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ORIGINAL ARTICLE

Expanding Indications for a Ketogenic Diet as an Adjuvant Therapy in Adult Refractory Status Epilepticus: an Exploratory Study Using Moderation Analysis

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Abstract

Refractory status epilepticus (RSE) requires multimodal treatment approaches to achieve rapid seizure cessation and neuroprotection. A ketogenic diet (KD) has demonstrated efficacy as a nutritional therapeutic option for adult RSE. However, the group of adult RSE patients who would benefit from adopting a KD needs to be determined to appropriately select the patients indicated for a KD. Therefore, we conducted a nonrandomized retrospective cohort study to explore the therapeutic efficacy of a KD by investigating the moderation effect of a KD on the association between the clinical characteristics of RSE patients and their functional outcomes. This study investigated 140 RSE patients, including 32 patients treated with a KD; among these patients, 28 (81%) achieved seizure cessation. We found that KD moderated the reduction in the modified Rankin scale (mRS) score at discharge among patients who were older, had higher seizure severity scores, were under continuous intravenous anesthetic therapy (CIVAD), and had super-RSE. Age and seizure severity scores, but not CIVAD or super-RSE, were associated with a KD-moderated change in mRS score at 3 months. Thus, we consider that our study provides evidence of a neuroprotective effect of KD in the most severe RSE patients with very few remaining therapeutic options, but future randomized controlled trials in these subgroups of KD patients are necessary.

Keywords Ketogenic diet · Refractory status epilepticus · Moderation analysis · Nutritional therapy · Neuroprotection

Introduction

Refractory status epilepticus (RSE) is one of the most challenging states of neuro-emergency among many neurocritical conditions and has a high mortality rate of 11–48% [1] and a heavy burden of disease [2]. The treatment of RSE requires rapid escalation of antiseizure medications (ASMs), a decision on the initiation of continuous intravenous anesthetic drugs (CIVADs), and application of various pharmacological, surgical, and nutritional therapeutics [3]. The goal of multimodal treatments for RSE is to achieve rapid seizure termination and neuroprotection.

A ketogenic diet (KD) has been considered an effective therapeutic option in patients with status epilepticus. KD possibly provides a beneficial effect by producing ketone bodies, which are known to have favorable properties in individuals with seizure disorders. Although the exact mechanism by which KD exerts its therapeutic effect is not well established, several hypotheses, such as enhanced gamma-aminobutyric acid production [4, 5], reduced proinflammatory cytokine levels [6], and neuroprotection against metabolic stress [7], have been proposed as potential mechanisms of KD. Thus far, a phase I/II trial and several retrospective studies have demonstrated the therapeutic efficacy of a KD, especially in super-RSE (SRSE) and febrile infection-related epilepsy syndrome (FIRES) [8–13], highlighting seizure cessation after KD implementation. However, no previous

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studies of RSE have included the potential neuroprotective properties of KD by assessing the functional outcome of RSE patients.

We conducted a nonrandomized retrospective cohort study to determine the target demographic that would benefit from KD implementation. We performed a moderation analysis to identify how KD moderates the association between diverse patient characteristics and functional outcomes. We hypothesized that the therapeutic efficacy of a KD would be different among heterogeneous RSE populations according to their clinical, electrographic, and treatment-related characteristics. Therefore, this study could provide information about the mechanism of the therapeutic effect of a KD on adult RSE and, further, suggest a rationale for its implementation.

Methods

Study Design and Patients

An extensive retrospective review of the medical records of all consecutive adult patients with RSE admitted to Ajou University Hospital from January 2015 to February 2021 was performed. Data were acquired through an electronic medical record system. The inclusion criteria for this study were as follows: (1) age 18 years or older; (2) RSE with electrographic evidence, including ictal-interictal continuum (IIC) or electroclinical/electrographic status epilepticus (ESE); and (3) an available mRS score at discharge. The exclusion criterion was RSE due to an anoxic-ischemic cause.

RSE was defined as persistent clinical, electroclinical, or electrographic seizures despite treatment with intravenous (IV) benzodiazepine and IV ASM [14]. Our institutional protocol for RSE indicates that all patients with suspected RSE should undergo continuous video-electroencephalogram (EEG) monitoring or repeated routine EEGs. For this study, patients who were documented with IIC or ongoing ESE were selected. The EEGs of each patient were reviewed by expert epileptologists and were reassessed if the findings were in concordance with the definitions proposed by the 2021 American Clinical Neurophysiology Society criteria [15].

