

Variability in Definitions of Vaso-Occlusive Crises (VOCs) in Sickle Cell Disease (SCD): A Targeted Literature Review of Global Real-World Evidence (RWE) Studies

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INTRODUCTION

- SCD is a **rare chronic hereditary blood disorder** characterized by the production of abnormal hemoglobin, causing sickle-shaped red blood cells that obstruct the blood flow.^{1,2} It primarily affects individuals of African, Middle Eastern, Indian, and Mediterranean descent.^{1,3}
- Globally, approximately 300,000 infants are born with SCD each year.¹ In the US, the condition affects around 100,000 individuals.⁴
 - A hallmark complication of SCD is the **occurrence of VOCs**, which are acute pain episodes caused by blocked blood vessels.^{2,3} VOCs are an important cause of ED visits, hospitalizations, and can result in long-term organ damage.^{2,3} VOCs severely impact patients' daily life, education, work, and emotional well-being.³
 - The economic burden of VOCs is substantial.^{5,6} Patients with >3 VOC episodes during 1-year follow-up period had the highest annual SCD-related costs, with a mean of US\$58,950, which is greater than the costs observed for patients with >2 VOC episodes.⁶
- Given the **significant impact of VOCs**, generating robust and reliable RWE is crucial for understanding and managing this complication. However, this is challenged by the lack of standardized definitions and measurement tools for VOCs across different RWE studies. This inconsistency complicates clinical management and hinders meaningful comparisons in research.

OBJECTIVE

- To conduct a **TLR of RWE studies/reviews** published between January 2020 and April 2025, focusing on how VOCs are identified and characterized globally within the RWE setting.
- To identify key gaps and inconsistencies in the current literature and provide insights that can support efforts toward the **standardization of VOC definitions** and metrics in SCD research and clinical practice.

