Department of Pharmacology and Clinical Pharmacy

School of Pharmacy

College of Health Sciences

Addis Ababa University

Treatment Outcomes of Nephrotic Syndrome and Associated Factors in Children; at selected hospitals in northern Ethiopia, a Retrospective Study

By: Yainu welegerima (B. Pharm)

Advisor: Teshome Nedi (Ph.D.)

Co-advisor: Mamo Feyissa (Ph.D. candidate)

October 2020, Addis Ababa, Ethiopia

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A thesis submitted to the Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University in partial fulfillment of the requirements for the degree of Master of Pharmacy in pharmacy practice

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Abstract

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Nephrotic syndrome is a glomerular disorder of childhood that is characterized by heavy proteinuria, hypoalbuminemia, hypercholesterolemia, and edema. Despite the availability of effective treatments, severe complication and relapse proteinuria which needs a prolonged corticosteroid treatment is the characteristic of the disease. The aim of this study was to evaluate the treatment outcome of nephrotic syndrome in children. A retrospective cross-sectional study was conducted among children diagnosed with nephrotic syndrome from 2010 to 2017 in Ayder Comprehensive Specialized hospital and Mekelle General Hospital. The data was entered and analyzed using SPSS version 22. Binary logistic regression statistical tests were performed. P-value <0.05 was considered statistically significant. A total of 159 nephrotic syndrome children were included from both Ayder Comprehensive Specialized hospital and Mekelle General Hospital. The mean age of participants at the initial diagnosis was 5.21 ± 2.66 years. A total of 150 (94.3%) of patients have shown response to initial steroid treatment. Remission was achieved in 80 (53%) of participants treated with steroids within 2 weeks of treatment. However, among patients who have remission in the first treatment episode 117(78%) of them have relapsed and only 33 (20.8%) patients remain in steroid sensitive nephrotic syndrome. 52 (32.7%) patients were categorized into infrequent relapse nephrotic syndrome while the remaining 65 (40.9%) patients have found to be steroid dependent/frequent relapse nephrotic syndrome. Early age at diagnosis, hematuria, acute kidney injury, infection, low serum albumin and remission time was found to significantly associate with poor prognosis. Despite good responses with steroid treatment have seen at initial treatment, the relapse rate was higher.

Key words: Nephrotic syndrome, Proteinuria, Prednisolone

Acknowledgment

By the grace of God, I have completed this intellectual academic attempt. I would like to express my gratitude to my research supervisor Teshome Nedi (Ph.D.) and co-supervisor Mamo Feyissa (Ph.D. candidate), for their patient guidance, enthusiastic encouragement and their advice of this starting from the research proposal. I would also like to thank the academic staff of the department of Pharmacology and Clinical practice Addis Ababa University for their constructive comments.

I would also like to sincerely thank the College of Health Science, Mekelle University for giving me this scholarship in continuing my education and conduct my research

I would also like to thank Addis Ababa universities for accepting me the opportunities for my scholarship and continuing my education.

My sincerely thanks also goes to Mekelle General Hospital for allowing me doing my research in their setting and the nurses and other supporting staff there for their help in the data collection time.

Finally, I would like to express my appreciation for my classmates for their valuable comment

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List of Acronyms and Abbreviations

ACSH	Ayder Comprehensive Specialized Hospital
ACTH	Adrenocorticotrophic Hormone
AH	Arterial Hypertension
AKI	Acute Kidney Injury
CKD	Chronic Kidney Disease
CNS	Congenital Nephrotic Syndrome
CNIS	Calcineurin Inhibitors
CYA	Cyclophosphamide
ESRD	End-Stage Renal Disease
FRNS	Frequent Relapse Nephrotic Syndrome
FSGS	Focal Segmental Glomerulosclerosis
GBM	Glomerular Basement Membrane
GFR	Glomerular Filtration Rate
ISKDC	International Study of Kidney Disease in Children
KDIGO	Kidney Diseases Improving Global Outcomes
IRNS	Infrequent Relapse Nephrotic Syndrome
MCD	Minimal Change Disease
MCNS	Minimal Change Nephrotic Syndrome
MN	Membranous Nephropathy
MRN	Medical Record Number
NS	Nephrotic Syndrome
SD	Standard Deviation
SDNS	Steroid Dependent nephrotic Syndrome
SLE	Systemic Lupus Erythematous
SRNS	Steroid Resistance Nephrotic Syndrome
SSNS	Steroid Sensitive Nephrotic Syndrome
USA	United State of America
UTI	Urinary Tract Infection

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1. Introduction

1.1. Background

Nephrotic syndrome (NS) is a chronic glomerular disorder of childhood characterized by heavy proteinuria (24-hour urine collection showing > 3 to 3.5 g protein) or a Nephrotic range proteinuria of early morning urine protein 3+/4+, hypoalbuminemia (<2.5gm/dl), hypercholesterolemia (> 200mg/dl) and edema (FMHACA, 2014, Cattran et al., 2012). Globally, the prevalence of NS approximately 16 cases per 100,000 and incidence of 2–7 cases per 100,000 children per year (Eddy & Symons 2003). The prospective studies across Canada and Netherlands revealed an incidence of 1.52 to 4.76/100,000 children (El Bakkali et al., 2011, Banh et al., 2016). The incidence of nephrotic syndrome is higher in south Asian, African-American and Arab children ranging 11.6/100, 000 upto 9.4/100,000 (McKinney et al., 2001, Elzouki et al., 1984, El Bakkali et al., 2011).

Histopathological, about 80% of NS children have a minimal-change disease (MCD) while the remaining others are focal segmental glomerulosclerosis (FSGS), congenital NS (CNS) and NS due to glomerulonephritis. MCD is characterized by changes in light microscopy that are minor or absent, and well respond to corticosteroid agents (Dinçel et al., 2015). Once the overall incidence of childhood NS is constant over the last many years (3.6 in this study), the histological pattern shown to be altering with a surge in the incidence of FSGS, reported 24.5% in this study in compare to previous which founds 6.9% (Srivastava et al., 1999).

NS is believed to be an inflammatory injury to the glomerular structures and results in few cells or cellular casts in the urine. It is related to abnormalities in T-cell and B-cell regulation. The syndrome may be the result of primary diseases of the glomerulus such as MCD, FSGS or MN and has no background disease (idiopathic) or be associated with systemic diseases such as diabetes mellitus, systemic lupus erythematous (SLE), amyloidosis, and preeclampsia and has any background disease. The presence of proteinuria indicates a defect of the size or charge-selective barriers within the glomerular basement membrane (GBM). In addition to kidney disease and systemic infection, NS may be caused by other factors such as genetic, environmental or certain medications (Joseph T. DiPiro, 2017). The property of the illness to relapse after infections or an atopic episode and the therapeutic response to steroids and

cyclosporine support the ‘immune dysregulation’ hypothesis be the pathogenesis of NS (Bagga and Mantan, 2005).

New-onset edema, particularly in the lower extremities, is the most common presenting symptom. Depending on disease severity, the edema can extend to the proximal lower extremities, lower abdomen, or genitalia. Other symptoms like ascites, periorbital edema, hypertension, and pleural effusion also present. Patients may report foamy urine, exertional dyspnea or fatigue, and significant fluid-associated weight gain (Siddall and Radhakrishnan, 2012).

Traditionally the treatment of NS relied on food-based where a high-protein, low-salt diet was recommended to increase albumin synthesis to make up for the urinary loss and to minimize edema formation. Other treatments like mercury as diuretics, induction of measles and malaria vaccines was also practiced (Robert C. Keisch, 1993, Kher et al., 2006). Before 1950, the mortality of NS in children was approximately 50% - 67%. Once the introduction of antibiotics sulphonamides and penicillin the mortality decreased to 40% and 35% respectively (Kher et al., 2006).

