Patient Journey with Status Epilepticus: Understanding Treatment Pathways, Outcomes, and Healthcare Burden Using Patient Level Real-World Hospital Data

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Introduction

- **Status epilepticus (SE) is a common life-threatening neurological emergency associated with high morbidity, mortality, and healthcare costs**[1,2]
- Management of SE requires rapid and sustained seizure control to minimize neurologic injury, identification and treatment of underlying etiologies, and the prevention or management of systemic complications[1]
- **Patients who do not respond to parenteral benzodiazepines (BZDs) and 1 intravenous (IV) anti-seizure medication (ASM)** are considered to have **refractory SE (RSE),** requiring additional pharmacotherapies including escalation to **IV anesthesia (IVA)**[3]
- There is **scant evidence** to guide treatment of RSE and **considerable unmet need** for safe and effective therapies[3,4]
- **Limited data** have been published regarding the **patient journey in the SE continuum in the United States in recent years** during the changing healthcare landscape and increased societal guidance on SE classification
- We **conducted a 5-year cross-sectional analysis to examine treatment dynamics in patients treated for SE in the United States**

Methods

- Hospital-based, service-level, all-payer **US data from PINC AI™ Healthcare Database (2018-2022)** and **Komodo Health Healthcare Map (2017-2022)** were analyzed for **hospitalized patients with SE admitted to the emergency department or an inpatient unit**
- Patients were included if encounter billing listed an **ICD-10 code for SE** at the admit, primary, or secondary diagnostic position over the 5-year study period
- Patient encounters were segmented according to parenteral BZD, IV ASM, and IVA exposures within PINC AI data into the following: **SE only, established SE (ESE), refractory SE with or without IVA (RSE-IVA, RSE-no IVA). Super-refractory SE (SRSE)** was included as a subcategory of RSE determined by duration of mechanical ventilation (MV) while on IVA
- Metrics that required complete visibility into the patient encounter (length of stay, discharge codes, setting of admission, treatment sequencing) were estimated using a subset of SE patients (n=92,322) who were not transferred to another center during their care, as the patient could not be tracked across facilities within the PINC AI™ Healthcare Database

Episode Classification Based on Treatment Paradigm

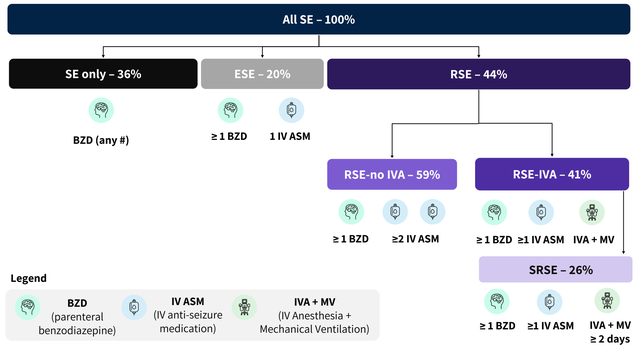

Figure 1: Categorization of SE episodes. This cross-sectional patient journey study examined a total of 140,538 SE episodes in 113,229 unique patients during the 5-year study period using PINC AI data. Episodes were categorized as SE only (n=51,066, 36%), ESE (n=27,685, 20%), and RSE (n=61,801, 44%). In patients with RSE, 59% (36,489) of episodes were not treated with IVA (RSE-no IVA) and 41% (n=25,312) were treated with IVA (RSE-IVA), and 26% (n=6,650) of RSE-IVA episodes progressed to SRSE.

References

1. Betjemann JP, Lowenstein DH. *Lancet Neurol.* 2015;14(6):615-24. **2.** Guterman EL et al. *JAMA Neurol.* 2021;78(5):588-95. **3.** Lu M et al. *Epilepsy Behav.* 2020;112:107459. **4.** Rossetti AO, Lowenstein DH. *Lancet Neurol.* 2011;10(10):922-30.

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Our cross-sectional analysis of admissions revealed that while prior history of epilepsy was a risk factor for SE, new onset SE remained a risk in hospitalized patients with or without acquired brain injury

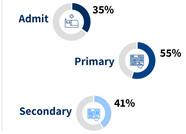
SE occurred in patients with or without a baseline epilepsy disorder and may have presented as a secondary complication to a primary illness

A.

