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META-ANALYSIS ON PREVALENCE OF SICKLE CELL DISEASE AT VARIOUS GEOGRAPHIC AND POPULATION LEVELS

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ABSTRACT

Sickle cell disease (SCD) is a severe inherited blood disorder where the mutated form of haemoglobin brings about modification in red blood cells making it rigid and shaped like a "C" or sickle, giving the disease its name. Sickle-cell disease is much more prevalent in African regions however population migration has spread these diseases to most countries. There is a wide discrepancy in data in the existing literature regarding the menace of SCD. These data require further analysis for better accuracy. This study aims at a comprehensive report regarding the prevalence of SCD compared at global, interstates of India and within districts of Odisha. This Meta-analysis is conducted under PRISMA guidelines. Statistical data collected from databases, reference resources and published articles were used for the systematic search. The scale-up of scientific interventions for the management of SCD to improve public health is briefly discussed.

Keywords: Sickle cell disease (SCD), Anemia, Meta-Analysis, Prevalence,Odisha

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INTRODUCTION

Sickle cell disease as a group of chronic autosomal recessive disorder affects haemoglobin that carries oxygen. It is a serious inherited disease among haemoglobinopathies in the world. The gene may be present in homozygous or heterozygous state. In this individuals who are homozygous for the β^S allele trait have Sickle cell anaemia as the most common form of SCD. The individuals heterozygous for the trait are Carriers and are generally symptomless. Other forms of SCD like HbSC, HbSβ-Thalassemia and HbAS are less common and differentiated if they are inherited with another HbS gene or with different gene mutation of β globin subunits. There is a mutation in the 11^{th}chromosome particularly the gene that encodes for β_2 globulin (Graham R Serjeant 2016). By single nucleotide substitution at sixth position of β globin chain of haemoglobin, glutamate residue is replaced with a valine residue (Atweh 2007). The deoxygenated β_2 cells causes polymerization of Haemoglobin making it Sickle haemoglobin HbS. Theerythrocytes having Sickle haemoglobin are prone to haemolysis due to membrane damage (Roshan B. Colah 2015). They are rigid and stick to the walls of blood vessels causing Vaso-occlusion (Gorakshakar n.d.)(Prithu Sundd 2019).The oxygen cannot reach the nearby tissues leading to pain crises and chronic organ dysfunction. Immune Deficiency is noticed in early childhood where the person gets easily affected to infections. Bacterial infections are major contributors to overall mortality in patients. The clinical complications including chest pain, musculoskeletal problems, stroke, pulmonary hypertension and septicaemia often co-exist. The sign and symptoms of SCD have discrete variations from patient to patient. The symptoms show varying levels of severity from mild to very severe requiring hospitalization (Paula Tanabe 2019).

It is important to note that Sickle Cell Disease is recently recognized as global disease by World Health Organization (WHO) and United Nations (Lucky L.MulumbaaL 2015). In fact it is estimated that 300,000 babies are born every year across the globe with SCD. The carrier gene frequency ranges from 5%-40%. The incidence of disease due to higher frequency of the β^Sallele, disproportionately affects sub Saharan Africa and part of Mediterranean, the Middle East and India, Spanish speaking region of South America and Central America, the Arabian Peninsula and parts of Caribbean. Estimations have revealed that 50% - 80% infants born in Africa with SCD die before the age of 5, which clearly indicates that SCD is associated with high childhood mortality. The epidemiology of Malaria resistance genes and migration of population lead to wider distribution of disease over countries (Banu Aygun 2012)(Kato 2018).