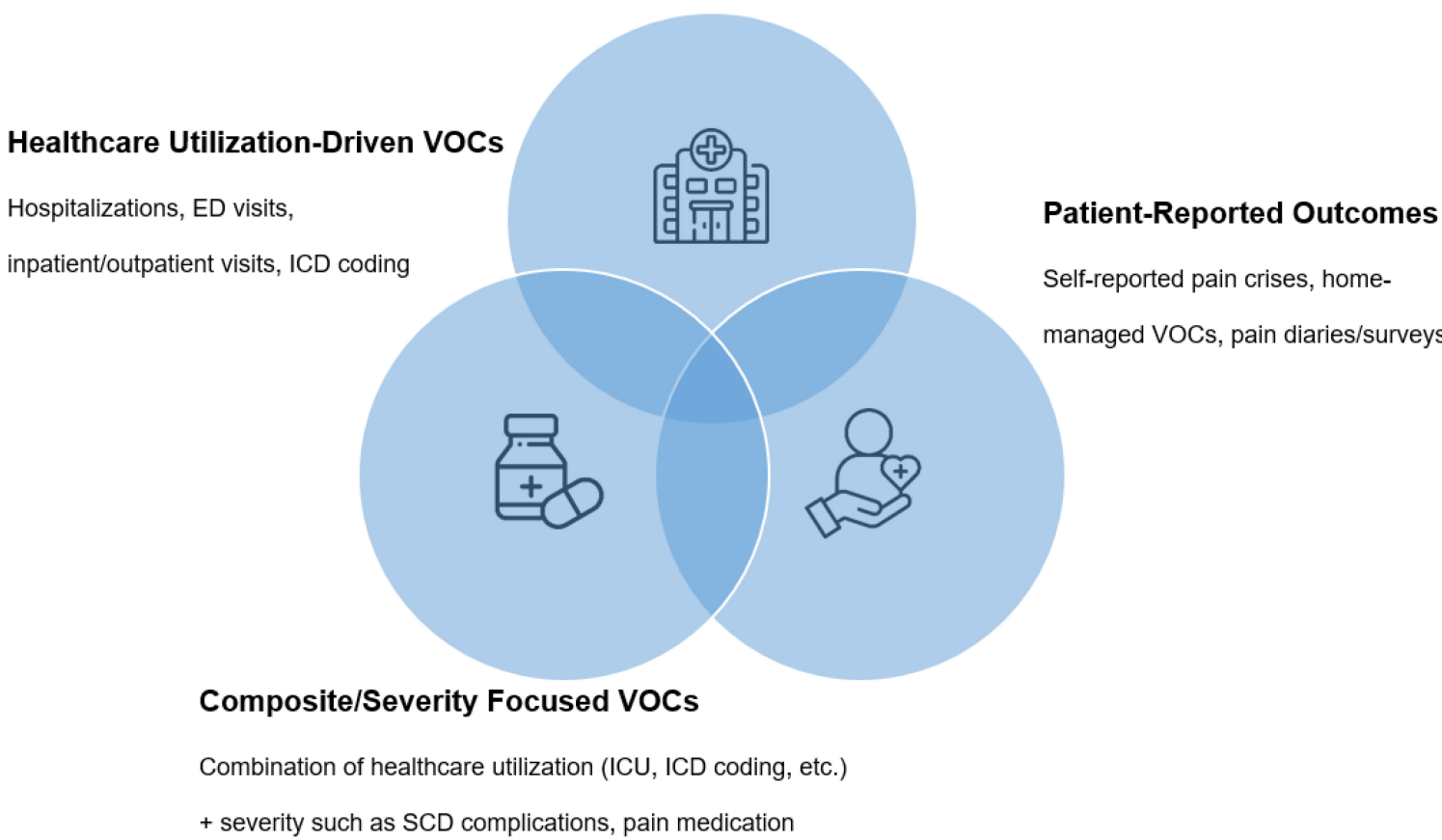
METHODS

- Studies published between January 2020 and April 2025 were identified through PubMed, Embase, and congress abstracts (EHA, ASH).
- Inclusion criteria** focused on RWE studies (observational, retrospective, prospective, cohorts, cross-sectional surveys, etc.) and SLRs describing VOC definitions through:
 - ICD codes** (e.g., ICD-9-CM and ICD-10-CM: D57.0-4)
 - Healthcare utilization metrics** (hospitalizations, ED visits, inpatient/outpatient visits, telehealth consultations, etc.)
 - PROs** (e.g., interviews, surveys).
- Exclusion criteria were clinical trials, published guidelines, and those outside the timeframe or lacking VOC definitions.
- Titles and abstracts were manually reviewed against inclusion criteria. Full-text articles of potentially relevant studies were evaluated for eligibility. Data extraction focused on:
 - VOC definition types (conceptual, operational)
 - Study design
 - Measurement tools (ICD codes, PROs, healthcare utilization)
 - Geographic location (US, Europe, Asia/Africa) and healthcare settings (inpatient, outpatient, ED).

RESULTS

- A total of 86 studies were identified, with 59 meeting the inclusion criteria and 27 excluded because they did not meet the inclusion criteria. Results were stratified into **three dimensions of VOC definitions**:

Figure 1. The Three-Dimensional Stratification Framework for VOC Definitions



Study Design & Data Sources Overview

- The distribution of study designs across all studies included is outlined below. *Table 1* summarizing the data sources:
 - Retrospective (including cohorts): 35 (59.3%) studies
 - Prospective (including cohorts): 5 (8.5%) studies
 - Cross-sectional: 4 (6.8%) studies
 - Literature reviews / SLRs: 9 (15.3%) studies
 - Other / unique methods (surveys, interviews, case studies, MAP studies, descriptive analyses, consensus): 6 (10.2%) studies

