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# Epidemiology and clinical impact of Sickle Cell Disease in India: Genetic diversity, regional inequities, and contemporary management approaches - A review

VENKATASWAMY MALLEPOGU[1], NAGALAKSHMAMMA VADABINGI[2], BALAJI MERIGA[3]
[1,3]*Department of Biochemistry, Sri Venkateswara University, Tirupati, Andhra Pradesh, India*
[2]*Centre of Excellence for Herbal and Synthetic drug development, RUSA-II, Sri Venkateswara University, Tirupati, Andhra Pradesh, India*

***Abstract-*** ***Sickle cell disease (SCD) is a hereditary hemoglobinopathy caused by a β-globin gene mutation leading to hemoglobin S polymerization, chronic hemolytic anemia, vaso-occlusion, and progressive multi-organ damage. India represents one of the largest global contributors to SCD burden, with pronounced geographic, ethnic, and socioeconomic heterogeneity, particularly affecting tribal and marginalized populations. This review aims to synthesize contemporary evidence on the epidemiology, genetic modifiers, clinical spectrum, and public health response to SCD in India, highlighting key disparities, challenges, and opportunities for disease control. A structured narrative review was conducted using peer-reviewed literature retrieved from PubMed, Science Direct, and allied databases, supplemented by government reports and national program documents. Studies published between 2000 and 2025 reporting epidemiologic, genetic, clinical, or therapeutic data on Indian SCD populations were included. Evidence was thematically synthesized, with findings summarized across geographic distribution, genetic modifiers, and clinical outcomes. India has over 215,000 confirmed SCD cases, with the highest burden concentrated in central, western, and eastern states, particularly among Scheduled Tribes and vulnerable communities. SCD in India is predominantly associated with the Arab–Indian haplotype, often linked to higher fetal hemoglobin levels, yet substantial phenotypic heterogeneity exists due to co-inheritance of α- and β-thalassemia, G6PD deficiency, nutritional factors, and environmental influences. Patients experience a wide spectrum of acute and chronic complications, including vaso-occlusive crises, infections, acute chest syndrome, and progressive organ damage. Expanded screening programs and hydroxyurea therapy have improved detection and outcomes, though gaps in access and continuity of care persist. SCD in India remains a major public health challenge characterized by marked regional and genetic diversity. Strengthening universal screening, integrating genotype-informed care, and reinforcing primary healthcare and national initiatives are essential to reduce morbidity and mortality and achieve sustainable disease control.***

***Keywords: Sickle Cell Disease, India, Epidemiology, Genetics, Tribal Health, Hydroxyurea Therapy***

***Abbreviations: SCD-Sickle Cell Disease; SCT-Sickle Cell Trait; HbS-Hemoglobin S; HbF-Fetal Hemoglobin; HPLC-High-Performance Liquid Chromatography; VOC-Vaso-occlusive Crisis; G6PD-Glucose-6-Phosphate Dehydrogenase; NSCAEM-National Sickle Cell Anaemia Elimination Mission; ST-Scheduled Tribe; PVTG-Particularly Vulnerable Tribal Group; ICMR-Indian Council of Medical Research; NHM-National Health Mission; BMT-Bone Marrow Transplant***

## I. INTRODUCTION

Sickle cell disease (SCD) is an inherited hemoglobin disorder caused by a single point mutation in the β-globin gene (β6 Glu→Val), which results in the production of abnormal sickle hemoglobin (HbS). Under hypoxic conditions, HbS undergoes polymerization, leading to erythrocyte deformation and reduced cellular flexibility (Piel et al., 2017). These pathophysiological changes give rise to chronic hemolytic anemia, recurrent vaso-occlusive episodes, and progressive multi-organ damage, collectively contributing to substantial morbidity and premature mortality worldwide. Globally, approximately 300,000 infants are born each year with severe forms of SCD, with the majority of cases occurring in low- and middle-income countries. Beyond sub-Saharan Africa, India represents one of the largest contributors to the global SCD burden, reflecting both its large population size and the high

prevalence of hemoglobinopathies within specific ethnic groups (Kato et al., 2018; Piel et al., 2021; Babu et al., 2023). India's complex demographic landscape, characterized by marked ethnic, linguistic, and geographic diversity, underlies pronounced regional and community-level variation in SCD prevalence (Colah et al., 2020; Hockham et al., 2021). High carrier frequencies and disease prevalence are predominantly observed among indigenous tribal and socially marginalized populations residing in central, western, and eastern regions of the country, whereas considerably lower rates are reported in other areas (Colah et al., 2020; Jain et al., 2024). Recent population-based studies and large-scale national screening programs have further demonstrated uneven disease distribution across gender, caste, and geographic boundaries, emphasizing the need for region-specific prevention and management strategies (Piel et al., 2021; Ministry of Health and Family Welfare, 2023). Historically, the elevated genetic burden of SCD among tribal populations, particularly in central and western India, has been attributed to selective evolutionary pressure related to malaria endemicity (Colah et al., 2015). The disease was first documented in India during the 1950s among tribal communities in the Nilgiri Hills and among tea garden workers in Assam, highlighting its long-standing association with socioeconomically disadvantaged populations.

