Introduction

Status epilepticus (SE) represents a frequent neurological emergency with an annual incidence of 10 to 20 per 100,000 inhabitants in Germany and an overall mortality rate of around 9 - 20 % [1-3]. It is defined by prolonged seizures or a series of seizures with only an incomplete return of consciousness in between [4]. Although all seizure types can evolve into SE, sufficient treatment evidence exists only for generalised convulsive SE (GCSE) [5, 6]. Therefore, the current treatment recommendations refer to this SE form and suggest adopting these recommendations for all other SE forms without further evidence [6, 7].

Benzodiazepines (BZDs) are best established as first-line treatments after several randomised controlled trials (RCTs), with equal efficacy throughout this drug class's different substances and application forms [8-13]. However, not all SE patients receive initial BZD therapy in clinical practice, and the reasons for this remain elusive. In the SENSE registry, a prospective multicentre registry for patients with SE from eight centres with particular expertise in SE treatment in German-speaking countries, it was previously shown that BZDs were only given in 86 % of GCSE and 73 % of non-GCSE. The current guideline's dosage recommendations for BZDs were violated in many cases, leading to reduced dosage applications and prolonged SE duration [14]. Possible explanations for deviations from existing treatment recommendations could be uncertainties as to whether these recommendations should be applied to all forms of SE. Besides, treating physicians might fear that higher dosing could lead to relevant side effects such as respiratory depression with the need for intubation and mechanical ventilation.

Guideline violations for first-line BZD treatment in SE appear to be pervasive even in prospective registries and trials [14, 15], suggesting a higher proportion in real-world settings and non-specialised centres. This study evaluated the extent and impact as well as possible reasons for refusal of BZD as first-line therapy in SE in a representative cohort of SE patients.

Methods

Patient selection

The *Project for Status Epilepticus in Cologne (PROSECO)* is a collaboration of all Neurology departments in Cologne that provide acute neurological care. *PROSECO* gathers information on adult SE patients. Cologne is the fourth largest city in Germany, with approximately one million inhabitants. All SE patients admitted between 03/2019 and 02/2021 to one of the three hospitals with an acute Neurology department in Cologne were retrospectively analysed. Previously, we addressed and excluded a relevant confounding impact of the Coronavirus Disease 2019 (COVID-19) pandemic during the last year of the observation period [16]. For drop-out handling and detailed epidemiological cohort data, we refer to [16]. This manuscript provides an in-depth analysis of the treatment practice of SE in the registry. The participating hospitals were the University Hospital of Cologne (UHC), the Cologne City Hospitals (CCH), and the Heilig Geist-Hospital Cologne (HGH).

All patients included in this study fulfilled the criteria for SE defined by the International League Against Epilepsy (ILAE) [4], with a seizure duration for GCSE ≥ 5 minutes and non-GCSE ≥ 10 minutes. In the case of generalised convulsive semiology at any timepoint during the SE episode, we labelled the SE as GCSE, otherwise as non-GCSE. The diagnosis for GSCE was made by typical clinical manifestation; in case of non-GCSE, the "Salzburg-EEG-criteria" were used additionally [17]. Patients with hypoxic encephalopathy and an age under 18 years were excluded. For detailed inclusion and exclusion criteria, refer to [16]. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were followed [18].

Data collection

Data were retrieved from electronic patient files. All SE patients were screened for the following *characteristics*: gender, age, care status before SE, known epilepsy, semiology and

aetiology of SE. SE aetiology was defined according to the ILAE proposal for SE classification in acute, remote/progressive or unknown [4]. For *therapy and outcome*, the following parameters were evaluated: initiation of prehospital treatment, drugs used for treatment and their concentrations, the mean number of drugs used, and duration of SE before hospital admission. Refractory SE was defined by the use of >2 anti-seizure therapies. We assessed further need and duration of assisted ventilation, duration of intensive care unit (ICU)-stay, duration of hospitalisation, Status Epilepticus Severity Score (STESS) [19] and modified Rankin-Scale (mRS) at discharge. A favourable outcome was defined as a patient's discharge without a decreased mRS relative to the premorbid level.