Demographics, premorbid modified Rankin scale (mRS) score, and initial seizure severity scores including Status Epilepticus Severity Score (STESS) [16], modified STESS (mSTESS) [17], and epidemiology-based mortality score in status epilepticus (EMSE) [18] were collected. Presumed etiologies of RSE were classified according to the International League Against Epilepsy classification [19]. Variables related to treatment, including CIVADs, immunotherapy, magnesium infusion, and the number of ASMs used, were included in the analysis. The duration of RSE was collected in days, which was determined according to the EEG findings. New-onset RSE (NORSE) was defined as RSE in previously healthy individuals without a clear acute or active structural, toxic, or metabolic cause. SRSE was defined as a persistent seizure lasting more than 24 h despite CIVAD or reemergence of seizure upon withdrawal of the anesthetic agent [20].

This study was reviewed and approved by the institutional review board of Ajou University Medical Center (AJIRB-MED-MDB-21–275). The requirement for informed consent was waived by the board due to the retrospective nature of the study.

KD's Moderation Effect on Outcome Measures

The main outcome measure in our study was set as the modified Rankin scale (mRS) score at discharge, and other supporting outcome measures included the mRS score and seizure frequency at 3 months. Missing data due to loss to follow-up were omitted from the analysis.

To explore the specific group of RSE patients who may benefit from KD, we performed a moderation analysis. The rationale behind the moderation analysis was to adjust for the inherent bias in our retrospective study, in which the decision regarding KD implementation was not random. The direct comparison of outcome measures between KD and non-KD cohorts would indicate worse outcomes in the KD cohort because the KD was implemented among the patients with more refractory seizures. Therefore, the moderating effect of KD in the association between the functional outcome of RSE and RSE characteristics was assessed.

When a particular RSE-related characteristic is associated with the outcome of RSE and KD changes the degree of its association with the outcome, KD is considered to have a moderating effect. Statistically, moderation analysis is a type of regression analysis using the regressor variable (X, RSE characteristics), moderator variable (M, KD), and interaction variable of regressor and moderator variables (X:M) as covariates. The presence of the moderation effect was defined as a statistically significant association between the interaction variable (X:M) and outcome measures (Y), along with the RSE characteristic (X) and KD (M). A graphical representation of the moderation analysis is shown in Fig. 1.

After selecting the regressors that were significantly associated with the moderation effect of the KD on the outcome, these clinical characteristics were incorporated into the moderated moderation analysis to adjust for the possible influence of other therapeutic modalities. A graphical representation of the moderated moderation analysis is depicted in Supplementary Fig. 1.

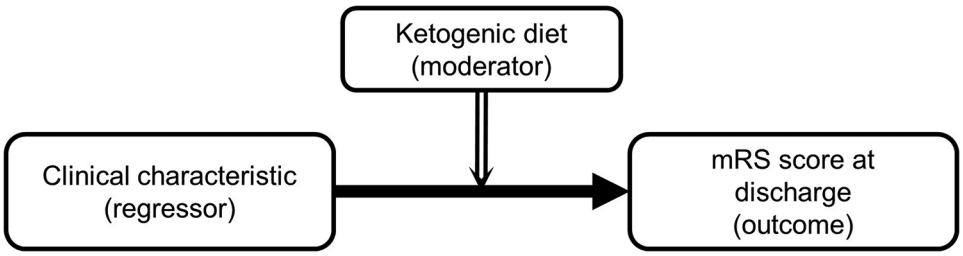

Fig. 1 A graphical representation of the moderation analysis. Abbreviations: mRS, modified Rankin scale

KD Protocol

The KD cohort included patients who received enteral or parenteral KD for at least 4 days. For enteral KD, a commercially available liquid formula (Namyang Ketonia; NAMYANG DAIRY PRODUCTS CO., LTD., Seoul, Korea) at a 4:1 (lipid:nonlipid) ratio containing 120 kcal per 100 ccs was administered via a nasogastric tube or percutaneous gastrostomy tube and later switched to oral administration when the patient regained consciousness. The dosage was carefully increased, starting with one-third of the target calorie intake and increasing daily until the target calorie intake was reached (5–7 days). For parenteral KD, a method involving a 16 h IV calorie infusion and 8 h fasting was chosen [21]. Briefly, one-third of the estimated 70% dietary energy requirement was administered on the first and second days using IV lipid emulsion and amino acid solution. In the next 2 days, two-thirds of the 70% energy requirement was provided, and the full dose was reached starting from the fifth day.

