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Recurrent Intradialytic Hypotension, Associated Risk Factors, and Outcomes in Northern Tanzania: A Retrospective Cohort Study

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ABSTRACT

Background and Aims: Intradialytic hypotension (IDH) is a common phenomenon during hemodialysis (HD), with profound complications and all-cause mortality. Data on IHD is scarce in Sub-Saharan Africa. The study aimed to evaluate the incidence, risk factors, and outcome associated with recurrent IDH among patients on maintenance HD.

Methods: This was a retrospective cohort study conducted at the Kilimanjaro Christian Medical Centre HD unit between August 1, 2021 and July 31, 2022. In the study, 39 met the inclusion criteria, and a total of 4706 HD sessions were analyzed. The predictor was the occurrence of recurrent IDH. The outcomes were mortality from IDH, hospital admission due to IDH, and termination of the respective HD session. Descriptive statistics for categorical and continuous variables. A χ^2 test was used to identify associations, and the receiver operating characteristics curve was used to determine the cutoff threshold for different parameters in determining risk factors for recurrent IDH.

Results: The incidence of IDH was 4.35%; 46.3% of these IDH episodes were recurrent. Risk of IDH was higher in patients with pre-dialytic serum inorganic phosphate levels > 1.8 mmol/L (RR: 2.33, 95% CI: 1.02–5.35, $p < 0.001$) with a predicted threshold of 1.27 mmol/L by ROC curve (AUC 0.618, CI: 0.541–0.694, sensitivity 60%, specificity 40%), among males (aRR: 9.65, CI: 2.27–40.85, $p = 0.002$). A systolic blood pressure of < 140 mmHg had a significant protective effect (aRR: 0.34, CI: 0.17–0.69, $p = 0.003$).

Conclusion: Recurrent IDH is more common in males, among patients with hyperphosphatemia, and shows seasonal variations. Systolic blood pressure of < 140 mmHg confers a protective effect against recurrent IDH.

1 | Introduction

Chronic kidney disease (CKD) affects 10% of the world population [1], and of these, two million globally receive hemodialysis (HD) treatment [2]. The global all-age mortality rate attributed to end-stage renal disease (ESRD) has increased by 41.5% between 1990 and 2017 [3], with predictions suggesting that it will become the fifth-highest cause of life loss by 2040 [4]. Studies done between 2019 and 2020 at Kilimanjaro Christian Medical Centre (KCMC) identified CKD as the leading cause of admission (6.2%) and ranked second as the leading cause of death, with a mortality rate of 11.1% in

the medical wards [5], and 54.9% in the medical intensive care unit [6].

As lifesaving as it is, HD-associated morbidity and mortality among ESRD patients have been increasing despite advancements in pharmacological and dialysis technology [7], not to mention intradialytic hypotension (IDH). An example seen in the USA, reported a 30%–56% greater adjusted risk of death for those with a systolic blood pressure (SBP) decline to < 90 mmHg during HD [8].

Multifactorial interactions result in IDH, and parameters including ultrafiltration rate (UFR), cardiac output, and arteriolar tone play an important role. Excessive UFR may result in reduced cardiac output, especially when compensatory mechanisms (increased chronotropy, inotropy, vascular tone, and redistribution of splanchnic blood flow) fail to be optimally recruited. It is noteworthy that in three-times-weekly HD patients in the USA, UFR goals are often in the range of 2.7–3.0 L [8].

With these changes, different interventional measures are implemented in HD units to prevent and manage IDH episodes by targeting the augmentation of defective compensatory mechanisms. Some include optimization of the dialysis prescription (cooling the dialysate below core temperature, UFR reduction, sodium profiling, high flux hemofiltration), intradialytic measures (midodrine prescription, isotonic saline fluid administration, avoiding food intake, intradialytic exercise, and intermittent pneumatic compression of the lower limbs), and inter-dialytic period interventions (lower interdialytic weight gain (IDWG) and blood pressure (BP) lowering drugs), as well as switching the modality to peritoneal dialysis [9].

Some of the risk factors associated with the occurrence of IDH include diabetes mellitus, cardiovascular disease, autonomic dysfunction, poor nutritional status, hypoalbuminemia, female sex, age > 65 years, pre-dialysis SBP < 100 mmHg, high body mass index (BMI), and severe anemia [10]. As most of these factors are modifiable, it is crucial to know the burden of IDH and establish risk stratification, as these can help prevent IDH episodes. Therefore, this study aimed to determine the cumulative incidence, risk factors and complications associated with recurrent IDH among maintenance HD patients at the KCMC HD unit.

