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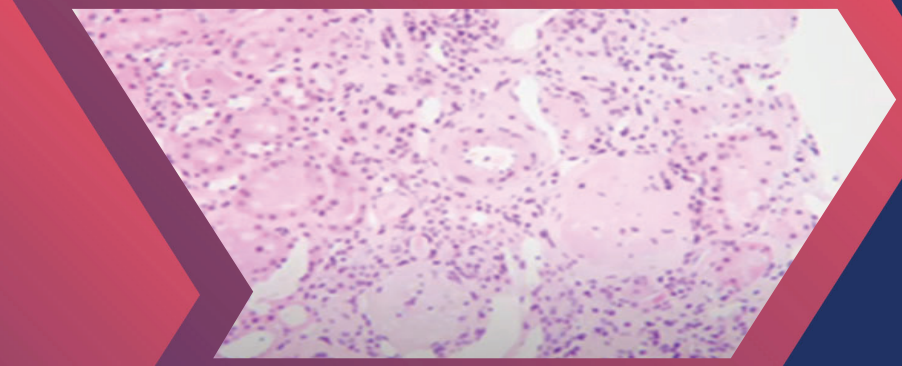

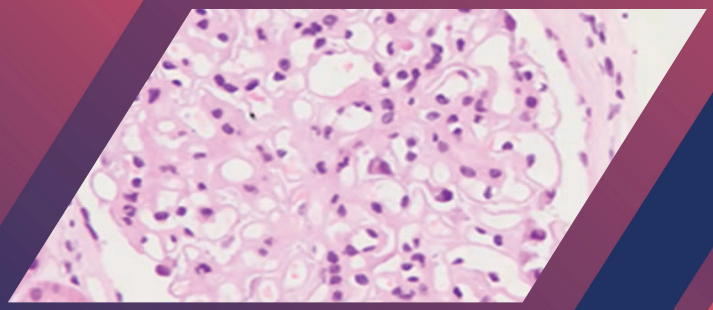

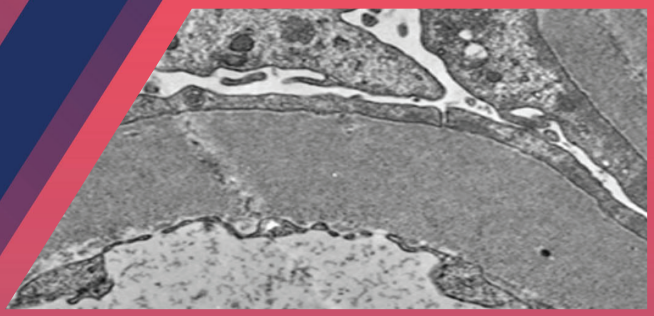

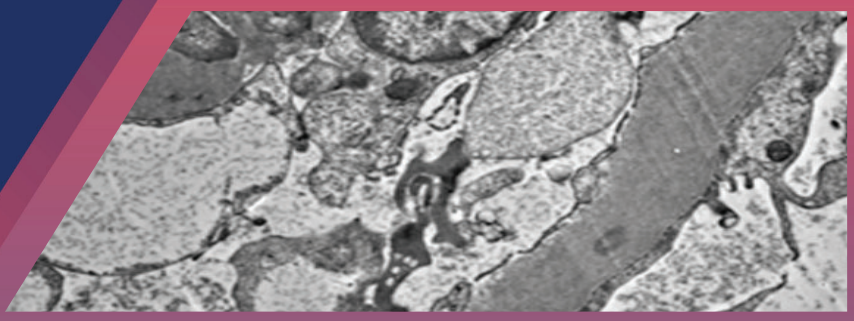

MALAYSIAN SOCIETY OF NEPHROLOGY

CASE REPORT

Myeloproliferative Disorder Associated with Focal Segmental Glomerulosclerosis - A Case Report