Patient cohorts

First, we divided all SE patients whether they received BZDs as initial therapy. We further analysed the BZD-receiving group for sufficient or underdosed BZD application [20]. Underdosing was defined as less than the dose for a person weighing 50 kg since all SE patients were adults. All groups were assessed for differences in characteristics, therapy and outcome as outlined above.

Statistical analysis

Statistical analyses were performed using SPSS 28.0 for Windows (IBM, Armonk, New York, USA) and Stata 16.1 software (StataCorp, Texas, USA). For comparisons of categorical independent data, chi-square tests or Fisher's exact tests (if less than 5 items) were performed. T-tests for unpaired variables were performed for comparisons of independent metrical data. All tests were performed two-tailed. Statistically significant different patient and therapy characteristics were further analysed with logistic regression analysis for the primary outcome parameters (dependent variables). P-values <0.05 were estimated as significant.

Ethics

The local ethics committee of the University of Cologne (21-1443-retro) approved the study. Due to the retrospective design and anonymous data collection, patient consent forms were waived.

Results

Selection process

Our multicentre database search resulted in a total of 485 hits. 157 patients had to be excluded from the analysis: 89 patients did not meet the ILAE-definition criteria for SE [4], five patients had developed SE during their inpatient stay, nine patients were not treated by Neurology departments, another 54 patients had a SE onset outside the urban area of Cologne. The remaining 328 patients were included for further analyses. Of these, 237 (72.3 %) received BZDs as initial therapy. The selection process is depicted in **Supplemental material 1**.

Patient and overall treatment characteristics

The detailed epidemiological data are provided in **Table 1.** The specific aetiologies of SE are summarised in **Supplemental material 2**. In the 237 (72.3 %) SE patients initially treated with BZDs, the most commonly used BZD was midazolam in 123 patients (37.5 %), followed by lorazepam in 72 (22 %). Rarely used were clonazepam in 13 (4 %) and diazepam in 29 patients (8.8 %).

Anti-seizure medication (ASM) was the drug of initial choice in 70 patients (21.3 %), with levetiracetam being used in 65 patients (19.8 %). Four patients were initially treated with lacosamide and one with valproic acid. Only three patients received anaesthetics as first-line treatment (0.9 %), two propofol and one thiopental.

Insert Table 1 here.

Characteristics of patients with and without BZD treatment

Comparisons between the BZD and the non-BZD group are detailed in **Table 2**. Patients receiving BZD treatment were younger (mean 61.7 years, to a mean 70 years, p-value **<0.001**), had more often known epilepsy (71.7 % to 45.2 %, p-value **<0.001**), more often arrived at the

emergency department within 30 minutes after ictal onset (23.6 % to 6.8 %, p-value **0.002**) and presented more often as GCSE (50.2 % to 21.9%, p-value **<0.001**). Prehospital therapy was started in only 14 of the 73 non-BZD patients (19.2 %) compared to 155 of the 237 BZD patients (65.4 %, p-value: **<0.001**). Notably, the mean number of drugs administered differed in both groups, with less medication in the non-BZD group than in the BZD group (2.2 to 2.7, p-value: **0.005**). SE outcome parameters showed, however, no significant differences between the groups.

Insert Table 2 here.

Characteristics of patients with sufficient versus underdosed BZD treatment

The SE patients initially treated with BZDs were further grouped dependent on whether their dosage was sufficient or underdosed per guideline recommendations [20]. Patient records did not mention initial BZD dosages in four patients (1.2 %). Therefore, they were excluded from this part of the analysis.

Only 71 of 233 patients (21.6 %) were treated sufficiently according to guideline recommendations with BZDs, while 162 patients (79.4 %) were underdosed.

Regarding all SE patients, most treatment and outcome parameters did not differ significantly for sufficient and underdosed BZD patients (see **Table 3a)**. Somewhat surprisingly, refractory SE, defined as a need for >2 anti-seizure therapies, was more often seen in the sufficiently treated BZD group (57.7 % to 42 %, p-value: **0.03**). The mean duration of ventilation was significantly prolonged in the underdosed subgroup (73.9 hours compared to 211.3 hours, p-value: **0.04**). Prehospital application rate and the number of drugs used did not differ significantly.

