

Exploring Prevalence and Predictors of Clinically Suspected Dialysis Disequilibrium Syndrome in End-Stage Kidney Disease Patients Initiating Hemodialysis

Budsarawadee Nookaew, M.D., Ussanee Boonsrirat, M.D., Suwikran Wongpraphairot, M.D., Sirihatai Konwai, M.D., Suntornwit Praditaukrit, M.D., Atthaphong Phongphithakchai, M.D.

Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.

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Abstract:

Objective: This study aimed to examine the prevalence and predictors of clinically suspected dialysis disequilibrium syndrome (DDS) in end-stage kidney disease (ESKD) patients starting their first hemodialysis session.

Material and Methods: Data was retrospectively collected from a university hospital; from december 2020 to July 2023. It included adult patients receiving their first session of hemodialysis. Patient demographics, comorbidities, medications, and laboratory results were analyzed. The primary objective was to identify clinically suspected DDS using predefined criteria. Multivariate logistic regression was used to identify independent risk factors for clinically suspected DDS.

Results: A total of 106 patients were enrolled. Among these, 18.8% had clinically suspected DDS, with nausea being the most prevalent symptom. The onset of symptoms varied, with a median of 240 minutes. Multivariate analysis revealed higher pre-hemodialysis serum creatinine as a risk factor for DDS (adjusted OR: 1.13; 95% CI: 1.02–1.25), while lower pre-hemodialysis serum sodium (adjusted OR: 0.90; 95% CI: 0.84–0.98) and capillary blood glucose levels (adjusted OR: 0.99; 95% CI: 0.97–1.0) were associated with increased risk. Notably, elevated blood glucose levels were protective against DDS.

Conclusion: Higher pre-dialysis serum creatinine, coupled with lower sodium and glucose levels significantly predicts DDS. These findings emphasize the necessity of tailored hemodialysis prescriptions and vigilant monitoring of patients likely to develop DDS.

Keywords: dialysis disequilibrium syndrome, end-stage kidney disease, hemodialysis, prevalence, risk factors, neurological symptoms

Contact: Atthaphong Phongphithakchai, M.D.
Division of Nephrology, Department of Internal Medicine, Faculty of Medicine,
Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand.
E-mail: ton331@hotmail.com

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Introduction

Dialysis disequilibrium syndrome (DDS) is a clinical syndrome characterized by neurological deterioration observed in patients undergoing hemodialysis. The occurrence of this phenomenon is more probable in patients either during or immediately following their initial treatment, although it can manifest in any patient undergoing hemodialysis. The etiology of this syndrome is believed to be attributed to alterations in fluid distribution during the process of hemodialysis, resulting in the development of cerebral edema and a diverse range of neurological manifestations¹.

There are two proposed mechanisms for this syndrome. First, the 'reverse urea effect' during hemodialysis rapidly removes small solutes like urea, which, although a freely diffusing ineffective osmole, cannot match the speed of removal from the serum. This creates a temporary osmotic gradient between the plasma and brain cells, leading to water movement into brain cells and subsequent cerebral edema¹⁻³. Additionally, the progression of chronic kidney disease itself can lead to an exacerbation of cerebral edema due to the upregulation of brain aquaporin channels and the downregulation of urea channels⁴. Second, intracerebral acidosis can develop in post-dialysis due to a drop in brain cell pH and increased carbon dioxide levels. This decrease in pH causes sodium and potassium ions to dissociate from proteins, which become osmotically active. Furthermore, the brain retains organic osmolytes like glutamine, glutamate, taurine, and myoinositol, which paradoxically lower intracellular pH, increase brain osmolality, and contribute to cerebral edema⁵⁻⁷.

As mentioned, although studies into the mechanisms of DDS exist, significant gaps remain concerning its prevalence and risk factors. While most reports suggest a decline in DDS incidents, some believe it is underreported due to its varied clinical manifestations^{8,9}. Additionally, although many risk factors for the development of DDS have been reported, the exact risk factors for DDS have

yet to be determined in terms of human studies. In all, the objective of this study was to explore the prevalence and predictors in end-stage-kidney-disease (ESKD) patients that receive the first session of hemodialysis initiation and to identify the extent to which some variables could predict DDS among them.

