute-on-chronic kidney injury, ACKI). [6] in different studies it has been recognized that AKI is a strong independent predictor of both in-hospital and 1-year mortality.[7]

The interaction between heart and kidney disease has been an area of considerable interest recently. CRS involves a bidirectional relationship between the heart and kidneys whereby

dysfunction in either may exacerbate the function of the other, but this syndrome has been difficult to precisely define because it has many complex physiologic, biochemical, and hormonal abnormalities. The pathophysiology of CRS is not completely understood, but potential mechanisms include reduced kidney perfusion due to decreased forward flow, increased right ventricular and venous pressure, and neurohormonal adaptations.

Treatment options include inotropic medications; diuretics; ultrafiltration; and medications, such as beta blockers, inhibitors of the renin-angiotensin- aldosterone system, and more novel treatments that focus on unique aspects of the pathophysiology. Recent observational studies suggest that treatments that result in a decrease in venous pressure and lead to hemocon- centration may be associated with improved outcomes. Patients with CRS that is not responsive to medical interventions should be considered for ventricular assist devices, heart transplantation, or combined heart and kidney transplantation.[8]

WRF is defined as an increase in the serum creatinine level by ≥0.3 mg/dL compared with the value at admission, and it has been established as the gold standard for the evaluation of acute renal failure in patients with ADHF [9]

However, there is no working or consensus definition in international heart failure management guidelines for worsening renal function. In addition, there appears to be no concordance or adaptation of chronic kidney disease guidelines by heart failure guideline development groups for the monitoring of chronic kidney disease in heart failure.[3]

There are five types of CRS; the classification reflects the presumed primary and secondary problem:

• Type 1: Acute heart failure causes acute kidney injury (AKI) –it is the focus of this study

• Type 2: Chronic heart failure causes CKD

• Type 3: AKI or acute renal failure causes acute cardiac failure

• Type 4: CKD causes chronic cardiac dysfunction, including heart failure

• Type 5: An acute or chronic systemic disorder causes both cardiac and renal failure (e.g. sepsis, diabetes mellitus, systemic lupus erythematosus)[10]

Among hospitalized ADHF patients, a rise in creatinine of 0.3 mg/dL has been clinically significant, but the time limits for worsening renal function have been variable in different literatures. [11]

Guideline directed treatment for HF have been shown to increase life expectancy, those treatments include ACE inhibitors (ACEIs), angiotensin receptor blockers (ARBs), sacubitril/valsartan, beta-blockers and mineralocorticoid receptor antagonists (MRAs) (together with appropriate device therapy). However, it is also known that most of the treatments used for CHF can cause worsening of renal function.[12]

It should also be noted that the same mechanisms that trigger ADHF, such as tachyarrhythmia, anemia, and infection can also predispose to WRF.[1]

In ADHF achieving clinical euvolaemia is a fundamental goal to improve symptoms and to improve outcome. Loop diuretics are first-line agents to alleviate congestive symptoms.

Unless they are diuretic naïve congested patients often need high doses of intravenous diuretics to achieve fluid loss. It is a common practice to decrease the dose of diuretics or even to stop it when renal impairment is observed but Patients with fluid overload should have their diuretics increased whether or not their renal function is impaired.[12]

Although use of loop diuretics is widespread for management of ADHF, there is little evidence of their influence in managing CRS. Their use may be associated with electrolyte abnormalities, further neurohormonal activation and worsening renal function. In addition, they may increase the risk to develop adverse effects of concomitant medications, such as ACEI, ARB, or spironolactone. [13]

In CARESS study doses as high as 30 mg furosemide per hour together with a thiazide was used successfully to treat difficult to treat congestions. It is common practice to prescribe low diuretic dose for the initial because of fear of an adverse impact on renal function. But fact is clinical assessment is should direct our management than renal function. If the patient is improving clinically, declines in renal function are of secondary importance. Current renal function should be assessed in the context of 'baseline' values (ideally reflecting longer-term serial evaluations).[12]

RAAS inhibitors may cause decline in renal function and/or hyperkalaemia, particularly during initiation and titration, intercurrent illness and during worsening of heart failure. [12] it is recommended by NICE for dose reduction or even stopping ACEI or ARB if serum creatinine rises by >30% without another explanation. [12]

Various patterns of WRF may have different prognostic implications and may require different therapeutic approaches. WRF may be initially classified by duration (transient vs. persistent) and by etiology (elevated venous pressures vs. arterial underfilling). Other critical contributing factors during hospitalization include progressive left ventricular dysfunction, neurohormonal activation, and medications. Transient WRF as a result of aggressive therapy targeting congestion may not be associated with poor outcomes. Persistent WRF seen in patients with severe hemodynamic derangements may be associated with poor post-discharge prognosis. Future investigations must clarify the pathophysiological correlates of various patterns of WRF. To date, there is an unmet clinical need to achieve adequate control over congestion while preserving renal function in HHF patients.[14]

1.2. Statement of the problem

Cardiorenal syndrome had become an active area of interest in the past decade. Numerous studies have demonstrated that renal dysfunction and worsening renal function (WRF) are common in patients who are admitted for heart failure and appear to be associated with poor in-hospital and post-discharge outcomes. Its etiology has not been completely understood, and its prediction during hospitalization remains challenging.

The evaluation of renal impairment during hospitalization should take into consideration the underlying renal substrate (e.g., predisposing clinical comorbidities such as diabetes and hypertension), initiating mechanisms (e.g., in-hospital therapies such as diuretics), and amplifying factors (neurohormonal and hemodynamic profile changes).

In patients with ADHF, worsening WRF is a common comorbidity with multifactorial mechanisms and heterogeneous prognostic impacts among studies. The development of decreased kidney function during treatment affects the response to diuretic therapy and is associated with important clinical outcomes, including mortality.

Further research into the causes of AKI among HF hospitalizations is, therefore, important as it will enable the development of treatment strategies to prevent AKI in HF hospitalizations and, consequently, benefit both the patients and health care system.

1.3 Significance of the Study

Even though the association between HF and renal dysfunction is well known there is a paucity of research on the incidence and consequences of AKI among patients hospitalized with HF generally and particularly in Africa and Ethiopia.

There is no research published on this particular subject matter in Ethiopia to date, so this will be the first study. The results of the study will be used as a baseline data for further research.

This study will contribute to the management of ADHF patients who are at increased risk of developing AKI (type 1 CRS). It will show the clinical profile of ADHF patients, their laboratory parameters and management and outcome. The results will help to improve the practice of treating ADHF patients in our set up.