During the KD period, daily laboratory tests and physical examinations were conducted to monitor the achievement of ketosis and the development of adverse events. Serum ketone body (beta-hydroxybutyrate) levels, serum glucose levels, urine ketone (acetoacetate) levels, and arterial blood gas were assessed daily during the KD period. The achievement of ketosis was defined as a serum ketone level ≥ 2.0 mmol/L or urine ketone level ≥ 40 mg, as described in the literature [10].

Adverse events of KD included hypoglycemia, metabolic acidosis, and gastrointestinal (GI) problems such as ileus. Hypoglycemia was defined as serum glucose or point-of-care glucose level < 60 mg/dl or a significant decrease in glucose from baseline resulting in hypoglycemic symptoms. Metabolic acidosis was defined as either arterial pH < 7.2 or serum bicarbonate level < 17 mEq/L. Point-of-care glucose tests were performed four to seven times a day. In addition, daily bowel sound auscultation and weekly abdominal radiography were performed to monitor the presence of ileus. Adverse events resulting in the discontinuation of KD were separately assessed. Data on concomitant carbonic anhydrase inhibitor or steroid use were also collected due to their potential effect on the achievement of ketosis or the development of an adverse event.

Statistical Analysis

Dichotomous variables are presented as numbers (percentages). Continuous variables were tested for normality using the Shapiro–Wilk test and are reported as medians (interquartile ranges, *IQR*s). Categorical variables were compared using the chi-squared test or Fisher's exact test. Continuous variables were compared using the Mann–Whitney *U* test. The mRS score was regarded as a continuous variable in all analyses but examined for proportionality when using graphical methods. All statistical analyses were performed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). The statistical significance level was set at $p < 0.05$.

Results

Patient Characteristics and Outcome

In total, 140 RSE patients (male: 87 [62.1%], age: 62 [*IQR*, 49–77]) were selected for inclusion in the analysis. Of these, 32 (22.9%) patients received a KD. Patient characteristics of each cohort are summarized in Table 1. Baseline clinical characteristics such as age, sex, premorbid mRS score, STESS, mSTESS, and EMSE were not significantly different between cohorts. RSE etiologies and EEG characteristics were also not different between cohorts.

The rate of ongoing RSE at 3 days was higher in the KD cohort (49.1% vs. 84.4%, $p < 0.001$) than in the non-KD cohort, which expectedly would have driven the vigorous treatments in the KD cohort, including the implementation of the KD itself. For example, the number of ASMs administered was higher in the KD cohort than in the non-KD cohort (2 [2–4] vs. 3 [2–5], $p = 0.009$); there was also a higher rate of CIVADs (20.4% vs. 53.1%, $p < 0.001$), immunotherapy (14.8% vs. 40.6%, $p = 0.004$), and magnesium infusion (8.3% vs. 43.8%, $p < 0.001$). Propofol, a CIVAD agent that is contraindicated during the KD period, was administered to four patients in the KD cohort. No overlap was present between the CIVAD and KD periods, except for in one patient, who showed a 3-day overlap between enteral KD administration and the tapering phase of propofol.