National burden and geographic distribution

Recent government-led surveillance and screening programs indicate that India has more than 215,000 confirmed cases of sickle cell disease (SCD), underscoring its status as a major public health concern outside sub-Saharan Africa. Odisha accounts for the highest documented burden, with approximately 96,080 registered patients, followed by Madhya Pradesh (~30,580), Gujarat (~28,150), Chhattisgarh (~26,104), and Maharashtra (~23,218) (Ministry of Health and Family Welfare, 2023; Colah et al., 2020). Additional states, including Rajasthan, Andhra Pradesh, and Jharkhand, also report substantial numbers of affected individuals, whereas several northern and northeastern states demonstrate comparatively lower prevalence, reflecting pronounced regional heterogeneity (Serjeant et al., 2016; Hockham et al., 2021; Jain et al., 2024).

Tribal and community disparities

The burden of SCD in India is disproportionately concentrated among Scheduled Tribes (STs) and Particularly Vulnerable Tribal Groups (PVTGs), where sickle cell trait frequencies range from 10% to 40% depending on the community and geographic location (Italia et al., 2009; Deshpande et al., 2015; Colah et al., 2020). Central Indian tribal populations, particularly the Gonds and Bhils, exhibit high HbS carrier rates ranging from 10% to 33%, while significant prevalence has also been documented among eastern and western tribes such as the Madias, Pawaras, and Pardhans (Hockham et al., 2021; Jain et al., 2024). School and community-based screening initiatives conducted in regions of Madhya Pradesh and Nagpur have identified carrier frequencies of approximately 5.75%, along with clinically affected individuals, highlighting the widespread rural distribution of the disease across socioeconomic strata (Italia et al., 2021). Marked ethno-geographic variation is further illustrated in southern Rajasthan, where the Garasia tribe demonstrates a substantially higher prevalence of SCD (~15.52%) compared with the Bhil tribe (~9.68%) (Jain et al., 2024). Collectively, these findings emphasize the necessity for targeted, culturally sensitive screening, counseling, and management strategies tailored to high-risk tribal communities.

Genetic modifiers and disease phenotype

Sickle cell disease (SCD) in India is predominantly associated with the Arab–Indian HbS haplotype, which has historically been linked to elevated fetal hemoglobin (HbF) levels and a relatively less severe clinical course compared with African haplotypes (Colah et al., 2014; Shivwanshi et al., 2019; Balgir, 2020). Nevertheless, accumulating evidence demonstrates wide phenotypic heterogeneity influenced by the co-inheritance of additional hemoglobinopathies and modifying genetic factors, as well as environmental and socioeconomic determinants (Colah et al., 2020; Piel et al., 2023). Co-inheritance of α-thalassemia alters red cell indices and hemolytic severity, while compound heterozygosity with β-thalassemia or HbD Punjab

significantly modifies hematologic parameters, transfusion requirements, and overall disease expression (Italia et al., 2019; Jain et al., 2024). Furthermore, interactions with enzymatic disorders such as glucose-6-phosphate dehydrogenase (G6PD) deficiency may exacerbate anemia and increase susceptibility to hemolysis, complicating clinical management (Balgir and Dash, 2020; Colah et al., 2020). The presence of these overlapping genetic abnormalities limits accurate prognostication and underscores the need for individualized, genotype-informed care models.

Gender-wise trends and sociodemographic factors

Although SCD is inherited in an autosomal recessive manner and is theoretically gender neutral, emerging Indian studies suggest potential sex-based differences in hematologic indices, frequency of vaso-occlusive episodes, and patterns of healthcare utilization (Panda et al., 2021; Italia et al., 2021). Variations in baseline hemoglobin levels, pain perception, and access to medical care between men and women have been reported; however, comprehensive gender-stratified analyses remain scarce, highlighting a critical gap in Indian SCD research.

Clinical Spectrum and health challenges

The clinical spectrum of SCD in India encompasses chronic hemolytic anemia, recurrent painful vaso-occlusive crises, febrile illnesses, acute chest syndrome, neurologic complications particularly stroke splenic dysfunction, and progressive end-organ damage (Colah et al., 2014; Kato et al., 2023). Infants and children frequently experience recurrent hospitalizations, transfusion dependence, and increased vulnerability to infections. Long-term complications such as avascular necrosis, pulmonary hypertension, and chronic kidney disease substantially impair quality of life and impose significant healthcare and socioeconomic burdens (Piel et al., 2021; Jain et al., 2025). India's clinical response includes preventive and therapeutic interventions such as newborn screening, prophylactic antibiotics, standardized pain management, hydroxyurea therapy, and, in selected cases, hematopoietic stem cell transplantation. Hydroxyurea has consistently demonstrated efficacy in increasing HbF levels, reducing vaso-occlusive events, and decreasing transfusion needs across multiple Indian cohorts (Italia et al., 2009; Budhbaware et al., 2026).

Public health initiatives

To address the substantial national burden of SCD, the Government of India launched the National Sickle Cell Anaemia Elimination Mission, 2025 (NSCAEM, 2025), with the objective of eliminating SCD as a public health problem by 2047 through large-scale screening, genetic counseling, and strengthening of healthcare infrastructure (Ministry of Health and Family Welfare, 2023). The mission emphasizes early diagnosis, community engagement, nutritional support, and research translation, particularly in high-burden tribal and rural regions, representing a major step toward equitable and sustainable SCD control in India.