Insert Table 3 here.

As there is still considerable controversy about how aggressive non-GCSE should be treated, and randomised trials are lacking for non-GCSE, we further stratified our cohort for SE semiology (**Table 3 b-c**) [21, 22].

Stratifications for patient characteristics showed that for GCSE sufficient BZD dosages were withheld in older (>65 years: 17.8 % to 48.1 %, **p-value 0.001**) and female patients (25 % compared to 48.1 %, **p-value 0.006**), while no differences were observed in non-GSCE patients (**Table 3 b-c**).

The 77 GCSE patients not treated sufficiently with BZDs had a higher Status Epilepticus Severity Score (STESS) (p-value: **0.01**), less often a refractory SE (24 % to 28 %, p-value: **0.02**), a prolonged mean ventilation duration (mean 37.1 hours compared to 208.6 hours, **p-value: 0.01**), stayed significantly longer in the ICU (mean 1.7 days to 5.0 days, **p-value: 0.01**) and had a prolonged mean overall in-hospital stay (4.1 days to 8.8 days, **p-value: 0.003**) compared to GCSE patients who were treated according to current guidelines (n=40). The parameters favourable outcome and mortality rate were comparable for GCSE patients with sufficient or underdosed BZD treatment.

In contrast, the subgroup analysis in patients with non-GCSE showed different results. Whereas most parameter did not differ whether BZD were given in sufficient (n=31) or underdosed dosages (n=85), mechanical ventilation was necessary more often in the sufficiently dosed BZD group (6 % to 5 %, **p-value: 0.04**). Sufficiently dosed BZD patients also had a prolonged mean in-hospital stay (9.2 days to 5.8 days, **p-value: 0.04**) and less often a favourable outcome at discharge (16 % to 63 %, **p-value: 0.03**). However, mortality rates were not different.

Binomial logistic regression analysis for BZD versus non-BZD treatment

In a next step, we aimed at identifying the predictive value of BZD treatment adherence compared to other statistically different patient characteristics in our SE cohort on the outcome

parameters by using a binomial logistic regression analysis. For this analysis, the categorial variable "duration of ventilation" was therefore processed to an ordinal form (duration of ventilation ≤ or >24 h) (**Figure 1**).

Binomial logistic regression analysis for BZD versus non-BZD treatment

BZD treatment was not predictive of any of the assessed outcome parameters for all SE patients. Favourable outcome at discharge was mainly observed in patients ≤ 65 years (**OR 4.40**) and with a known history of epilepsy (**OR 1.90**). Mechanical ventilation was seen in patients with GCSE semiology (**OR 10.31**). A SE onset <0.5 hours at arrival decreased the odds (**OR 3.02**). The odds that SE was refractory decreased with the patient's arrival <0.5 hours in the emergency department (**OR 0.48**). None of the analysed variables influenced the duration of ventilation. Further analysis details are given in **Figure 1.**

Insert Figure 1 here.

Binomial logistic regression analysis for sufficient versus underdosed BZD treatment

Analogously, we also assessed the BZD treatment group for the variable sufficient versus underdosed treatment to unmask any dosage-related influences on the outcome parameter (**Figure 2**) with comparable results as for the above-mentioned BZD versus non-BZD treatment. The odds for a favourable outcome at discharge were significantly increased with age ≤ 65 years (**OR 5.33**), while no mechanical ventilation was associated with a SE onset <0.5 hours before the patient's arrival (**OR 3.06**). The odds for mechanical ventilation increased with a GCSE semiology (**OR 3.16**). Sufficient BZD dosages were associated with a refractory SE (**OR 2.02**). A refractory SE was seen in patients with a delayed arrival after SE onset (**OR 2.18**). Due to the small sample size, binary logistic regression analyses were not applicable for the semiological subgroup.

Insert Figure 2 here.

Discussion

Our study offers clinically relevant insights into the current treatment practice and guideline adherence concerning the treatment of adult SE patients in Germany. To this end, we evaluated a representative cohort in the urban area of Cologne encompassed by *PROSECO*.