Table 1 Clinical characteristics of the KD and non-KD cohorts

	Non-KD ($N=108$)	KD ($N=32$)	p value
Age, median (*IQR*), years	62 (49.75–77)	62 (44.25–77)	0.81
Male sex, no. (%)	72 (66.67%)	15 (46.88%)	0.07
Premorbid mRS, median (*IQR*)	1 (0–3)	2 (0–3.25)	0.50
Seizure severity scores			
STESS, median (*IQR*)	3 (2–5)	4 (3–5.25)	0.39
mSTESS, median (*IQR*)	4 (3–5)	4 (3–6)	0.46
EMSE 4 strata, median (*IQR*)*	84 (66.5–92)	85 (77.5–100.5)	0.09
EMSE 6 strata, median (*IQR*)*	123 (110.5–137)	128 (120–145.75)	0.10
NORSE, no. (%)	25 (23.15%)	13 (40.62%)	0.08
Etiological classification, no. (%)			
Acute	37 (34.26%)	13 (40.62%)	0.28
Remote	19 (17.59%)	5 (15.62%)	
Progressive	7 (6.48%)	5 (15.62%)	
Cryptogenic	45 (41.67%)	9 (28.12%)	
Specific etiologies, no. (%)			
Acute vascular disease	8 (7.41%)	2 (6.25%)	0.22
Remote vascular disease	41 (37.96%)	9 (28.12%)	
Brain tumor	4 (3.7%)	4 (12.5%)	
Drug withdrawal	5 (4.63%)	0 (0%)	
Alcohol-related	3 (2.78%)	0 (0%)	
Metabolic cause	9 (8.33%)	1 (3.12%)	
Autoimmune encephalitis	16 (14.81%)	10 (31.25%)	
Infectious encephalitis	3 (2.78%)	1 (3.12%)	
Cryptogenic	18 (16.67%)	4 (12.5%)	
Others	1 (0.93%)	1 (3.12%)	
EEG, no. (%)			
Electroclinical/electrographic seizure	58 (53.7%)	23 (71.88%)	0.10
Ictal-interictal continuum	77 (71.3%)	25 (78.12%)	0.59
Number of antiseizure medications (*IQR*)	2 (2–4)	3 (2–5)	0.009
CIVAD, no. (%)	22 (20.37%)	17 (53.12%)	< 0.001
Midazolam	21 (95.45%)	17 (100%)	> 0.99
Pentobarbital	2 (9.09%)	6 (35.29%)	0.06
Propofol	1 (4.55%)	4 (23.53%)	0.15
Ketamine	0 (0%)	6 (35.29%)	0.004
Immunotherapy, no. (%)	16 (14.81%)	13 (40.62%)	0.004
Methylpredisolone pulse therapy	16 (14.81%)	13 (40.62%)	0.004
Intravenous immunoglobulin G	11 (10.19%)	8 (25%)	0.04
Rituximab	4 (3.7%)	6 (18.75%)	0.01
Tocilizumab	0 (0%)	3 (9.38%)	0.01
Other immunotherapies	1 (0.93%)	1 (3.12%)	0.41
Magnesium infusion, no. (%)	9 (8.33%)	14 (43.75%)	< 0.001
Duration of seizure, median (*IQR*), days	3.14 (2–6)	7 (4.75–19.25)	< 0.001
Super-RSE, no. (%)	20 (18.52%)	16 (50%)	< 0.001
Short-term outcome			
mRS scores at discharge, median (*IQR*)	4 (2–5)	5 (3–5)	0.13
In-hospital mortality, no. (%)	15 (13.89%)	5 (15.62%)	0.78
Long-term outcome			
mRS score at 3 months, median (*IQR*)	2 (1–5)	3.5 (2–5)	0.44
Seizure frequency (/month) at 3 months, median (*IQR*)	0 (0–0.5)	0 (0–0.5)	0.64
Recurred SE within 3 months, no. (%)	2 (3.51%)	3 (17.65%)	0.08

CIVAD continuous intravenous anesthetic drugs *EEG* electroencephalogram, *EMSE* epidemiology-based mortality score in status epilepticus, *IQR* interquartile range, *KD* ketogenic diet, *mRS* modified Rankin Scale, *mSTESS* modified STESS, *NORSE* new-onset refractory status epilepticus, *SE* status epilepticus, *STESS* Status Epilepticus Severity Score

*The four strata of EMSE include etiology, comorbidity, EEG findings, and age. The six-strata EMSE additionally includes the duration of seizure and level of consciousness

Patients in the KD cohort showed a longer RSE duration (days, 3.14 [2–6] vs. 7 [4.75–19.25], $p < 0.001$), along with a higher rate of SRSE (18.5% vs. 50.0%, $p < 0.001$), than the non-KD cohort. However, no significant differences were seen between the cohorts in mRS score at discharge (4 [2–5] vs. 5 [3–5], $p = 0.13$). Three-month mRS scores were available in 97 (69.29%) patients and did not show significant differences between cohorts. The median seizure frequency at 3 months was similar between the cohorts (0 [0–0.5] vs. 0 [0–0.5]); however, recurrent SE within 3 months was more frequently observed in the KD cohort (3.51% vs. 17.65%, $p = 0.08$).