## II. METHODOLOGY

This review adopted a structured narrative synthesis to collate and critically examine published evidence on sickle cell disease (SCD) in India. Peer-reviewed literature was systematically retrieved from PubMed, Science Direct, and allied biomedical databases. To capture evolving epidemiological trends and implementation perspectives, additional sources included regional health surveys, government reports, and documentation from national public health programs (Weatherall, 2010; Ministry of Health and Family Welfare, 2023). Studies published between 2000 and 2025 were eligible for inclusion. The review considered original research articles, population-based prevalence studies, observational and cohort studies, interventional trials, and systematic or narrative reviews that reported epidemiologic, genetic, clinical, or therapeutic data specific to Indian SCD populations, without restriction on age or sex. Articles were excluded if they were non-English, outside the defined time period, or lacked disaggregated data relevant to India (Weatherall and Clegg, 2001; Colah et al., 2014).

Data extraction focused on sickle cell trait and disease prevalence, demographic and community characteristics, gender-stratified outcomes where reported, genetic modifiers, clinical manifestations,

therapeutic approaches, and intervention outcomes. Diagnostic and screening methodologies commonly reported across studies included high-performance liquid chromatography (HPLC), solubility or sickling tests, and confirmatory hemoglobin electrophoresis or molecular analyses in selected cohorts (Mukherjee et al., 2010; Colah et al., 2020). Information on regional screening programs and national initiatives was synthesized from both peer-reviewed literature and official government publications. Extracted evidence was analyzed thematically. Epidemiological patterns and genotype distributions were summarized in tabular form, while clinical features and management outcomes were narratively synthesized. Three core tables were developed to illustrate geographic and community-specific prevalence, genetic modifiers with clinical implications, and major SCD-related complications in Indian settings. This methodological approach aimed to ensure comprehensive coverage while maintaining analytical clarity, and to identify critical gaps in epidemiology, service delivery, and future research priorities.

## III. RESULTS

### Epidemiology and prevalence of sickle cell disease in India

Sickle cell disease (SCD) is one of the most prevalent inherited hemoglobinopathies in India and represents a major public health concern due to its extensive geographic reach and pronounced socio-demographic variability. Unlike many monogenic disorders with relatively uniform population distribution, SCD in India demonstrates marked heterogeneity driven by ethnicity, geography, ecology, and social structure. The disease burden is disproportionately concentrated among tribal and socioeconomically marginalized populations, particularly those residing in central, western, and selected southern regions of the country. This distribution reflects long-standing demographic and cultural practices, including endogamy, consanguinity, and genetic isolation, which have facilitated the persistence and amplification of the sickle hemoglobin (HbS) allele over generations (Colah et al., 2015; Gupta etal., 2024; Obeagu and John 2025). Recent national registry data and programmatic estimates indicate that by 2025, more than 215,000 individuals had been formally diagnosed with SCD in India. However, these figures likely represent a conservative estimate, as systematic screening remains incomplete and access to diagnostic services is uneven across states. Odisha accounts for the highest proportion of documented cases, with approximately 96,000 individuals identified through large-scale screening initiatives. Madhya Pradesh and Gujarat follow, reporting over 30,000 and 28,000 confirmed cases, respectively. These state-wise differences highlight both true epidemiological variation and disparities in screening coverage and health system capacity. Community-based screening surveys across high-burden regions have reported SCT prevalence ranging from 5% to over 30% in certain tribal groups, emphasizing the magnitude of the carrier pool and the sustained transmission of the HbS allele (Piel et al., 2017). Despite the expansion of state and national screening programs, underdiagnosis remains substantial, particularly in geographically remote and underserved regions where confirmatory testing, specialized care, and follow-up services are limited. Consequently, many affected individuals are diagnosed only after the onset of severe clinical manifestations, contributing to preventable morbidity and mortality.

### Regional distribution and geographic heterogeneity

The synthesis of data presented in Table 1 reveals striking geographic heterogeneity in the distribution of sickle cell trait and disease across India. Central and eastern regions bear a disproportionate share of the national burden, particularly in areas with high concentrations of tribal populations. States including Odisha, Chhattisgarh, Madhya Pradesh, Gujarat, Maharashtra, Rajasthan, Jharkhand, and parts of Andhra Pradesh and Telangana consistently report elevated HbS carrier frequencies, ranging from moderate to exceptionally high levels (Rao et al., 2009; Colah et al., 2015; Singh et al., 2018; Balgir et al., 2020). Odisha emerges as the state with the highest documented SCD burden nationally, reflecting both genuinely high prevalence and the impact of extensive population-based screening programs that encompass tribal and non-tribal communities. Central Indian states, particularly Madhya Pradesh and Chhattisgarh, report some of the highest SCT frequencies in the country, with carrier

rates approaching one-third of screened individuals in certain tribal subgroups. This elevated prevalence corresponds with ecological and evolutionary factors, including historical malaria endemicity, which is believed to have exerted selective pressure favoring HbS heterozygosity.