We show that real-world treatment of SE patients wildly deviates from current treatment guidelines as an initial treatment with BZDs was only performed in 72.3 % of all adult SE patients, with a significant proportion of patients being underdosed.

Based on epidemiological data with an annual incidence of 10–20 patients with SE per 100,000 inhabitants in Germany, 200–400 cases were expected for the urban area of Cologne within the assessed two-year period [1]. Our cohort size of 328 patients is within the predicted range, indicating that we explored a representative cohort of adult SE patients.

We confirm prior reports of BZD treatment refusal as first-line therapy in SE in a relevant proportion. In the SENSE registry, a prospective multicentre non-interventional registry of centres with expertise in epilepsy in German-speaking countries, about 20% of SE patients did not receive BZD as a first-line agent [14]. Our study shows that the proportion of SE patients not initially treated with BZDs even increases when different care levels are involved. The reluctance to use BZDs is surprising as their high efficacy and good applicability for SE termination in early stages have been demonstrated in several large prospective trials for prehospital [10, 12] and in-hospital management [9, 11]. First-line treatment with BZDs was superior to other ASM [9]. Besides, the combination of levetiracetam and clonazepam as initial prehospital SE therapy did not provide treatment benefits, which led to the premature termination of the respective French SAMUKeppra study [23]. Based on this data, BZDs are unequivocally recommended as first-line therapy in SE treatment guidelines [8, 20].

The reasons for not using BZDs were not documented in the patient files or emergency service protocols. However, indirect conclusions can be drawn from our epidemiological data, as BZDs

were given more frequently in GCSE, in patients with known epilepsy and who were younger. BZD treatment occurred regularly in the prehospital initial therapy setting. This points toward more formally implemented prehospital therapy schemes. As levetiracetam is a listed medication in the ambulances of the Cologne emergency services, its less frequent use in the prehospital setting is not explained by lack of opportunity.

The preference for initial treatment with ASM in elderly patients may point toward a feared respiratory depression due to excessive BZD application, thus influencing treatment decisions. Respiratory depression can occur as an adverse effect, especially in the elderly with opioid comedication [24-26]. Next to polypharmacy, possible reasons include drug accumulation due to prolonged BZD half-life in patients with impaired renal or liver function [27].

Another possible explanation for withholding BZDs is the often challenging diagnosis of a non-GCSE, as no specific clinical or electroencephalographic features exist, especially if epilepsy is not known in the patient history [28]. Furthermore, it is still a matter of debate whether non-GCSE is equally harmful as GCSE regarding cerebral and extracerebral consequences. This, combined with fear of BZD-induced respiratory depression, could have led to preferring ASM in these cases. The most often used ASM was levetiracetam (93 % of the cases) in a substantial number of patients (overall 19.8 %). SE patients initially treated with ASM were significantly older, had a missing history of epilepsy, and presented more often with a non-GCSE than a GCSE. These parameters are associated with a worse functional outcome in the literature [29-31]. Astonishingly, the significant differences in SE management and patient characteristics in our cohort did not translate into relevant outcome differences.

Not only refusal of BZDs appears to be persistent, also underdosing of BZDs is a well-documented problem in SE treatment [14, 15, 28], and significant outcome differences might be masked by insufficient BZD treatment observed in different prospective epidemiological studies [14, 15]. In our cohort, nearly two-thirds of the patients with SE – if treated with a BZD

– did not receive sufficient dosing [8, 20]. In a former study, prolonged SE was ascribed to this [14]. By analysing all SE patients who received BZDs for relevant in-hospital and functional outcome parameters, we observed that sufficient BZD treatment of SE patients significantly shortened the mean ventilation time in our cohort. However, other outcome parameter showed no significant differences whether BZDs were dosed adequately or not, as seen in the study by Rossetti et al. [32]. Both Rosetti et al.'s study [32] and ours included large patient groups and were not solely focused on GCSE but also included non-GCSE. Instead, as described by our binary regression analysis, other parameters like age, aetiology and SE severity were strong predictors for functional SE outcome (**Figure 1 and 2**). The odds for a favourable SE outcome decreased in the elderly and patients without a known history of epilepsy, while the need for ventilation in SE patients was related to a generalised convulsive semiology and a prolonged arrival time to the hospital. This could misdirect to the hypothesis that treatment deviations from guidelines recommendations have only minor impact on SE outcome.