Material and Methods

Study design and population

This was a retrospective observational cohort study conducted at a university hospital in southern Thailand from 1st December 2020 until 31st July 2023. Adult patients aged over 18 years, diagnosed with ESKD; as defined by a GFR under 15 ml/min/1.73 m² (category G5) according to the KDIGO 2024 Clinical Practice Guidelines for Chronic Kidney Disease¹⁰, and receiving their first session of conventional hemodialysis were eligible for inclusion. Several exclusion criteria were applied; including patients receiving renal replacement therapy (RRT) in the previous 3 months before the time of enrollment, hemodynamic instability, which was defined by receiving vasopressors before or during hemodialysis, as patients having hypotension requiring dopamine >15 µg/kg/min or epinephrine/norepinephrine >0.1 µg/kg/min, cardiac arrhythmia requiring therapies, and pregnancy patients. The study adhered to the principles of the Declaration of Helsinki. Approval for the research was granted by the Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University; code REC. 66-330-14-4. Because no further interventions were conducted and the analysis was performed on anonymized data, informed consent was not required.

Data collection

Hospital electronic medical records were reviewed to collect demographic data, including gender, age, height, weight, body mass index (BMI), comorbidities, and current medications. Laboratory values before hemodialysis

(referring to values obtained within 24 hours prior to hemodialysis) and after hemodialysis (referring to values obtained within 24 hours following the hemodialysis session); such as complete blood count (CBC), blood urea nitrogen (BUN), serum creatinine (Cr), sodium (Na), potassium (K), bicarbonate (CO_2), calcium (Ca) and glucose, were collected. Additionally, details of the hemodialysis prescription were documented; including dialyzer surface, blood flow rate (BFR), dialysate flow rate (DFR), temperature, duration, the composition of dialysate (Na, K, Ca, HCO_3 , glucose) as well as the ultrafiltration rate.

Since DDS is diagnosed by exclusion, we have adopted the term: 'clinically suspected DDS.' Criteria to define this condition has been developed and this is detailed in Table 1. The definition of clinically suspected DDS, which was defined in this study, is the presence of 4 criteria as following; 1) New onset of at least one neurological symptom or sign during or after hemodialysis at less than 24 hours, 2) No recent use of medications that induced encephalopathy at the time of DDS diagnosis, 3) No recently explained diseases or conditions that affect the neurological system, 4) No neurological radiographic evidence indicating that the neurological symptoms are caused by anything other than DDS at the time of DDS diagnosis (Table 1). The primary objective was the prevalence of clinically suspected

DDS among patients having received first hemodialysis initiation. The secondary objective was to determine factors associated with clinically suspected DDS.

Statistical analysis

Statistical analyses were conducted using R software version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria) and RStudio 1.2.5001 (RStudio, Inc., Boston, MA). Categorical variables were presented as frequencies and percentages, while continuous variables were reported as mean±standard deviation (S.D.) or as median with interquartile range. To compare continuous variables between the two groups (clinically suspected DDS and no clinically suspected DDS), a t-test or Mann-Whitney U-test was used as appropriate. The Chi-square or Fisher exact test was used for comparing categorical variables between groups. Risk was presented as an unadjusted odds ratio (OR), along with the corresponding 95% confidence interval (CI). In univariate analysis, factors with a p-value equal to or less than 0.1, in addition to other factors of interest, were included in multivariable logistic regression analyses to assess the relationship between clinically suspected DDS. Only significant factors in the final model of multivariate analysis were reported. Statistical significance was defined as a p-value<0.05.

Table 1 Diagnostic criteria for clinically suspected dialysis disequilibrium syndrome

Diagnostic criteria
1. New onset of at least one neurological symptom or sign during or after hemodialysis at less than 24 hours: Symptoms or signs: Nausea, Emesis, Headache, Disorientation, Confusion, Asterixis, Coma and Death.
2. No recent use of medications that induced encephalopathy at the time of DDS diagnosis.
3. No recently explained diseases or conditions that affect the neurological system; including subdural hematoma, cerebral infarction, intracerebral hemorrhage, meningitis or encephalopathy, were present at the time of DDS diagnosis.
4. No neurological radiographic evidence indicating that the neurological symptoms are caused by anything other than DDS at the time of DDS diagnosis.

DDS=dialysis disequilibrium syndrome

Results

A total of 106 patients were enrolled in this study, with 86 patients showing no signs of clinically suspected DDS and 20 patients (18.8%) meeting the diagnostic criteria for clinically suspected DDS. Baseline characteristics are presented in Table 2. More than half of the patients in both groups were male. Notably, patients who did not develop clinically suspected DDS were significantly older compared to those with clinically suspected DDS (73 years vs. 62 years; p -value=0.006). However, there were no significant differences in height, weight, BMI, comorbidities, or current medication usage between the two groups.