- *Nurnadiah Kamarudin, Christopher Thiam Seong Lim*

ORIGINAL ARTICLE

Continuous Kidney Replacement Therapy in Critically Ill Intensive Care Unit Patients with Acute Kidney Injury in a District Hospital Without Nephrologist

- *Xue Meng Lim, Nor Haslina binti Abdul Rahman, Mohd Kamil bin Ahmad*

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Original Paper Open Access

MYELOPROLIFERATIVE DISORDER ASSOCIATED WITH FOCAL SEGMENTAL GLOMERULOSCLEROSIS - A CASE REPORT

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ABSTRACT

We report a rare case of focal segmental glomerulosclerosis (FSGS) with Myelofibrosis. A 57-year-old man with underlying Idiopathic Membranous Nephropathy (IMN) presented to us with chief complaints of frothy urine and leg swelling. Urine quantification showed nephrotic-range proteinuria. The patient underwent renal biopsy due to rapidly declining renal function and persistent proteinuria, in which the electron microscopy (EM) revealed the diagnosis of focal segmental glomerulosclerosis (FSGS) although initial light microscopy showed thickening of capillary loops which suggested MN. He was started on immunosuppressive therapy which consisted of calcineurin inhibitor and steroids, and his renal function and proteinuria improved. We wish to highlight the importance of incorporating EM as part of the routine histopathological assessment to yield a precise diagnosis.

Keywords: *Focal Segmental Glomerulosclerosis, Membranous Nephropathy, Myelofibrosis, Nephrotic syndrome, Electron Microscopy*

INTRODUCTION

FSGS is a clinical-pathologic syndrome of proteinuria associated with focal and segmental sclerotic glomerular lesions that are characterized by podocyte damage. The pathologic classification of FSGS is categorized as primary and secondary, the latter of which is caused by HIV-associated, drug toxicities, but also by structural-functional adaptations to glomerular hyperfiltration such as obesity, hypertension, reflux nephropathy, and so on. Several morphologic variants of primary and secondary focal sclerosis are now recognised, based on a 2004 Columbia classification system, including FSGS-not otherwise specified (NOS), perihilar, cellular, tip, and collapsing variants.

To date, the exact nature of FSGS superimposed on Idiopathic MN remains unclear. Uchika Gupta et al. suggested that FSGS may be secondary to membranous nephropathy and may be an indication of poor prognosis however the mechanism is still unknown. Glomerulopathy is even more unusual in myeloproliferative neoplasm (MPN). According to the literature, there are only a few reported cases of glomerular disease with myelofibrosis, hence we present an interesting case of focal segmental glomerulosclerosis with myelofibrosis

CASE REPORT

A 57 years old Malay Gentleman with underlying Idiopathic Membranous Nephropathy (IMN) was diagnosed in 2010. He is also obese with a BMI of 30 kg/m2. He was previously on mycophenolate mofetil (MMF) since 2010 and was off after achieving remission in 2014. But unfortunately, he had relapsed nephrotic syndrome in 2015 and MMF was restarted. At that time, he was offered cyclophosphamide but he refused. He was then on prednisolone tapered dose and T MMF 500mg BD. His urine protein creatinine index remains in the range of 1-3 grams per day. However, in early June 2021, he presented with abdominal distension

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with splenomegaly and bone marrow aspiration and trephine was done which unfortunately he was diagnosed with myelofibrosis. He was started on thalidomide and ruxolitinib but thalidomide was stopped in April 2023 due to infection. Currently, he was on ruxolitinib and monthly blood transfusion. He was planned for allotransplant but unfortunately, he has no matched donor and was deemed not suitable for mud transplant due to his underlying glomerulopathy. He is currently still under haematology team follow-up.