KD Cohort

KD-related findings in the KD cohort are summarized in Table 2. In the KD cohort, 25 (78.1%) patients received enteral KD, 4 (12.5%) received parenteral KD, and 3 (9.4%) started with parenteral KD and were later switched to enteral KD. The initiation of KD occurred 4 (2–9.25) days after admission and was maintained for 11.5 (9.75–24) days. Ketosis was achieved in 28 (87.5%) patients in 2.5 (1–4.25) days. The peak serum ketone level was 3.37 ± 1.72 mmol/L. Seizure cessation was achieved in 26 (81.3%) patients within 3 (2–9) days from the initiation of KD.

Adverse events associated with KD were observed in 19 (53.1%) patients; only seven (21.9%) patients experienced adverse events resulting in the discontinuation of KD. Of all adverse events, the most common was metabolic acidosis (63.2%), followed by hypoglycemia (21.1%), and ileus (21.1%). The adverse events resulting in the discontinuation of KD were ileus ($n = 4$), suspected GI bleeding ($n = 1$), metabolic acidosis ($n = 1$), and pancreatitis ($n = 1$). Notably, one patient died due to GI sepsis following ileus. The patient who experienced pancreatitis during KD showed normal triglyceride levels. A detailed description of each patient in the KD cohort is graphically presented in Supplementary Fig. 2.

Moderation Effect of KD

Through moderation analysis, several clinical and treatment-related characteristics were identified, and KD showed a significant moderation effect on age, STESS, mSTESS, CIVAD, and SRSE. The core result of the moderation analysis is summarized in Table 3. The full result of the moderation analysis is shown in Supplementary Table 1.

The moderation analysis revealed that KD moderated the mRS score at discharge by −0.04 (−0.07 to 0.00) per 1-year increase in age. Similarly, the implementation of a KD was associated with a reduced mRS score at discharge

Table 2 KD-related findings in the KD cohort

	KD cohort ($N = 32$)
Time to initiation of KD, days (*IQR*)	4 (2–9.25)
KD type, no. (%)	
Enteral	25 (78.1%)
Parenteral	4 (12.5%)
Parenteral to enteral	3 (9.4%)
Achievement of ketosis, no. (%)	28 (87.5%)
Time to ketosis achievement, days (*IQR*)	2.5 (1–4.25)
Peak serum ketone level, mean ± SD, mmol/L	3.37 ± 1.72
Duration of KD, days (*IQR*)	11.5 (8.75–19.5)
Achievement of seizure cessation, no. (%)	26 (81.3%)
Time to seizure cessation from KD initiation, days (*IQR*)	3 (2–9)
Concomitant drug use, no. (%)	
Topiramate	17 (53.1%)
Zonisamide	3 (9.4%)
Steroid	13 (40.6%)
Rate of adverse events, no. (%)	19 (59.4%)
Metabolic acidosis	12 (63.2%)
Hypoglycemia	4 (21.1%)
Ileus	4 (21.1%)
Gastrointestinal bleeding	1 (5.3%)
Pancreatitis	1 (5.3%)
Adverse events resulting in the discontinuation of KD, no. (%)	7 (21.9%)

IQR interquartile range, *KD* ketogenic diet, *SD* standard deviation

Table 3 Moderation analysis of clinical characteristics and KD on the outcome measures