In terms of pre-hemodialysis laboratory tests, Cr levels were significantly lower in the no clinically suspected DDS group compared to the clinically suspected DDS group (7.2 mg/dL vs. 12.3 mg/dL; p -value=0.013). Additionally, patients without clinically suspected DDS had significantly lower levels of serum Na, Cl, and glucose compared to those with the condition (Na, 135.5 mmol/L vs. 129.9 mmol/L; p -value=0.002), (Cl, 95.9 mmol/L vs. 90.5 mmol/L; p -value=0.018), (Glucose, 159.1 mg% vs. 134.7 mg%; p -value=0.043). Regarding post-hemodialysis laboratory tests, only serum Na was significantly higher in the group without clinically suspected DDS (135.4 mmol/L vs. 130.5 mmol/L; p -value=0.002). Hemodialysis prescription did not reveal any significant differences between the two groups (Table 3).

A density plot displaying the distribution of Na concentration in mEq/L for Dialysate Na and pre-hemodialysis Na is presented in Figure 1. As shown, it appears that the distribution of Dialysate Na is quite narrow, with concentrations ranging approximately from 137 to 143 mEq/L; peaking sharply around 140 mEq/L. On the other hand, the pre-hemodialysis Na shows a much wider distribution, with concentrations spanning from around 125 to 145 mEq/L; with the highest density around 135 mEq/L. The most common dialysate Na prescription was 138 mEq/L,

accounting for 76% of patients without clinically suspected DDS and 65% of patients with the condition; as shown in Figure 2.

Among the 20 patients with clinically suspected DDS, a collective presentation of five signs and symptoms were observed; including nausea, emesis, disorientation, confusion, and asterixis (Figure 3). Nausea was the most reported symptom, accounting for 15.1% of all signs and symptoms, followed by emesis at 12.3%. Disorientation was experienced by 3.8% of patients, confusion by 1.9%, and asterixis was present in 0.9% of the cases. The median onset time for developing DDS was 240 minutes. The quickest onset was recorded at 30 minutes, and the longest observed onset occurred 1,440 minutes (24 hours) after initiating hemodialysis.

Multivariate logistic regression was performed to determine risk factors that predicted clinically suspected DDS; as shown in Table 4. The final model revealed the significant independent risk factors of developing clinically suspected DDS included serum Cr pre-hemodialysis (adjusted OR: 1.13; 95% CI: 1.02–1.25; p -value=0.013), serum Na pre-hemodialysis (adjusted OR: 0.9; 95% CI: 0.84–0.98; p -value=0.007) and serum glucose pre-hemodialysis (adjusted OR: 0.99; 95% CI: 0.97–1.0; p -value=0.035). Moreover, the ROC curve, with an area under the curve (AUC) of 0.783 having a 95% CI of 0.726 to 0.840 and a p -value of less than 0.001, demonstrated that the ultimate model exhibited satisfactory discrimination between the two classifications of the outcome variable: “clinically suspected DDS: yes/no”.

Discussion

In this retrospective cohort analysis, we explored the prevalence and predictors of clinically suspected DDS in ESKD patients undergoing their first hemodialysis session. It was found that 18.8% of patients met the criteria for clinically suspected DDS. Nausea was the most common symptom,