The modern treatments became available in the mid-1900s with the advent of steroids, antibiotics, diuretics, and other immunomodulators. Corticosteroids have been used to treat childhood NS since 1950. Large doses of adrenocorticotrophic hormone (ACTH), cortisone was given for two to three weeks and induce diuresis with loss of edema and proteinuria (Arneil, 1971). The standard medication for treatment is prednisolone or prednisone which replaced the previously used medication of cortisone as they could be administered orally without the need for daily injections. It was since the advent of this steroid therapy, mortality from nephrotic syndrome dramatically decreased to 9%- 3% (ISKD-c, 1984).

Eight weeks therapy of prednisolone was recommended after substantial study between January 1967 and June 1974 by International Study for Kidney Diseases in Children (ISKD-c) which continues for three decades (Barnett et al., 1981). Controlled studies later suggested that prolongation of initial steroid therapy for 12 weeks or longer claiming it was associated with reduced risk for subsequent relapses (Ueda et al., 1988). Based on different evidence and opinion, it was recommended an initial episode of prednisolone at a dose of 2 mg/kg per day

(maximum 60 mg in single or divided doses) for 6 weeks followed by 1.5 mg/kg (maximum 40 mg) as a single morning dose on alternate days for the next 6 weeks then therapy is discontinued (Lombel et al., 2013, Książek and Wyszyńska, 1996, Beck et al., 2013).

Steroid responsiveness and frequency of relapses provide the best guide to therapy in idiopathic NS. Around 80%–98% of patients achieve remission in initial treatment (Elzouki et al., 1984). Over 50% - 80% of the patients' experience one or more relapses (Anochie et al., 2006, Koskimies et al., 1982) and around 50% suffer from frequent relapses thereby needing additional courses of corticosteroid therapy (Constantinescu et al., 2000, Pasini et al., 2017).

In any case, in terms of renal function, response to steroids is associated with a good long-term prognosis irrespective of the kidney histology type (Niaudet, 2009). Steroid-resistant nephrotic syndrome (SRNS) may occur with initial steroid therapy or as a late event month to years after initial steroid sensitivity. Significant morbidity, including a progressive decline of kidney function, and development of end-stage kidney disease is well-documented in childhood SRNS (Bagga and Mantan, 2005, Crawford and Gipson, 2017).

Patients who relapse from initial treatment are declared as infrequent relapse nephrotic syndrome (IFRNS) if the occurrence of <2 relapses within the first six months or <4 relapses during any 12 months. Frequently relapsing nephrotic syndrome (FRNS) is the occurrence of >2 relapses within the first six months or >4 relapses during any 12 months. Steroid dependent nephrotic syndrome (SDNS) is the occurrence of a relapse while the child is still on steroid treatment or within 2 weeks after its cessation (Cattran et al., 2012). Relapses are treated with prednisolone 60 mg/m2 until the urine protein is negative for three consecutive days and then followed by 40 mg/m2 on alternate days for further 4 weeks. Frequent relapses, steroid dependence or steroid resistance are treated with steroid-sparing agents including Cyclophosphamide (CYA), Levamisole, Rituximab and Calcineurin inhibitors (CNIS) like tacrolimus and cyclosporine (Lombel et al., 2013).

1.2. Statement of the problem

Idiopathic NS is common primary kidney disease among children. It causes considerable illness as it stereotypically rounds a relapsing course dispersed with extended periods of corticosteroids and other immunosuppressive medication. It affects about 2-7 incidence of children per 100,000, and prevalence of 16 children per 100,000 worldwide (Eddy and Symons, 2003) , with higher rates reported among children from the Asian, Arabs and African, ranging 11.6/100, 000-9.4/100,000 (El Bakkali et al., 2011, McKinney et al., 2001, Elzouki et al., 1984).

Information about NS is scarce in Africa. Common infections in the continent such as malaria, schistosomiasis, hepatitis B and HIV have been suggested as major causes of NS (Doe et al., 2006). Compared to white Caucasian children, there is higher incidence of NS in black-African, which is explained by higher Hepatitis B infection to cause this disease. There is also higher incidence of the resistant type of in black children (Srivastava et al., 1999, Bhimma et al., 1997).

Regardless of corticosteroid therapy have shown favorable remission rate in the initial treatment, relapse proteinuria which needs a prolonged corticosteroid treatment is common. . Around 80% of initial responders experience one or several relapse and will need additional courses of steroid therapy. Furthermore, approximately 10% of children with nephrotic syndrome are steroid-resistant (Tarshish et al., 1997).

A study from the USA revealed that NS resulted in an estimated 48,700 inpatient days and charges totaling $259 million nationally in the years 2006 and 2009. Furthermore, 16% of the discharges had at least one severe complication, including thromboembolism, septicemia, peritonitis, pneumonia, or diabetes (Wang et al., 2017). Quality of health of children with nephrotic syndrome is affected by the characteristic chronic relapsing nature. Patients who were not sensitive to treatment, CKD and longer duration of illness scores poor quality of life (Solarin et al., 2019). The impact of NS goes beyond direct economic burden to family and care givers. NS care givers scores higher rate of depression and expends around 60% their total income to manage the disease (Mitra and Banerjee, 2011).

It is well documented that patients with steroid-responsive MCD had the best outcome and those with steroid-resistant NS had the worst outcome. Studies showed that Steroid resistant nephrotic syndrome (SRNS) is an important cause of chronic kidney disease (CKD) in children that often

progresses to end-stage renal disease (ESRD) (Constantinescu et al., 2000). Around 21% ESRD was found in unremitting proteinuria during the initial 8 weeks of treatment. When unremitting proteinuria continued through the subsequent 6 months, ESRD reaches 35%. Although 95% of children with MCNS do well, 4 to 5% die from complications (Srivastava et al., 1999). Black children have a lower incidence of MCNS, higher incidence of FSGS and more aggressive form of FSGS which responds poorly to corticosteroid and other immunosuppressive treatment (Doe et al., 2006, Ingulli and Tejani, 1991). More black Children develop CKD stages 4 and 5 or ESRD compared to white children and have higher mortality compared to white children (Van Biljon, 2011).

Although treatment with glucocorticoids remains the mainstay of therapy, significant morbidity is associated with prolonged glucocorticoid therapy and Steroid sparing agents initially and in frequent relapses. Treatment complications from prolonged treatment corticosteroids and CNIs like hypertension; cushiongous syndrome, infection, acute leukemia, renal carcinoma, and osteoporosis have been reported (Sinha et al., 2015).

Large inter-individual variation of clinical course of the disease, treatment response, intensity and spectrum of side effects of its treatment make the disease difficult to predict its outcome (Abdulmalek, 2017, Schijvens et al., 2019). Though remission of proteinuria following steroid therapy has greater prognostic value in relation to long-term outcome, variance in the disease make difficult to predict its treatment outcome and generally affect the management protocol. Since there is a considerable variation in disease burden by country of origin and steroid responsiveness pattern all over the world, it is crucial to study the characteristics and treatment outcome of the disease in the institution. To my knowledge there are no studies on the treatment outcome and risk factors for steroid responsiveness in northern Ethiopia, particularly in the selected hospital of Mekelle town. It is likely that genetic and environmental risk factors play a substantial role in explaining this ethnic difference. It can also have different factors that need further study. We have investigated the basic demographics, laboratory and clinical aspects of the patients and their effects on the response to treatment.