In September 2022, he had relapsed nephrotic syndrome again with a urine protein of up to 9.1g per day. Therefore, he was counselled for re-biopsy and was restarted with high-dose prednisolone 60mg daily (1 mg/kg), and the MMF dose was increased to 1g BD. He underwent renal biopsy and light microscopy (LM), immunofluorescence (IF) and electron microscopy (EM) were performed. Light microscopic examination disclosed 35 glomeruli, 4 of which were globally sclerotic and 3 glomeruli disclosed segmental glomerulosclerosis associated with hyalinosis. 3 other glomeruli show periglomerular fibrosis with increased urinary space and mild wrinkling of glomerular tufts. There is the presence of global and diffuse thickening of the basement membrane and most of the glomeruli show mild mesangial hypercellularity and mesangial matrix expansion (Fig. 1).

Immunofluorescence staining of glomeruli revealed granular staining of IgM (1+) within the mesangium and C3 accentuation at the area of sclerosis. There is non-specific deposition at C3, IgA, IgM, IgG and C1q. Kappa and lambda light chains were negative. Electron microscopy showed thickened basement with diffuse foot processes effacement (Fig. 2). There were no electron-dense deposits or fibrils.

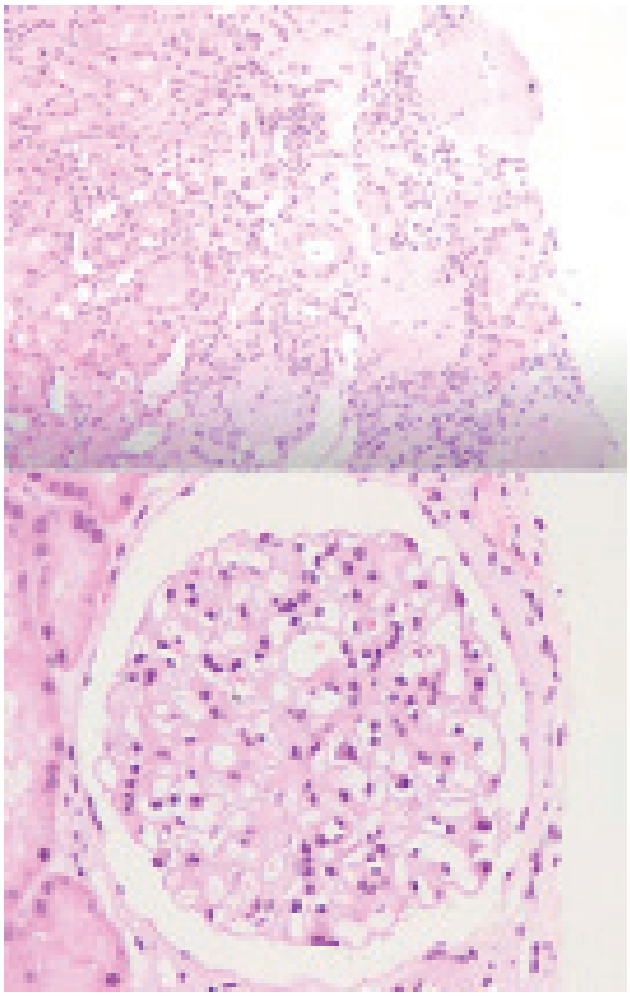

Fig. 1. The light microscopic appearance of a renal biopsy demonstrated global (top) glomerulosclerosis with thickened basement and mesangial hypercellularity (below) (H & E stains).