Table 2 Baseline characteristics of the study population

Variables	No clinically suspected DDS (N=86)	Clinically suspected DDS (N=20)	Total (N=106)	p-value
Age (years)	73 (65–80.8)	62 (43–71)	71 (61–79)	0.006
Male (%)	52 (60.5)	11 (55)	63 (59.4)	0.845
Height (cm)	161±8.7	159±9.7	160±8.8	0.471
Weight pre-HD (cm)	56 (49.1–63.1)	57.9 (51.9–64.7)	57 (49.1–63.1)	0.701
BMI (kg/m ²)	21.7 (19.4–23.7)	23.7 (19.8–25.4)	21.9 (19.4–24.2)	0.156
Current medication				
ACEI	3 (3.5)	0 (0)	3 (2.8)	1
ARB	4 (4.7)	1 (5)	5 (4.7)	1
CCB	48 (55.8)	9 (45)	57 (53.8)	0.532
Beta blocker	32 (37.2)	3 (15)	35 (33)	0.101
Short-acting insulin	4 (4.7)	1 (5)	5 (4.7)	1
Long-acting insulin	8 (9.3)	1(5)	9 (8.5)	1
Mixed insulin	10 (11.6)	0 (0)	10 (9.4)	0.202
Glipizide	4 (4.7)	1 (5)	5 (4.7)	1
Comorbidities				
Hypertension	55 (64)	10 (50)	65 (61.3)	0.369
Diabetes Mellitus	45 (52.3)	10 (50)	55 (51.9)	1
Dyslipidemia	65 (75.6)	11 (55)	76 (71.7)	0.118
Cardiovascular disease	16 (18.6)	2 (10)	18 (17)	0.515
Pre-HD laboratory test				
Hemoglobin (g/dL)	8.8±1.6	8.8±1.8	8.8±1.6	0.891
Platelet count (10 ³ /μL)	195 (109–447)	174 (161–254)	187 (135–247)	0.409
Albumin (g/dL)	3.1±0.5	3±0.5	3.1±0.5	0.375
Serum Cr (mg/dL)	7.2 (5.2–11.7)	12.3 (7.5–17.8)	8 (5.3–12.3)	0.013
BUN (mg/dL)	113 (96–133)	103 (74.9–136)	111 (92.3–134)	0.422
Serum Na (mmol/L)	135±7.2	129±7	134±7.5	0.002
Serum K (mmol/L)	3.9 (3.6–4.4)	4 (3.6–4.7)	3.9 (3.6–4.5)	0.654
Serum Ca (mg/dL)	9.1 (8.8–9.6)	8.8 (8.4–9.8)	9.1 (8.7–9.6)	0.417
Serum glucose (mg%)	159±49.9	134±37.7	154.2±48.5	0.043
Serum osmolarity (mOsmo/L)	315±38.2	304±29.2	311±34.5	0.566
Post-HD laboratory test				
Hemoglobin (g/dL)	8.4 (7.7–9.4)	8.8 (7.2–9.7)	8.5 (7.7–9.6)	0.976
Platelet count (10 ³ /μL)	161 (113–243)	189 (130–254)	169 (116–247)	0.617
Albumin (g/dL)	2.9±0.5	3±0.3	2.9±0.5	0.615
Serum Cr (mg/dL)	5.6 (4.1–8.3)	7.8(4.6–11.1)	5.7(4.1–8.7)	0.151
BUN (mg/dL)	80.9±22	84.5±33.4	81.6±24.3	0.580
Serum Na (mmol/L)	135±5.6	130±6	134±5.9	0.002
Serum K (mmol/L)	3.7 (3.5–4.2)	4 (3.6–4.2)	3.8 (3.5–4.2)	0.706
Serum Ca (mg/dL)	9.4 (8.7–9.8)	8.9 (8.7–9.5)	9.4 (8.7–9.7)	0.486

values are presented as number (percentage), median (interquartile range) or mean±standard deviation (S.D.)

ACEI=angiotensin converting enzyme inhibitors, ARBs=angiotensin receptor blockers, BUN=blood urea nitrogen, Ca=calcium, CCB=calcium channel blockers, CKD=chronic kidney disease, Cr=creatinine, CVD=cardiovascular disease, HD=hemodialysis, K=potassium, Na=sodium DDS=dialysis disequilibrium syndrome, N=number

Table 3 Hemodialysis prescription according to patients with or without clinically suspected DDS

Prescription	No clinically suspected DDS (N=86)	Clinically suspected DDS (N=20)	Total (N=106)	p-value
Dialyzer surface (m ²)				0.614
1.4	5 (5.8)	2 (10)	7 (6.6)	
1.8	81 (94.2)	18 (90)	99 (93.4)	
BFR (ml/min)	150 (150–200)	150 (150–200)	150 (150–200)	0.588
DFR (ml/min)	300 (300–300)	300 (300–425)	300 (300–300)	0.109
Dialysate temperature (°C)	36.5 (36.5–36.6)	36.5 (36.5–36.6)	36.5 (36.5–36.6)	0.915
Session length (minutes)	120 (120–120)	120 (120–120)	120 (120–120)	0.569
Dialysate Na (mEq/L)	138 (138–138)	138 (131.5–138)	138 (138–138)	0.079
Dialysate K (mEq/L)	3 (3–3)	3 (3–3)	3 (3–3)	0.968
Dialysate Ca (n, %)				0.951
2.5 mEq/L	44 (51.2)	11 (55)	55 (51.9)	
3.5 mEq/L	42 (48.8)	9 (45)	51 (48.1)	
Dialysate HCO ₃ (mEq/L)	28.3±1.4	30.4±4.6	29.2±3.1	0.268
Dialysate glucose (mg%)	200 (200–200)	200 (200–200)	200 (200–200)	0.295
UF (ml)	0 (0,1000)	760 (0,1000)	0 (0,1000)	0.224
UF rate (ml/kg/hr.)	10.2±4.6	8.2±2.9	9.7±4.2	0.190