2. Literature Review

A total of 2,010,095 hospitalizations for HF were identified from the National Inpatient Sample database (USA) from January 2012 through September 2015, it was found that that incidence of new-onset AKI was ~ 20%. In this study in-hospital mortality was higher in the HFwAKI group (adjusted OR 3.63, P ≤ 0.001) and higher among patients with HFrEF (adjusted OR 3.85), as opposed to patients with HFpEF (adjusted OR 3.21). Similarly, length of stay and cost of care for the HFwAKI group were significantly higher as well. New-onset AKI among hospitalizations for HF poses a significant health problem, since the prevalence of HF is increasing globally.[15]

A systematic search of MEDLINE revealed 8 studies on the relationship between WRF and mortality in 18,634 patients with HF. WRF developed in 4,734 (25%) patients and was associated with a higher risk for mortality (odds ratio [OR] 5 1.62; 95% confidence interval [CI] 1.45e1.82, P < .001) and hospitalization (OR 5 1.30, 95% CI 1.04e1.62, P 5 .022). The severity of WRF was also associated with greater mortality. Patients with impaired renal function at baseline were more prone to progressive renal function loss. In this systematic search it was concluded that WRF predicts higher rates of mortality and hospitalization in patients with HF.[16]

Across 2002–2013, the incidence of D-AKI doubled from 0.51% to 1.09%. It was found that male sex, younger age, African-American and Hispanic race, and various comorbidities and procedures, such as sepsis and mechanical ventilation, to be independent predictors of D-AKI in HF hospitalizations. D-AKI was associated with higher odds of in-hospital mortality and adverse discharge. In conclusion the incidence of D-AKI in HF hospitalizations doubled across 2002–2013. Despite declining in-hospital mortality, LoS, and cost, D-AKI was associated with worse outcomes.[17]

In one study old age, diabetes, hypertension and acute coronary syndromes increased the risk of WRF. In-hospital furosemide doses as well as discharge treatment were similar in WRF and no-WRF patients. Serum creatinine elevation was the strongest independent determinant of a longer hospital stay. [18]

In a prospective cohort of 412 patients hospitalized for heart failure, comparison of a spectrum of worsening renal function definitions (absolute creatinine elevations ≥0.1 to ≥0.5 mg/dL and 25% relative elevation from baseline) and associations with 6-month mortality, readmission, and functional decline were looked at. Larger creatinine elevations predicted the highest risk of death, yet even minor changes in renal function were associated with adverse outcomes. [19]

In a nested case-control study on 382 subjects who were hospitalized with HF the association of medications, fluid intake/output, and weight with WRF was assessed. It was shown that several medical strategies, including the use of CCBs and a higher dose of loop diuretics, but not ACE inhibitors, were associated with a higher risk of WRF. Although assessment of in hospital diuresis was limited, WRF could not be explained by greater fluid loss in these patients. [20]

The in-hospital mortality was significantly higher among patients with AKI than in those without AKI. Hospital stays were longer for patients with AKI than for patients without AKI.[21] [19]

In a study in Argentina a retrospective analysis of data on 200 patients admitted with ADHF was done, WRF was defined as increment of the serum creatinine level during hospitalization by 0.3 mg/dL and by ≥25% from admission. 23% of patients developed WRF. On multivariate analysis, age >80 years (odds ratio [OR] = 2.72; 95% confidence interval [CI], 1.86-3.42), admission glomerular filtration rate <60 mL/min per 1.73 m2 (OR=2.05; 95% CI, 1.53-2.27) and admission systolic pressure <90 mm Hg (OR=1.61; 95% CI, 1.17-3.22) were independently associated with WRF. The rate of mortality or readmission for heart failure (HF) at 1 year was higher in the WRF group (P<.01 by log-rank test). The median hospital stay was 9 days for patients with WRF and 4 days for those without (P<.05). On multivariate analysis, WRF remained independently associated with mortality or HF rehospitalization (hazard ratio = 1.65; 95% CI, 1.12-2.67; P=.003).[1]

In prospective study which enrolled 299 patients across eight European countries. Nearly one-third of patients [72 of 248 patients, 29% (95% CI 26–32%)] developed WRF during hospitalization. The risk of WRF in this group was independently associated with serum creatinine levels on admission, pulmonary oedema, and a history of atrial fibrillation. Although the mortality of WRF patients was not increased significantly, the length of stay was 2 days longer [median 11 days (90% range (4–41) vs. 9 days (4–34), P ¼ 0.006]. The re-hospitalization rate was similar in both groups.[14]

In a population based study in Spain a total of 30 529 patients with HF were included. There were 5294 AKI episodes in 3970 patients (13.0%) and incidence of 3.3/100 HF patients/year were recorded. They were more frequent in women with diabetes and hypertension. The study demonstrated the worse prognostic value of sudden renal function decline in HF patients and pointed to those with more future risk who require review of treatment and closer follow-up.[22]

At University of Glasgow UK, data from a post hoc analysis of the Diuretic Strategies in Patients with Acute Decompensated Heart Failure trial, in which patients who were hospitalized with congestion were randomized to a high versus low dose intravenous diuretic regimen. Improvement in eGFR at 72 hours was independently associated with increased risk of the composite end point of death, hospitalization for HF or visit to the emergency department. The association may reflect inadequate optimization of fluid balance.[12]