1.3. Literature Review

Treatment outcome and associated risk factors for poor prognosis

Study was done in Australia on children aged below 15 years with new-onset nephrotic syndrome. Twelve-month follow-up data found that out of 129 participants 107 (83 %) achieved remission and 22(17 %) had steroid-resistant nephrotic syndrome. Median time to achieve remission was 12 day. Eighty-six (80 %) of 107 children experienced one or more relapses. Of 86 children with relapse, clinicians classified 41 (48 %) children as having infrequent relapses, 24 (28 %) as having frequent relapses, and 21 (24 %) as being steroid dependent. Male gender (HR 3.30; p<0.001) and Time to relapse (HR0.92; p0.002) was the two significant predictor for Frequent relapse (Sureshkumar et al., 2014).

On a prospective cohort Study conducted between December 3, 2007 and May 31, 2010 in France of 188 children, the male to female ration were 1.8:1. The age range was between 6 months and 15 years. Of these 188 patients, 174 (93%) have remission by the 4^{th} week. 139 patients (79%) experienced one or more relapse. Of these relapsers, 43 patients (31%) were frequent relapsers and 95 patients (69%) were non-frequent relapsers. Age at diagnosis less than 4 year was associated with risk of early relapse and frequent relapse ($p < 0.001$)(Dossier et al., 2019).

In course of 2 years study with 347 Patients in Germany, steroid-resistant was found to stay longer time in hospital than children with steroid-sensitive (25.2 vs. 13.3 d). Patients with bacterial/viral infections stayed longer in hospital (24.9 d vs 19.5d) than children without an infection (14.2 d vs 14.9 d). Additionally, children with arterial hypertension (AH) and acute renal failure (ARF) stayed significantly longer in hospital. Patients with SRNS had frequent complications such as bacterial infections, AH, UTI and AKI (Franke et al., 2019).

In a retrospective study of 54 NS patients in Denmark, 56% (30/54) develop FR/SD. FR/SD patients were significantly younger at debut than non-FR/SD patients (3.5 vs. 8.5 years, respectively). Males were overrepresented in the FR/SD group (69% vs. 38%). There were no differences in terms of hematuria, hypoalbuminemia, or days to achieve remission. In total, 31 and 23 patients were on a 6 + 6-week (pred-long) and 4 + 4-week (pred-short) steroid treatment

regimen, respectively. There was a reduction in the number of FR/SD patients in the pred-long group relative to the pred-short group (38 vs. 80%, respectively) (Andersen et al., 2010a).

In a randomized, double-blind, placebo-controlled trial of 150 Netherlands' children treated with equal doses of prednisolone but different duration of treatment, 18 patients from both groups developed hypertension, 16 patients develop infection and 35 patients develop cushiongous syndrome. Prolongation of initial prednisolone treatment from 3 to 6 months while maintaining equal cumulative dose, was associated with risk of development of side effect without reducing risk of relapse.(Teeninga et al., 2013).

A study done in Poland comparing toxic effect and different initial treatment duration on relapse and remission in the first 2 years follow up found, frequency of corticosteroid side effects did not increase after the prolongation of the initial treatment. More than half of the patients 123/184 developed side effects. Recurrent infection occurs in 66, Cushiongous occurred in 31 patients, hypertension in 16 patients and 10 of the participants were found with retarded growth. Prolonged initial therapy was found with reduced risk of relapse. 65.3% children who had been treated for 6 months remained relapse-free within the first 6 months and 50% remained free of relapse over the entire 2-year follow-up period. Children treated 2 and 3 months were found 36.4% and 32.4% for the 6-month period; 27.3% and 20.6% for the 2-year period with free of relapse respectively (Książek and Wyszyńska, 1996).

In retrospective study of 50 patients in Germany, 43(86%) patients get into remission and the remaining 7(14%) were resistant to treatment. The mean age of patients at onset was 4.7 were years ranging 1.2–14.5 years. Of the 43 patients, 36 (83.7%) patients have relapsed at least once and 7(16.3%) patients did not. 11 (25.6%) patients of these become frequent relapser in the follow up. Cataracts and arterial hypertension as steroid toxicity were seen on long time exposure to prednisolone. A younger age at onset less than 4 years ($p = 0.042$) and relapse within 6 months after remission ($p<0.001$) was a risk factor for frequent relapses(Aydin et al., 2019).

In study of 325 Indian children, 213 were IRNS and 112 were FRNS/SDNS. Adequate treatment duration (≥12 weeks) of the first episode and shorter time took (<5.5month) to the first relapse were found an independent predictors of poor prognosis (Mishra et al., 2018).

Study done in Turkey found 150 infrequent relapsers and 120 frequent relapsers from 270 patients who were followed up for at least 1 year. Compared with infrequent relapsers, frequent relapsers had a significantly lower age at onset (4 year vs 5 year), lesser time to first relapse (5 month vs. 23months) and a higher number of relapses with infection. Males were less likely to be frequent relapser (Dakshayani et al., 2018b).

In study of 84 Iranian NS children, 62 children with MCNS, 11 FSGS, and 11 children with diffuse mesangial proliferation (DMP) were followed for 5 years. In this study 57.1% were found with SSNS/IRNS, 22.6% were FRNS/SDNS, and 20.2% were SRNS. Non-responder and risk of developing FRSNS/SDNS was associated with time span between initial presentation and remission, initial presentation of hypertension, hematuria, patients older than six years, increasing number of infections and time period for the first relapse (Davutoglu et al., 2007).

A 35 (49%) of participants SDNS/FRNS, 30(41%) SSNS and the remaining 7(10%) of resistant to treatment was found in a retrospective study of 72 patients done in Japan. Longer time to get remission after initial steroid therapy, and early relapse within 6 months after starting the initial remission and early age at diagnosis was to be a significant predictor of none response and risk of relapse (Fujinaga et al., 2011).

In a retrospective study of 165 Iranian children under 14 years of age in the Children's Hospital of Tabriz, 124 patients (75.2%) responded to steroids, and 41 patients (24.8%) were steroid resistant. Girls were found with higher Frequency of hematuria and steroid resistance than boys. 32.7% of their histopathological finding was focal segmental glomerulosclerosis. Of those who achieved remission for initial treatment, 62.3% experienced at least one recurrence episode, 10.3% were frequent relapsers, and 8.2% were steroid dependent. Old age at onset of was significantly associated with lower relapse rate (Mortazavi and Khiavi, 2011).

A retrospective study at tertiary care hospital of India consisting of children aged 1-15 years were conducted in 88 patients. 25% of the total participants were found with hematuria and 14.7% were hypertensive at initial diagnosis. The male to female ratio were 2.1:1. The mean age at presentation was 5.9 years±2.2. In one year follow up, 26% of the participants develop frequent relapse and 76% develop infrequent relapse. Time to remission ($p<0.041$), presence of

hematuria($p<0.033$), and hypertension($p<0.002$) at presentation were associated with development of frequent relapse (Prasun et al., 2017).

A retrospective cross-sectional study of Indonesian children aged 1−14 years old was done in 90 patients. Boys: Girl ratio in this study was 4.6:1. It was found 50% patients develop IRNS and 50% FRNS. Time spent on remission ≤6 months (OR: 37.113; $P<0.001$) and age at diagnosis ≤5 years (OR: 8; $P<0.001$) was associated with frequent relapse (Situmorang et al., 2016).

Retrospective study from Iraq with enrollment of 80 children age range of 1- 14 years were done. The male to female ratio was 2.2:1. Of the total, 51 patients (63.7%) were within the age-group at presentation 1–5 years. Of them, 45 patients had FR (56.3%) and 35 patients had IFR (43.7%). A total of 15 (18%) patients present with hematuria at diagnosis with majority of these 13 (28%) were from the frequent relapsers ($P=0.008$). Majority of infrequent relapser have (n = 33, 94.3%) responded to steroid therapy in <2 weeks, while most patients with frequent relapsers get into remission (n = 23, 51.1%) within two to four weeks ($p=0.001$) (Ali et al., 2016).