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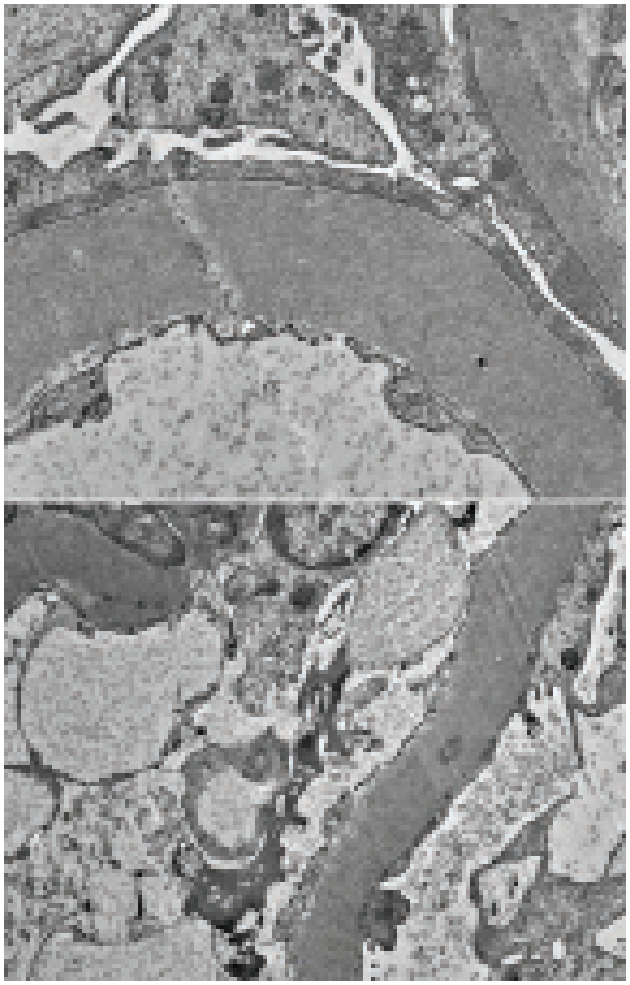

Fig. 2. Electron microscopy showed thickened basement with diffuse foot processes effacement and without any depositions.

DISCUSSION

This is a case of a diagnostic challenge. This patient was diagnosed as MN earlier at another centre but unfortunately, we were not able to retrieve his slides and nor could we retrieve any prior Phospholipase A2 Receptor (PLA2R) antibody results in view of it was in different centre and more than 10 years. The current biopsy sample, although showed rigid capillary loops that were suggestive of IMN, the EM has failed to show any subepithelial deposits. Instead, the EM revealed features of FSGS. The patient's prior IMN could have resolved as evidenced by the dissolution of the immune deposits. Nevertheless, segmental glomerulosclerosis can occur in the course of membranous nephropathy. Several studies have reported the effect of lesions on the clinical characteristics and renal prognosis of Idiopathic MN patients with FSGS, but the conclusions varied. Some studies have shown that the incidence of FSGS in IMN patients is between 12.8% and 43% [1,2,3]. Several prognostic factors including age, sex, degree of proteinuria, the extent of tubulointerstitial changes, hypertension and stage of glomerular disease, have been identified in IMN patients [1,3].

Additionally, glomerular lesions also have been described in some malignant diseases especially myeloproliferative disorder [4]. MN is the most widely described glomerulopathy associated with solid organ tumours while FSGS associated with haematological tumours is infrequent and, when it occurs, it is not clear whether the occurrence of FSGS in these patients is related to the primary haematological disorder or just a coincidence. In our case, glomerulopathy was present at a later stage after diagnosis of myelofibrosis compared to a case described by Rajasekaran et al with early MPN-related glomerulopathy in a 60-year-old man. However, the pathogenesis of glomerulopathy in MPN is still unclear. The most prominent histological findings that are associated with myeloproliferative disorder included double-contoured glomerular basement membranes (71%), acute endothelial damage (68%), intracapillary platelet aggregation (62%), mesangiolysis (21%), thrombotic microangiopathy (24%), segmental glomerulosclerosis (66%), mesangial hypercellularity and sclerosis, extramedullary haematopoiesis (17%), and also IgA nephropathy (21%) and glomerulonephritis (GN) with features of infection-related GN (21%).

Therefore, this case highlights the importance to have EM to accurately diagnoses renal disease. In any case, the prognosis of MPN-related FSGS remains poor despite immunosuppressive therapy and treatment of underlying neoplasm. However, in our case, the patient improved after 2 months of steroid therapy. Long-term follow-up is required to better define the exact clinical course of glomerulopathy in MPN. It remains to be seen whether FSGS is a part of the wider spectrum of MPN-associated glomerulopathy.

CONCLUSION

The mechanism of development of FSGS lesions in IMN and associated with myelofibrosis is still uncertain. Therefore, more studies are needed to elucidate the overlap of these primary glomerulopathies and their association with malignancy.