2 | Methods

2.1 | Study Design and Setting

The study was a retrospective cohort conducted at the KCMC HD unit. Data collection started on November 1, 2022 and ended on April 30, 2023, with the information collected over 1 year from August 1, 2021 to July 31, 2022. The hospital is located at the foothills of the tallest mountain in Africa, Mount Kilimanjaro, displaying annual weather variations, with the highest temperatures reaching 30.0°C from January to March and the lowest recorded temperatures between June and July reaching 25.0°C.

A patient on maintenance HD attends three sessions per week, each session takes 4 h to complete. The unit accommodates about 60 patients every day on three shifts per day. The unit comprises of 37 dialysis chairs, run primarily by a team of one nephrologist, one consultant physician, two registrars, two internal medicine residents, 16 registered nurses, two dieticians, one social worker and three biomedical engineers. The unit serves natives of Kilimanjaro region and neighboring regions with a catchment population of over 15 million.

The study obtained approval from the Kilimanjaro Christian Medical College Research Ethics and Review Committee (No. PG142/2022), as well as from the hospital and the head of the department. Patients younger than 18 years old were excluded from this study. Informed consent was not obtained, as this was a retrospective study. Confidentiality was observed, and all data were stored unlinked to patient identifiers.

2.2 | Definitions

IDH: is a decrease in SBP by more than 20 mmHg or a decrease in mean arterial pressure by 10 mmHg, accompanied by symptoms including, but not limited to, abdominal discomfort, yawning, sighing nausea and/or vomiting, muscle cramping, restlessness, dizziness/fainting, or anxiety [11].

IDWG: is defined as the total weight gained during the interval between subsequent HD or peritoneal dialysis sessions [12].

Recurrent IDH: is defined as a condition in which IDH events cumulate by > 30% of total sessions [8].

2.3 | Study Variables and Analysis

The inclusion criteria were ESRD adult patients on maintenance HD who underwent ≥ 3 HD sessions per week. Patients with acute kidney injury, chronic liver disease, suboptimal treated chronic or advanced heart failure, pre-dialytic SBP of < 90 mmHg or on vasopressor support, and evidence of sepsis at the time of the HD session were excluded from the study. Patients with chronic hypotension are complex and difficult to manage; hence, this study looked into factors involved only in hypotension linked to large variations in BP and volume. The primary endpoint was the occurrence of recurrent IDH, mortality from IDH, hospital admission due to IDH, and termination of the respective HD session.

Each selected patient was followed up within 1 year and included all HD sessions that occurred for each of the patients to identify IDH. The variables included socio-demographic characteristics, comorbidities, venous access, date and month of each HD session, and laboratory markers. During each HD session, the data collected included pre- and post-HD body weight, height, BP, pulse rate, and axillary temperature. Each respective HD session prescriptions (UFR, sodium, bicarbonate, blood flow rate, and pump speed) were entered into the automated machine, and the session commenced. Each session was monitored and included vitals and clinical symptoms from the beginning to the end, with respective records being documented

in the electronic hospital management system. For each HD session that occurred in the mentioned timeframe, the relevant clinical and laboratory data were collected from the HD database and the electronic hospital management system.

Laboratory information was categorized as per the 2019 Tanzania standard operating procedure and protocol for dialysis, as well as KDIGO general recommendations for HD patients. They included results of; serum albumin in the last 3 months, which was categorized as < 35 g/L and > 35 g/L, hemoglobin (Hb) level in the last 1 month (categorized as < 8 g/dL, 8–11 g/dL and > 11 g/dL) and third monthly serum inorganic phosphate (categorized into < 1.8 mmol/L and > 1.8 mmol/L) as well as adjusted serum calcium (categorized into < 2.15 mmol/L, 2.15–2.55 mmol/L, > 2.55 mmol/L) [13].

Each HD session data included SBP, access type and functional status, HD prescription details including solute concentration, prescription, and temperature, duration of HD, time at the onset of IDH, and outcome of HD session. Kt/V (categorized into < 1.2, 1.2–1.6 and > 1.6), blood flow rate (categorized into < 300 and ≥ 300), UFR (categorized into < 850 mL/h and > 850 mL/h) [13].

The data were collected, cleaned, and entered into the Statistical Package for Social Science (SPSS) v26 (IBM; https://www.ibm.com/analytics/spss-statistics-software). Descriptive data and continuous variables were summarized using narration, tables, and figures. A χ^2 test was used to identify associations, and the receiver operating characteristics curve was used to determine the cutoff threshold for different parameters in determining risk factors for recurrent IDH. A p-value of < 0.05 was considered statistically significant, and a confidence interval of 95% will be used. Exposure variables were fitted against the dependent variable, one at a time, and the significant variables with $p < 0.05$ with a corresponding confidence interval were considered in the multivariate analysis.