values are presented as number (percentage), median (interquartile range) or mean±standard deviation (S.D.)

BFR=blood flow rate, Ca=calcium, DFR=dialysate flow rate, HCO₃=bicarbonate, K=potassium, Na=sodium, UF=ultrafiltration
 DDS=dialysis disequilibrium syndrome, N=number

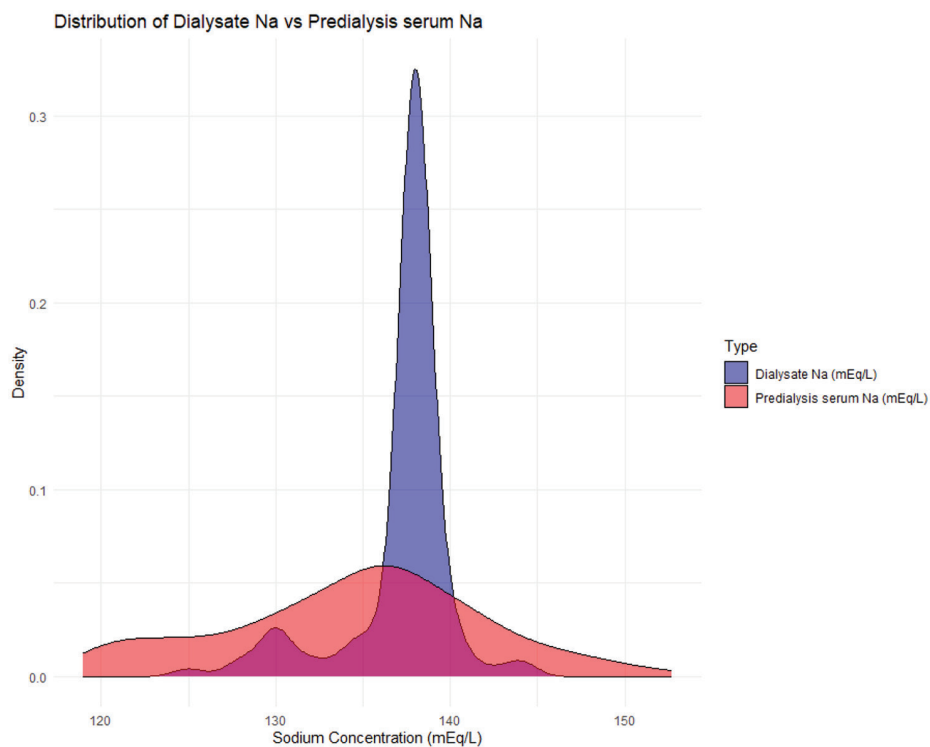
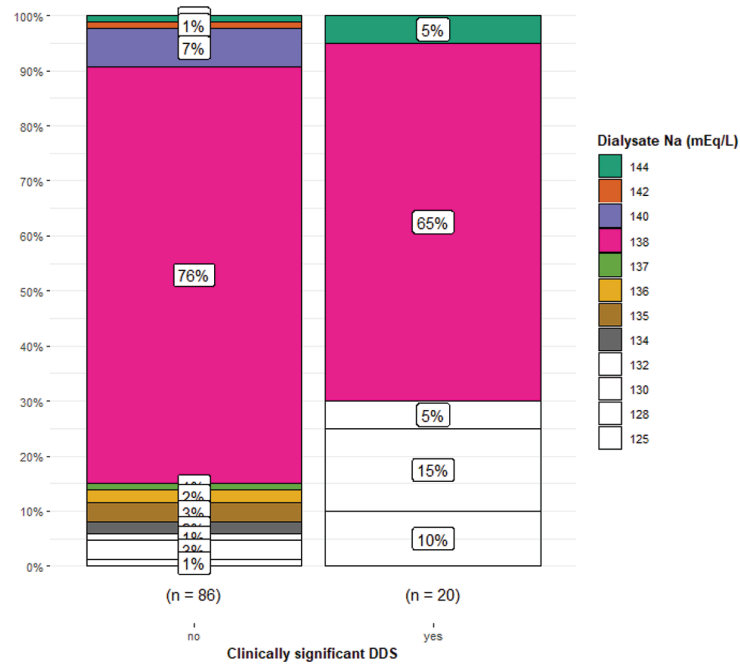
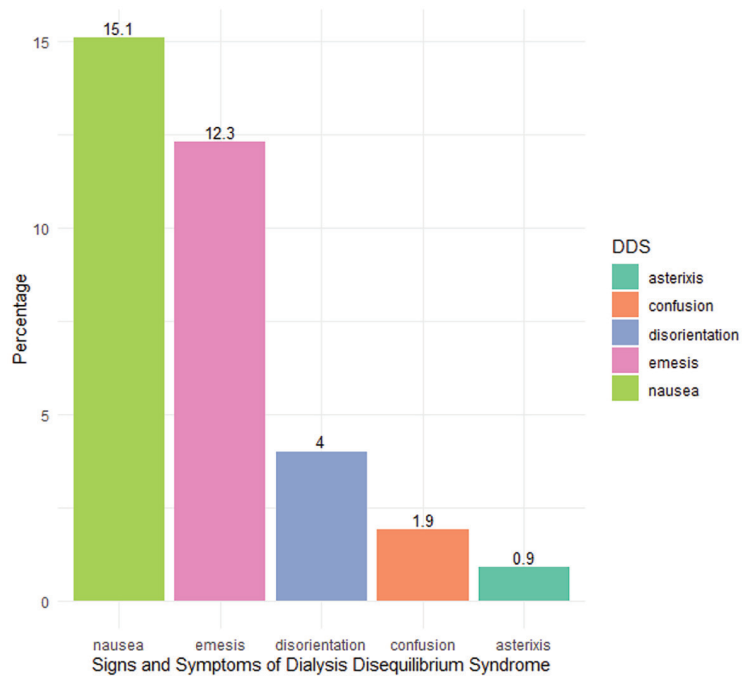