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CONTINUOUS KIDNEY REPLACEMENT THERAPY IN CRITICALLY ILL INTENSIVE CARE UNIT PATIENTS WITH ACUTE KIDNEY INJURY IN A DISTRICT HOSPITAL WITHOUT NEPHROLOGIST

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ABSTRACT

Introduction: Acute kidney injury in critically ill patients is associated with increased mortality. This paper describes the characteristics of intensive care unit (ICU) patients who required continuous kidney replacement therapy (CKRT), properties of CKRT, and outcomes i.e. length of ICU stay, mortality and renal recovery.

Method: Retrospective descriptive review was conducted on 13 septic patients who underwent CKRT in an ICU in a district hospital without an in-house nephrologist between May 2022 to March 2023. Treatment indications were refractory fluid overload, severe metabolic acidosis (pH<7.1), hyperkalaemia (>6.5mEq/l), and symptomatic uraemia. We describe patients' characteristics, their disease severity with Sequential Organ Failure Assessment (SOFA) score, the timing of CKRT initiation, characteristics of CKRT, and outcomes such as length of ICU stay, mortality and renal recovery.

Results: There were 13 critically ill ICU patients with sepsis and multiorgan failure who underwent CKRT. There were five males and eight females, with a mean age of 46 years (SD 13.6). Pre-morbidly, eight patients had diabetes mellitus (61.5%), six had hypertension (46%), three had heart failure (23%), and one for stage V chronic kidney disease, coronary artery disease and bronchial asthma (8%). Four patients had no prior illness (31%). Twelve patients (92%) had severe disease; the mean SOFA score was 16 (SD 3.2). Time to nephrology referral were between <1 day to 2 days, and treaments were initiated within 2 hours. All received continuous venovenous hemodiafiltration using the Prismaflex-Baxter machine. The mean treatment duration is 38 hours (SD 31.8). Incomplete treatment was due to seven clotted circuits and four deaths. Two patients who used anticoagulated circuits completed their treatments. The mean length of ICU stay was 10 days. Three patients survived with renal recovery, and the mortality rate was 77%.

Conclusion: CKRT provides hemodynamic stability for critically ill patients. We aim to increase circuit patency and improve the mortality rate by expanding treatment availability to a wider range of patients. This review provides insight for improvement and encourages CKRT initiation in other centres.

Keywords: *CKRT, CVVHDF, AKI, haemodialysis, ICU*

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INTRODUCTION

Acute kidney injury (AKI) is common among critically ill patients, with varied incidences due to different diagnostic definitions. A study among Asians reported an incidence of 57% among those admitted into the intensive care unit (ICU) (1). KDIGO defined AKI as either an increase in serum creatinine by ≥0.3 mg/dl (≥26.5 mmol/l) within 48 hours, or an increase in serum creatinine to ≥1.5 times baseline within the prior 7 days, or urine volume ≤0.5 ml/kg/hour for 6 hours (2). It can be divided into pre-renal causes, due to reduced blood flow to the kidney in shock, renal causes such as glomerular and tubulointerstitial diseases, and post-renal causes such as urinary tract obstruction. Medications can lead to all three categories of AKI. AKI is associated with an increased risk of mortality (3,4). The aim of this paper is to describe the characteristics of critically-ill patients admitted into the ICU of a district hospital without a nephrologist, who required continuous kidney replacement therapy (CKRT), and the property of CKRT delivered, as well as the outcomes in terms of length of ICU stay, mortality and renal recovery.