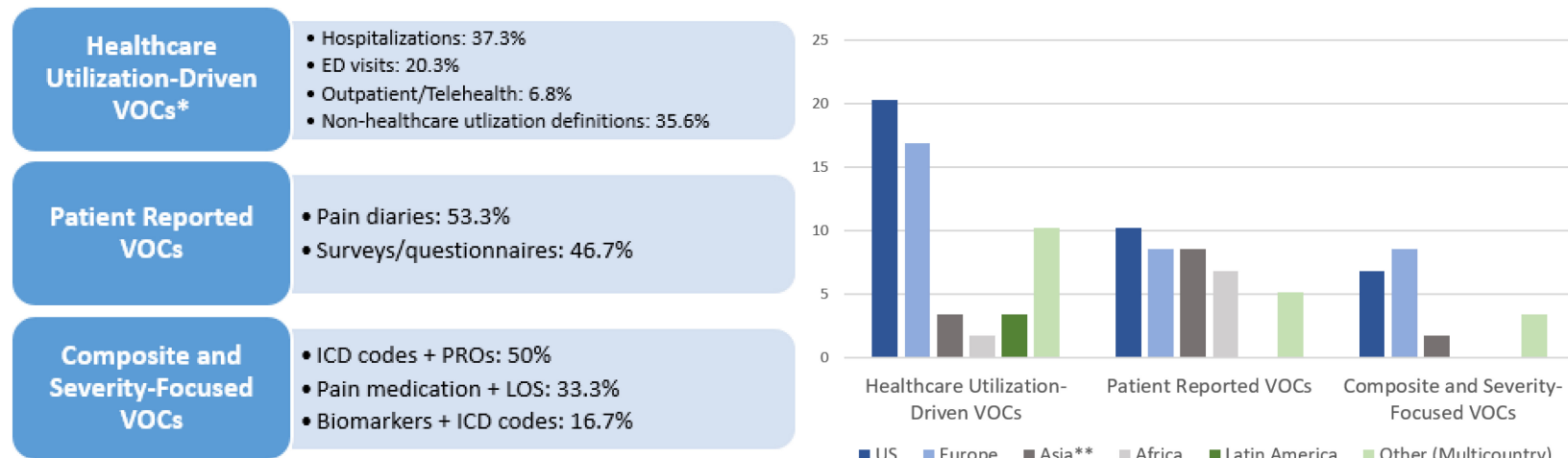
Table 1. Data Source Distribution for All Studies Included (N=59)

| Data Source Type | Definitions/Examples | Distribution, N (%) |
|-----------------------------------|---|---------------------|
| Administrative Databases | Claims/billing data, national health data systems, insurance records (e.g., SNDS, Medicaid, CPRD + HES) | 19 (32.2) |
| EHRs/Hospital or Clinical Records | Electronic/paper hospital records, chart reviews, clinical notes, hospital-based data | 9 (15.3) |
| Patient Surveys/PROs | Patient- or caregiver-completed surveys, pain diaries, self-reported outcomes | 10 (16.9) |
| Registries | SCD-specific or national disease registries (e.g. Saudi MOH SCD registry, CSSCD) | 6 (10.2) |
| Mixed/Other Sources | Studies using more than one of the above (e.g. EHR + survey; registry + claims, or literature reviews/SLRs) | 15 (25.4) |

Three Dimensions of VOC Definitions

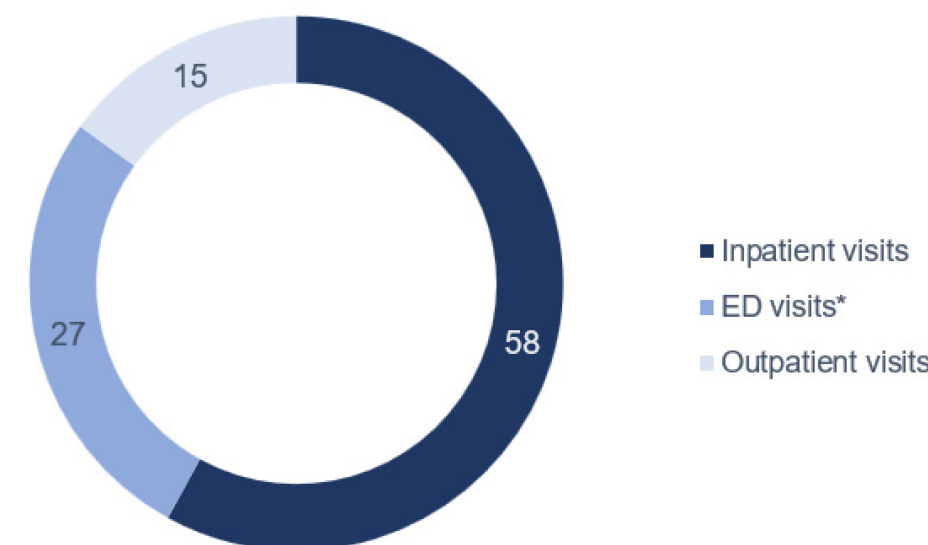
- To address inconsistencies in the literature and better capture the full spectrum of VOC experiences, definitions of all 59 studies were categorized into three key dimensions:
 - Healthcare utilization-driven VOCs:** 38 (64.4%) studies
 - Patient-reported VOCs:** 15 (25.4%) studies
 - Composite and severity-focused VOCs:** 6 (10.3%) studies
- There was high variability with many studies using healthcare utilization-driven approaches and notable global variations in the application of these dimensions (*Figure 2*).
 - In studies from US and European countries, the use of hospitalization metrics and ICD codes to define VOCs was common, reflecting the accessibility of real-world data sources such as insurance claims and EHRs that prioritize healthcare utilization metrics.