The consistent detection of homozygous HbSS cases in these regions underscores the ongoing transmission of the sickle gene and highlights the urgent need for early-life screening, genetic counseling, and structured long-term care. Western India, notably Gujarat and Maharashtra, demonstrates substantial yet variable SCT prevalence. These states have benefited from long-standing community-based, school-based, and antenatal screening initiatives, which have facilitated early identification of carriers and affected individuals. The effectiveness of these decentralized screening models underscores their potential scalability to other high-burden regions. Southern Rajasthan exhibits marked intra-tribal variation in SCT and SCD prevalence, illustrating the influence of micro-population structure, marriage practices, and localized genetic drift. In contrast, Jharkhand and the tribal belts of Andhra Pradesh and Telangana report moderate SCT prevalence and lower HbSS frequencies. However, these estimates may partially reflect under-ascertainment due to limited registry coverage and uneven access to diagnostic services. Urban migrant populations show comparatively lower prevalence of SCT and SCD, yet increasing detection in metropolitan settings suggests that internal migration is reshaping the epidemiological landscape of SCD in urban India. Northern and north-eastern regions report very low prevalence; however, the lack of systematic screening in these areas raises concerns regarding potential underestimation. Overall, these findings confirm that SCD in India is geographically clustered and socio-ethnically patterned, necessitating region-specific public health strategies and culturally adapted interventions.

Genetic background of SCD in Indian populations

The molecular epidemiology of SCD in India is distinct from that observed in African, European, and Middle Eastern populations. The majority of Indian patients harbor the Arab–Indian haplotype of the β-globin gene cluster, which exerts a significant influence on disease expression. This haplotype is frequently associated with elevated fetal hemoglobin levels, a factor known to inhibit hemoglobin S polymerization and reduce red cell sickling under hypoxic conditions (Mukherjee et al., 2010; Italia et al., 2019). Elevated HbF levels represent a key protective modifier in many Indian SCD cohorts and are often associated with delayed onset of severe complications, reduced vaso-occlusive crisis frequency, and milder hemolysis. Nevertheless, clinical expression remains highly variable, indicating the influence of additional genetic modifiers. Co-inheritance of α-thalassemia is particularly prevalent among Indian tribal populations and represents one of the most significant contributors to phenotypic heterogeneity. While α-thalassemia reduces hemolysis by lowering intracellular hemoglobin concentration, it may increase blood viscosity, leading to complex and sometimes paradoxical effects on vaso-occlusive risk (Colah et al., 2014). Interactions with β-thalassemia mutations further diversify clinical outcomes. Compound heterozygous states, including sickle $\beta^0$- and $\beta^+$-thalassemia, are associated with more severe anemia, increased transfusion dependence, and greater clinical complexity. Additional hemoglobin variants, such as HbD Punjab, contribute to regional variation in disease severity, particularly in north-western India. Polymorphisms in HbF-regulating loci including BCL11A, the HBS1L–MYB intergenic region, and the XmnI γ-globin promoter variant play a central role in modulating HbF expression and further contribute to inter-individual variability (Thein, 2013; Makani et al., 2020).

Genetic and environmental modifiers of disease severity

The analysis of genetic modifiers summarized in Table 2 highlights the multifactorial determinants of disease severity in Indian SCD populations. Beyond globin gene interactions, several non-globin modifiers significantly influence clinical outcomes. Glucose-6-phosphate dehydrogenase (G6PD) deficiency frequently coexists with SCD in tribal populations, particularly in central India. This enzymatic defect increases susceptibility to oxidative stress–induced hemolysis, exacerbates anemia during

infections, and complicates newborn screening and therapeutic decision-making (Fasola et al., 2019). Nutritional factors represent an additional and often under-recognized modifier of disease severity. Iron deficiency is highly prevalent among Indian women and children and frequently coexists with SCD, compounding baseline anemia and increasing morbidity. Environmental pressures, particularly historical malaria exposure, continue to shape HbS allele frequencies and contribute to observed geographic clustering. Emerging evidence implicates epigenetic regulation and red cell dehydration pathways in the pathogenesis of vaso-occlusion and chronic organ damage. Collectively, these findings underscore the high genetic heterogeneity of SCD in India and the limitations of genotype-based prognostication alone, supporting the integration of molecular profiling into routine clinical care.

Gender, age, and demographic characteristics

Systematic gender-disaggregated data on SCD in India remain limited. Available hospital-based and regional cohort studies suggest subtle sex-based differences in hematologic indices, pain perception, and health-seeking behavior, although these findings lack confirmation from large population-based analyses (Patel et al., 2012). Social determinants, including delayed access to care among women and girls, further influence observed outcomes. Age-stratified analyses consistently demonstrate early onset of clinical manifestations. Severe anemia, splenomegaly, and infection-related morbidity frequently present during infancy and early childhood, underscoring the importance of newborn screening and early linkage to care (Patel and Serjeant 2014; Jain et al., 2024). Adolescents and young adults often experience cumulative organ damage, chronic pain syndromes, and psychosocial challenges that impair educational attainment and workforce participation. Nutritional deficiencies, including iron, folate, and vitamin B12 insufficiency, intersect with SCD-related anemia in many Indian settings, with women of reproductive age being particularly vulnerable (Obeagu and Obeagu 2024; Kochhar and McGann 2025).