METHOD

A retrospective descriptive review was conducted in 13 patients aged >18 years who underwent CKRT in an intensive care unit of a district hospital without a nephrologist between the period of May 2022 to March 2023. All critically ill patients with kidney failure resulting from sepsis and require CKRT support were included. Indications for CKRT initiation were refractory fluid overload, severe refractory metabolic acidosis (pH <7.1), hyperkalemia (>6.5 mEq/l), and symptomatic uremia. The exclusion criteria are patients without complete records. We report the characteristics (age and gender) and comorbidities (chronic kidney disease, hypertension, diabetes mellitus, heart failure, coronary artery disease, lung disease and liver disease) of the patients, severity of disease calculated according to Sequential Organ Failure Assessment (SOFA) score, timing of nephrology referral, characteristics of the CKRT delivered (duration, modality, membrane used, anticoagulation), as well as outcome in terms of length of ICU stay, mortality and renal recoverys.

RESULTS

A total of 13 critically-ill patients who were admitted into ICU of a district hospital underwent CKRT between May 2022 to March 2023. All of them were diagnosed with sepsis with multiorgan failure. There were 5 males (38.5%) and 8 females (61.5%), with a mean age of 46 years (SD 13.6 years). One patient had stage V chronic kidney disease (CKD) before presentation, while the others either have normal baseline serum creatinine or had no premorbid disease. Most patients had diabetes mellitus (8 patients, 61.5%) as a pre-morbid condition, followed by six hypertensive patients (46%), three heart failure patients (23%), one coronary artery disease patient and one with bronchial asthma (8%). Four patients had no prior illness (31%). A total of 12 patients (92%) had severe disease as indicated by an SOFA score of ≥12, and a mean SOFA score of 16 (SD 3.2). Time from diagnosis of AKI to nephrology referral was evenly spread among groups of <1 day (4 cases), 1 day (4 cases) and 2 days (5 cases). All treatments were initiated within 2 hours of the decision.

All the patients received continuous venovenous hemodiafiltration (CVVHDF) using the Prismaflex-Baxter machine and with a prescribed dose of 30 ml/kg/hour. Seven patients used the oXiris membrane, and the others used the standard membrane. The mean duration of the CKRT delivered is 38 hours (SD 31.8). Seven patients had premature clotting of the membrane before the completion of 72 hours. Only two patients, who completed their prescribed 72-hours treatment, had their lines anticoagulated with heparin infusion at the rate of 10 units/kg/hour. Death in four of our patients is another important cause of incomplete CKRT. The outcome of these patients was categorized into length of ICU stay, 30-day mortality and renal recovery. The mean duration of ICU stay was 10 days, with the longest stay of 32 days. Out of 13 patients, three survived with total renal recovery, and the mortality rate is 77%.

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Patient	Characteristics and comorbidities								
	Gender	Age (years)	CKD	Hypertension	DM	Heart failure	Coronary artery disease	Lung disease	Diease severity (SOFA score)
1	Female	38	X	X	X	X	X	X	15
2	Male	72	X	X	✓	X	X	X	16
3	Female	28	X	✓	✓	X	X	X	20
4	Male	40	X	✓	✓	X	X	X	14
5	Male	35	X	X	✓	X	X	X	10
6	Male	65	X	X	X	X	X	X	17
7	Female	44	X	X	X	X	X	X	13
8	Female	36	X	X	X	X	X	✓	11
9	Female	43	X	✓	✓	X	X	X	19
10	Male	55	✓ Stage V	✓	✓	✓	✓	X	16
11	Female	35	X	X	X	✓	X	X	20
12	Female	68	X	✓	✓	X	X	X	20
13	Female	41	X	✓	✓	✓	X	X	15
% or mean	**38.5% males, 61.5% females**	**Mean 46 (SD 13.6)**	**8%**	**46%**	**61.5%**	**23%**	**8%**	**8%**	**Mean 16 (SD 3.2), 92% severe disease**

Table 1: Patient characteristics, comorbidities, and disease severity.

CKD, chronic kidney disease; DM, diabetes mellitus, SOFA, Sequential Organ Failure Assessment.