However, a more detailed look into our SE cohort revealed that SE semiology might be crucial for further treatment decisions. In particular, patients with a GCSE benefited from sufficient dosing as it was significantly associated with a reduced overall duration of ventilation and both ICU and overall in-hospital stay. However, these results should be interpreted with caution as age and gender as possible confounders deviated significantly in this subgroup analysis. Age is a well-described determinant of SE outcome, as described in our regression analysis and in the literature [25, 32].

However, the short-term outcome in patients with non-GCSE did not benefit from high dosages of BZD treatment. In contrary, sufficiently dosed patients with non-GCSE had less often a favourable outcome than underdosed patients, suggesting that aggressive BZD treatment could be harmful for non-GCSE patients. There is an ongoing controversy how aggressively non-GCSE should be treated, mainly to the lack of evidence, especially as treatment recommendations are either adapted from GCSE [22] or not covered at all [6, 8]. In Cologne,

treatment recommendations for non-GCSE are derived from GCSE. Notably, only 11.2 % of the 116 non-GCSE patients treated with BZDs arrived within 30 minutes in the emergency ambulances, compared to 36.8 % of the GCSE patients. This suggest that non-GCSE may not be easy to identify and treatment might often be delayed, possibly impacting the outcome. However, there was no statistical difference in arrival time between the non-GCSE patients who were treated sufficiently or who were underdosed (**Table 3**). Our data indicates that SE semiology might be crucial for treatment decision and that further treatment evidence especially in non-GCSE is urgently needed.

Several limitations of the current study need to be considered. First, this is a retrospective analysis, with no insights into the duration of SE until cessation nor time-to-treatment which both are possible confounders and could have influenced the outcome of SE [4, 5, 33]. A prospective study design would allow a more detailed assessment of SE treatment. Second, though all neurological emergency departments in Cologne participated in this study, patients treated by other departments or hospitals in Cologne and not directly referred to a neurological emergency department were excluded. This practice could result in a potential underrepresentation of non-GCSE patients. Third, a possible explanation for the missing impact of BZD use and underdosing on SE patient's functional outcome in our cohort is that the compared numbers are too small relative to the effect sizes to be expected, and, therefore, statistically significant effects were masked. Although we cannot provide nationwide epidemiologic data, we consider the study size described to be sufficiently large and representative compared to existing data [32, 34, 35]. In particular, we combined all levels of care of a region, whereas in previous publications, data were derived from specialised epilepsy centres, which might neglect a relevant number of patients [14]. No long-time follow-up of the patients was provided, and therefore the study could miss any long-term functional outcome changes. Fourth, there are several questions regarding the role of levetiracetam and its

effectiveness in SE compared to BZD treatment. A recent study showed a comparable outcome in an RCT pilot study in GCSE patients who received either lorazepam or levetiracetam [36], whereas adjunctive levetiracetam to clonazepam did not show an additional benefit [23]. The role of levetiracetam as an initial treatment of SE seems insufficiently explored to date. Well-designed and adequately powered studies are warranted.

Conclusion

In summary, we report real-life data for guideline adherence in an European urban area. Initial BZD therapy in SE was withheld in about a quarter of all cases. This occurred mainly in older patients, non-GCSE, and if the treatment was initiated at the emergency department. Guideline recommendations for BZD dosages were violated in about three of four SE patients. In GCSE, BZD underdosing resulted in prolonged ventilation duration, ICU stay and overall in-hospital stay. However, our data indicate that aggressive BZD treatment might negatively affect the outcome in non-GCSE. Our findings highlight the urgent need for further treatment evidence especially in non-GCSE.

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Author Contributions

Study concept and design: FK and MPM. Data acquisition and analysis: FK, MM, EFB, LB, and MPM. Drafting the manuscript: FK and MPM. All authors participated in the critical revision of the manuscript and approved the final version.