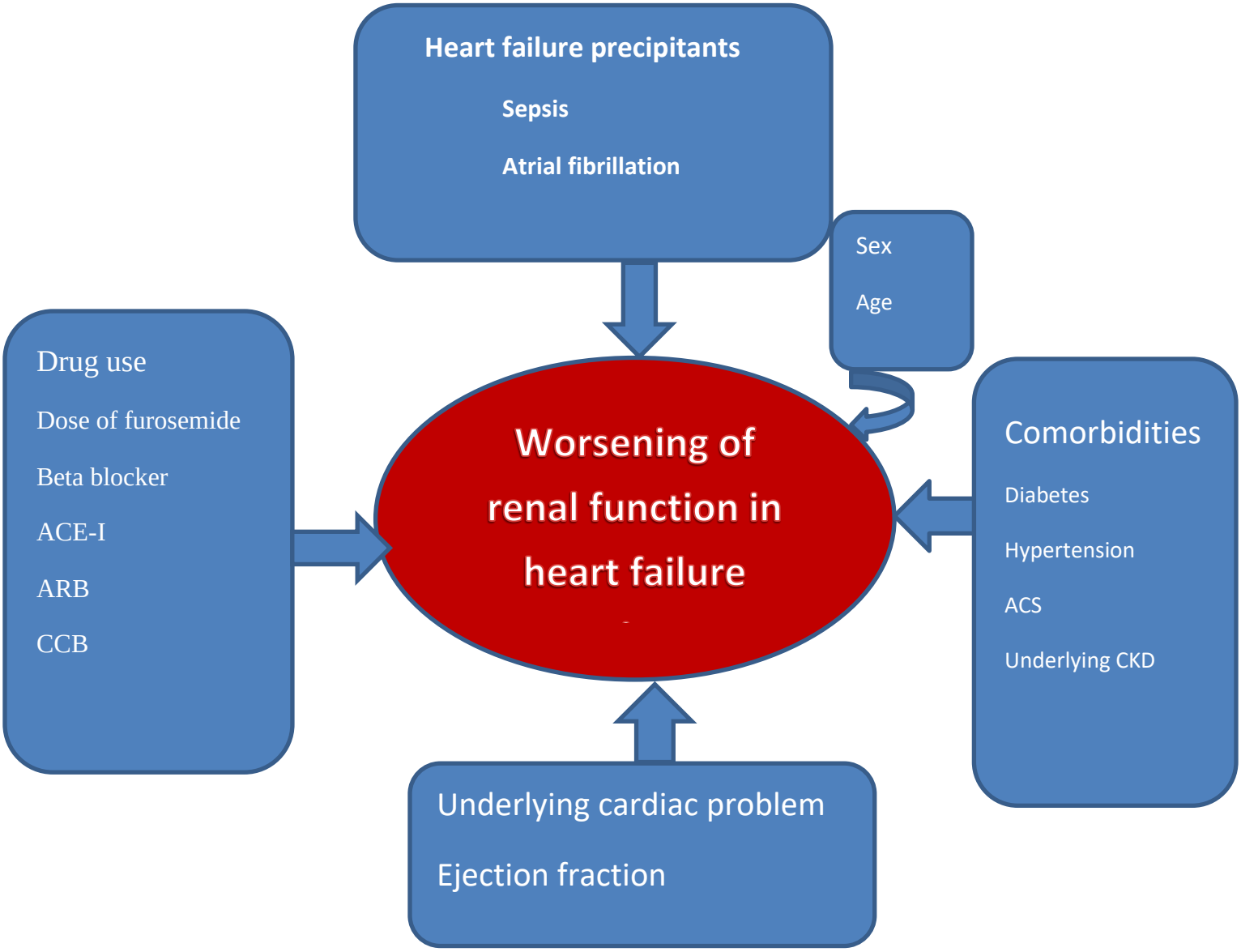
In a study done in Romania ,AKI was associated with a higher risk of mortality in patients with HFmrEF when compared with those with HFrEF, suggesting a stronger prognostic impact of AKI in patients with HFmrEF.[23]

In a study done in China a total of 1,005 patients were enrolled. The incidence of ACKI was higher than that of AKI. The proportion of patients with diuretic resistance was higher among patients with pre-existent CKD than among those without CKD (16.9% vs. 9.9%, P = 0.002). Compared with AKI, ACKI was associated with higher risk for in-hospital mortality,

long hospital stay, and failure in renal function recovery. Pre-existent CKD and development of acute worsening of renal function during hospitalization were the independent risk factors for in-hospital death after adjustment of the other risk factors. The RIFLE classification predicted all-cause and cardiac mortality in both AKI and ACKI. Patients with ACKI were at greatest risk of adverse short-term outcomes in ADHF.[6]

In a cohort of 196 patients admitted for AHF to the Cardiology Department at Nhan Dan Gia Dinh Hospital, Viet Nam, from July 2016 to March 2017 WRF developed in 43.4%. In 80.0% of patients, WRF occurred within 48 hours of admission. [24]

3. Conceptual Framework



4. Objectives

4.1 General Objective

The general objective of this study was to assess the prevalence and risk factors associated with worsening of renal function among heart failure patients admitted at Tikur Anbessa Specialized Hospital.

4.2 Specific Objectives

Specific objectives of this study were:

- To identify baseline characteristics of heart failure patients who develop worsening of renal function
- To assess prevalence of AKI/or worsening of renal function in heart failure patients
- To assess for specific risk factors associated with worsening of renal function

5. Methodology

5.1 Study Area and Study Period

Addis Ababa is the capital city of Ethiopia. Tikur Anbessa Specialized Hospital (TASH) is the country's largest teaching and tertiary hospital with more than 400,000 patients seen at an outpatient follow up clinic annually. The study was conducted over four month's period from June to October of 2021.

5.2 Study Design

A prospective cross sectional study design was used.

5.3 Population

5.3.1 Source Population

All heart failure patients admitted to the cardiac ward from June to October, 2021 were included.. On average 30-33 patients are admitted to the cardiac ward monthly.

5.3.2 Study Population

All heart failure patients admitted to the ward from June to October, 2021.

5.4. Eligibility Criteria

5.4.1 Inclusion Criteria

All heart failure patients admitted to TASH who fulfill the following eligibility criteria:

- All Men or women age >=18

-patients with HF of any cause admitted for ADHF and AHF

5.4.2 Exclusion Criteria

- Patients with established ESRD with eGFR of <=15 on RRT or not

-patients who received IV iodine containing contrast during time of admission

5.5 Sampling

5.5.1 Sample Size Determination

The sample size was calculated using the single proportion formula

$$\boldsymbol{n = \frac{Z^2_{\alpha/2} pq}{d^2}}$$

Z α/2 = is standard normal variant (at 5% type 1 Error (P <0.05) it is 1.96

d = margin of error was taken as 0.03.

p = expected proportion of the population with the event of outcome (prevalence) –the prevalence of WRF in HF patients in a similar set up is 43.4%. [24]

q =1-p: the probability of non-occurrence of the event of interest.

The calculated sample size is **377** patients.

The calculated sample size is 377 patients.

Since the population size is less than 10,000 we need additional correction with

$$\mathrm{n} = \frac{\mathrm{n0}}{1 + \frac{n0}{N}}$$

n= Final sample size

n_0= Initial sample size (377)

N= Source population size (155)

The final calculated sample size is 1**04** patients with10% loss added.

5.5.2Sampling Technique

Convenience sampling method was used.

5.6 Data Collection Method

Data on sociodemographic variables and comorbidity was collected by interview, chart review and electronic record review. Heart failure and renal injury related factors were collected by chart and electronic record review. The data were collected by trained physicians and medical students.

5.7 Variables

5.7.1 Outcome Variables

- Prevalence of AKI and worsening of renal function in heart failure patients

- Risk factors associated with worsening of renal function in heart failure patients

5.7.2 Explanatory Variables

-age

-comorbidities (DM, hypertension)

- Drug use (diuretics, ACE-I, ARB, beta blockers)

- Specific causes of heart failure

-precipitant of heart failure

5.8 Operational Definitions

AKI: AKI was defined according to KDIGO (kidney disease improving global outcome)

According to the KDIGO criteria, AKI is defined by "[a]n abrupt (within 48 hours) reduction of kidney function, defined as an absolute increase in serum creatinine of more than or equal to 0.3mg/dl, a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5ml/kg per hour for more than six hours).

WRF: Worsening of renal function defined as increment in serum creatinine value by >=0.3 gm/dl within 07 days of hospital stay and creatinine value difference between initial and last cr determination of >= 0.3gm/dl in patients who are discharged or deceased.

