

## The 66th ASH Annual Meeting Abstracts

### POSTER ABSTRACTS

#### 114. SICKLE CELL DISEASE, SICKLE CELL TRAIT, AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: CLINICAL AND EPIDEMIOLOGICAL

##### Data Driven Research through the European RADeep Registry and the Use of Artificial Intelligence Towards Personalized Medicine in Sickle Cell Disease

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### Background:

Sickle cell disease (SCD) is a life-threatening genetic inherited disease considered rare in the European Union (EU). Its complex mechanisms lead to highly variable clinical expression, encompassing in a majority of patients severe acute events and progressive organ damage with premature death. The lack of large datasets combining standardized clinical and research data in real settings hampers the identification of reliable biomarkers and endpoints to monitor disease progression, assess safety and efficacy of new therapies and regulatory decision making.

The RADeep, Rare Anemia Disorders European Epidemiological Platform, aims to collect large amount of highly standardized clinical data to enable data driven outcome research through the linkage of real-world data (RWD) repositories across EU.

Artificial Intelligence (AI) based models for SCD progression, severity classification, response to treatments and generation of synthetic data are being developed through Genomics and Personalized Medicine for all (GenoMed4All) and Synthetic Generation of Haematological Data Over Federated Computing Frameworks (SYNTHEMA) EU-funded projects.

### Methodology:

The first large EU SCD dataset includes clinical (n=100), laboratory (n=65) and research data i.e. GWAS, tNGS, metabolomics and rheology from 5 repositories (France (2), Italy, Spain and The Netherlands); all data has been generated through standardized methodologies. To ensure relevance, coherence, timeliness, completeness, coverage and reliability of the minimal dataset for the development of the AI models, a data management and quality analysis plan were applied at data source and centrally. Descriptive analysis of a) hemolysis related parameters b) hydroxyurea uptake and c) number of vaso-occlusive events (VOE) have been performed dis-aggregated by age ranges 0-11yo and  $\geq 12$ yo, beta and alpha globin genotypes and sex.

### Results:

Standardized data on 1,150 SCD patients has been gathered through RADeep. The cohort is representative of all age groups: 0-11yo=29.5%, 12-17yo=17.8%, 18-54yo=45.6% and  $\geq 55$ yo =7.1%. Sex at birth distribution is balanced (F=53.4%) except for  $\geq 55$ yo (F=73.2%). SCD subdiagnosis resulted on 864 SS (75%), 151 SC (13%), 113 Sbeta (9.8%), 17 SOtherHb (1.5%) and 5 S-HPFH (0.4%). Beta and alpha globin genotypes are collected in 97% and 87% of the patients respectively (missing data is being generated). Discrepancies between SCD subdiagnosis and beta globin genotype reported data, initially found in 6.1% of the records, were solved after data source verification. Proportions of one alpha and two alpha deletions were 21 and 3.5%, respectively.

Dis-aggregated descriptive analysis showed higher hydroxyurea uptake rates and Hb concentration levels across all genotypes and age groups than previously reported. Age group 0-11yo: SS=HU89.4%, Hb9.0g/dL; SC=HU20%, Hb11g/dL; Sbeta0=HU84.6%, Hb10g/dL and Sbeta+=HU11.1%, Hb10.4g/dL. Age group  $\geq 12$ yo: SS=HU80.5%, Hb9.0g/dL; SC=HU22.6%, Hb11.5g/dL; Sbeta0=HU78.9%, Hb9.9g/dL and Sbeta+=HU35.7%, Hb11.3g/dL.

The proportion of patients aged 0-11yo with at least 1 VOE in the last 2 years was SS =25%, SC=20%, Sbeta0=15.4% and Sbeta+=0%. For patients  $\geq 12$ yo SS =46%, SC=33%, Sbeta0=28.9% and Sbeta+=21.4%. Interestingly SC genotype in  $< 12$ yo showed similar frequencies as SS while in  $\geq 12$ yo was markedly lower.

SS male patients  $\geq 12$ yo presented with higher values of total Hb if  $\alpha\text{-}/\alpha\text{-}$  or  $\alpha\alpha/\alpha\text{-}$  was associated whereas this difference was not evident in the female group.

### Conclusions

Standardization and quality assurance of RWD from multiple cross border data sources is a crucial step to advance data driven clinical research and improved care pathways in SCD; RADeep EpiData reported 26,892 patients with SCD in regular follow-up from 324 clinical sites in 12 EU countries.

The RADeep SCD dataset will enable to validate hypothesis on clinical outcome research and open the door for personalized medicine in SCD through the development of AI models for recurrent VOs, acute chest syndrome and cerebral silent infarct. Resulting models can be validated in clinical settings at data providers contributing to the RADeep, currently 87 medical centres in 8 EU countries, that have collected standardized clinical data for 3,000 SCD patients in 2024. RADeep is currently working to get datasets qualified by EMA for regulatory purposes and to integrate patient self-reported outcomes in SCD.

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