Potential Conflicts of Interest

FK is supported by the Koeln Fortune Program / Faculty of Medicine, University of Cologne (472/2020). The funding is not related to this project. GRF received royalties from Spinger, Thieme and Hogrefe. He declared speaker honoraria from Bayer, Desitin, Ergo DKV, Forum für medizinische Fortbildung (FomF) GmbH, GSK, Medica Academy Messe Düsseldorf, Medicbrain Healthcare, Novartis, Pfizer, and Sportärztebund NRW. The remaining authors have no conflicts of interest.

Abbreviations:

ASM = anti-seizure medication

BZD = benzodiazepine

CCH = City Hospitals Cologne-Merheim

COVID-19 = Coronavirus Disease 2019

GCSE = generalised convulsive status epilepticus

HGH = Heilig Geist-Hospital Cologne

ICU = intensive care unit

ILAE = International League Against Epilepsy

mRS = modified Rankin scale

PROSECO = Project for Status Epilepticus in Cologne

RCT = randomised controlled trial

SE = status epilepticus

UHC = University Hospital of Cologne

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Tables

Table 1: Characteristics, therapy, and outcome of all patients with status epilepticus (SE) (n=328).

Characteristics	
Female, n (%)	150 (45.7)
Age >65 years, n (%)	171 (52.1)
Median age in years (SD, range)	66.4 (18.8, 18.4-93.5)
Admitted from home, n (%) from nursing home, n (%)	 233 (71.0) 95 (29.0)
Known epilepsy, n (%)	213 (64.9)
Semiology, n (%) GCSE Non-GCSE	 142 (43.3) 186 (56.7)
Aetiology of SE, n (%) Acute Remote/progressive Unknown	 37 (11.3) 264 (80.5) 27 (8.2)
STESS (SD, range)	2.0 (1.5, 0-6)
STESS <2, n (%)	179 (54.6)
Therapy and outcome	
Prehospital initial treatment, n (%)	169 (51.5)
SE duration <0.5h at arrival, n (%)	65 (19.8)
Initial therapy, n (%) BZD, n (%) MDZ LZP CZP DZP ASM, n (%) LEV Valproic acid Lacosamide Anaesthetic, n (%) Propofol Thiopenthal	310 (94.5) 237 (72.3) 123 (37.5) 72 (22.0) 13 (4.0) 29 (8.8) 70 (21.3) 65 (19.8) 1 (0.3) 4 (1.2) 3 (0.9) 2 (0.6) 1 (0.3)
BZD dosages, n (%) Sufficient Underdosed Unknown	237 (72.3) 71 (21.6) 162 (49.4) 4 (1.2)
Refractory SE (>2 drugs)	134 (40.9)
Median number of drugs (SD, range)	2 (1.4, 0-7)
ICU admission, n (%)	247 (75.3)
Mechanical ventilation, n (%)	49 (14.9)
Median duration ventilation in hours (SD, range)	54.6 (210, 0-921)
Median duration ICU stay in days (SD, range)	1.3 (6.6, 0-63.2)
Median duration in-hospital stay in days (SD, range)	4.3 (11.0, 0.1-103.9)
Favourable outcome at discharge, n (%)	225 (68.6)
Death, n (%)	20 (6.1)

Semiology was defined as generalised convulsive SE (GCSE) or non-GCSE. Therapies were sorted by their drug classes: benzodiazepines (BZD), anti-seizure medications (ASM), and anaesthetics. Abbreviations: MDZ = midazolam, LZP = lorazepam, CZP = clonazepam, DZP = diazepam, LEV = levetiracetam, ICU = intensive care unit, STESS = Status Epilepticus Severity Score. Standard deviation (SD) is provided if applicable.

Table 2: Status epilepticus (SE) patients with or without benzodiazepine (BZD) treatment were compared for characteristics and outcomes.