AKI staging according to KDIGO-

- stage 1: 1.5–1.9 times baseline (i.e. an increase of 50% to 99% from baseline)
  OR ≥0.3 mg/dl (≥26.5 µmol/l) increase
- stage 2: 2.0–2.9 times baseline
- stage 3: 3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6 µmol/l)
  OR Initiation of renal replacement therapy

ADHF; based on clinical diagnosis of ADHF documented on the patients' medical record

ADHF was defined as either new-onset HF or decompensation of chronic HF with symptoms sufficient to warrant hospitalization.

5.9 Data Quality Control

Regular checkup of data collection methods and study protocol adherence were undertaken. Regular checkup for completeness and consistency of the collected data was done by the primary investigato.

5.10 Data Processing and Analysis

Data was checked for completeness, edited, coded and entered into SPSS version 26.0 statistical software for cleaning and analysis. Frequencies and proportion are used to describe study subjects and socio-demographic characteristics. Continuous variables are expressed as means ± standard deviation. Tables and graphs are used to present results. Bivariate and multivariate binary logistic regression analyses was done to identify factors associated with AKI and WRF, Statistical significance was considered at the level of significance of 0.05%, and adjusted odds ratio (AOR) with 95% confidence interval (CI) was used to present the estimates of the strength of the association.

5.11 Ethical Approval

Data collection was carried out after approval of the research proposal by institutional review board of College of health Sciences, Addis Ababa University. Appropriate measures were taken to protect confidentiality of the collected information. Written informed consent was taken from eligible patients. Patients were provided with information on the objectives of the study and confidentiality issues.

5.12 Dissemination of Result

Findings of the research will be communicated to TASH, CHS and AAU University research offices. The findings of the study will be distributed to health workers and health care institutions managing AKI or heart failure patients. The findings will also be presented in different seminars; meetings and workshops and finally efforts will be made to publish on reputable journal.

6. Result

6.1 General Characteristics of patients

A total of 104 patients admitted with ADHF were included in the study. Among them 64 (61.5%) were male and 40(38.5%) were female.

The age of patients included in the study ranged from 18-84 years. The mean age of patients was 47.38±18.323 years. The median age was 60yrs (interquartile range 18-84 years).

Characteristics of the study participants are displayed in table 1.

Table 1: Characteristics of ADHF Patients admitted to TASH, Addis Ababa 2021

Variable	Frequency	Percentage
Sex		
Male	64	60.5
Female	40	39.5
Age (Mean(±SD)	64 (61.5%)	
<65	92	88.5
>=65	12	1.5
Smoking status		
Ex- smoker	27	26.0
Current smoker	2	1.9
Never smoker	75	72.1
Serostatus for HIV		
Negative	33	31.7
Positive	3	2.9
Unknown	68	65.4
DM		
Yes	25	24
No	79	76
Hypertension		
Yes	29	27.9
No	75	72.1

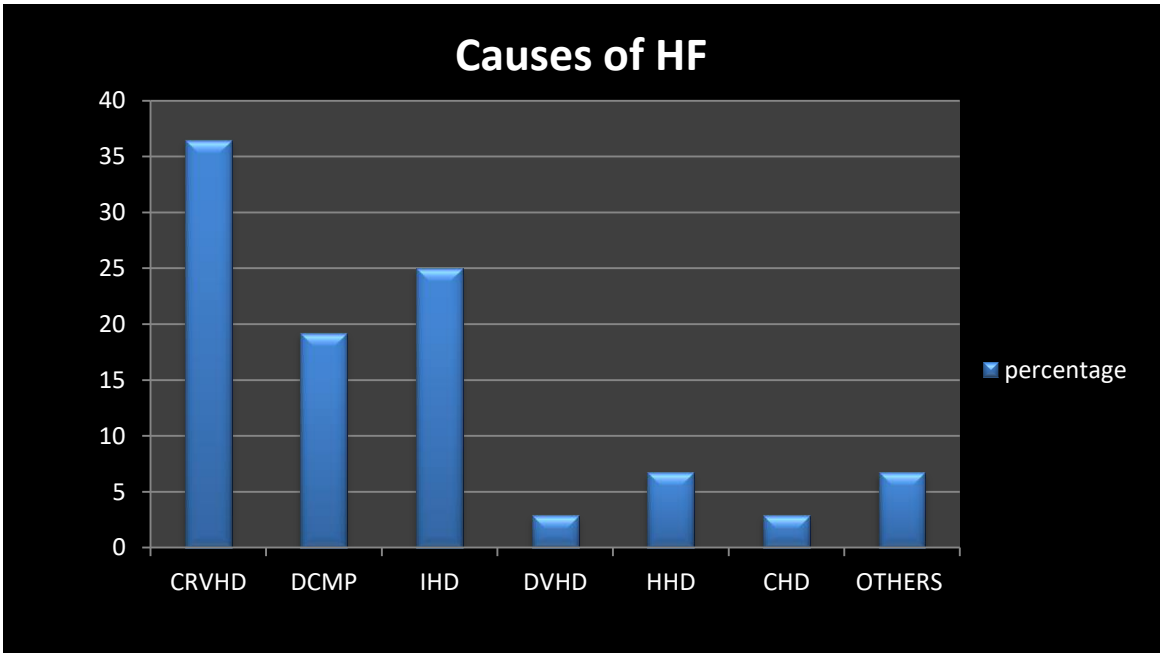
From all studied patients 25 (24%) were diabetic. All patients with diabetes were on treatment 18 patients (72 %) were taking insulin, 18 patients (72%) were taking metformin, only 2 patients were taking SGLT2 inhibitor and 6.7 % were taking SU.

From all patients studied 29 (27.9%) were hypertensive. Among hypertensive patients 93% of them were taking antihypertensive medications,15 patients (55.6%) were on ACE inhibitors,4 (14.8%) on ARBs, 9 (33.3%) taking CCB and 6(22.2%) thiazide diuretics and 4(16%) beta blocker.

6.2 Clinical Profile

The commonest cause of HF among all studied patents was chronic rheumatic heart disease (CRVHD) with prevalence of 36.5% followed by IHD 25% and DCMP19.2% respectively.

Graph 1. Cause of heart failure



The commonest precipitant of HF identified was infection accounting 45.2% followed by drug discontinuation 19.2%.