3 | Results

At the beginning of the study period, there were 51 patients with CKD on maintenance HD; 39 met the inclusion criteria and were recruited for the study. During the study period, among the 39 recruited patients, five moved out of the HD unit, and four died during the follow-up period. Three patients who were transferred from other facilities to the KCMC HD unit and six others who were on maintenance HD were recruited to compensate for the discrepant number when qualified for the inclusion criteria. Among the 39 patients, a total of 4706 HD sessions were analyzed.

Four thousand seven hundred and six sessions were reviewed for 1 year; out of these, 205 (4.35%) sessions met the criteria for IDH. Out of the 205 sessions, 95 (46.3%) sessions were recurrent IDH. The median age of study patients was 60 years. The majority (61.5%) were males with a sex ratio of 1.6:1, aged > 50 years (82.1%), and patients with diabetes mellitus (58.3%); the median duration on HD was 8 months. As shown in Table 1, the majority of these IDH sessions occurred in males (64.7%), < 65 years (58.8%), patients with BMI 18–24 (58.4%), and those with both diabetes mellitus and hypertension (52.9%). Vascular access in these sessions was 38.5% through a fistula and 61.5% through a central venous catheter.

Mean monthly Hb was 9.7 (SD $\pm$ 1.9) g/dL, mean inorganic phosphate was 1.4 (SD $\pm$ 0.5) mmol/L, mean serum calcium

TABLE 1 | Social demographic and clinical characteristics of patients undergoing HD ($N = 39$).

Characteristics	Total *n* (%)	IDH *n* (%)
Gender		
Male	23 (61.5)	22 (64.7)
Female	16 (38.5)	12 (35.3)
Age (years); median (IQR)	64 (57–64)	64 (57–69)
< 65	23 (61.5)	20 (58.8)
≥ 65	16 (38.5)	14 (41.2)
Education Level* ($n = 23$)		
Primary	6 (26.1)	6 (26.1)
Secondary	7 (30.4)	7 (30.4)
Higher education	10 (43.5)	10 (43.5)
BMI (kg/m^2)* ($n = 24$)		
18–24	14 (58.4)	14 (58.4)
25–29	5 (20.8)	5 (20.8)
> 30	5 (20.8)	5 (20.8)
Comorbidities		
Hypertension	11 (28.2)	8 (23.5)
Diabetes mellitus	3 (7.7)	4 (11.8)
Hypertension and diabetes mellitus	20 (51.3)	18 (52.9)
Others (HIV/AIDS, SLE, BPH, Alport syndrome)	5 (12.8)	4 (11.8)
Number of antihypertensives ($n = 33$)		
1	16 (48.5)	16 (48.5)
2	12 (36.4)	12 (36.4)
≥ 3	5 (15.1)	5 (15.1)
Class of antihypertensives ($n = 33$)		
CCB/ACEi/β-blocker	22 (66.7)	22 (66.7)
CCB and vasodilator	8 (24.2)	8 (24.2)
Vasodilator	3 (9.1)	3 (9.1)
Vascular access		
Arteriovenous fistulae	15 (38.5)	13 (37.1)
Central venous catheter	24 (61.5)	21 (62.9)
Duration on HD (month); median (IQR)	8.0 (3.0–12.0)	5.0 (3.0–13.0)

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; AIDS, acquired immuno-deficiency syndrome; BPH, benign prostate hyperplasia; CCB, calcium channel blocker; HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus.

TABLE 2 | Dialysis parameters and time distribution of IDH episodes.

Variables	*n* (%)
IDWG (kg); mean (SD)	1.86 (1.16)
UFR (mL/h); median (IQR)	590.0 (550.0–715.0)
UFR > 850 mL/h	23.0 (11.2)
UFR volume (mL); median (IQR)	2060.0 (1380.0–2537.0)
IDH diagnosis time	
1st hour	80 (39)
2nd hour	55 (26.8)
3rd hour	59 (28.8)
4th hour	11 (5.4)
Kt/V; mean (SD)	1.3 (0.3)

Abbreviations: IDH, intradialytic hypotension; IDWG, interdialytic weight gain; UFR, ultrafiltration rate.

was 2.04 (SD ± 0.28) mmol/L, and mean serum albumin was 37.1 (SD ± 4.8) g/L. In sessions with IDH, the mean interdialytic weight gain was 1.86 (SD ± 1.16) kg, the median UFR was 590.0 (550.0–715.0) mL/h, and the higher UFR > 850 mL/h prescribed was 23.0 (11.2%), as seen in Table 2. In general, the highest number of IDH episodes (39%) occurred during the first hour of dialysis. Out of all IDH episodes, 18 (8.8%) had the respective HD session time extended beyond 4 h, and 26 (12.7%) of all IDH episodes had the respective HD sessions terminated.