Figure 2. Components of the Three Dimensions of VOC Definitions (Top), and Percentage Distribution by Continent of VOC Definition Dimensions (Bottom), Across All Studies Included (N=59)



*The percentages reflect the proportion of studies including each non-mutually exclusive component, so they do not add up to 100%.
**The 'Asia' category represents studies conducted in India and Saudi Arabia, as the burden of SCD is minimal or absent in most other Asian countries.

Figure 3. Percentage Distribution of VOC Definition Dimensions Across All Healthcare Utilization-Related Studies (N=38 studies)



Hospitalization metrics, represented by inpatient visits, were the primary basis for VOC definitions [22 (58%) studies], with ED visits also common [10 (27%) studies], but outpatient/telehealth less so [6 (15%) studies] (*Figure 3*).

*Of the 27% studies with ED visits, there was an overlap of 89% of these studies having inpatient visit as part of the VOC definition.

Conceptual and Operational Definitions

- Operational VOCs:** 47 (79.7%) studies used measurable criteria (e.g., hospitalization, ICD codes, ED visits, pain scales, etc.).
- Conceptual VOCs:** 12 (20.3%) studies focused on a deeper understanding of the biological mechanism underlying VOC pathophysiology [e.g., "ischemic tissue injury from sickled erythrocytes", "periods of excruciating pain"].

RESULTS (cont.)

Pain Medication

- Opioids (e.g., morphine, hydromorphone, and fentanyl) were the primary pain management strategy for VOCs, reported in 78% of included studies that could function as criteria for defining VOCs
- Non-opioid analgesics (e.g., NSAIDs) were used as adjuncts to opioids in 30% of studies, particularly for mild to moderate VOCs.

CONCLUSION

- Significant heterogeneity exists in VOC definitions across RWE studies, hindering comparability and **highlighting the need for a standardized, multi-dimensional framework that integrates healthcare utilization, PROs, and biomarkers**.
 - In US and Europe, the availability of claims and EHR data drives reliance on healthcare utilization metrics, which may overlook home-managed VOCs—especially in low-resource settings, where access to care is limited.
 - This geographic disparity, along with the underrepresentation of PROs and composite definitions, highlights critical gaps in VOC measurement. Furthermore, most studies included only operational definitions, falling short of regulatory and HTA RWE guidelines to incorporate both conceptual and operational components.
- Addressing these gaps is essential to accurately assess disease burden, treatment outcomes, and to guide future validation studies.
 - Before developing and standardizing VOC algorithms (RWE phenotypes), the next step should be to achieve expert consensus on conceptual and operational definitions of VOCs-using a modified Delphi panel or similar consensus approach to ensure best practices and facilitate subsequent validation and implementation across real-world data platforms.

Abbreviations: ACS, Acute chest syndrome; ED, Emergency department; EHR, Electronic health record; ICD, International Code of Diseases; LOS, Length of stay; PRO, Patient-reported outcome; RWE, Real-World Evidence; SCD, Sickle cell disease; SLR, Systematic literature review; TLR, Targeted literature review; VOC, Vaso-occlusive crisis

References: 1. Elendu, C. *Medicine (Baltimore)*. 2023. 102(38): p. e35237; 2. Udeze, C. *Clinical Therapeutics*. 2025. 47(1): p. 29-36; 3. Khurana, K. *Cureus*. 2024. 16(3): p. e56389; 4. Kavanagh, P.L. *JAMA*. 2022. 328(1): p. 57-68; 5. Udeze, C. *Adv Ther*. 2023. 40(8): p. 3543-3558; 6. Shah, N. *J Health Econ Outcomes Res*. 2020. 7(1): p. 52-60.

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