Clinical manifestations and multisystem involvement

SCD is a multisystem disorder driven by hemoglobin polymerization, red cell dehydration, chronic hemolysis, and recurrent microvascular occlusion. Indian patients exhibit a clinical spectrum broadly comparable to global patterns, though severity and complication profiles vary according to genetic and environmental modifiers (Rees et al., 2010; Ware et al., 2017). Vaso-occlusive crises remain the hallmark acute manifestation and are the leading cause of emergency visits and hospital admissions. Chronic hemolytic anemia contributes to persistent fatigue, jaundice, and reduced physical endurance, significantly impairing quality of life (Serjeant 2013). Acute chest syndrome is among the most serious complications and is a major cause of intensive care admission and mortality. Functional asplenia predisposes patients to recurrent infections, particularly in early childhood, with delayed presentation and incomplete vaccination coverage contributing to high infection-related mortality (Tubman and Makani 2017; Makani et al., 2020). Chronic complications include renal dysfunction, pulmonary hypertension, avascular necrosis, gallstone disease, leg ulcers, and progressive cardiopulmonary impairment. Neurological complications, including overt and silent strokes, are increasingly recognized and associated with long-term cognitive impairment (Kinney et al., 1999; Elendu et al., 2023).

Spectrum of acute and chronic complications

The clinical spectrum summarized in Table 3 demonstrates substantial variation in complication frequency and severity across age groups and healthcare settings. Chronic hemolytic anemia is universally present and underpins most disease manifestations. Vaso-occlusive crises are the primary drivers of healthcare utilization and psychosocial burden. Acute chest syndrome, although reported at moderate frequency, carries a disproportionately high mortality risk and is frequently underdiagnosed. Infectious complications remain a major cause of early mortality, particularly in tribal and rural populations. Progressive organ damage becomes more prominent with age, leading to long-term disability and reduced survival. Gender- and life-stage-specific complications, including priapism and

pregnancy-related risks, highlight the need for specialized multidisciplinary care.

Symptoms and Lived Experiences of Patients

Beyond clinically defined complications, individuals with SCD experience persistent symptoms that profoundly affect daily life. Chronic fatigue, recurrent pain, reduced physical stamina, growth retardation, delayed puberty, and psychosocial distress are common and often under-recognized (Smith et al., 2011; Elendu et al., 2023; Jonani et al., 2025). Pregnancy in women with SCD is associated with increased maternal and fetal risks, necessitating specialized care (Elendu et al., 2023).

Screening, diagnosis, and early detection

Population-based screening remains the cornerstone of SCD control in India. High-performance liquid chromatography and hemoglobin electrophoresis are the diagnostic gold standards, while solubility tests are widely used for community-level screening (Colah et al., 2017). Newborn screening programs have demonstrated feasibility and effectiveness, with pilot initiatives in Maharashtra and Gujarat showing improved survival and reduced early childhood morbidity (Patel et al., 2014).

Management strategies and public health initiatives

Hydroxyurea therapy has emerged as the cornerstone of disease-modifying treatment for SCD in India, with low fixed-dose regimens proving effective and safe in resource-constrained settings (Italia et al., 2009; Patel et al., 2012). Supportive care, transfusion therapy, and infection prophylaxis remain essential components of management (Ware et al., 2017). Primary healthcare workers play a central role in India's National Sickle Cell Anaemia Elimination Mission, launched in 2023, which emphasizes universal screening, access to essential medicines, genetic counselling, and digital integration (Ministry of Health and Family Welfare, 2023). Early programmatic outcomes indicate improved case detection and treatment uptake in high-burden states (Babu et al., 2023; Jain et al., 2024).

## IV. DISCUSSION

This review synthesizes contemporary evidence to illustrate the multifaceted and evolving burden of sickle cell disease (SCD) in India, revealing both substantial progress and persistent systemic challenges. SCD in the Indian context extends beyond a monogenic hematological disorder to represent a complex public health condition shaped by ethnicity, geography, socioeconomic inequities, and health system capacity. The consolidation of national registry data and large-scale screening initiatives has substantially improved quantification of disease burden, with more than 215,000 confirmed patients and several million individuals identified as carriers. These data underscore the magnitude of SCD as a national priority while also highlighting the likelihood of continued underdiagnosis, particularly in remote and underserved regions (Colah et al., 2020; Jain et al., 2024). Earlier characterizations of an inherently "mild" Indian SCD phenotype are increasingly challenged by recent clinical and epidemiological evidence. While the predominance of the Arab–Indian haplotype is associated with elevated fetal hemoglobin (HbF) levels, contemporary studies demonstrate that Indian patients experience the full spectrum of disease severity observed globally, including recurrent vaso-occlusive crises, acute chest syndrome, stroke, and progressive organ damage (Mukherjee et al., 2018; Ware et al., 2020). The wide variability in clinical outcomes reflects the influence of genetic modifiers such as α-thalassemia, β-thalassemia mutations, and glucose-6-phosphate dehydrogenase deficiency, which together generate marked phenotypic heterogeneity even within the same communities (Italia et al., 2009; Fasola et al., 2019).

Geographically, the tribal belt across central and western India remains the epicenter of SCD burden, shaped by historical genetic isolation and endogamy. However, increasing detection of SCD in non-tribal and urban populations reflects patterns of internal migration, intercommunity marriage, and improved screening coverage. This epidemiological transition reinforces the need to view SCD as a nationwide concern rather than a condition confined to tribal populations alone (Piel et al., 2017). Despite these

advances, gender-specific analyses remain sparse. Available studies suggest possible sex-based differences in disease expression, health-seeking behavior, and access to care, but the absence of systematically disaggregated data limits definitive conclusions and represents a critical research gap. Therapeutically, the expanded use of hydroxyurea has been one of the most important advances in SCD management in India. Multiple Indian cohort studies have confirmed its effectiveness in reducing vaso-occlusive episodes, hospital admissions, and transfusion requirements, even at relatively low fixed doses suitable for resource-limited settings (Patel et al., 2012; Italia et al., 2019). Despite its inclusion in national essential medicine lists, population-level impact remains constrained by barriers such as inconsistent drug availability, limited laboratory monitoring, concerns regarding long-term safety, and challenges with patient adherence. These gaps are particularly pronounced in rural and tribal regions, where health infrastructure and specialist access are limited.