Males (52.6%) had a significantly higher risk of recurrent IDH compared to their female counterparts even when adjusted for other risk factors (aRR: 9.65, CI: 2.27–40.85, $p = 0.002$). Age > 65 years showed a higher chance for recurrence by 1.48 times, even though statistically insignificant (aRR: 1.48, CI: 0.71–3.09, $p = 0.28$). BMI > 30 kg/m^2 were notably less at risk compared to the lower subgroups, even though statistically insignificant, but the risk of recurrent IDH within this subpopulation was 28% less (aRR: 0.82, CI: 0.18–3.65, $p = 0.8$). However, the majority of recurrent IDH episodes (59.7%) were within 18–24 kg/m^2 (Table 3).

Severely anemic patients (Hb < 8 g/dL) had a higher risk of recurrent IDH by 1.47 times; however, when adjusted for other factors, this effect's significance dropped (aRR: 0.78, CI: 0.28–2.19, $p = 0.64$). Hypercalcemia (> 2.55 mmol/L) and hyperphosphatemia subgroups (> 1.8 mmol/L) had higher risk even though statistically insignificant (aRR: 1.10, CI: 0.16–7.42, $p = 0.91$ and aRR: 1.01, CI: 0.36–2.81, $p = 0.977$, respectively). In patients with lower *Kt/V* dialysis values (< 1.2), the risk of recurrent IDH was higher compared to their counterparts; however, this was statistically insignificant (RR: 1.38, CI: 0.52–3.6, $p = 0.5$) (Table 3). Patients with low albumin (< 35 g/L) had a higher risk of IDH recurrency compared to their counterparts; however, this was statistically insignificant (aRR: 1.32, CI: 0.66–2.64, $p = 0.42$). Higher UFR (> 850 mL/h) during dialysis had a lower risk of IDH recurrency even when adjusted, but this was not statistically significant (aRR: 0.82, CI: 0.30–0.20, $p = 0.69$). However, in patients with blood flow rates ≥ 300 mL/h during HD, the risk was higher by 1.11 of IDH recurrency, but this effect dropped when adjusted for other factors and was statistically not significant (aRR: 0.83, CI: 0.27–2.52, $p = 0.74$).

There was a significant reduction in risk for IDH recurrency by 66% among patients with SBP < 140 mmHg during HD, and this was statistically significant even when adjusted for other factors (aRR: 0.34, CI: 0.17–0.69, $p = 0.003$). Among hypertensive patients, risks were highest in those with > 3 anti-hypertensive medications by 3.19 times even when adjusted for other factors. Patients with hydralazine had higher risks of IDH recurrency compared to other drug combinations by 1.7-folds; however, this was statistically not significant. (aRR: 3.19, CI: 0.82–12.40, $p = 0.09$).

The area under the ROC curve for phosphate was 0.618, CI: 0.541–0.694, and that of SBP was 0.34, CI: 0.265–0.415 (Figure 1). A cut-off of 1.27 mmol/L was optimal for predicting recurrent IDH associated hyperphosphatemia, with a sensitivity of 60% and a specificity of 40%.

The weather component was another risk factor for IDH assessed. There was a significant monthly variation of IDH events during the entire 1-year duration of the study with the highest incidences occurring in August (33) and the lowest in March (7) (Figure 2).

The risk of termination of HD sessions was higher in patients with recurrent IDH compared to non-recurrent patients (69.2% vs. 30.8%), and access failure (thrombosis) was higher in the non-recurrent group (56.5% vs. 43.5%) (Table 4).

4 | Discussion

Numerous studies have been conducted to investigate risk factors for IDH, but there is limited data to guide the prevention of IDH in the local setting. With the results being used to predict the at-risk group, this will improve the quality of HD sessions and thus improve quality of life, as well as reduce morbidity and mortality by reducing IDH episodes.

In this study, the IDH incidence was 4.35%, which coincides with studies done in Nepal (4.5%) [14], Morocco (5%) [15], and Mexico (5.4%) [16]; however, it is lower compared to Nigeria (8.6%) [10]. The low incidence of IDH in this study could be due to the exclusion of multiple confounders for hypotension during HD, for example, sepsis, which was not the case in Nigeria [10]. It is noteworthy, that despite being in developing countries, the incidence of IDH in this study is minimal in comparison to studies from high-income countries with the same definition criteria. This could be partly explained by stringent exclusion criteria used to minimize confounders but still falls under the general observation of less than 12% prevalence per definition used as observed in the meta-analysis study [17].