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Patient	Prismaflex CKRT						
	Time to neprology referral	Duration of CKRT (hours)	Type of CKRT and dosage prescribed (ml/kg/hour)	oXiris membrane	Premature clotting	Heparin use	Cause of termination
1	<1 day	3	CVVHDF, 30	✓	X	X	Death
2	2 days	38	CVVHDF, 30	X	✓	X	Clot
3	2 days	45	CVVHDF, 30	✓	✓	X	Clot
4	2 days	13	CVVHDF, 30	X	✓	X	Clot
5	1 day	3	CVVHDF, 30	✓	✓	X	Clot, access problem
6	1 day	102	CVVHDF, 30	X	X	✓	Completed
7	<1 day	33	CVVHDF, 30	✓	X	X	Death
8	<1 day	5	CVVHDF, 30	✓	X	X	Death
9	1 day	44	CVVHDF, 30	X	✓	X	Clot
10	2 days	86	CVVHDF, 30	✓	X	✓	Completed
11	1 day	9	CVVHDF, 30	✓	X	X	Death
12	<1 day	58	CVVHDF, 30	X	✓	X	Clot
13	2 days	53	CVVHDF, 30	X	✓	X	Clot
% or mean	**Mean 1 day**	**Mean 38 hours (SD 31.8)**		**54%**	**54%**	**15%**	**54% clotted, 31% deaths, 15% completed**

Table 2: Time to nephrology referral and characteristic of CKRT delivered.

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Patient	Length of ICU stay (days)	30-day mortality	Renal recovery
1	1	✓	X
2	15	✓	X
3	4	✓	X
4	3	✓	X
5	5	X	✓
6	25	✓	X
7	8	✓	X
8	2	✓	X
9	10	X	✓
10	8	✓	X
11	32	✓	X
12	6	✓	X
13	20	X	✓
% or mean	**Mean 10 days**	**Moratlity rate 77%**	**Recovery rate: 23%**

Table 3: Outcomes of patients in terms of length of ICU stay, 30-day mortality and renal recovery.

DISCUSSION

This paper summarizes our experience in treating 13 patients since the initiation of CKRT in May 2022 in our district hospital without a nephrologist. All cases were reviewed by resident physicians and were discussed with nephrologists from a tertiary hospital before initiation of therapy. CKRT is performed in cooperation between the internal medicine and anaesthesiology teams. We received one Prismaflex machine in May 2022. CKRT is delivered via 14F catheters inserted into the femoral vein or right internal jugular vein. The choice of membrane used is based on their availability. KDIGO recommends CKRT as the modality of choice in haemodynamically unstable patients (2), although studies have failed to demonstrate better renal recovery or lesser mortality compared to intermittent haemodialysis (IHD) or prolonged intermittent renal replacement therapy (PIRRT) (5-9). Some studies indicated that CKRT is associated with more stable cerebral perfusion and better negative fluid balance in critically ill patients (10-11). CVVHDF is our modality of choice because it combines the benefits of both continuous venovenous hemodialysis (CVVHD) and continuous venovenous hemofiltration (CVVH), providing optimal solute clearance including those of higher molecular-sized, delivers better haemodynamic stability and reducing filter clot. We initiate CKRT in critically ill patients who depended on more than two inotropes. Most of our patients are relatively young, with one to two co-morbidities. One patient had CKD stage V before illness and all patients were kidney replacement therapy (KRT)-naïve.

Timing of CKRT initiation is a delicate balance between its benefit in correction of fluid balance, solute clearance and stabilizing acid-base status, versus the risks associated with the treatment and resources available. The Effect of

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Early vs Delayed Initiation of Renal Replacement Therapy on Mortality in Critically Ill Patients with Acute Kidney Injury (ELAIN) trial reported that early initiation of kidney replacement therapy (KRT) improves 90-day mortality, shorter duration of KRT, reduced ventilator time, and shortened duration of hospitalization (12). However, the Artificial Kidney Initiation in Kidney Injury (AKIKI) trial reported no difference in 60-day mortality between early and late KRT initiation, with the benefit of reduced KRT in late strategy (13,14). This is supported by the Initiation of Dialysis Early Versus Delayed in the Intensive Care Unit (IDEAL-ICU) trial, which also reported no difference in 90-day mortality, ventilator duration, inotrope support duration, length of hospitalization and dependence on KRT (15). The timing of KRT initiation is still debatable due to the innate differences among these studies in criteria used for initiation of KRT, modality of KRT used, and characteristics of patients included in the trials, with a preference towards late initiation in absence of absolute indications such as severe fluid overload or hyperkalemia (16).