Baseline epilepsy diagnosis was reported in **67%** of episodes, while **33%** showed no previous history of epilepsy

Median patient age was 51 years at SE diagnosis

B. SE diagnostic position



Point of origin for most SE episodes was the home

C. Point of origin all SE (pre-admit)

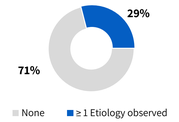
*Includes clinics, ambulatory surgery centers, court/law enforcement, born outside of hospital

Considerable proportion of episodes with RSE progressed beyond initial treatment lines

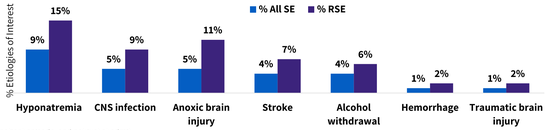
D. Treatment distribution across all RSE episodes**

**Note, these are not mutually exclusive and excludes treatments administered by emergency medical services or at home; complete patient sample (n=92,322 total) was used to determine treatment distribution

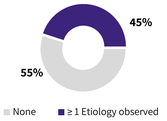
E. Proportion of all SE episodes with an acute etiological factor***



~⅓ of all SE episodes presented with an acute etiological factor of interest; comorbid conditions were more common in patients with RSE



Proportion of RSE episodes with an acute etiological factor***



***Etiology flag was picked up at any point during the patient episode, and not just at admit

Figure 2: Characterization of patients with SE. A. Baseline epilepsy diagnosis was reported in 67% (n=97,631) of episodes (Komodo Healthcare Map – Closed Claims Data), and the median (IQR) age at SE diagnosis was 51 (28,66) years (complete patient sample, n=92,322, PINC AI data). **B.** SE was the admit, primary or secondary diagnosis in 35% (n= 32,666), 55% (n=51,066), and 41% (n=37,772) of episodes, respectively (complete patient sample, n=92,322, PINC AI data). **C.** Prior to admission, SE patients' point of origin was mainly the home (n=76,174, 83%), followed by SNF/ICF (n=2,341, 3%), and other (n=13,316, 14%). Total patient N is from the adjusted complete patient sample (n=92,055, PINC AI - adjusted complete sample for data visibility, missing values, and cleanliness to track patient origin). **D.** Majority of all RSE episodes received 1st/2nd line therapy, with treatment distribution as follows: received ≥1 BZD (n=38,135, 97%), received ≥1 IV ASM (n=39,409, 100%), received ≥2 IV ASMs (n=36,116, 92%), received ≥3 IV ASMs (n=17,675, 45%), received MV+IVA > 2 days (n=11,515, 29%), and received MV+IVA ≥ 2 days (n=4,125, 10%) (from PINC AI data). **E.** Approximately ¾ (n=27,018, 29%) of all SE episodes presented with an underlying etiological factor, while 71% (n=68,553) did not. Amongst the etiological factors, hyponatremia ranked the highest (n=8,087, 9%), followed by both CNS infection (n=4,708, 5%) and anoxic brain injury (n=4,925, 5%), stroke (n=3,770, 4%), alcohol withdrawal (n=3,516, 4%), hemorrhage (n=1,220, 1%) and traumatic brain injury (n=792, 1%). Approximately half (n=17,624, 45%) of RSE episodes presented with an underlying etiological factor, while 55% (n=21,785) did not. Amongst the etiological factors, hyponatremia ranked the highest (n=5,732, 15%), with anoxic brain injury (n=4,150, 11%), CNS infection (n=3,566, 9%), stroke (n=2,876, 7%), alcohol withdrawal (n=2,376, 6%), CNS tumor (n=1,772, 4%), hemorrhage (n=965, 2%), and traumatic brain injury (n=623, 2%) following. All etiologies were from the adjusted patient sample (SE n=92,055, RSE n=39,409) from PINC AI data.