A profound high risk was noted among males, who had almost 10-times higher risks of recurrent IDH compared to females, and this was statistically significant. This contrasts with what is known about the classical risk factor for IDH being female. A similar finding was seen in Shanghai, whereby the prevalence

TABLE 3 | Risk factors for recurrent IDH among patients undergoing HD at KCMC HD unit ($N = 205$).

Variables	Total	Recurrent IDH *n* (%)	cRR (95% CI)	*p* value	aRR (95% CI)	*p* value
Age group (years)						
< 65	110	56 (50.9)	Ref			
> 65	95	39 (41.1)	1.48 (0.85–2.59)	0.15		
Sex						
Male	175	92 (52.6)	9.97 (2.91–34.10)	< 0.001	9.65 (2.27–40.85)	0.002
Female	30	3 (10.0)	Ref		Ref	
BMI (kg/m^2) ($n = 144$)						
18–24	88	40 (59.7)	Ref			
25–29	36	16 (23.9)	0.68 (0.25–1.81)	0.44		
> 30	20	11 (16.4)	0.65 (0.21–1.96)	0.45		
Hemoglobin (g/dL)						
< 8	27	11 (40.7)	1.47 (0.63–3.41)	0.36		
8–11	135	68 (50.4)	0.86 (0.32–2.31)	0.76		
> 11	43	16 (37.2)	Ref			
Serum calcium (mmol/L)						
< 2.15	147	79 (53.7)	0.58 (0.12–2.80)	0.37		
2.15–2.55	50	13 (26.0)	Ref			
> 2.55	8	3 (37.5)	1.93 (0.44–8.40)	0.50		
Phosphate (mmol/L)						
< 1.8	177	77 (43.5)	Ref		Ref	
> 1.8	28	18 (64.3)	2.33 (1.02–5.35)	0.04	1.33 (0.48–3.64)	0.58
Kt/V						
< 1.2	71	38 (53.5)	1.38 (0.52–3.6)	0.5		
1.2–1.6	110	47 (42.7)	Ref			
> 1.6	22	10 (45.5)	0.89 (0.35–2.24)	0.81		
Comorbidities						
Diabetic	166	80 (48.2)	0.67 (0.32–1.37)	0.27		
Non Diabetic	39	15 (38.5)	Ref			
HbA1c (%) ($n = 157$)						
< 6	73	28 (38.4)	Ref			
6.0 – 8.9	46	21 (45.7)	1.19 (0.52–2.71)	0.66		
> 9	38	13 (34.2)	1.61 (0.66–3.92)	0.28		
Serum albumin (g/L)						
< 35	65	27 (41.5)	1.32 (0.734–2.40)	0.34		
> 35	140	68 (48.6)	Ref			
UFR (mL/h)						
< 850	182	84 (46.2)	Ref			
> 850	23	11 (47.8)	0.93 (0.39–2.22)	0.88		
SBP (mmHg)						
< 140	46	31 (67.4)	0.32 (0.16–0.65)	0.002	0.34 (0.17–0.69)	0.003
> 140	159	64 (40.3)	Ref		Ref	
IDWG (kg) ($n = 110$)						

(Continues)

TABLE 3 | (Continued)

Variables	Total	Recurrent IDH *n* (%)	cRR (95% CI)	*p* value	aRR (95% CI)	*p* value
< 3	88	33 (37.5)	Ref			
> 3	22	7 (31.8)	1.28 (0.47–3.47)	0.62		
Number of anti-hypertensives						
None	19	6 (31.6)	Ref			
1–3	168	82 (48.8)	0.72 (0.18–2.80)	0.64		
> 3	18	7 (38.9)	1.49 (0.55–4.05)	0.42		
Type of anti-hypertensive						
None	20	6 (30.0)	Ref			
CCB/ACEi/β-blocker	114	60 (52.6)	0.67 (0.21–2.10)	0.49		
Vasodilator	30	13 (43.3)	1.73 (0.83–3.59)	0.13		
CCB and vasodilator	41	16 (39.0)	1.19 (0.45–3.11)	0.71		
Blood flow rate (mL/h)						
< 300	25	11 (44.0)	Ref			
≥ 300	180	84 (46.7)	1.11 (0.48–2.58)	0.80		

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; CCB, calcium channel blocker; HTN, hypertension; SBP, systolic blood pressure.