On study of 166 children from Japan followed for two years, 87.3% children were steroid-sensitive and 12.7% children were steroid-resistant. Of 145 steroid-sensitive nephrotic syndrome, 22.1% children experienced frequent relapses. The time to initial remission was longer (10 versus 7 days) in the frequent relapsers than the non-frequent relapsers. The time taken to first relapse was significantly shorter (2.6 versus 6.1 months) in the frequent relapsers than in the infrequent relapsers (Nakanishi et al., 2013b).

Study in Nigeria of Fifty children with median age at onset of 4.8 years was followed for 31.1 (12.1–79.8) months. The relapse status was 23 (46%) and 24 (70.6%) in the 1st and 2nd year after diagnosis respectively. In the 1st-year, 10% had FR/SD while in the 2nd year 11.8% had FR/SD, respectively. Despite more than half of children with NS experience relapse in the follow–up period, proportions experienced FR and SD in these periods was less. None of the commonly reported demographic and clinical factors (like age at onset, gender, time to first remission, serum creatinine or presence of hypertension or microscopic hematuria) was associated with NS relapse (Esezobor et al., 2016).

A retrospective study done in South Africa achieved remission in 81% white vs 56% black children of MCNS and 33% white vs 20% black children of FSGS. Those who failed to oral

corticosteroid treatment were treated with intravenous methylprednisolone of whom only 4 (one white and 3 black child) went into complete remission and hundred children were treated with cyclophosphamide. The response rate was statistically significantly different in the white and black children and sustained remission was achieved in 80% white and in 43% black children. Throughout the follow up more black children (19%) developed stage 4 or 5 CKD compared to white children (3.8%) (Van Biljon, 2011).

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2. Objective

2.1. General objective

- ✓ To assess the treatment outcome of nephrotic syndrome and associated factors in children in in selected hospitals of northern Ethiopia

2.2. Specific objectives

- ✓ To assess steroid treatment response of NS patients in children
- ✓ To identify factors that influence the steroid treatment response of NS patients in children

3. Methodology

3.1. Study area and period

This study was conducted in Ayder Comprehensive Specialized Hospital (ACSH) and Mekelle General Hospitals both located in Mekelle, Tigray Regional State, Ethiopia 783 Kilometers away from Addis Ababa, Ethiopia. ACSH commenced rendering its referral and non-referral services to the 8 million populations in its catchment areas of the Tigray, Afar and Southeastern parts of the Amhara Regional States. It provides a broad range of medical services to Patients of all age groups. ACSH is the second-largest hospital in the nation with the total capacity of about 500 inpatient beds. The hospital has four major departments and other specialty units and with the day by day rising patient flow that has already exceeded 100,000 per year. The four major departments in the teaching hospital are department of surgery, internal medicine, gynecology and pediatrics. Mekelle general hospital gives almost a comparable service to ACSH. The hospital contains more than 100 beds for inpatient and is serving for referral nearby primary hospitals and health centers and nearby woredas including afar region. Both hospitals have the largest patient flow.

3.2. Study Design

A retrospective cross-sectional study was conducted on nephrotic syndrome patient from September 2010 to September 2017.

3.3. Source population

The source of populations was pediatric patients on nephrotic syndrome cases at ACSH and Mekelle General Hospital admitted in the study period.

3.4. Study population

All patients with NS who have treated in the pediatric ward of ACSH and Mekelle General Hospital

3.5. Inclusion and exclusion criteria

Inclusion criteria

- ✓ All patients who undergo treatment with in the period of study, age <18 years and with complete medical record were included in this study

Exclusion criteria

- ✓ Patients who have not completed one year follow up and those who does not take steroid treatment for their condition for any reason.

3.6. Sample size determination and sampling technique

All patients who have been treated with nephrotic syndrome from September 2010 to September 2017 were included. While the event is rare; the sample includes all patients' within the period of study that had undergone treatment of nephrotic syndrome in ACSH and Mekelle General Hospital. Of all the charts found, six were excluded because of nephritic nephrotic diagnosis (reported as NS in the MRN retrieve but the patient was not treated for nephrotic syndrome at all). 10 patients were used for the pilot study. Finally, 159 charts were used in the final data collection for the study. All pilot study samples were used from ACSH. Modification in the data abstraction tool was made after the pilot study. Infection was rearranged in the data collection tool to be included in the initial presentation rather than complication or side effects of the steroid therapy. This was made because the pilot study found infection as initial presentation and physician diagnosed steroid induced infection was not written in the assessment. Information's on place of residence, body mass index and Height of the patients was not also recorded in most of the pilot study, hence to remove these from the data abstraction tool for the study. In recording the steroid induced side effects; it was only used if there is a physician diagnosis written in the chart saying like "steroid induced hyperglycemia" and or on treatment for that side effect. A baseline measures and the higher measure after starting treatment of each laboratory characteristic were taken.

3.7. Study variable

3.7.1. Dependent variable

- ✓ Treatment outcome of steroid treatment

3.7.2. Independent variable

- ✓ gender, age of onset, time to remission, prolonged treatment of first episode, occurrence of comorbid disease, presence of renal complication, hematuria, infection at diagnosis, the frequency of steroid administration, serum albumin, time to first relapse and total cholesterol

3.8. Ethical consideration

Ethical clearance was obtained from the Ethical Review Committee of School of Pharmacy, Addis Ababa University. A support letter was also written by department of pharmacology and clinical pharmacy to ACSH and Mekelle General Hospital for cooperation. The confidentiality of data collected was maintained by omitting the name and address of the patient.

3.9. Data collection process

Data was collected from medical records using data abstracting format which includes demographic data, clinical information, number of prescribed drugs, the duration of therapy and the treatment outcome. The patient registration book was used for retrieving the MRN (Medical record number) of NS patients admitted from September 2010–september 2017. Four data collectors were recruited among clinical pharmacists who were working in hospitals. Training in overall the data collection was given for the data collectors. They were trained one day on the objectives of the study and how to use the data abstraction form to collect data from patient records/charts. Data were collected between 26 July 2019– October 13, 2019 in ACSH and from October 20 -November 10, 2019, in Mekelle general hospital.

3.10. Data analysis and interpretation

The collected data were organized, categorized, entered and analyzed using Statistical Package for the Social Sciences (SPSS) version 22. In the analysis, simple descriptive statistics such as frequencies, proportions, and percentages were used to describe demographic and clinical characteristics of participants. Data analysis and interpretation were done using Binary Logistic regression to identify the factors that are statistically associated with the treatment outcomes. At a 95% confidence interval, $p<0.05\%$ was considered statistically significant in all tests.

3.11. Operational definition

Steroid sensitive nephrotic syndrome (SSNS): NS patients who have been trace or +1 of proteinuria after four week of therapy

Steroid dependent nephrotic syndrome (SDNS): patients who have relapsed following dose reduction or within two weeks steroid discontinuation and came with unremitting proteinuria of +3 or +4 on dipstick urine test

Remission: refers to disappears of protein in the urine and swelling in tissues within one to four weeks of steroid treatment.

Relapse: reappearance of proteinuria 3+ or 4+ for 3 consecutive days and can be either frequent or infrequent. Infrequent relapse means less than 2 relapses in 6 months or less than 3 relapses in one year while frequent relapse means 2 or more relapses in the initial 6 months or more than 3 relapses in any 12 months or one year.