	Clinical characteristic (regressor)			Ketogenic diet (moderator)			Characteristic: ketogenic diet (interaction)		
	Beta	95% *CI*	*p* value	Beta	95% *CI*	*p* value	Beta	95% *CI*	*p* value
On mRS score at discharge									
Age	0.0537	(0.0351, 0.0723)	< 0.001	2.3944	(0.8896, 4.9792)	0.0131	−0.0363	(−0.0689, −0.0036)	0.0308
STESS	0.4930	(0.3235, 0.6626)	< 0.001	1.8549	(0.4722, 3.2376)	0.0089	−0.3472	(−0.6841, −0.0104)	0.0434
mSTESS	0.5888	(0.4501, 0.7275)	< 0.001	2.2683	(1.0085, 3.5280)	0.0005	−0.3991	(−0.6594, −0.1389)	0.0029
CIVAD	1.1032	(0.1944, 2.0119)	0.0177	1.2810	(0.3002, 2.2617)	0.0109	−1.7385	(−3.2753, −0.2016)	0.0269
SRSE	1.0363	(0.0795, 1.9932)	0.0340	1.2238	(0.2670, 2.1807)	0.0126	−1.6613	(−3.2296, −0.0931)	0.0380
On mRS score at 3 months									
Age	0.0586	(0.0321, 0.0850)	< 0.001	3.5781	(0.7706, 6.3857)	0.0131	−0.0537	(−0.1023, −0.0051)	0.0308
mSTESS	0.6808	(0.4701, 0.8915)	< 0.001	2.3165	(0.4210, 4.2119)	0.0172	−0.4810	(−0.8965, −0.0655)	0.0238

CI confidence interval, *CIVAD* continuous intravenous anesthetic drug, *mRS* modified Rankin scale, *mSTESS* modified STESS, *SRSE* superrefractory status epilepticus, *STESS* status epilepticus severity score

by −0.35 (−0.68 to −0.01) and −0.40 (−0.66 to −0.14) for each one-point increase in STESS and mSTESS scores, respectively. In patients who received CIVAD, KD moderated the mRS score at discharge by −1.74 (−3.28 to −0.20) compared to that in the patients without CIVAD. Patients who converted from RSE to SRSE showed a moderating effect of KD on the reduction in mRS score at discharge by − 1.66 (− 3.23 to − 0.09). This indicates that in older patients, those with higher STESS and mSTESS scores, those who underwent CIVAD, and those who converted to SRSE, a reduction in mRS score at discharge was observed compared to that in the non-KD cohort. A visualization of this finding is depicted in Fig. 2, which shows the least-squares regression line and confidence intervals between the RSE characteristics and mRS score at discharge.

Furthermore, moderation analysis on the mRS score and seizure frequency at 3 months was performed, and the results are also summarized in Table 3. RSE characteristics that were associated with the moderation effect of KD on the 3-month mRS were age and mSTESS. With a 1-year increase in age, KD moderated the 3-month mRS score by −0.05 (−0.10 to −0.01); with a one-point increase in mSTESS, KD moderated the 3-month mRS score by −0.48 (−0.90 to −0.07). These values suggest a slightly stronger moderation effect than that for the mRS score at discharge. KD did not show a significant moderation effect on the 3-month mRS score in association with CIVAD and SRSE. In the moderation analysis with seizure frequency at 3 months as the outcome measure, no definite RSE characteristic was identified to be associated with the significant moderating effect of KD.

Therapeutic modalities other than KD, such as immunotherapy, magnesium infusion, and CIVAD, were frequently used in the KD cohort. To adjust for the possible influence of these potential confounders, a moderated moderation analysis was conducted. The specified RSE characteristics from the moderation analysis above were included in the moderated moderation analysis, and outcomes were set as mRS scores at discharge and at 3 months. We found that no other treatment exhibited a significant moderated moderation effect on the outcomes. The result of the moderated moderation model is summarized in Supplementary Table 2.

Discussion

Our study explored the moderating effect of KD on outcomes in adult RSE patients based on the hypothesis that KD's therapeutic efficacy would be different across heterogeneous RSE characteristics. We found that KD moderated the functional outcome at discharge in patients with an older age, with higher STESS and mSTESS scores, under CIVAD, and with SRSE.

Despite the growing need for a higher level of evidence on the utilization of KD in RSE patients, the lack of knowledge on this specific therapeutic option makes it difficult to determine the ideal patient selection criteria or primary outcome for the design of the desired randomized controlled trial. Our study showed that particular subgroups of RSE patients benefited from KD, thereby suggesting potential patient selection criteria for future randomized controlled trials.