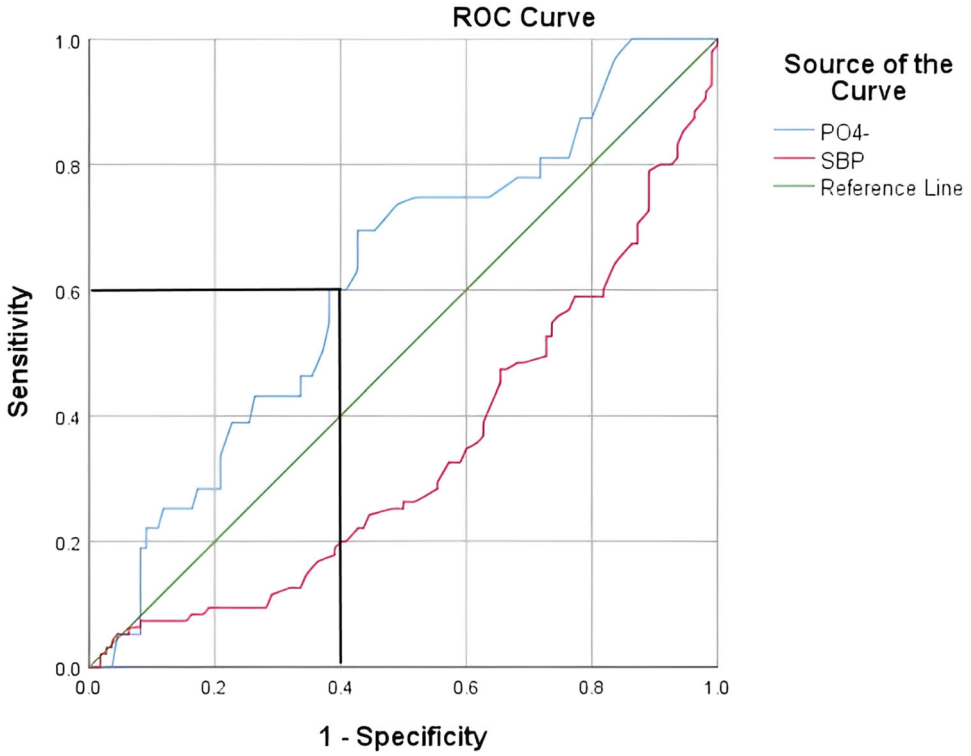

FIGURE 1 | Diagnostic accuracy of PO4- and SBP in predicting IDH.

of IDH was higher in males by 63.4% [18]. This could have been largely explained by the male gender predominance of 61.5% in this study as well as the fact that the majority of the female patients were postmenopausal, hence the decline in estrogen levels, which in turn affects the regulation of vascular reactivity, enhanced inflammation, a decline in endothelial function, and coronary atherosclerosis.

An interesting finding was the low incidence of recurrent IDH among patients with a low pre-dialytic SBP of < 140 mmHg. In this study, there was a highly significant protective effect of 66%, and the finding was statistically significant ($p = 0.003$). A possible explanation for this is the higher prevalence of diastolic, systolic, and endothelial dysfunction among hypertensive patients, which predisposes to impaired compensatory

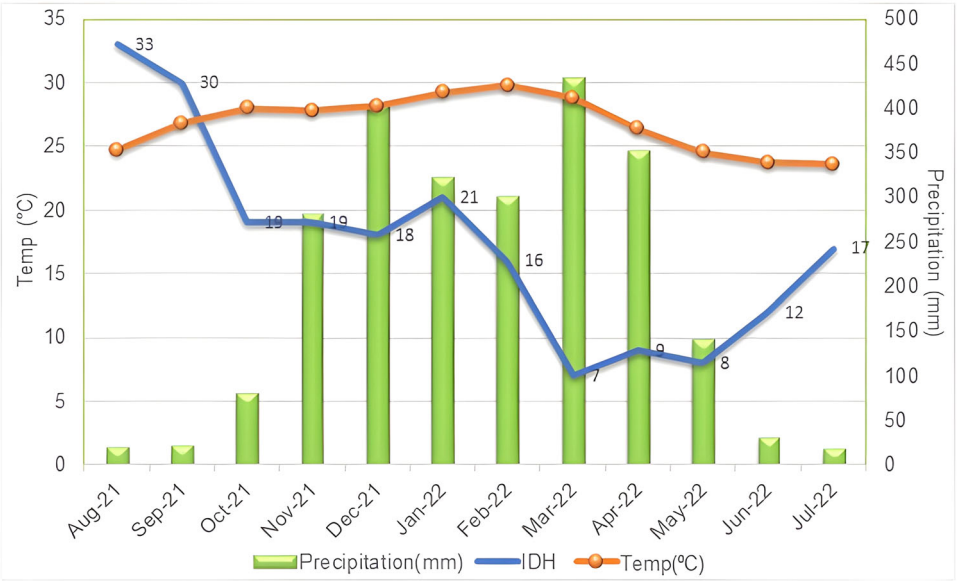

FIGURE 2 | Monthly variations of IDH episodes among HD sessions ($N = 205$).