Steroid resistance: refers to the failure to respond to initial steroid treatment or failure to achieve remission despite 4 weeks of prednisolone therapy.

Poor prognosis: frequent relapse and steroid dependent nephrotic syndrome patients are used as good outcome.

Good prognosis: infrequent relapse and steroid sensitive nephrotic syndrome patients are used as good outcome

4. Results

4.1. Sociodemographic and clinical characteristics

In this study as presented below (table 1), a total of 159 children treated for NS were included from two hospitals located in Mekelle town. Of these; 104 (65.4%) were boys and the mean age at initial diagnosis was 5.21 ± 2.66 years. The majority, 124 (78%) of patients were presented with +3 proteinuria and 68 (42.8%) patients presented with hematuria (+1 and above blood) on urine dipstick at the time of diagnosis. Nearly half 79 (49.7%) of patients were found with infection at diagnosis before starting a treatment for NS. Prolonged steroid therapy was prescribed in 131 (82.4%) patients. Two times a day frequency of administration was prescribed in 130 (81.8%) of the NS patients. All patients were presented with edema at their first diagnosis. Besides, 32 (20.1%) patients were found with a comorbid disease at the first presentation. A renal complication which is an acute renal failure was found in 25 (15.7%) of the participants. Remission was achieved in 80 (53.3%) participants within 2 weeks of treatment with steroids.

Table 1: Sociodemographic and clinical characteristics of NS patients (n=159) Mekelle, in selected hospitals of northern Ethiopia from September 2010–september 2017

Variables	Frequency (n)	Percent (%)
Gender		
Male	104	65.4
Female	55	34.6
Age at diagnosis (Mean ± SD) (5.21±2.65)		
1 -4years	68	42.8
4 -8years	76	47.8
8 -15years	15	9.4
Urine protein		
+3	124	78
+4	35	22
Hematuria		
Yes	68	42.8
No	91	57.2
Duration of treatment		
12 weeks	131	82.4
8 weeks	28	17.6
Frequency of administration		
Once-daily	29	18.2
Twice daily	130	81.8
Comorbid Diagnosis		
Present	32	20.1
Absent	127	79.9
Renal complication		
Yes	25	15.7
No	134	84.3
Remission		
Within 2 weeks	80	53.3
Beyond 2 weeks	70	46.7
Infection		
Present	79	49.7
Pneumonia	32	40.52
Meningitis	10	12.6
Upper respiratory tract infection	14	17.72
Urinary tract infection	7	8.86
Spontaneous bacterial infection	5	6.32
Sepsis	8	10.12
Osteomyelitis	3	3.79
Absent	80	50.3
Edema at presentation		
Yes	150	100
No	0	0

SD; standard deviation

4.2. Laboratory Characteristics

On the blood lipid panel, Serum total cholesterol and triglyceride (TG) values were recorded for the initial measures. The mean serum triglyceride (TG) and serum total cholesterol were 162.92 mg/dL (±44.79 SD) and 252.75 mg/dL (± 57.05 SD) respectively. Baseline mean for creatinine level was 0.66 mg/dL (± 0.25 SD). Mean Serum albumin at baseline was measure to be 2.03 gm/dl (± 0.46SD). The mean blood sugar at baseline was 85.61 mg/dl (± 16.96 SD). Last visit of hospitalization while in treatment for relapse or initial steroid was recorded. An average of 13.37 days length of stay was found with a range of stays 5-35 length of hospitalization stay days (Table 2).

Table 2: Laboratory findings of the NS patients at first admission; Mekelle, in selected hospitals of northern Ethiopia from September 2010–september 2017

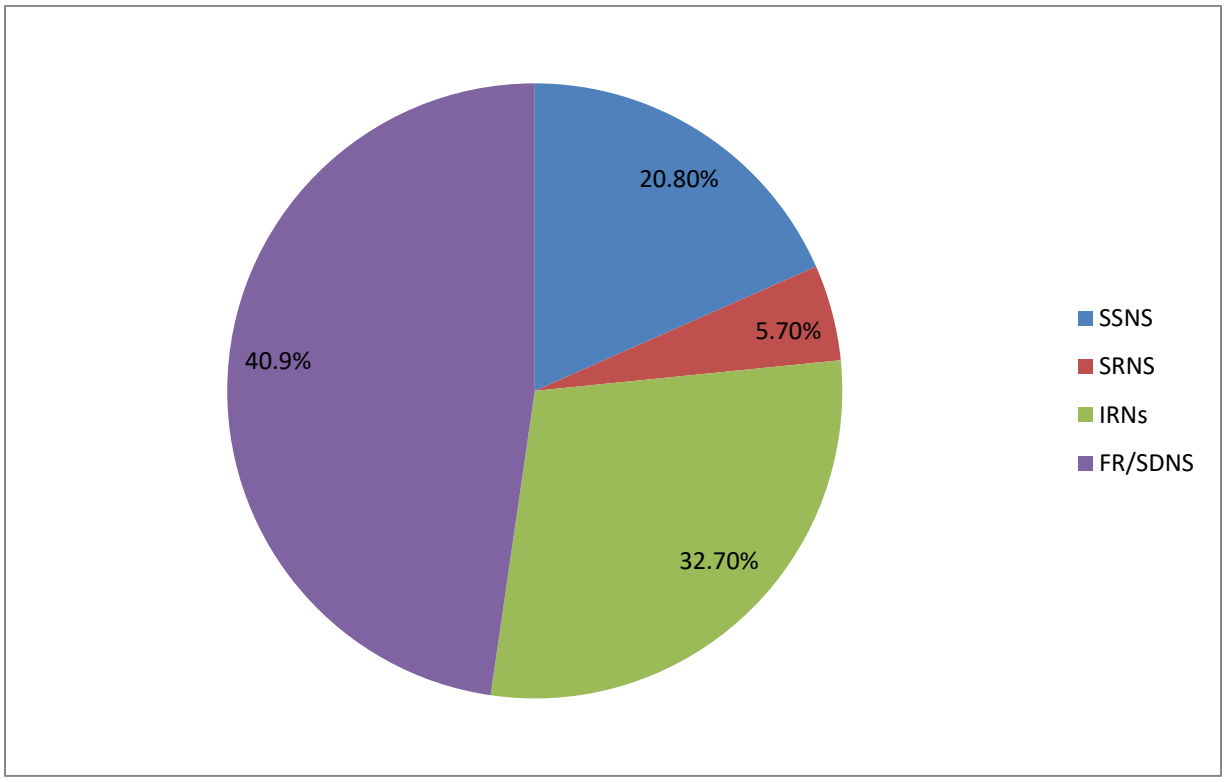
Variables	Range	minimum	maximum	Mean ± SD
Blood sugar	102	56	158	85.6101 ± 16.96 mg/dL
Total cholesterol	334	138	472	252.7484 ± 57.05 mg/dL
Serum TG	556	103	659	162.95 ± 44.79 mg/dL
Serum album	2.00	1.20	3.20	2.0254 ± 0.46 gm/dl
Serum creatinine	1.30	0.20	1.50	0.6597 ± 0.25 mg/dL
SDB				89.59 ± 12.80 mmHg
DBP				62.51± 10.63 mmHg

SD: Standard Deviation; LOS: length of stay; SBP-systolic blood pressure; DBP-diastolic blood pressure; TG: Triglyceride; gm: gram; mg: milligram; dl: deciliter; mmHg: millimeter mercury

4.3. The outcome of NS patients after their course of steroid therapy

As shown in figure 1, Following the treatment with steroids, 150 (94.3%) of NS patients have shown remission at the initial treatment. Generally, 33 (20.8%) patients remained steroid-sensitive during the follow up period. 52 (32.7%) patients were infrequent relapser (IRNS). The remaining 65 (40.9%) patients have found to be relapsing more than two times in six months or more than three times in one year and/or get into steroid dependency. 9(5.7%) patients did not response at all. Of the 150 patients who have shown remission in the first treatment episode,

more than two-third 117(78%) have relapsed at least once and/or become steroid-dependent (SDNS) in the next follow-up period.