Newborn and early childhood screening programs represent another critical opportunity for improving outcomes. Evidence from pilot initiatives demonstrates that early diagnosis, combined with prophylactic interventions and caregiver education, significantly reduces childhood morbidity and mortality (Jain et al., 2024). However, implementation remains uneven across states, and linkage between screening and sustained care is frequently weak. Similarly, genetic counselling an essential component of SCD prevention is underutilized, especially in high-prevalence tribal regions where cultural beliefs, stigma, and limited awareness may hinder uptake (Obed et al., 2017). The launch of India's National Sickle Cell Anaemia Elimination Mission represents a landmark policy response, emphasizing universal screening, community engagement, free treatment, and integration with existing public health programs. Early reports from high-burden states indicate improved case identification and treatment initiation, suggesting that large-scale, government-led interventions can yield tangible benefits (Jain et al., 2024). Nonetheless, translating national policy into effective community-level impact will require sustained financing, workforce training, digital health integration, and culturally sensitive communication strategies tailored to diverse populations.

Beyond clinical morbidity, SCD imposes a substantial societal and economic burden. Recurrent hospitalizations, chronic pain, disability, and reduced productivity significantly affect patients and families, particularly those already facing poverty and social marginalization. Tribal populations often experience compounded disadvantages, including limited access to quality healthcare, lower literacy levels, and economic insecurity, which collectively exacerbate disease outcomes and delay timely interventions (Babu et al., 2022). Looking ahead, advances in curative therapies such as hematopoietic stem cell transplantation and emerging gene-based approaches offer long-term promise. However, their high cost, infrastructural requirements, and ethical considerations raise concerns about equitable access in low- and middle-income settings like India (Kanter et al., 2020). In the interim, strengthening primary healthcare capacity, embedding SCD services within maternal and child health programs, and fostering community participation are likely to yield the greatest population-level benefits.

Limitations and Future Research Directions

This review also highlights important limitations within the existing evidence base. Heterogeneity in study design, screening methodologies, and outcome reporting complicates cross-regional comparisons. Inconsistent gender-disaggregated data and a paucity of longitudinal cohort studies limit understanding of life-course disease progression. Strengthening standardized national registries, conducting long-term community-based cohorts, and promoting participatory research approaches will be essential to inform targeted interventions and achieve sustainable disease control.

## V. CONCLUSION

Sickle cell disease in India constitutes a complex and enduring public health challenge shaped by marked genetic diversity, substantial disease concentration among tribal populations, and heterogeneous clinical expression across regions. Although significant

progress has been achieved through expanded screening programs, wider adoption of hydroxyurea therapy, and the implementation of national control initiatives, major gaps persist in equitable access to diagnosis, long-term care, and preventive services. Strengthening primary healthcare systems, integrating genetic counselling and newborn screening, and ensuring continuity of care in rural and tribal settings remain critical priorities. Sustained policy commitment, adequate resource allocation, and community-centered implementation strategies are essential to translate national goals into meaningful health outcomes. With coordinated, evidence-based interventions and robust health system strengthening, India has the potential to substantially reduce sickle cell disease–related morbidity and mortality and move toward effective disease control by 2047.

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## VI. TABLE LEGENDS

Table 1 Geographic Distribution of Sickle Cell Disease (SCD) and Sickle Cell Trait (SCT) in India

Table 2 Genetic Modifiers Influencing the Phenotype of Sickle Cell Disease in Indian Populations

Table 3 Major Clinical Complications Observed in Indian Sickle Cell Disease (SCD) Cohorts