	BZD (n=237) n(%)	**Non-BZD (n=73) n(%)**	**Significance**
Patient characteristics			
Female, n (%)	109 (46.0)	33 (45.2)	1.0†
Age > 65 years, n (%)	114 (48.1)	48 (65.8)	**0.01**
Admitted from home, n (%)	160 (67.5)	58 (79.5)	0.06†
Known epilepsy, n (%)	170 (71.7)	33 (45.2)	**<0.001**†
GCSE, n (%)	119 (50.2)	16 (21.9)	**<0.001**†
Aetiology of SE, n (%) Acute Remote/progressive Unknown	 24 (10.1) 198 (83.5) 15 (6.3)	 13 (17.8) 52 (71.2) 8 (11.0)	0.1†
STESS <2, n (%)	137 (57.8)	34 (46.6)	0.1†
Management and outcome			
Prehospital initial therapy, n (%)	155 (65.4)	14 (19.2)	**<0.001**†
SE onset <0.5 h at arrival, n (%)	56 (23.6)	5 (6.8)	**0.002**†
Refractory SE (>2 drugs)	109 (46.0)	25 (34.2)	0.1†
Mean number of drugs (SD)	2.7 (1.3)	2.2 (1.4)	**0.005**‡
ICU admission, n (%)	182 (76.8)	54 (74.0)	0.6†
Mechanical ventilation, n (%)	39 (16.5)	10 (13.5)	0.6†
Mean duration ventilation in hours (SD)	162.0 (228.3)	61.0 (77.8)	0.2‡
Mean duration ICU stay in days (SD)	3.3 (7.2)	3.0 (5.5)	0.8‡
Mean duration in-hospital stay in days (SD)	6.9 (9.4)	9.4 (15.8)	0.1‡
Favourable outcome at discharge, n (%)	165 (69.6)	45 (61.6)	0.3†
Death, n (%)	14 (5.9)	6 (8.2)	0.6†

Abbreviations: ICU = intensive care unit, GCSE = generalised convulsive SE. Standard deviations (SD) are provided if applicable. †chi-square test or Fisher's exact test. ‡t-test for unpaired variables.

Table 3 a-c: Characteristics, therapy, and outcome of sufficiently versus underdosed benzodiazepine (BZD) treated status epilepticus (SE) patients.

Dosage BZD	**Sufficient**	**Underdosed**	**Significance**
a. All SE (n=233)	**n=71**	**n=162**	
Patient characteristics			
Female, n (%)	22 (31.0)	84 (51.9)	**0.004**
Age > 65 years, n (%)	23 (32.4)	88 (54.3)	**0.003**
Admitted from home, n (%)	49 (69.0)	108 (66.7)	0.8
Known epilepsy, n (%)	55 (77.5)	113 (69.8)	0.3
Aetiology of SE, n (%) Acute Remote/progressive Unknown	 5 (7.0) 59 (83.1) 7 (9.9)	 18 (11.1) 136 (84.0) 8 (4.9)	0.2