SSNS: Steroid sensitive nephrotic syndrome; **SRNS**: steroid-resistant nephrotic syndrome: **IRNS**; infrequent relapse nephrotic syndrome; **FRNS**: frequent relapse nephrotic syndrome; **SDNS**: steroid-dependent nephrotic syndrome.

Figure 1: The outcome of childhood NS patients after their course of steroid therapy; Mekelle, in selected hospitals of northern Ethiopia from September 2010–september 2017

4.4. Common Steroid Treatment-associated Adverse Effects

Side effects secondary to steroid treatment for NS were recorded from each patient chart during their follow up period. There was a total of 109 adverse effected associated with steroids treatment of NS reported. The four common side effects were increase in blood glucose and blood pressure, dyspepsia and moon face. Moon face was seen in 25 patients, rises in BP and sugar level were found with 28 and 29 patients respectively, and 20 patients develop dyspepsia.

Table 3: Common steroid treatment-associated adverse effects reported in NS patients; Mekelle, in selected hospitals of northern Ethiopia from September 2010–september 2017

Variables	Frequencies,(n)	Percentage (%)
Increase BP		
yes	28	17.6
no	131	82.4
Increase blood sugar		
yes	29	18.2
no	130	81.8
Dyspepsia		
yes	20	12.6
no	139	87.4
Moon face		
yes	25	15.7
no	134	84.3
Others		
yes	7	4.4
no	152	95.6

BP: Blood Pressure; **Others**: Glaucoma/conjunctivitis (4); Psychosis (3);

4.5. Factors associated with frequent relapse/steroid dependency (Poor prognosis)

As shown in table 4, Binary logistic regression was used within variables of possible predictors of poor prognosis like gender, age of onset, time taken to remission, prolonged treatment of first episode, occurrence of comorbid disease, presence of renal complication, hematuria, infection at diagnosis, the frequency of steroid administration, serum albumin, time to first relapse and total cholesterol. Variables that have p values of < 0.25 in Univariate-binary logistic regression analysis were taken to multivariable-binary logistic regression analysis. Multivariable-binary logistic regression was used for the factors having a significant association in univariate binary logistic regression to decrease the effect of confounders.

Age of children six and below at initial diagnosis showed 3.16 times higher odds of poor prognosis as compared to age of children above six (AOR=3.16; 95% CI: 1.225-8.156). Children who had hematuria of +1 and above were found to be 6.74 times higher odds of poor prognosis than those without hematuria (AOR=6.741; 95% CI: 2.530-17.958). Children who get remission within the first 2 weeks after start of treatment had a 0.271 times odds of poor prognosis than those who responded after the first 2 weeks (AOR=0.27; 95% CI: 0.113-0.646). A significant association was found between poor prognosis children and the infection at diagnosis. Children

who have infection at initial diagnosis were found to be 3.275 higher odds of poor prognosis than without infection. (AOR=3.275; 95% CI: 1.345-7.973). The odds of poor prognosis were 6.092 times higher among patients found with renal complication compared to those without (AOR=6.092; 95% CI: 1.606-23.103). A low measure of albumin (below 1.5 g/dl) at baseline was associated with 8.376 odds of higher having the chance of poor prognosis compared to a higher measure of serum albumin.

Table 4: Common factors affecting frequent relapse/steroid dependency of NS patients; Mekelle, in selected hospitals of northern Ethiopia from September 2010–september 2017

Predictive Variables	Steroid treatment outcome		AOR (95% CI)	P-value
	Good prognosis n (%)	Poor prognosis n (%)		
Gender			1.053(0.410-2.703)	0.915
Male	49 (50.5)	48 (49.5)		
Female	36 (67.9)	17 (32.1)		
Age cate			3.161(1.225-8.156)	0.017
1-6yr	51 (50.49)	50 (49.51)	*	
>6 year	34 (69.4)	15 (30.6)		
Hematuria			6.741(2.530-17.958)	<0.0001
Present	20 (32.8)	41 (67.2)	*	
Absence	65 (73)	24 (27)		
Infection			3.275(1.345-7.973)	0.009
Yes	29 (40.8)	42(59.2)	*	
No	56 (70.8)	23(29.2)		
Ren. comp			6.092(1.606-23.103)	0.008
Yes	6 (30)	14 (70)	*	
No	79 (60.8)	51 (39.2)		
FOA			1.125(0.360-3.516)	0.840
QD	20 (72.4)	8 (27.6)		
BID	65 (53.3)	57 (46.7)		
Remission			0.271(0.113-0.646)	0.003
≤ 2wks.	60 (75)	20 (25)	*	
>2 wks.	25 (35.7)	45 (64.3)		
Serum albumin			8.376(1.706-41.134)	0.009
<1.5	3 (21.4)	11 (78.6)	*	
>1.5	82 (60.3)	54 (39.7)		

*: P< 0.05; AOR: Adjusted odds ratio, CI: Confidence interval, QD: once daily, BID: twice a day

5. Discussion

This study revealed that 94.3% of children have achieved remission within 4 weeks of steroid treatment. This is similar to another finding where 98% and 97% remission was found within 28 days of treatment in Libya and Italy respectively (Vivarelli et al., 2010, Elzouki et al., 1984). Similar study from japan also found a higher response rate of 95.8% (Shinzawa et al., 2013). The response rate in our finding is higher than in Iran which found a remission of 66% (Safaei and Maleknejad, 2009), 83% in Australia (Sureshkumar et al., 2014) and 75.2% in Iran (Mortazavi and Khiavi, 2011). A total of 90 patients get into remission within 2 weeks. The remaining 60 patients get into remission in the next third and fourth weeks. 5.7% of the study participants did not get into remission in the specified treatment duration. The unresponsive rate is as low as reports from Netherlands (Barnett, 1982) which reports 7% non-response. Non response rate in this study was very low as compared to other study which have found as high as 20% from Turkey (Davutoglu et al., 2007), 17 % in Australia (Sureshkumar et al., 2014), and 24.8% in Iran (Mortazavi and Khiavi, 2011) their participants did not respond. This variation could be attributed to the difference in histological, racial or environmental variation which basically affects the steroid-response. The time to declare the patient is resistance to treatment and disease severity at initial treatment can also be a reason for such discrepancies.

More than two third, 78% of patients have relapsed at least once in the follow up period. This finding is comparable to other previous works that have found a relapse rate of 60% in Nigeria (Anochie et al., 2006), 75% in Iran (Mortazavi and Khiavi, 2011) and 93% in Netherlands (Tarshish et al., 1997). Around 43.3 % of the relapsers in this study were frequent relapser or steroid-dependent nephrotic syndrome. Previously studies also found poor prognosis in 44% of Turkey (Dakshayani et al., 2018a) , in 60% of Japan (Hiraoka et al., 2000), and in 58% of USA (Constantinescu et al., 2000) children. Frequent relapse and steroid dependency were reported 21% in India (Mishra et al., 2018), 28% in Germany (Ehrich and Brodehl, 1993) and 32% in Netherlands (Tarshish et al., 1997), which is low as compared to our study. This discrepancy could be due to the difference in follow up period of patients to be included in the study. Short follow up period could be underestimating the incidence of poor prognosis in these studies. Minimum of one year on follow up were included in our study. Children with six month follow up period were included in other study which underestimates the poor prognosis finding. The

other reasons could be the severity of disease at presentation, late or early visit of hospital, referral hospital cases represented as in our case can overestimate the number of poor prognosis.