Figure 1 The distribution of pre-hemodialysis serum sodium concentrations and dialysate sodium concentrations of the entire cohort



DDS=dialysis disequilibrium syndrome

Figure 2 The distribution of dialysate sodium concentrations in patients with and without clinically suspected DDS



DDS=dialysis disequilibrium syndrome, N=number

Figure 3 The percentage of symptoms in patients with clinically suspected DDS

Table 4 Univariate and multivariate logistic regression models for variables predicting clinically suspected DDS

Variables	Univariate			Multivariate		
	ORs	95% CI	p-value	ORs	95% CI	p-value
BMI (kg/m ²)	1.13	0.90–1.42	0.302			
Dyslipidemia	0.64	0.13–3.23	0.585			
Beta blocker usage	0.42	0.06–2.71	0.361			
Pre-HD serum Cr (mg/dL)	1.11	1.00–1.23	0.134	1.13	1.02–1.25	0.013
Pre-HD serum Na (mmol/L)	0.88	0.81–0.96	0.048	0.90	0.84–0.98	0.007
Pre-HD platelet count (10 ³ /μL)	1.01	0.98–1.03	0.476			
Pre-HD serum glucose (mg%)	0.99	0.98–1.01	0.180	0.99	0.97–1.00	0.035
UF rate (ml/kg/hr.)	1.00	0.99–1.00	0.676			

BMI=body mass index, Cr=creatinine, HD=hemodialysis, Na=sodium, ORs=odd ratios, UF=ultrafiltration, DDS=dialysis disequilibrium syndrome

affecting 15.1% of cases, followed by emesis, disorientation, confusion, and asterixis. The median onset time for DDS was 240 minutes. Additionally, higher pre-hemodialysis serum Cr levels were associated with a greater risk of DDS, while lower serum Na and serum glucose levels before hemodialysis also indicated a higher risk of the syndrome.