Over a 5-year period, 20% of patients had recurrent SE; 26% of RSE-IVA episodes progressed to SRSE, which was linked to worse outcomes

A. 1 in 5 patients with SE were observed to have **more than 1 episode** across the 5-year study period

B. 1 in 4 RSE-IVA episodes **progressed to SRSE**

Figure 4: Frequency of recurrent SE. A. Recurrent SE was observed in 20% (n=28,801 out of 117,607 patients; from Komodo Healthcare Data – Closed Claims), regardless of episode type. **B.** SRSE was observed in 26% (n= 6,650) of RSE-IVA episodes, which was characterized by prolonged ICU and hospital LOS (median 10 and 15 days, respectively) and increased inpatient mortality (39%). From all-patient sample (n=140,538) – PINC AI data.

Limitations

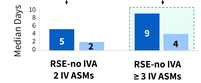
- **SE-related diagnosis and comorbid conditions were reliant on ICD-10 coding** by providers and we were unable to differentiate between SE subtypes or offer definitive assessment of etiologic factors
- Due to limitations in treatment reporting, we were **unable to determine exact timing, dose, and responses to medications used to treat SE**
- **SE refractoriness was determined by exposure to IV ASMs and IVA using previously established methods**, however we were **unable to confirm the clinical context for which medications were started** during SE episodes
- **It is possible that not all treatments** within an SE episode were **captured within PINC AI**, especially if the **patient received initial management in emergency medical services** or was **transferred in from another setting**; therefore, patients who were transferred during their course of care were excluded from medication-related analyses

RSE-IVA episodes were characterized by worse outcomes and longer inpatient/ICU length of stay (LOS); even in the absence of IVA, increased IV-ASM use was associated with increased LOS

RSE episodes that required IVA were characterized by considerably worse outcomes and longer IP/ICU length of stay

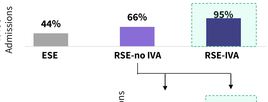
A. Increased hospital and ICU LOS in RSE-IVA episodes

B. Increased hospital and ICU LOS for RSE-no IVA episodes that required multiple IV ASMs

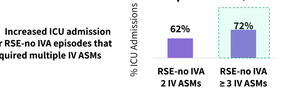


Even in the absence of IVA exposure, increased use of IV ASMs for SE management was associated with worse outcomes and increased healthcare utilization

C. Increased ICU admission in RSE-IVA episodes



D. Increased ICU admission for RSE-no IVA episodes that required multiple IV ASMs



E. Both IVA and increased IV ASM utilization was associated with increased mortality and decreased discharge to home

Discharge Status	ESE	RSE–no IVA	RSE–no IVA 2 IV ASMs	RSE–no IVA ≥3 IV ASMs	RSE–IVA
	% (n)	% (n)	% (n)	% (n)	% (n)
To Home	**72%** (12,333)	**51%** (12,253)	**61%** (7,981)	**40%** (4,272)	**41%** (6,358)
To SNF /ICF	10% (1,690)	19% (4,621)	17% (2,182)	23% (2,439)	15% (2,404)
To LTC / Rehab	3% (433)	6% (1,504)	5% (599)	8% (905)	10% (1,523)
To Hospice	3% (599)	8% (1,797)	5% (697)	10% (1,100)	5% (840)
In-Hospital Mortality	**6%** (989)	**12%** (2,738)	**8%** (988)	**16%** (1,750)	**25%** (3,912)
Other*	7% (1,122)	4% (833)	4% (586)	3% (297)	4% (576)

*Other discharge locations include court/law enforcement, swing bed, nursing facility, left against medical advice, expired in medical facility (for hospice), still a patient - expected to return, or information not available

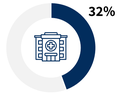
Figure 3: ICU and hospital LOS and mortality outcomes. Statistics reported as n, median (IQR). **A.** RSE-IVA episodes had longer ICU LOS (n=14,830, 5.0 days [3,11]) vs. RSE-no IVA (n=15,887, 3.0 days [2,6]), or ESE (n=7,608, 2.0 days [1,3]). RSE-IVA episodes had longer hospital LOS (n=15,597, 9.0 days [5,18]) vs. RSE-no IVA (n=23,137, 6.0 days [3,12]), and ESE (n=14,439, 3.0 days [2,6]). **B.** In the absence of IVA, RSE episodes treated with ≥ 3 IV ASMs (n=7,821) had longer ICU LOS (4.0 days [2,8]) compared to episodes treated with ≥ 2 IV ASMs (n=8,066, 2.0 days [1,4]), and longer hospital LOS (n=10,657, 9.0 days [5,16] vs. n=12,480, 5.0 days [3,9]). **C.** RSE-IVA episodes had increased ICU admissions (n=14,830, 95%) compared to RSE-no IVA episodes (n=15,887, 67%), and ESE episodes (n=7,608, 44%). **D.** RSE-no IVA episodes treated with ≥ 3 IV ASMs (n=7,821, 73%) had increased ICU admissions compared to RSE-no IVA episodes that were treated with 2 IV ASMs (n=8,066, 62%). **E.** RSE-IVA episodes had the highest mortality rate and similar rate of discharge to home as RSE-IVA episodes treated with ≥3 IV ASMs. Total patient N is from the adjusted complete patient sample from PINC AI (n=92,055, adjusted complete sample for data visibility, missing values, and cleanliness to track patients in their stays and discharge statuses).