Graphical abstract

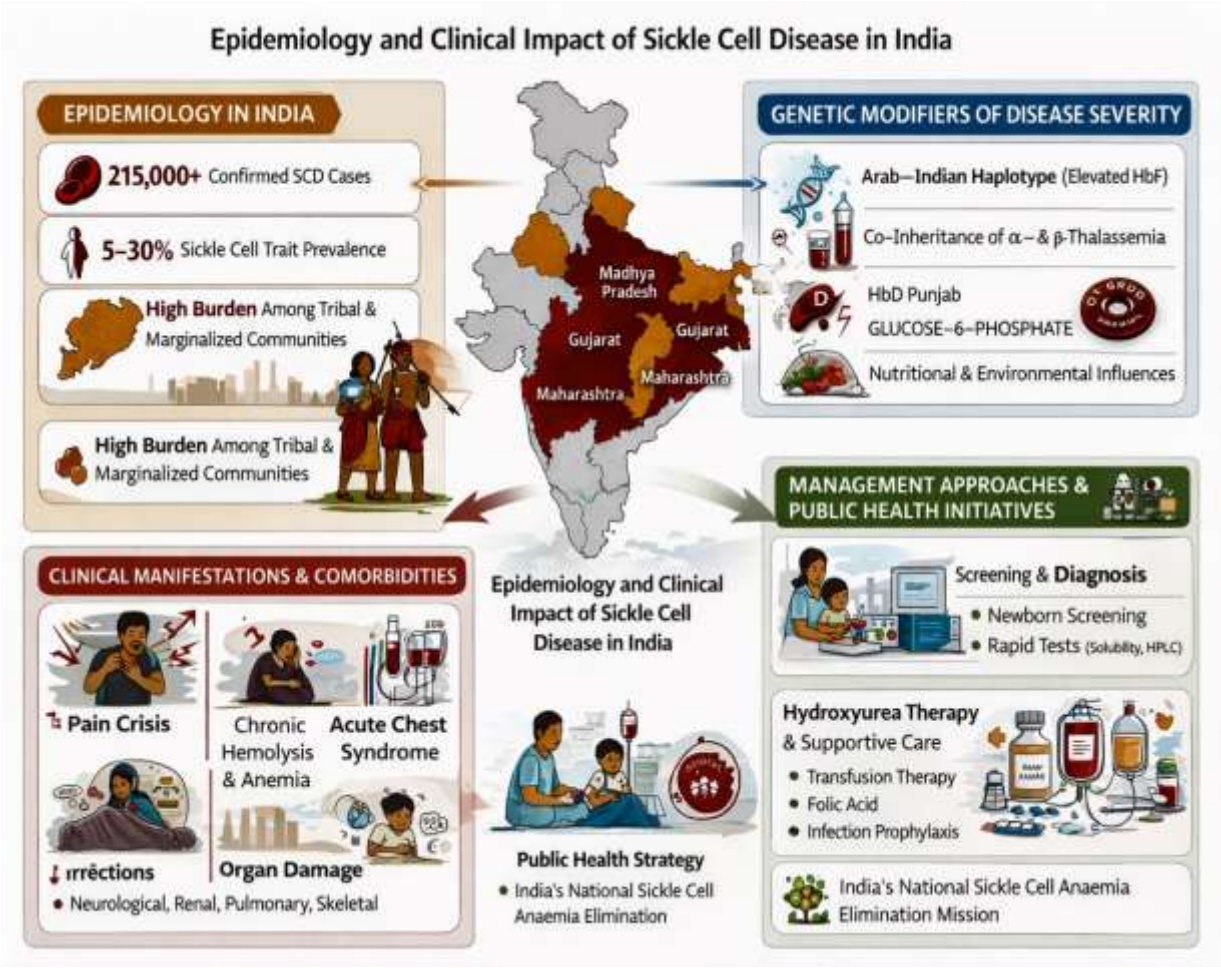

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Table 1 Geographic Distribution of Sickle Cell Disease (SCD) and Sickle Cell Trait (SCT) in India

| S. No | Region / Study | Population stidied | HbS Carrier (SCT) (%) | SCD (HbSS) (%) | Indian Evidence/Notes | Reference |
|---|---|---|---|---|---|---|
| 1 | Odisha state (screening, 2025) | Tribal and non-tribal communities | 8-17 | ~1.7 | Highest registered SCD burden nationally; extensive mass screening under state programs | Times of India, 2025, Colah et al., 2025. |
| 2 | Madhya Pradesh (Central India) | Gonds, Bhils, rural populations | 10–33 | 0.8-1.9 | High tribal concentration; early childhood detection common | Colah et al., 2015, Balgir et al., 2020. |
| 3 | Gujarat (Western India) | Tribal belts (Bhils, Rathwas | 6-18 | 0.5-1.5 | Long-standing community screening initiatives; significant SCT prevalence | Times of India, 2025, Colah et al., 2015. |
| 4 | Chhattisgarh | Scheduled Tribes | 10-33 | 1.0-2.0 | High HbS frequency linked to malaria-endemic ecology | Shrikhande et al., 2007; Balgir et al., 2020. |
| 5 | Maharashtra (Vidarbha region) | Mixed tribal–rural populations | 5-14 | 0.6-1.4 | School- and antenatal-based screening identifies both SCT and HbSS | Kamble and Chaturvedi, 2000. |
| 6 | Rajasthan (Southern districts) | Garasia and Bhil tribes | 9-16 | 0.7–1.6 | Marked intra-tribal variation in prevalence | Singh et al., 2018. |
| 7 | Jharkhand | Tribal populations | 5–10 | 0.3–0.9 | Moderate prevalence; limited registry coverage | Balgir et al., 2020 |
| 8 | Andhra Pradesh / Telangana | Scheduled Tribes | 4-12 | 0.3–1.0 | Regional heterogeneity with clustered tribal burden | Rao et al., 2009. |
| 9 | Urban migrant cohorts | Mixed ethnic groups | 1-4 | <0.5 | Increasing detection due to rural–urban migration | Piel et al., 2021. |
| 10 | North & North-East India | General population | <1 | Rare | Low reported prevalence; under-screening possible | Colah et al., 2015. |