TABLE 4 | Outcomes of IDH among patients undergoing HD ($N = 205$).

Outcomes	Total	IDH	
		Non-recurrent *n* (%)	Recurrent *n* (%)
Access failure	23 (11.2)	13 (56.5)	10 (43.5)
Termination of HD	26 (12.7)	8 (30.8)	18 (69.2)

mechanisms. Another possibility is more careful, pre-emptive care to prevent IDH by maneuvers like profiling the UFR to prevent rapid declines of BP in normotensive patients compared to hypertensive patients, which permits the caregiver more room for higher ultrafiltration due to permissible higher pre-dialytic SBP. Nevertheless, IDH is also known to occur in both normotensive and hypertensive patients, as per KDOQI and ERBP guidelines. This observation was similarly observed in Portugal [19] and Nigeria [10].

Using the ROC curve in estimating potential cut-off points at which phosphate posed a risk for recurrent IDH was shown to be at 1.27 mmol/L with 60% sensitivity and 40% specificity (AUC 0.618). Similarly in Portugal [19], Korea [20], and the USA [21], hyperphosphatemia was shown to be an independent risk factor in recurrent IDH. Higher phosphate levels could potentially induce symptomatic hypocalcemia due to calcium-phosphate precipitations in tissues, with cardiovascular effects including hypotension, endothelial dysfunction, valvular calcification, atherosclerosis, and heart failure. In this study, higher than acceptable phosphate levels of 1.8 mmol/L pose a 2.3-times higher risk of recurrent IDH, and this was statistically significant. However, upon adjusting for other factors, there was a loss of statistical significance, even though individuals still had a higher risk of recurrent IDH by 1.3 times. Since there are limited studies on mitigating hyperphosphatemia as a risk factor for IDH, further research may influence a treatment protocol change to attempt to lower the threshold of pre-dialytic serum inorganic phosphate in recurrent IDH in the risk group at levels beyond the general HD patients' recommendations, considering the associated clinical implications. With regard to this study, a cut-off of 1.27 mmol/L may be optimal for predicting recurrent IDH associated hyperphosphatemia.

This study showed that there was no significance to serum calcium and recurrent IDH. However, studies have shown that hypocalcemia has been associated with a higher risk of IDH [22]. However, lower dialysate calcium concentrations are associated with a greater risk of IDH, and using higher dialysate calcium concentrations may reduce the risk of IDH. Not the same can be said about potassium as studies have shown no association [23]. Studies have shown that metabolic acidosis increases the risk of IDH, as acidosis causes cutaneous vasodilatation and reduces the effective blood volume and BP [24]. However, the effects have reduced as a result of bicarbonate as a dialysate buffer.

This study found that anti-hypertensive medications, and the number of medications, were not associated with recurrent IDH. Studies have shown that due to the dialyzability of certain anti-hypertensive medications, this may have an impact on IDH. Among β-blockers, atenolol and metoprolol are cleared by HD, but carvedilol is not. Additionally, calcium channel blockers and angiotensin-receptor blockers are not cleared by HD, but most angiotensin-converting enzyme inhibitors are cleared by HD [25]. To avoid complications, due to low dialyzability, calcium channel blockers and direct vasodilators are withheld on the morning of HD in certain patients prone to hypotension, with autonomic dysfunction due to diabetes, and who are on a low-sodium diet [25].

An interesting finding in this study was the observation of IDH episode occurrences every month. This study was conducted at the HD unit setup located at the footsteps of Mount Kilimanjaro, the tallest mountain in Africa, with clear, dry, and cold seasons annually. The cold season of the year lasts for approximately 8.1 months, from October to June (the highest precipitation season). Similar to the study in Japan, results from this study showed significant seasonal variation, with the highest episodes of IDH occurring during August and September, a plateau from October to January, and the lowest incidences occurring in March through June [26]. This variation is noticeably attributed to seasonal changes in outside temperatures and rates of precipitation. High temperatures may result in vasodilatation, leading to a decrease in peripheral vascular resistance and ultimately a reduction in pre-dialytic SBP. Another hypothesis, as a predictor of outcomes in HD patients, is related to the malnutrition-inflammation-atherosclerosis syndrome, whereby C-reactive protein, serum albumin, phosphorus and normalized protein catabolism rate, peak in the winter and nadir in the summer, suggesting that increased protein intake leads to increased production of uremic toxins. Furthermore, season variation might be correlated with higher comorbidity and poorer nutritional status in HD patients [27]. However, seasonal variations as risk factors for IDH are not well understood, and no studies have yet been published to control HD unit temperatures in attempts to offset this effect. This is an emerging concept with limited data, as such further research may influence a treatment protocol change that may indicate strictly regulating the temperature and humidity of the HD unit and tie them to the seasons with the lowest incidence, as indicated by the IDH monthly curve.