Interhospital transfers during SE management were common; patients with RSE that required intense treatment had a higher rate of transfer, suggesting challenges in managing these patients with current care options

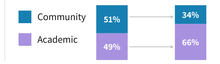
A.

Interhospital transfers were associated with **32% of all SE episodes**

Most transfers occurred after 1st/2nd line treatments

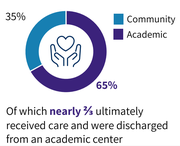


B. A high proportion of community admits were ultimately transferred to an academic facility



C.

41% of patients with RSE were treated at multiple institutions



Of which **nearly ¾** ultimately received care and were discharged from an academic center

D. RSE-IVA episodes had the highest rate of transfer

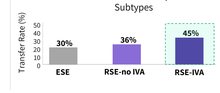


Figure 5: Care setting and transfer characteristics. A. Inter-hospital transfers (n=65,545 out of 203,176 transfers) accounted for 32% of all episodes. Across treatments, transfer rates were as follows: 1 IV ASM (n= 6,981, 50%), 1 BZD + 1 IV ASM (n=3,634, 26%), 2 IV ASMs (n=2,678, 19%), and sedation (MV) (n=1,311, 9%) from a total of n=13,839 transfers (Komodo data) – indicating that nearly all transfers occurred after 1st/2nd line therapy. **B.** Of SE episodes with ≥1 transfer, the first care site of admission was evenly split between academic (n=32,402, 49%) and community (n=33,143, 51%) settings. However, the majority were discharged from an academic facility (n=42,974, 66%) compared to community (n=22,571, 34%). **C.** Approximately 41% (n=2,252) of patients with RSE were treated at multiple institutions during an episode. Approximately 2/3 (n=1,461, 65%) of episodes treated at multiple institutions ultimately received final care and were discharged from an academic medical center compared to community (n=791, 35%). (Subanalysis of 5,475 patients with linked data between Komodo Claims and KHI Chargemaster databases) **D.** RSE-IVA episodes had the highest rate of transfer (n=1,533, 45%), followed by RSE-no IVA episodes (n=719, 36%), and ESE episodes (n=614, 30%). All samples in this figure are from the Komodo Healthcare Map – Closed Claims Data.

Conclusions

- **Patients who progressed to RSE-IVA faced long ICU/hospital stays and poor outcomes, highlighting urgent need for specialized care and rapid treatment solutions**
- **44% of all SE cases advanced to refractory status;** a **high proportion** of RSE cases (41%) **were treated with IVA**. Approximately **26% of RSE-IVA episodes progressed to SRSE**
- **RSE episodes that required IVA** were associated with increased ICU admission rates, **longer ICU and hospital LOS,** and **high mortality**
- Even in the **absence of IVA treatment**, **RSE episodes that were treated with ≥ 3 IV ASMs** had **worse outcomes** and **longer LOS** compared to those treated with 2 IV ASMs
- **Increased treatment intensity (e.g., RSE-IVA) was associated with increased need for interhospital transfers** compared to other segments. A **high proportion of community admits were transferred to academic institutions,** highlighting need for coordinated efforts between both centers to provide optimal care

Patients with SE had complex care pathways that required specialized care and multi-institutional interactions. Increased treatment with IV ASMs and exposure to IVA in SE were associated with increased hospital resource utilization and overall worse outcomes. Rapidly effective anti-SE treatments remain an urgent unmet need in this patient population.