The male: female ratio in this study was 1.89:1, which sounds similar to other findings from France and Turkey in which they report NS is two times as common in males than in females (Letavernier et al., 2008, Dakshayani et al., 2018a). Some studies report male sex as a significant predictor of poor prognosis (Andersen et al., 2010b). In our study, we do not found this variable to be a significant predictor of poor prognosis. A possible explanation for this could be the initial presentation of these patients, basically similar histopathological findings. This is supported by the higher number of initial steroid treatment remission rate in this study.

The mean age of patients was found to be 5.21 ± 2.66 years; where also the majority (68.6%) of these children was within the age category six and below. This finding was similar to other studies (4.37±6 .4 years) in USA (Constantinescu et al., 2000) and (5.4±3.1 years) in Denmark (Andersen et al., 2010a) that the majority of the patient's age at diagnosis was within six years and below. In this work, age category of six and below was found to be significantly associated with poor prognosis by a 3.161 higher factor (95% CI: 1.225-8.156). A study from India in agreement to our study found 2.99 times (95% CI: 1.573-5.680) (Mishra et al., 2013) higher odds early age at inial diagnosis was significantly associated with poor prognosis. Another study from Denmark (P=0.002) (Andersen et al., 2010b) also found early age at initial diagnosis was significantly associated with poor prognosis. It is mentioned that nephrotic syndrome is caused by impaired function of T cells. These abnormal T cells produce the chemical mediators like glomerulotoxic and lymphokines which increase the permeability of the basement membrane and cause proteinuria. This abnormal T cell was supposed to be produced in the thymus, most actively in children of young age and infancy stage (Situmorang et al., 2016). Other studies did not found early age at diagnosis associated with poor prognosis. A different histological character at diagnosis which matters the response to steroid can explain to findings early age can explain these discrepancies ($p>0.05$) (Dakshayani et al., 2018a, Kanwal et al., 2018).

Hematuria of +1 and above on urine dipstick was found in 68 patients which accounts for (42.8 %). This is similar to other findings, where 38.9% patients in Denmark (Andersen et al., 2010a), 44% in Nigeria (Ladapo et al., 2014), and 46.4% in USA (Constantinescu et al., 2000) found with hematuria at initial diagnosis . Hematuria in this study is higher as compared to others who

found 16% in India (Mishra et al., 2013) and 25% from Iran (Mortazavi and Khiavi, 2011) and 19.1% in Sudan (Ali et al., 2018) at initial diagnosis. Measurement difference could be the reason for such disagreement. Unlike to other studies which used only macro hematuria (Mishra et al., 2013, Ali et al., 2018), our study used both micro and macro hematuria hence found with higher percentage of hematuria. Other reason like the laboratory technique can bring a difference in hematuria of dipstick test. Significant association was found between poor prognosis and the presentation of patients with hematuria at initial diagnosis. Our study found that patients who have hematuria at initial diagnosis develop poor prognosis 6.092 times higher odds compared to without hematuria (AOR: 6.741; 95% CI: 2.530-17.958). This finding is supported by previous works who found 56.3% FRNS in Iraq (p= 0.008) (Ali et al., 2016) and 50% FRNS in Bangladesh (Sarker et al., 2012) found hematuria to be a significant predictor of poor prognosis. Blood can have end products produced by oxidative stress which then causes harm to the kidney (Tracz et al., 2007). In addition of this hematuria, additional problems like proteinuria can potentiate the poor prognosis (Viteri and Reid-Adam, 2018). No association between hematuria in the first episode and frequent relapses was found in some previously studies from Indonesia and Singapore (p>0.05) (Noer, 2005, Yap et al., 2001).

Around 49.3% of concomitant infections were found at the time of diagnosis in this study. This is in line with studies found infection at presentation 55% in Bangladesh (Sarker et al., 2012), 48% in Singapore (Yap et al., 2001). Our finding but is lower as compared to 71.8% in Sudan (Ali et al., 2018), and 70% in India (Mishra et al., 2013). The low albumin nature of the disease cause insufficient immunoglobulin production, inadequate antibody responses, and inadequate defective cell-mediated immunity. This condition make children at risk to develop infection easily (Bernard, 1988). This high number of infection at presentation could be due to the environmental factor where these reports are from developing country with a high prevalence of infection and also delayed hospitalized which make children at risk for infection. Conversely, other reports found a lower incidence of infections (32.3%) in their cases at first presentation (Noer, 2005).

Infection at initial presentation in this study was associated with risk of developing poor prognosis. It was found that patients with infection at initiation presentation develop 3.275 times higher odds of poor prognosis compared to those without infection (AOR=3.275 95% CI: 1.345-

7.973). This is comparable with the findings from scholars which founds infection at initiation presentation can trigger a relapse. Sarker and his coworkers from Bangladesh found infection at presentation was associated with poor prognosis (p=0.001) (Sarker et al., 2012). Similarly to this study, others scholars have also found infections at initial presentation as predictor of poor prognosis. Studies from Turkey (p=0.001) (Davutoglu et al., 2007) and Singapore (p=0.01) (Yap et al., 2001) also supported our finding. Injury to the podocyte can indeed occur with a viral and bacterial infection. The incidence of relapse is related to infection, and this is believed to be due to increased interleukin-13 messenger ribonucleic acid (mRNA) expression in response to infection. This interleukin may act on monocytes to produce vascular permeability factors involved in the pathogenesis of proteinuria in patients with relapse and early diagnosis (Uwaezuoke, 2015). Infection as trigger of relapse and pathogenesis of the NS was supported by intervening with supplementation of zinc and prednisolone at the time of infection. It was found with low risk of relapse when the maintenance doses of prednisolone is increased at the onset of viral upper respiratory infections, prednisolone is given during onset of viral upper respiratory infections and zinc was supplemented (Uwaezuoke, 2015).

Our study revealed 53% of patients achieved remission within two weeks. This response was almost similar to the response rate of NS patients to steroid treatment within fifteen days in turkey which found a 46% response rate (Davutoglu et al., 2007) and 57% in Egypt (Abdel-Hafez et al., 2017). We found patients who showed early remission within two weeks of steroid treatment to have 0.271 times odds (AOR: 0.271; 95% CI: 0.113-0.646) of poor prognosis in the follow up. The finding of our study is consistent with the available studies from Japan (P<0.001) (Nakanishi et al., 2013a, Fujinaga et al., 2011), France (AHR: 4.1, CI: 1.9–8.6,) (Harambat et al., 2013), Italy (OR=1.39 CI:1.17-1.66,) (Vivarelli et al., 2010), Egypt (p=0.001) (Abdel-Hafez et al., 2017) and Turkey (p<0.001) (Davutoglu et al., 2007) in approving that the longer the time takes to become proteinuria free, the more have the risk of poor prognosis. This is supported by the fact that frequent relapsers are more immunologically affected hence need prolonged-duration steroid treatment to achieve remission. There may be also a histological difference among the patients. No correlation was also reported between time to remission and risk of poor prognosis in previous studies done in Denmark (p=0.36) (Andersen et al., 2010b) and France (p>0.05) (Dossier et al., 2019). Differences in the ethnic/racial characteristics of the patients or histopathological findings can be the reason for such discrepancies. The other possible plausible

reason for such discrepancy cans also the dosage of the prednisolone. Some of the study uses lower daily dose (40 mg/day) in the initial daily treatment and once daily frequency of administration which both produce insufficient concentration in blood.