Our study is different from previous research because the functional outcome, represented by the mRS score, was set as the primary outcome. Since the exact mechanism by which KD assists in RSE treatment is not fully understood, our study exemplifies various outcome measures to accurately select patients who could benefit from a KD. Previous studies demonstrated the KD's efficacy in SRSE and FIRES, which are thought to be immune-mediated, and therefore suggested the anti-inflammatory properties

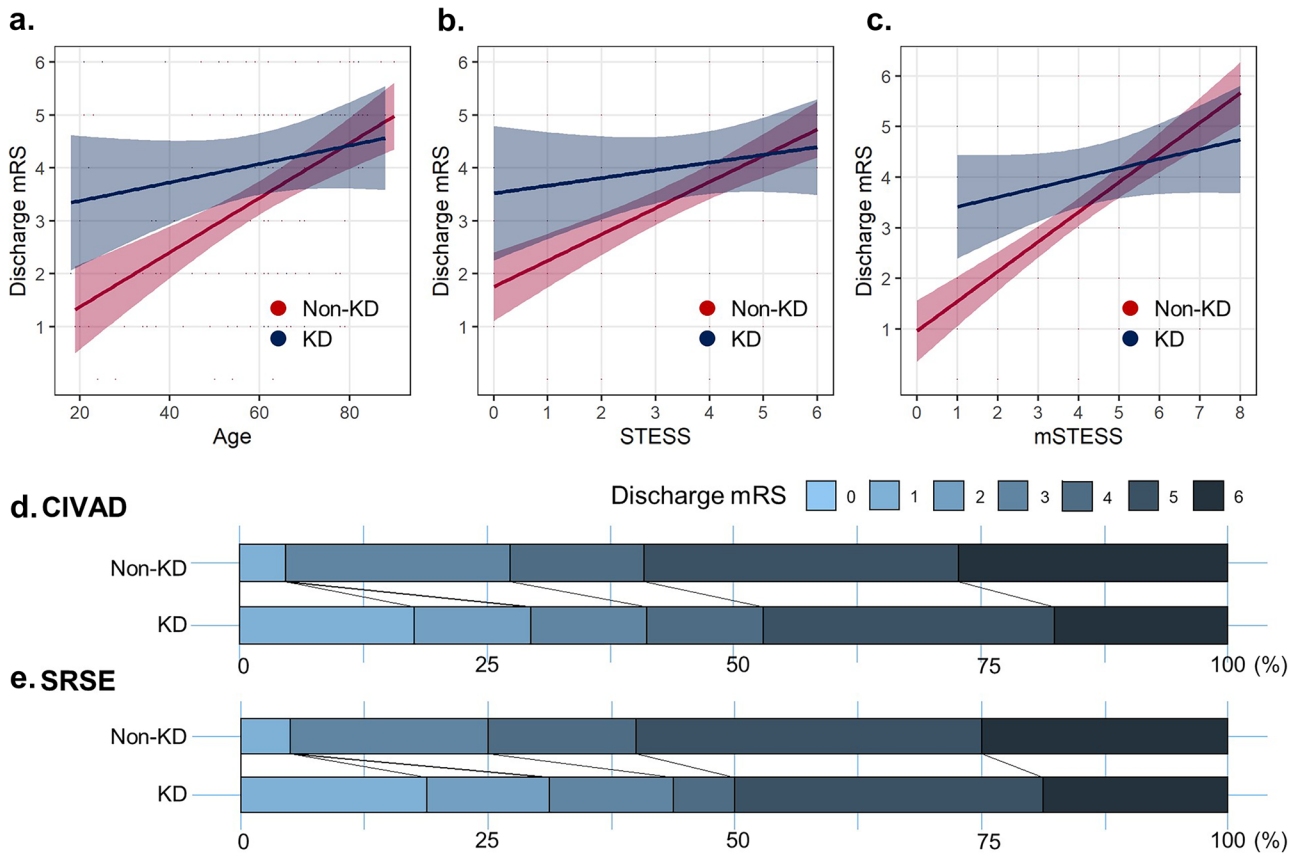

Fig. 2 mRS score at discharge according to the RSE characteristics. **a**, **b**, **c** Least-squares regression lines of mRS score on age, STESS, and mSTESS score in non-KD and KD cohorts. **d**, **e** Distribution of mRS scores at discharge in specific subgroups of IV anesthetic therapy and SRSE. The upper stacked bar plot shows the mRS score at discharge in the non-KD cohort, and the lower stacked bar plot shows the mRS score in the KD cohort. Abbreviations: CIVAD, continuous intravenous anesthetic drugs; KD, ketogenic diet; mRS, modified Rankin Scale; mSTESS, modified Status Epilepticus Severity Score; SRSE, superrefractory status epilepticus; STESS, Status Epilepticus Severity Score