Interestingly, a high prevalence of patients with clinically suspected ODS, up to 18%, was observed. This contradicts the findings of a study conducted by Raja and Seyoum¹¹, which reported a lower prevalence of DDS, occurring in less than 3% of cases. The explanation for this disparity may stem from the wide range of clinical manifestations associated with DDS. These can span from milder symptoms; such as nausea, to severe outcomes, including, seizures, coma, and even death. Consequently, milder symptoms might not be reported as DDS, as they can be self-limiting and typically dissipate within several hours, leading to an underreporting of these symptoms¹². Another potential reason for underreporting could be attributed to the timing of DDS onset. Typically, Classic DDS manifests during or shortly after hemodialysis¹³. However, this study's findings underscore the variability in the onset of neurological symptoms following hemodialysis initiation, which may occur later than expected. Hence, there is a possibility of underdiagnosis in such cases.

Recognition of high-risk patients developing DDS has been underscored for many years. These populations include the young and elderly, predisposing neurological disease, uremia, hypernatremia, hyperglycemia, and first hemodialysis⁷. However, the evidence of exact risk factors remains limited due to the lack of clinical studies in humans. To our knowledge, this is the first report on the predictors of clinically suspected DDS from real clinical practice. Higher pre-hemodialysis serum Cr was found to be associated with clinically suspected DDS. In contrast, pre-hemodialysis BUN levels showed no correlation with this condition. It was therefore hypothesized that elevated pre-hemodialysis serum Cr levels, indicative of reduced renal function, may cause retention of osmolytes like glutamine, glutamate, and myoinositol. The significant reduction of these osmolytes in plasma post-dialysis could lead to their accumulation in the brain, increasing brain water content and contributing to the development of DDS¹⁴. Lower pre-dialysis serum sodium levels were associated with a higher probability of DDS. This contradicts some studies that reported high sodium dialysate can minimize DDS^{15,16}. Therefore it was hypothesized that the most prescribed dialysate sodium level was 138 mmol/L, whereas the median serum sodium level in the DDS group was only 129 mmol/L. This significant discrepancy between dialysate and serum Na levels may contribute to DDS. Additionally, higher serum glucose typically act as

a protective factor against DDS by reducing the osmotic gradient during hemodialysis. However, hyperglycemia can paradoxically increase the risk of DDS⁷.

The study's rigorous methodology and comprehensive data analysis contribute to the existing knowledge on DDS, addressing a significant knowledge gap in the field. The findings have implications for clinical practice, potentially guiding healthcare professionals in identifying and managing patients at risk of developing DDS during hemodialysis initiation. It is suggested that hemodialysis prescriptions should be prescribed to each patient individually, including appropriate dialysate Na levels that correlate with the patient's condition. It's important to be cautious with patients who have high serum Cr levels, as they may require slow clearance hemodialysis. Additionally, monitoring blood sugar levels consistently is crucial to minimize the risk of DDS.

This study acknowledges several limitations. First, its retrospective design and reliance on publicly available data may introduce selection bias. Second, it lacked data on osmolarity during and after dialysis, which limits its ability to perform a direct quantitative assessment of osmolarity changes. However, it did evaluate other variables that indirectly affect osmolarity; such as electrolytes and glucose, in relation to clinically suspected DDS. Third, this study lacked a precise diagnostic tool for DDS, relying instead on: 'clinically suspected DDS,' which may not be accurate. Nonetheless, in clinical practice, this syndrome is typically diagnosed by exclusion. Finally, the study was conducted at a single center, limiting the generalizability of the findings to other healthcare settings. Further prospective studies involving a larger and more diverse patient population are warranted to validate the identified risk factors in addition to enhancing the understanding of DDS in the context of hemodialysis initiation. However, the lack of prior studies investigating clinically suspected DDS and its associated factors in this specific patient population emphasizes the importance and originality of our findings.

Conclusion

In conclusion, approximately 18.8% of the patients studied developed symptoms consistent with DDS, suggesting potential underreporting and variability in the clinical recognition of DDS symptoms. Additionally, key findings indicated that higher pre-hemodialysis serum creatinine levels, along with lower sodium and glucose levels, significantly increased the risk of DDS. These results highlight the importance of personalized hemodialysis prescriptions and vigilant monitoring of at-risk patients to mitigate the risk of DDS. This study advocates for further research; particularly through multi-center prospective studies, to validate these findings and enhance management strategies for ESKD patients starting on hemodialysis, thereby improving patient outcomes and reducing DDS incidences.

Conflict of interest

All authors declare no conflicts of interest.

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