This study showed that vascular access failure was present by 11.2%, more in the non-recurrent group (56.5% vs. 44.5%). These findings are consistent with what is generally known about IDH complications in relation to vascular access thrombosis. Similar findings were seen in the HEMO study, where the highest quartile of IDH had ~twofold higher independent relative rate of native arteriovenous fistula thrombosis [28]. No clear explanation has been established as the reason for vascular thrombosis in these patients; however, stasis of blood due to poor cardiac output during IDH could play an important role. The higher prevalence of access thrombosis in the non-recurrent IDH group could be due to the presence of other risk factors for access thrombosis in general, like advanced age, surgical expertise, high serum lipoprotein, peripheral vascular diseases, and diabetes mellitus.

The limitations of this study were that it was a single-centered study, and therefore the generalizability of the results could be limited. Although there were over 4500 adequate HD sessions, this study only included 39 patients, which may have limited the power of the findings. Patients with chronic hypotension would have been interesting to investigate, as considering the protective effect of low BP at the start of treatment could also be a bias. Interdialytic weight measurements were not done in all patients attending the HD unit, as this poses a risk in true risk assessment for IDH-related events. Utilization of electrocardiogram and echocardiography results could not be done as not all patients were screened, and not all procedures were done by the same operator or machine, and the results of which could have subjected significant bias in interpretation and utilization in this study. Dialysate electrolyte concentration could not be monitored due to the retrospective nature of this study which would have further assessed the risk of IDH. Other IDH-related complications, such as neurological complications, could not be assessed retrospectively since there was no routine brain imaging done on patients with IDH. The carry-over and delayed washout effects among risk factors for IDH could lead to errors in establishing temporal relationships.

5 | Conclusion

This is one of the few studies on the incidence and outcomes of IDH in Sub-Saharan Africa. The incidence of IDH in northern Tanzania is 4.35%. Male sex and hyperphosphatemia were noticeably higher risk factors for recurrent IDH, with a significant protective effect on lower SBP, while traditional risk factors for IDH like female sex, age > 65 years, diabetes mellitus, and anemia were not significant for recurrent IDH. A clear seasonal variation in the incidence of IDH has been shown, with the highest episodes occurring during dry seasons and the lowest during high rainfall months. The clear seasonal variation of IDH is an effect that poses more research interest and if a temporal relationship exists, amelioration of HD unit setup in weather labile settings should be implemented, as this can be done in more settings with extended duration of studies. A higher burden of HD session termination prevails within the recurrent IDH group in comparison to the non-recurrent group. More studies establishing solid evidence in this subgroup will shed more light on causality and temporal relationships in risk factor assessment.

Author Contributions

Fuad H. Said: conceptualization, formal analysis, writing – original draft, methodology, investigation, and data curation. **Venance P. Maro:** visualization, writing – review and editing, and methodology. **Abid M. Sadiq:** data curation, formal analysis, writing – review and editing, methodology, and investigation. **Faryal M. Raza:** writing – review and editing, investigation, and data curation. **Annette A. Marandu:** investigation, writing – review and editing, and data curation. **Sarah K. Gharib:** data curation, investigation, writing – review and editing. **Sophia S. Muhali:** data curation, investigation, writing – review and editing. **Norman Jonas:** data curation, investigation, writing – review and editing. **Elichilia R. Shao:** methodology, writing – review and editing. **Elifuraha W. Mkwizu:** methodology, writing – review and editing. **Furaha S. Lyamuya:** methodology, writing – review and editing. **Huda F. Akrabi:** conceptualization, methodology, writing – review and editing, visualization, validation, and supervision. **Nyasatu G. Chamba:** methodology, writing – review and editing. **William P. Howlett:** methodology, writing – review and editing. **Kajiru G. Kilonzo:** conceptualization, formal analysis, visualization, writing – review and editing, project administration, supervision, methodology, and validation.

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Ethics Statement

The study obtained approval from the Kilimanjaro Christian Medical College Research Ethics and Review Committee (No. PG142/2022), as well as from the hospital and the head of the department.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

Transparency Statement

The lead author Fuad H. Said affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.