Graph 2. Precipitants of heart failure

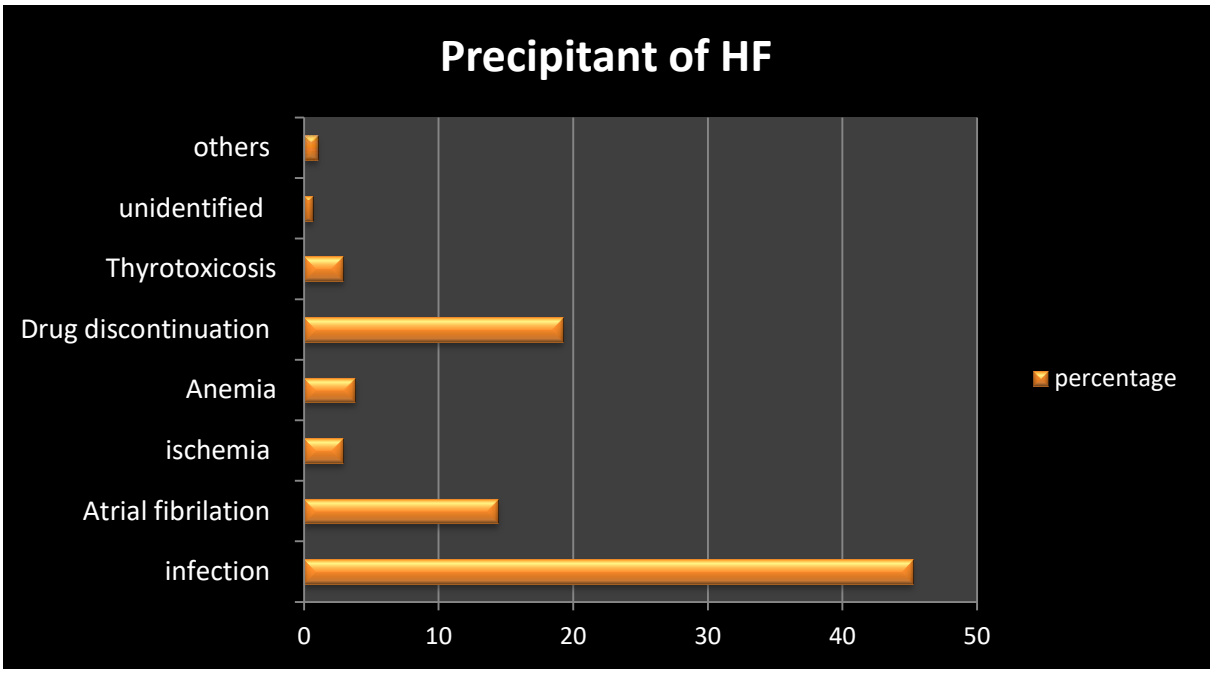


Table 2: Clinical Profile of ADHF Patients admitted to TASH, Addis Ababa 2021

Variables	Frequency	Percentage
Cause of HF		
CRVHD	38	36.5
DCMP	20	19.2
IHD	26	25
DVHD	3	2.9
CHD	3	2.9
HHD	7	6.7
Others	7	6.7
Precipitant of HF		
Infection	47	45.2
Drug discontinuation	20	19.2
Atrial fibrillation	15	14.4
Ischemia	3	2.9
Anemia	4	3.8
Unidentified	11	10.6
Thyrotoxicosis	3	2.9
NYHA class		
II	2	1.9
III	32	30.8
IV	70	67.3
Ejection fraction		
<20	22	21.1
20-40	29	27.9
40-55	24	23.1
>=55	29	27.9
Infecctive endocarditis		
Yes	6	5.8
No	98	94.2
Salt restriction		
Yes	31	29.8
No	73	70.2
Atrial fibrillation		
Yes	35	33.7
No	69	66.3
Pulse rate at initial presentation		
Normal	58	55.8
Bradycardia	4	3.8
Tachycardia	38	36.5
Feeble	4	3.8

SBP at initial presentation		
Hypotensive	5	4.8
Normotensive	82	78.8
Hypertensive	12	11.5
Unrecordable	5	4.8
DBP at initial presentation		
Hypotensive	10	9.6
Normotensive	85	81.7
Hypertensive	4	3.8
Unrecordable	5	4.8

From all patients 31 (29.8%) had severe LV systolic dysfunction with EF <30%, among which 22 (21.2%) had EF <20% and, 29(27.9%) have preserved ejection fraction. Majority of HF patients were NYHA class III and IV 30.8% and 67.3% respectively.

From all admitted patients 5(4.8%) had cardiogenic shock at admission and required IV fluids and vasopressors ,all the patients were out of shock on the same day od admission and received furosemide. 35(33.7%)had atrial fibrillation.

6.3 laboratory Profile of ADHF Patients

Table 3: laboratory Profile of ADHF Patients admitted to TASH, Addis Ababa 2021

Variables	**Frequency**	**Percentage**
Serum sodium at admission		
Normal value	21	20.2
Hyponatremia	36	34.6
Hypernatremia	0	0
Not determined	47	45.2
Serum potassium at admission		
Normal value	48	46.2
Hypokalemia	10	9.6
Hyperkalemia	1.0	1.0
Not determined	45	43.3
Preexisting CKD		
Yes	3	2.9
No	92	88.5
Unknown	9	8.7

Only 3 patients (2.9%) had pre-existing CKD. 36(34.6%) of patients had hyponatremia at initial presentation, 21(20%) of patients had normal sodium value no one of the patients were hypernatremic. 48(46.2%) of patients had normal value of potassium , 10(9.6%) had hypokalemia and only 1 patient had hyperkalemia.

6.4. Treatment of patients

Table 4 : list of medications the patients admitted to TASH with ADHF received, Addis Ababa 2021

Variables	Frequency	Percentage
ACE inhibitors		
Yes	39	37.5
No	65	62.5
ARB		
Yes	5	4.8
No	99	95.2
Spironolactone		
Yes	59	56.7
No	45	43.3
Beta blocker		
Yes	58	55.8
No	46	44.2
Antibiotics		
Yes	55	52.9
No	49	47.1
Antiplatelet		
Yes	46	44.2
No	58	55.8
Anticoagulant		
Yes	34	32.7
No	70	6.3
Furosemide at day of admission		
<80mg IV	43	41.3

80-160mg IV	29	27.9
160-240	28	26.9
240-320	2	1.9
>320	2	1.9

Among all admitted ADHF patients majority received initial dose of IV furosemide less than 80mg at the day of admission over 24 hours, 43(41.3%). Only two patients received dose of furosemide >320mg ,the highest dose of furosemide was 720mg .