Due to the retrospective nature of this paper, there is inadequate data to confirm the actual delivered dose of the CKRT for every patient. Although the recommended dosage of CKRT is between 20 to 25 ml/kg/hour, a higher dosage prescription of 30 ml/kg/hour is often required to achieve the target dose (2). Both the VA/NIH Acute Renal Failure Trial Network (ATN) study and The Randomized Evaluation of Normal versus Augmented Level (RENAL) Replacement Therapy Study reported no difference in mortality, renal recovery or extra-renal organ failure between more and less intensive therapy (17,18). Seven of our patients had premature circuit clotting which resulted in a reduced delivered dose of CKRT. Most of our patients did not receive anticoagulation due to coagulopathy associated with severe sepsis. In practice, anticoagulation usage varies, with 30% to 60% omitting them (17, 19). To improve circuit patency in the future, we should consider the usage of regional citrate anticoagulation (RCA), along with increasing blood flow rate, reducing filtration fraction to <20%, replacing fluid prefilter, and ensuring good catheter flow (17). One patient had a catheter problem causing the termination of treatment after only 3 hours. However, he survived with good renal recovery. Retrospectively, he had a less severe disease (SOFA score 10) and may have been started on treatment too early. Another outlier is a patient who stayed for 32 days in ICU and was treated with PIRRT before changing modality to CKRT for nine hours before her demise. Usage of oXiris membrane provides endotoxin adsorption and some studies have reported that it reduces inflammation and improve organ function, but these are not supported by randomized control studies (20,21).

The mean length of stay in ICU among our patients was 10 days, similar to another retrospective study (22). Mortality in patients treated with CKRT in ICU has been described as ranging between 37%-75% (23, 24), but the higher mortality rate of our patients at 77% may be attributed to the fact that our small population of septic patients were significantly ill requiring more than two inotropic support and mechanical ventilation. Renal recovery is defined as a return of serum creatinine to baseline or normalized, good urine output of >0.5 ml/kg/hour and haemodialysis independent. The Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study reported that urine output >400 ml daily without diuretics is associated with successful termination of CKRT (25). All 3 of our patients who had renal recovery did so within 30 days. The decision to discontinue CKRT is up the discretion of the physician.

Compared with hospitals without in-house nephrologist, it has been reported that treatment delivered by a specialized team consisting of nephrologist and staff specifically trained in CKRT lead to the reduction of red cells transfusions, earlier initiation of CKRT, better CKRT filter usage with less downtime, shortened length of ICU stay, and resulted in better 90-day survival (26-28). The availability of a nephrologist may improve our treatment delivery by optimizing the timing for initiation of KRT, ensuring adequate vascular access for CKRT, selecting the best modality required by patients which is dynamic and require ongoing clinical assessment, providing specifics of the prescription, handling possible complications which may arise with the treatment, and educating the team on the advances in the field, among many important roles.

The weakness of this review is our small sample size, limited by resource availability, precludes the usage of appropriate analysis tools to determine predictors associated with clinical outcomes. However, this is an audit of our performance to guide future improvement. We hope that this sharing of our experience can lead to the initiation of CKRT in other district hospitals without nephrologists.

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CONCLUSION

CKRT provides better hemodynamic stability for critically ill patients who require haemodialysis support. The optimal timing for initiation remains debatable. We can improve the patency of the circuit in the future with various methods, one of which is the usage of regional citrate anticoagulation. The mortality rate may be improved if we have more resources to administer this treatment to a wider range of patients. The sharing of our experience may provide insight for future improvement and encourage initiation of CKRT in other district hospitals without nephrologists.

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