Table 2 Genetic Modifiers Influencing the Phenotype of Sickle Cell Disease in Indian Populations

| S. No | Genetic Modifier / Variable | Frequency / Burden in India | Indian Description | Evidence / Notes | Reference |
|---|---|---|---|---|---|
| 1 | Arab–Indian HbS haplotype | Predominant (>85%) | Characteristic Indian HbS background | Associated with relatively higher HbF and delayed complications | Mukherjee et al., 2010; Colah et al., 2020. |
| 2 | Elevated fetal hemoglobin (HbF) | Common (8–20%) | Seen in many Indian HbSS patients | Modulates disease severity and reduces VOC frequency | Thein 2013. |
| 3 | α-Thalassemia co-inheritance | 30–60% in tribal belts | Frequent deletional α-thalassemia | Reduces hemolysis but may increase blood viscosity | Mukherjee et al., 2010; Italia et al., 2020. |
| 4 | β-Thalassemia co- | Region-specific | $S\beta^0/S\beta^+$ genotypes | Increases anemia | Colah et al., 2020 |

| | | | | | |
|---|---|---|---|---|---|
| | inheritance | | reported | severity and transfusion need | |
| 5 | HbD Punjab interaction | Low–moderate (NW India) | Compound heterozygosity (HbSD) | Produces variable clinical severity | Gorakshakar and Colah 2009 |
| 5 | G6PD deficiency | 5–20% in tribal groups | X-linked enzymopathy | Increases hemolysis and neonatal jaundice risk | Balgir et al., 2020; Jain et a., 2022. |
| 6 | BCL11A polymorphisms | Moderate | HbF regulatory gene variants | Associated with HbF persistence | Lettre et al., 2008. |
| 7 | HBS1L–MYB intergenic variants | Moderate | Erythropoietic regulator | Influences anemia severity | Thein 2013. |
| 8 | XmnI polymorphism (γ-globin) | Common | Promoter variant of HBG2 | Linked with higher HbF expression | Mukherjee et al., 2010. |
| 9 | Iron deficiency coexistence | High in women/children | Nutritional modifier | Worsens anemia independent of genotype | Pasricha et al., 2010. |
| 10 | Malaria exposure | Endemic regions | Historical selective pressure | Explains high HbS frequencies | Balgir et al., 2020 |
| 11 | Epigenetic regulation | Emerging evidence | DNA methylation effects | Potential target for novel therapies | Lettre et al., 2008. |
| 12 | Red cell dehydration pathways | Variable | Ion channel dysregulation | Contributes to VOC risk | Rees et al., 2010. |
| 13 | Genetic heterogeneity | High | Multiple interacting modifiers | Limits phenotype prediction | Piel et al., 2021. |
| 14 | Need for molecular profiling | Increasing | Precision medicine approach | Essential for individualized care | Kanter et al., 2021 |

Table 3 Major Clinical Complications Observed in Indian Sickle Cell Disease (SCD) Cohorts

| S. No | Complication / Variable | Frequency / Burden in India | Indian Context | Impact on Disease | Description | Evidence / Notes | Reference |
|---|---|---|---|---|---|---|---|
| 1 | Chronic hemolytic anemia | Universal | All age groups | Baseline morbidity | Persistent anemia due to red cell destruction | Leading cause of hospitalization | Rees et al., 2010; Colah et al., 2020. |
| 2 | Vaso-occlusive crises (VOC) | Very common | Children and adults | Major morbidity driver | Painful ischemic episodes affecting bones/chest | Leading cause of hospitalization | Ware et al., 2017; Jain et al., 2012. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 3 | Acute chest syndrome (ACS) | Moderate | Often underdiagnosed | High mortality risk | Pulmonary infiltrates with fever/hypoxia | Requires early intervention | Vichinsky et al., 2000. |
| 4 | Severe infections | High in childhood | Tribal and rural settings | Major cause of death | Functional asplenia-related susceptibility | Vaccination gaps worsen outcomes | Booth et al., 2010; Colah et al., 2020. |
| 5 | Functional asplenia | Common | Early childhood onset | Infection risk | Loss of splenic immune function | Underpins sepsis risk | Rees et al., 2010 |
| 6 | Stroke (overt/silent) | Low–moderate | Increasing recognition | Long-term disability | Cerebrovascular occlusion | Often under-screened | DeBaun et al., 2016. |
| 7 | Avascular necrosis | Moderate | Adolescents/adults | Chronic disability | Bone ischemia, hip involvement | Limits mobility | Jain et al., 2012; Ware et al., 2017 |
| 8 | Pulmonary hypertension | Underreported | Adults | Reduced survival | Chronic hemolysis-related vasculopathy | Needs systematic screening | Gladwin and Sachdev 2012. |
| 9 | Renal dysfunction | Progressive | Adolescents/adults | Chronic morbidity | Proteinuria, CKD | Late diagnosis common | Nath and Hebbel 2015. |
| 10 | Gallstone disease | Common | Adults | Surgical burden | Pigment stones from hemolysis | Frequently incidental | Rees et al., 2010 |
| 11 | Growth retardation | Moderate | Pediatric cohorts | Developmental impact | Chronic anemia/nutrition deficit | More severe in rural areas | Pasricha et al., 2010. |
| 12 | Chronic pain syndromes | Common | Adolescents/adults | QoL reduction | Persistent nociceptive pain | Psychosocial impact | Smith and Scherer 2010. |
| 13 | Leg ulcers | Low–moderate | Adults | Chronic morbidity | Vascular insufficiency | Poor wound healing | Minniti et al., 2010. |
| 14 | Priapism | Low | Males | Urologic morbidity | Painful prolonged erection | Underreported | Burnett et al., 2012. |
| 15 | Pregnancy complications | Moderate | Women with SCD | Maternal–fetal risk | Preterm birth, anemia | Needs specialized care | Boafor et al., 2016. |