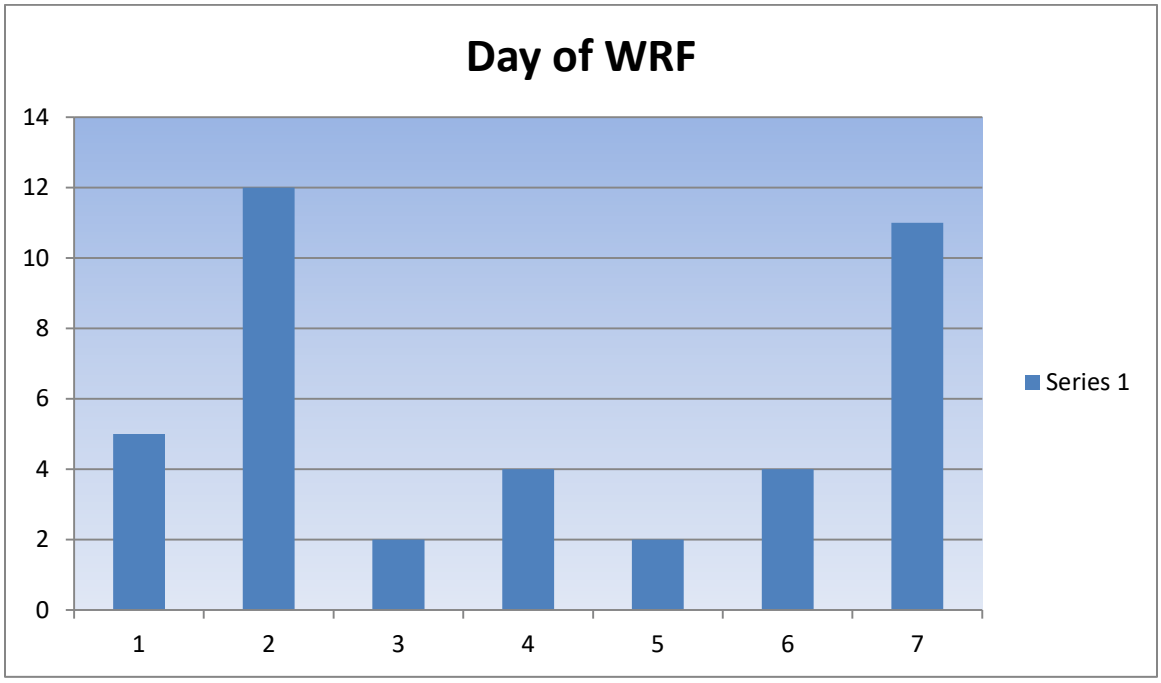
Mean of IV furosemide administered was 142.5 mg ±88.95 mg , with the lowest dose of 40mg and highest dose of 720mg over 24 hours.

6.5. which patients developed WRFAKI

From all admitted patients with the diagnosis of ADHF 22 patients (21.2%) developed AKI according to KDIGO criteria and 39 patients (37.5%) developed WRF within the 07 days of follow up period with increment of serum creatinine >=0.3. The average day that WRF occur is 4 days.

Majority of patients who developed AKI had stage 1 AKI accounting 26(66.7%) of all patients,8(20.5%) stage 2 and 5(12.8%) had stage 3. At the day of admission 32(30.8%) of patients had serum creatinine value of >1.0mg/dl.

Graph 3. Day of WRF occurrence



6.6 Associated factors

In bivariate logistic regression model, each variable was tested and those variables with p value less than 0.25 were entered in to multivariate binary logistic regression model. Multivariate binary logistic regression was conducted after checking the model fitness test called Hosmer and Lemeshow. Bivariate logistic regression was performed to assess the association of each independent variable with the outcome variable (development of AKI or not and WRF or not), the variables that showed a P-value of <0.25 for AKI were smoking, serosataus for HIV (HIV positivity), infection, atrial fibrillation, pre- existing CKD and dose of furosemide at the initial day of admission.

In multivariate binary logistic regression, only the variables smoking was significantly associated with AKI after controlling for other variables at p-value < 0.05.

However, HIV status, atrial fibrillation, infection, preexisting CKD and dose of furosemide were not significantly associated with development of AKI in multivariate binary logistic regression.

Table 5: Associated factor for AKI in admitted ADHF in TASH, Addis Ababa 2021

Variable	Bivariate Binary Logistic Regression		Multivariate Binary Logistic Regression	
	COR (95% CI)	P-Value	AOR (95% CI)	P-Value
Smoking	**3.55(1.32,9.52)**	**0.01**	**3.71(0.86, 13.18)**	**0.04***
Serostatus for HIV (positive)	8.10 (0.69, 93.85)	0.09	20.01(0.86,465.68)	0.06
Atrial fibrillation	0.51(0.17,1.52)	0.22	0.97(0.25,3.65)	0.96
Infection of any source	1.83(0.69,4.85)	0.21	2.7(0.84,911)	0.09
Preexisting CKD	8.10(0.699,93.85)	0.09	0.18(0.01,6.70)	0.35
Dose of furesemide at admission	1.00 (0.99,1.00)	0.11	1.00 (0.99, 1.01)	0.08

The variables that showed a P-value <0.2 for WRF were age >70 years, male sex, smoking, hypertension, initial systolic BP, higher initial creatinine, lower ejection fraction <20% and dose of furesemide at admission.

In multivariate binary logistic regression none of the above variables had statistically significant association with WRF.

Table 6: Associated factor for WRF in admitted ADHF in TASH, Addis Ababa 2021

Variable	Bivariate Binary Logistic Regression		Multivariate Binary Logistic Regression	
	COR (95% CI)	P-Value	AOR (95% CI)	P-Value
Age >70	**3.33(0.90,12.25)**	**0.06**	2.27(0.53, 9.66)	0.26
Sex (male)	8.10 (0.69, 93.85)	0.09	1.77(0.58,5.36)	0.30
Smoking	3.55(1.32,9.52)	0.01	1.39(0.62,5.72)	0.58
Hypertension	2.27(0.94,5.46)	0.06	2.7(0.42,4.60)	0.09
SBP	18(1.8,170)	**0.01**	1.01(0.98, 1.03)	0. 47
Ejection fraction (<=20%)	0.36(0.95,1.36)	0.13	0.18(0.01,6.70)	0.35
Initial creatinine level (>1)	1.95(0.85,4.63)	0.12	1.21(0.44,3.35)	0.70
Dose of furesemide at admission	1.00 (0.99,1.00)	0.20	1.00 (0.99, 1.00)	0.91

7. Discussion

The aim of the study was to assess the incidence and risk factors associated with AKI and WRF in admitted ADHF patients in TASH. The gender distribution in this study was a bit dominated by males 64 (61.5%) compared to female 40(38.5%). The age of patients included in the study ranged from 18-84 years. The mean age of patients is 47.38±18.32 years. The median ages of patients included in a systemic review done in Argentina ranged from 56–78 years. [25] [26] [27]In a similar prospective study done in Vietnam the mean age of the patients was 68.3 years, and 40.3% were men. Similarly in study done in Japan 65.4% male with a median age of 74 years.[28] In a study done over eight European countries mean age 68, 74% men).[14]