of KD. Additionally, these studies have focused on seizure termination resulting from KD, and the short-term/long-term outcomes of RSE in the context of KD utilization were not highlighted. To assess the short-term/long-term functional outcome, the presence of a control cohort is essential. Due to the lack of control groups in previous studies on the KD, the generalization of the results was limited. Although the absence of randomization, with patients having been treated and selected according to experts' medical decisions, makes it difficult to draw firm conclusions from this retrospective analysis, our study is the first to incorporate a non-KD cohort to investigate the efficacy of KD in adult RSE patients. Another noteworthy strength of our study is that seizure cessation, one of the essential immediate outcomes in RSE, was achieved in 81% of the KD cohort, supporting the beneficial role of KD in the most urgent circumstances, such as in the intensive care unit.

The clinical and treatment-related characteristics selected from our moderation analysis, which are age, STESS and mSTESS, CIVAD, and SRSE, are not pathomechanistically homogenous features. In turn, this suggests that KD acts on the severity or refractoriness of RSE itself and subsequent treatment-related conditions rather than the underlying etiopathology of RSE. The neuroprotective effect of ketosis has been suggested to be mediated by metabolic resistance in vitro [7] and preservation of cellular integrity in vivo [22] without a direct seizure-attenuating effect. Similarly, we speculate that KD's efficacy is accentuated in regard to protection against long-lasting seizures in aged, anesthetized, vulnerable brains. Therefore, these findings emphasize the value of KD in the treatment of patients with the most severe form of continuing RSE with very few remaining treatment options.

Looking at each RSE characteristic, older age was selected as one of the clinical characteristics that might be used to select patients who could benefit from KD. However, it should be acknowledged that this study was conducted only on adult RSE patients and therefore does not translate into a comparison between adults and children

with RSE. Because there are considerable data from previous studies on KD for SRSE in children that support the utilization of a KD in the pediatric population, large-scale studies to provide a mechanistic explanation for KD's moderation effect in older patients across various age groups, including children, are necessary. Among the other RSE characteristics, CIVAD and SRSE were also associated with KD's moderating effect on the outcome, but these findings do not indicate that only late administration of KD be considered after CIVAD has already failed. Since there were no data on whether early or late administration of a KD is beneficial in RSE patients, future studies addressing the timing of KD implementation in RSE patients are needed.

The safety of the adoption of a KD is a prominent issue, especially in the context of treating critically ill RSE patients. In a prior phase I/II trial of KD in SRSE, adverse events were reported in 67% of participants [10]. In our study, 53.1% of patients experienced adverse events, while adverse events resulting in the discontinuation of KD occurred in only 21.9% of participants. Metabolic acidosis was the most common adverse event; however, it was manageable in almost all patients. Conversely, ileus was the most common cause of KD discontinuation. Routinely administered GI motility drugs and laxatives were ineffective in preventing or managing ileus in these patients. Ileus in critically ill patients is a serious problem leading to systemic infections by translocated intestinal bacteria.

Our study is not without limitations. First, although this study was conducted in a comparatively large KD cohort of RSE patients, multiple confounding factors could not be adjusted for in the moderation analysis. Especially considering that the KD cohort received more diverse treatment modalities due to their higher intrinsic severity, we have demonstrated, in part, that other treatments in the KD cohort did not significantly explain the outcomes through the moderated moderation analysis. However, the statistical power of this analysis was limited due to the small sample size. Therefore, the findings regarding the selected RSE characteristics should be cautiously interpreted, and they do not directly represent the therapeutic indication for KD. A future randomized controlled trial on a KD in RSE patients is warranted to obtain a higher level of evidence, preferably using the patient selection criteria presented in our study. Second, the missing data due to loss to follow-up at 3 months accounted for 30.7% of data, resulting in poorer model fit. The regression estimates generated in the moderation analysis on the 3-month mRS score cannot be directly compared with the analysis on the mRS score at discharge. Therefore, whether KD's moderating effect was more robust in the long term could not be evaluated.

In conclusion, KD moderates the functional outcome in selected subgroups of adults with RSE. KD's therapeutic efficacy is associated with older age, higher STESS and mSTESS scores, CIVAD usage, and SRSE. Future prospective trials are warranted to explore the practical application of a KD in RSE patients.

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