STESS ≤2, n (%)	47 (66.2)	88 (54.3)	0.1
Management and outcome			
Prehospital initial therapy, n (%)	49 (69.0)	104 (64.2)	0.6†
SE onset <0.5 h at arrival, n (%)	14 (19.7)	42 (25.9)	0.3
Refractory SE (>2 drugs), n (%)	41 (57.7)	68 (42.0)	**0.03**†
ICU admission, n (%)	59 (83.1)	120 (74.1)	0.2†
Mechanical ventilation, n (%)	14 (19.7)	25 (15.4)	0.5†
Mean duration ventilation in hours (SD)	73.9 (135.2)	211.3 (256.0)	**0.04**‡
Mean duration ICU stay in days (SD)	2.5 (3.8)	3.7 (8.3)	0.1‡
Mean duration in-hospital stay in days (SD)	6.3 (7.1)	7.2 (10.4)	0.5‡
Favourable outcome at discharge, n (%)	46 (64.8)	117 (72.2)	0.3†
Death, n (%)	1 (1.4)	13 (8.0)	0.1
b. **GCSE (n=117)**	**n=40**	**n=77**	
Patient characteristics			
Female, n (%)	10 (25.0)	41 (53.2)	**0.006**
Age > 65 years, n (%)	7 (17.9)	37 (48.1)	**0.001**
Admitted from home, n (%)	26 (65.0)	54 (70.1)	0.7
Known epilepsy, n (%)	29 (72.5)	49 (63.6)	0.4
Aetiology of SE, n (%) Acute Remote/progressive Unknown	 3 (7.5) 33 (82.5) 4 (10.0)	 11 (14.3) 63 (81.8) 3 (3.9)	 0.3
STESS ≤2, n (%)	24 (60.0)	26 (33.8)	**0.01**
Management and outcome			
Prehospital initial therapy, n (%)	36 (90.0)	58 (75.3)	0.1
SE onset <0.5 h at arrival, n (%)	12 (30.0)	31 (40.3)	0.3
Refractory SE (>2 drugs), n (%)	24 (60.0)	28 (36.4)	**0.02**
ICU admission, n (%)	34 (85.0)	62 (80.5)	0.6
Mechanical ventilation, n (%)	8 (20.0)	20 (26.0)	0.5
Mean duration of ventilation in hours (SD)	37.1 (39.8)	208.6 (266.5)	**0.01**
Mean duration of the ICU stay in days (SD)	1.7 (1.6)	5.0 (10.7)	**0.01**
Mean duration in-hospital stay in days (SD)	4.1 (2.7)	8.8 (13.0)	**0.003**
Favourable outcome at discharge, n (%)	30 (75.0)	54 (70.1)	0.7
Death, n (%)	1 (2.5)	3 (3.9)	1
c. **NGCSE (n=116)**	**n=31**	**n=85**	
Patient characteristics			
Female, n (%)	12 (38.7)	43 (50.6)	0.3
Age > 65 years, n (%)	16 (51.6)	51 (60.0)	0.5
Admitted from home, n (%)	23 (74.2)	54 (63.5)	0.4
Known epilepsy, n (%)	26 (83.9)	64 (75.3)	0.5
Aetiology of SE, n (%) Acute Remote/progressive Unknown	 2 (6.5) 26 (83.9) 3 (9.79	 7 (8.2) 73 (85.9) 5 (5.9)	 0.8
STESS ≤2, n (%)	23 (74.2)	62 (72.9)	1
Management and outcome			
Prehospital initial therapy, n (%)	13 (41.9)	46 (54.1)	0.3
SE onset <0.5 h at arrival, n (%)	2 (6.5)	11 (12.9)	0.5
Refractory SE (>2 drugs), n (%)	17 (54.8)	40 (47.1)	0.5
ICU admission, n (%)	25 (80.6)	58 (68.2)	0.2
Mechanical ventilation, n (%)	6 (19.4))	5 (5.9)	**0.04**
Mean duration ventilation in hours (SD)	122.9 (200.6)	222.4 (236.3)	0.5
Mean duration ICU stay in days (SD)	3.5 (5.4)	2.5 (5.0)	0.3
Mean duration in-hospital stay in days (SD)	9.2 (9.7)	5.8 (6.9)	**0.04**
Favourable outcome at discharge, n (%)	16 (51.6)	63 (74.1)	**0.03**
Death, n (%)	0 (0)	10 (11.8)	0.1

Abbreviations: SE: status epilepticus; STESS: status epilepticus severity score; GCSE: generalised status epilepticus; NGCSE: non-generalised status epilepticus; ICU = intensive care unit. Standard deviation (SD) is provided if applicable. †chi-square test or Fisher's exact test. ‡t-test for unpaired variables.

Figure legends

Figure 1: Binomial logistic regression analysis of all status epilepticus (SE) patients.

Eighteen patients received no therapy and were not included in this analysis. For each of the outcome parameters favourable outcome at discharge, mechanical ventilation and refractory SE, 310 patients were assessed. 39 patients were included for the outcome parameter ventilation duration. The odds ratio and 95 % confidence interval on a logarithmic scale is shown. Abbreviations: GCSE = GCSE = generalised convulsive SE, BZD = benzodiazepine.

Figure 2: Binomial logistic regression analysis of all status epilepticus (SE) patients treated with benzodiazepines (BZDs).

The odds ratio and 95 % confidence interval on a logarithmic scale are depicted. For favourable outcomes at discharge, mechanical ventilation and refractory SE 237 patients were included. Further, 39 patients were analysed for the outcome parameter ventilation duration. Abbreviation: GCSE = GCSE = generalised convulsive SE.