Only 2(1.9%) patients were NYHA class II HF in this study the rest majority accounting for NYHA class III and IV 32(30.8%) and 70 (67.3%) respectively. While all of the patients admitted with AHF in the Vietnam study were in NYHA III (44.9%) and NYHA IV (55.1%) which is more or less similar with this study. [24]In a study done over eight European countries 87% of patients were in NYHA class III or IV. [14] [9]

In this prospective study 37.5% of patients admitted with ADHF developed WRF, and similarly 85(43.4%) patients with ADHF developed WRF during hospitalization a prospective study done in Vietnam. WRF was more likely to occur in older patients, those with acute decompensated heart failure or chronic kidney disease, those who had a lower sodium level, those using renin- angiotensin system blockers and those on oral loop diuretics: This conclusion is in line with our prospective study. In china 44.3% patients developed WRF.[6] Incidence of CRS1 was 52.56% in china.[29] WRF developed in 33% patients.[14] Worsening renal function occurred in 360 patients (33.2%) in 05 days follow up period in a study done in Japan. [9]

The average day that WRF occurred is 4 days in this study which is similar to most of the studies. In the Vietnam study 80.0% developed WRF within the first 48 hours and 92.9% developed during 96 hours after admission. [24] The median time from admission to the development of WRF in the whole group was 4 days (90% range 1–12 days)in a study done over eight European countries.[14] In a cohort done in Ohio 58 subjects (40%) developed

WRF during their hospitalization, predominantly within the first 5 days of hospitalization. [30]

WRF was defined by an increase in serum creatinine of >0.3 mg/dL, this cut off value is used by many authors.[31] [32] [1] [14] [33] [30]the definition of WRF after day of hospital admission ranged from 02-15 days. [2] [1] [34] [30] [9]

In relation to the severity of WRF, the majority of WRF cases were graded as KDIGO stage 1 AKI 26(66.7%), 8(20.5) stage 2 and 5(12.8%) stage 3. Similarly in the Vietnam study the majority had stage1 AKI (89.4%). KDIGO stage 2 and stage 3 were 9.4% and 1.2% of cases, respectively. [24]

When WRF occurred within the first 2 day after admission, our study indicated that smoking has strong association.

The odds of developing AKI in smokers was 3.7 times higher [AOR= 3.7; 95% CI: (0.86, 13.18)] Smoking has no significant association with WRF in study done over eight European countries and Ohio.[14]

The cumulative dose of furosemide at admission has no significant association with the development of WRF, [AOR= 1.00; 95% CI: (0.99, 9.42) p=0.91]. Similarly the Vietnam study has supported this outcome (OR 1.01, 95% CI 0.99 to 1.01) in the first 48 hours after admission cumulative dose of furosemide did not contribute to the deterioration of kidney function significantly.

Systolic blood pressure on admission <90 mm Hg is significantly associated with WRF in Argentina but not in this study.[26]

The rate of use of remodeling agents (beta blocker, ACE inhibitor,spironolactone) for patients with reduced ejection fraction is lower in this study as compared with other studies because majority of patients were new patients and it was not possible to start those medications because of raised creatinine value at presentation.

8. Limitation of the study

The limitation of this study is the small sample size which made it difficult to do a more reliable subgroup analysis and the sampling technique used was a convenience sampling method. Serial Creatinine value determination was not done based on standard time frame; it was done based on the convenience of the treating physician even though the primary investigators of the study had involvement.

9. Conclusion

In this prospective study of ADHF, when WRF was defined according to specific criteria, the incidence of acute kidney function deterioration or worsening was found to be higher.

10. Recommendation

In this study it was found that smoking has increased risk of developing WRF so smoking cessation should be advised for our patients and it should be advocated to the public generally. Also the dose of furosemide that patients are using is lower in our study compared to other studies and cumulative dose of furosemide did not have significant association with renal function deterioration so we should diures patients optimally by using clinical parameters rather than using their creatinine value. We should start remodeling agents as early as possible when the renal function stabilizes.

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12. Annex

1. English Version Questionnaire

Prevalence and risk factors associated with worsening of renal function among heart failure patients admitted in Tikur Anbessa specialized hospital, Addis Ababa, Ethiopia

After taking written informed consent and ethical approval, the following data will be retrieved by reviewing patient's charts and interviewing patients

Eligibility criteria

Inclusion Criteria	
- Is the patient aged >=18 years	Yes□ No□
- Does the patient have ADHF or worsening of HF	Yes□ No□
Exclusion Criteria	
-Does the patient have established ESRD with eGFR of <=15 on RRT or not	Yes□ No□
Did the patent receive intravenous iodine mediated contrast during time of admission	Yes□ No□

A. Sociodemographic factors

No	Variables	Response
101	Card number	_____
102	Place of admission	Ward □ ER □ ICU□
103	Age	_____

104	Sex	Male□ Female□
105	Living area	Urban□ Rural□ Semi urban□
106	Region	Addis Ababa□ □Tigray Oromiya□ Amhara□ SNNRP□ Others:____

B. Physical measures ,behavioral risk factors and comorbidities

No	Variables	Response
201	Smoking status	Current smoker□ Ex-smoker□ Never smoker□
202	How many pack years(For ex and current smokers)	_____
203	Does the patient chew chat?	Yes□ No□
204	Does the patient drink alcohol?	Yes□ No□
205	If yes to Q5, bottles of beer (equivalent) per week?	_____
206	Serostatus for HIV?	Positive□ Negative□ Unknown□
207	DM	Yes□ No□
208	If yes to Q7, Is the patient on treatment?	Yes□ No□
209	If yes to Q8, What medication/s?	Insulin□ Metformin□ Sulfonylurea□ SGLT2i□ DPP4i□ Others:_____
210	Hypertension	Yes□ No□
211	If yes to Q10, Is the patient on treatment?	Yes□ No□

212	If yes to Q11, What medication/s?	ACEIs □ ARBs □ Calcium channel blockers□ Diuretics□ Beta blockers□ Others:_____
213	Is the patient on lipid lowering drugs?	Yes□ No□
214	If yes to Q13, what medication/s?	Statin□ Ezetimibe□ Fibrates□ Niacin□ Others:_____