The mean serum albumin was 2.023 ± 0.46 g/dl. Similarly study in Nigeria also found a mean of albumin 2.05 g/L ± 0.82 (Ladapo et al., 2014). Low serum albumin at onset has been found as a significant risk factor for frequent relapses in this study. Patients with serum albumin below 1.5g/dl at diagnosis were associated with 8.376 times higher odds of becoming poor prognosis (AOR: 8.376; 95%, CI: 1.706-41.134) compared to measure of above 1.5g/dl at initial. This finding is consistent with previous studies done in Bangladesh (P <0.001) (Sarker et al., 2012) and Japan (2.71; CI, 1.27– 5.78) (Takeda et al., 1996). A study from USA also show higher serum albumin (>3g/l) level at the time of diagnosis was independently associated with more favorable renal outcomes and a lower risk of relapse (HR: 1.58 CI: 1.26–1.98) (Lee et al., 2020). This is explained by that severely affected nephrotic patients leak protein and hence end up with lower serum albumin. However, many other studies from Turkey (Dakshayani et al., 2018b, Davutoglu et al., 2007) and Japan (p>0.05) (Nakanishi et al., 2013b) showed no association with serum albumin and frequency of relapse. Albumin administration in the first presentation before starting treatment could bring such difference, whereas none of the above studies have information on this.

Acute kidney injury (AKI) occurs at the time of the first episode of NS or months later in case of relapse. A complication of AKI at initial was found in 13.3% of our patients. Our finding is higher as compared to an incidence of 9.7% in USA (Gipson et al., 2013), 1% in Poland (Kiliś-Pstrusińska et al., 2000), and 8.5 in USA (Rheault et al., 2014), and lower as compared to 34% in China (Chen et al., 2011), 23.6% in India (Sharma et al., 2018), 17.8% in USA (Waldman et al., 2007). Such discrepancies can be due to counting AKI at first admission and after treatment is begun and operationalizing AKI, as in our case only physician diagnosis was used. Out of the 20 patients found with AKI at initial episode, 14(70%) was found to become poor prognosis. Compared to patients with normal renal function, patients with AKI at initial episode of NS treatment had 6.092 times higher odds of poor prognostic development (AOR: 6.092; 95%, CI: 1.606-23.103). Acute renal injury in the nephrotic syndrome might be caused by impaired glomerular permeability. The pathophysiological mechanism proposed to explain this syndrome

was severe edema of the kidney (Cameron et al., 2004), which is in line to our study that all patients were found with edema. An effect of endothelin-1-induced vasoconstriction at the onset of proteinuria has been proposed to explain tubular cell ischemic necrosis which leads to the development of AKI. Infection, diuretic-induced hypervolemia, and other factors also contribute to the development of AKI in nephrotic syndrome. Studies showed that corticosteroid responsiveness can also be hindered or delayed if presented with AKI at initial (Meyrier and Niaudet, 2018). Low albumin, infection, and a severe form of NS were risk factors for the development of ARF (Kiliś-Pstrusińska et al., 2000). Higher numbers of children were found with infection and low albumin at presentation in this study, which can be a reason for the AKI. The time to response and hospital stay was longer in patients who have AKI which intern this results in poor prognosis ($p < 0.05$) (Rheault et al., 2015, Sutherland et al., 2013).

There were a total of 109 adverse effects associated with steroids. The common side effects found were moon faces, dyspepsia, BP and blood sugar increment. This finding was similar to findings from other studies where these common steroid associated adverse effects were mostly seen in their participants (Sinha et al., 2015, Książek and Wyszyńska, 1996).

6. Strengths and limitation of the study

This study has included all childhood NS patients treated with steroids at the specified hospitals. However, this study may not reflect the total community as it was conducted in only two hospitals located in one town which are the same population. Besides, it was a retrospective study based on the chart of the patient, which could lack strong association.

7. Conclusion

Despite good response at initial, a significant number of patients develop a relapse. The development of frequent relapse and/or steroid-dependent is significantly associated with early age at onset, low serum albumin, infection at presentation, hematuria, and AKI at presentation. Many of the common side effects of the steroid treatment like dyspepsia, hypertension, cushiongous effect and diabetics were also seen in many patients.

8. Recommendation

Renal biopsy should be done if possible, for early preparation and best management. Multicenter research, in a different part of the country and different ethnicities should be done for its generalization. Prospectively study should be done so that the basic clinical and laboratory measurement be accurate. Identification of some treatment-related adverse effects can be easy when studied prospectively unlike retrospectively which is mostly not written. Health institutions and policymakers should look into the disease burden especially on the risk of developing chronic kidney injury and end-stage renal failure as a complication of the disease. Long term and adult hood outcome should be studied as none of the children in this research have studied their adulthood.

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10. Annex I: Data abstraction tool/format

Part-1: Socio-demographic variables

1. Patient card no _____ 2. Age at diagnosis of NS _____year

3. WT___kg; 4. Sex A. Male ☐ B. Female ☐

6. Religion A. Muslim ☐ B. Orthodox ☐ C. Protestant ☐ D. Catholic ☐

Part-2: Steroid associated Toxicity/side effects/complication:

1. Diabetes/increase appetite ☐ 2. BP increment from baseline/HTN ☐

3. Moon face/striae ☐ 4. Psychiatric/emotional liability ☐

5. Dyspepsia/GI bleeding ☐ 6. Eye problem/glaucoma/cataract ☐

7. Obesity/weight increment ☐

Part-3: Renal and Extra-Renal complications of nephrotic syndrome

1. Thrombosis ☐ 3. Hyperlipidemia ☐

2. Chronic kidney disease ☐ 4. Acute kidney injury O

Part-4: Treatment status/clinical status of nephrotic patient

1. Steroid sensitive nephrotic syndrome ☐
2. Steroid resistant nephrotic syndrome ☐
3. Relapse nephrotic syndrome: **A**. Infrequent relapse ☐ **B**. Frequent relapse ☐
4. Steroid dependent nephrotic syndrome ☐

Part-5: Baseline patient initial presentation NS information

1. BP at initial _____mmhg
2. 24-hour urine protein/proteinuria/ urine dip stick_____ (+1, 2, 3, 4)
3. Edema at presentation A. Yes ☐ B. No ☐
4. Presence of infection at presentation_____

5. Presence of microhematuria/hematuria A. Yes ☐ B. No ☐

6. Sugar level at initial_____mg/dl

6. Presence of comorbidity A. Yes ☐ B. No ☐

If yes what_____

Part -6: baseline basic laboratory results

1. Serum creatinine_____ 5. Serum urea/BUN_____

2. Serum albumin_____ 6. Serum Total cholesterol_____

3. Serum triglyceride_____

4. Serum HDL/LDL_____

Part-7: Number of admissions/hospitalization history

1. Number of admissions since diagnosis: A. < 2 times B. >2 times

2. Reasons for admission_____

3. Length of stay during last hospitalization _____

Part-8: Medications received during hospitalization for nephrotic syndrome

s. no	Medication name; dose; frequency;	Duration of each treatment	Number of exposed
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

Part 9: Corticosteroid dosage information

1. Daily dose in A. mg/kg_____ B. mg/m^2 _____
2. Duration of treatment in the first episode_____wks. (daily)
3. Duration of treatment in the second episode_____wks. (every other day)

4. Frequency of administration A. once daily **O** B. Twice daily **O**
5. Total steroid dose exposure since diagnosis (number of relapse)_____
6. Time to response: A. ≤1 wk ☐ B. 2 wks ☐ C. 3wks ☐ D. ≥4wk☐ F. no response **O**
7. Time to first relapse: A. within 6month ☐ B. 6month-12 month ☐
   C. 12month-24-month ☐ D. > 24 months ☐