C. Clinical characteristics, lab parameters and medications used

No	Variables	Response
301	Cause of heart failure	□ RVHD□ DCMP□ IHD□ DVHD □ Unknown□ Others:_____
302	If RVHD type of the lesion, which valve is affected and severity	□ stenotic lesion □ regergitant lesion □mixed □MS □MR □TR □AS □AR others _____ □ mild □ moderate □ severe
303	Ejection fraction	
304	Precipitant of heart failure	□ infection □ ischemia □ anemia □ thyrotoxicosis □ Afib □ others _____
305	NYHA class	□ 1 □ 2 □3 □4
306	Stage of heart disease	□ A □ B □ C □ D
307	blood pressure at initial presentation	_____
308	pulse rate at initial presentation	_____
309	Does the patient have	Yes□ No□

	peripheral edema?	
310	If yes to Q09, how severe?	Grade1□ grade 2 □ grade 3 □ grade 4□
311	Level of dyspnea	Grade1□ grade 2 □ grade 3 □ grade 4□
312	Is the patient on diet containing Salt	Yes□ No□
313	Atrial fibrillation	Yes□ No□
314	Infective endocarditis	Yes□ No□
315	Dose of furosemide at admission	_____
316	Dose of furosemide at day 07 or discharge which eve comes first	_____
317	Is the patient on Beta blocking agent	Yes□ No□
318	Is the patient on ACE-I	Yes□ No□
319	Is the patient on ARB	Yes□ No□
320	Is the patient on Spironolactone	Yes□ No□
321	Is the patient on Digoxine	Yes□ No□
322	Is the patient on any anti-coagulant	□warfarin □NOACs □ASA □UFH □LMWH □not taking any □others specify
323	Does the patient have infection of any source	Yes□ No□
324	Is the patient on Antibiotics	Yes□ No□
325	If yes to question number 24 specify	_____
326	Preexisting CKD	Yes□ No□

327	If yes to Question number 26 what is the eGFR	_____

D. Serum electrolyte follow up

Day	0	1	2	3	4	5	6	7
Na+								
K+								

E. Serial serum Creatinine value follow up

Day	0	1	2	3	4	5	6	7
Cr value								

F. Conclusion

Does the patient have AKI according to AKIN based on the above Cr values	Yes□ No□
If yes what is the change in serum cr value	_____
Does the patient have WRF	Yes□ No□
If yes what is the change in serum cr value	_____

2. Information Sheet

Title of Project: Prevalence and Risk Factors associated with worsening of renal function among heart failure Patients admitted to TikurAnbessa Specialized Hospital, Addis Ababa, Ethiopia: A prospective Cross Sectional Study

Name of the Investigators: Eyerusalem Yalew

My name is Dr._____, and I am a final year internal medicine resident. I want to investigate the prevalence and Risk Factors associated with worsening of renal function among heart failure Patients admitted to Tikur Anbessa Specialized Hospital. You are invited to participate in this study. Before you decide to take part it is important for you to understand why this research is being done and what it involves. Please take time to read/listen to the following information carefully. Raise question if there is anything not clear. Thank you for the time you have spent already.

Background to the study.

I would like to investigate the Prevalence and Risk Factors associated with worsening of renal function among heart failure Patients admitted to Tikur Anbessa Specialized Hospital.

Renal dysfunction is often associated with heart failure and portends adverse outcomes. Identifying heart failure patients at risk of renal dysfunction is important in preventing progression to chronic kidney disease or worsening renal function, informing adjustment to medication management and potentially preventing adverse events.

Also, there is no research done on this particular matter in Ethiopia. You will be interviewed with a prepared questionnaire; your chart will be revised for clinical, laboratory and imaging findings.

Possible harms. There is no harm in participating in this study.

Benefits. You will not directly benefit from this study. However, the findings of the study may help plan for care of patients with HF who develops AKI or worsening of renal function.

Confidentiality. All information which is collected about you during the course of the research will be strictly confidential.

Autonomy. All the information you give us is highly valuable to the study. It is up to you to decide whether to take part or not. If you decide to participate, you will be given this information sheet to keep and be asked to sign a consent form. Whether you consent or do not consent to be part of the study, your rights for care in the health care facility will not be compromised and you can withdraw from the study any time.

What will happen to the research? The data will be collected over five to six months period and the result will be available in 8-9 months time, and I hope to disseminate the result publishing it on national and/or international journals.

Who is organizing and funding the research? Research is funded by Addis Ababa University. The research will be reviewed by the Institutional Review Board of College of health Sciences, Addis Ababa University.
Thank you in advance!

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Informed Consent Form

Renal dysfunction is often associated with heart failure and portends adverse outcomes. Identifying heart failure patients at risk of renal dysfunction is important in preventing progression to chronic kidney disease or worsening renal function, informing adjustment to medication management and potentially preventing adverse events.

For this reason, I kindly request you to participate in the study by responding to the interview, allowing to review your medical record and to undergo some investigations. We assure you that confidentiality of the information obtained is kept. If you have any questions, we will be so happy to entertain them.

I confirm that I have understood what has been read/what I have read has been clear to me, and I have agreed to participate in the study.

Name_____

Signature_____ Date_____

በጥናቱ ላይ ለመሳተፍ በፈቃደኝት ላይ ተመስርቶ የተደረገ የስምምነት ቅጽ

የኩላሊት መዛባት/ድክመት አብዛኛውን ጊዜ ከልብ ድካም ጋር የተያያዘ ሲሆን ይህም መጥፎ ውጤት እንደሚያስከትል ጥናቶች ያሳያሉ። የኩላሊት ችግር ሊገጥሟቸው የሚችሉ የልብ ድካም ያለባቸውን ሕሙማን በጊዜ ለይቶ ማወቅ ሥር የሰደደ የኩላሊት በሽታ ወይም የኩላሊት አሠራር እንዳይባባስ በመከላከል፣ መድኃኒቶችን በማስተካከል ረገድ ማስተካከያ ለማድረግና መጥፎ ሁኔታዎችን ለመከላከል ይረዳል። ስለዚህም ለቃለ መጠይቁ/ለጥናቱ ምላሽ በመስጠት በጥናቱ እንድትካፈሉ በትህትና እንጠይቃችኋለን፤ በተጨማሪም የእርስዎን የሕክምና መዝገብ ለማየት አንዳንድ የተደረጉ የምርመራ ውጤቶችን ማየት ለመቻል ፈቃድዎን እንጠይቃለን። ያገኘነው መረጃ በምሥጢር እንደምንይዝ እናረጋግጥላችኋለን ። ማንኛውም ጥያቄ ካለዎት መልስ ለመስጠት ዝግጁ ነን።

የተነበበውን/ያነበብኩትን ነገር የተረዳሁ መሆኔን አረጋግጣለሁ። በጥናቱም ለመሳተፍ ተስማምቻለሁ።

ስም _____

ፊርማ _____

ቀን _____

Investigators Signature Form

I agree to conduct the study in accordance with the relevant, current protocol and will not make changes to the protocol without permission of Department of Internal Medicine, except when necessary to protect the safety, rights, or welfare of study participants. I agree to personally conduct or supervise this study. I will ensure that the requirements relating to obtaining informed consent and Ethics Committee (EC) or Institutional Review Board (IRB) review and are met. I agree to maintain adequate and accurate study records and to make those records available for inspection by the department or unit heads, hospital administrators, and/or other applicable regulatory entities. I also agree to promptly report to the EC/IRB all changes to the study and all unanticipated problems involving risks to human subjects or others. I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator: _____

Signature: _____ Date: _____