One-fifth of the world population is credited to India, which consists of a wide ranging diversity on the basis of ethnicity, geography and genetics. It is a serious disease among haemoglobinopathies in the world and has second highest burden of disease in India (Carinna Hockham 2018). The β^S gene variant found belonging to ethnic groups such as scheduled caste and scheduled tribe who are socioeconomically backward and medically underserved in India (Deepak Saxena 2017). These subpopulations are genetically isolated from other populations over generations based on factors including religion, caste, culture, language, gotra etc. and amplified founder effects. The genetic variation is comparatively much less and is vulnerable to genetic recessive disorders

(Sharma 2017). Sickle cell haemoglobin was first discovered by Lehman and Cutbush in 1952 in tribal population of Nilgiri hills in South India (Roshan B. Colah 2015). The tribal population of India as per the latest Census of 2011 is 8.6% of total population and scattered over 30 states and 8 union territories which is about 67.8 million people (Carinna Hockham 2018). SCD is most prevalent in the central part of India (Roshan B. Colah 2015). It stretches from Gujurat to Odisha including Maharashtra, Madhya Pradesh, Chhattisgarh, Jharkhand referred as 'Sickle Cell Belt' (Graham R Serjeant 2016). It is estimated that about 5,200 babies are born in India per year affected in Sickle Cell Disease (Verma 2000). The average gene frequency of sickle cell anaemia disease in India is 4.3% (Neha Ghai 2015).There are many reasons behind these inherited diseases such as large population, high birth rate, consanguineous marriage etc. that are favoured in many communities while lack of proper public health services further escalates the burden of disease(Verma 2000).

In the tribal map of the Country, the state of Odisha occupies largest Tribal communities of 62 tribes including 13 primitive tribes (Prasanta Purohit 2014). In Odisha the prevalence of sickle cell disease for the homozygous state found to be 3.03% in Western regions and in adjacent areas near Chhattisgarh. The percentage of prevalence differs in different communities (Sujata Dixit 2015). The tribals of Odisha have common gene pool which is relatively in isolation with that of the non-tribal community. We have high burden not only in the terms of numbers but also burden in terms of impact the individuals living with the disease. It is burdensome to society in many ways. It is very hard to take care of individuals with a chronic condition particularly in recent history of us not having much in the way of treatment options. It is very expensive. It is estimated that it costs on an annual basis in the United States about 2 billion Dollars just to take care of acute care costs associated with SCD (NHLBI Evidence Report).

There is a wide discrepancy between epidemiological data in the existing literature regarding the menace of SCD. These data require further analysis for better accuracy. The present study documents the information regarding the prevalence of disease at various sets of populations at global level, interstates of India and within districts of Odisha. Knowledge of the geographical distribution and burden of SCA is necessary for implication of public health policies and planning. Community based approach and scientific interventions are inadequate. This study aims at better management of SCD in areas of high prevalence to reduce the burden of disease.

METHOD

SEARCH STRATEGY AND SELECTION CRITERIA

An in depth literature review was conducted with the PRISMA guidelines. Systematic searches in Medline, Embase (Elsevier), PubMed, Web of Science, Google Scholar, and ScopeMed were carried out. The reference lists of all the potential articles were screened to explore various aspects of SCD. Searches were limited to January 2000 and March 2022. There was no language restrictions applied. All published articles, government reports and policies related to SCD were collected from government portals were gathered. Articles were cross-checked for duplication. Later articles were finalised based inclusive criteria.

DATA EXTRACTION

From each study data were extracted based on the study duration, sample size, geographic location, WHO region birth prevalence, burden of diseases, mortality from SCD and interventions included. From the reports having overlapping data, the most recent study was used.

QUALITY ASSESSMENT

All the full text articles were checked further and depending upon the case ascertainment, statistical analysis and sampling (represented population at global, national and sub-national); the articles were included with high degree of quality. Low quality articles were excluded.

RESULTS

Based on the inclusion criteria, 45 articles were included in this Meta- Analysis. Majority of the published literature are cross-sectional studies conducted among tribal, non-tribal and infants with maternal carrier. The result of the literature search is shown in the flowchart of PRISMA. Of the 1876 records identified on different Databases, 569 were removed before screening. Titles of 1307 articles were screened and 659 were excluded. Abstract of 648 articles were screened from which 184 were assessed on full text. Due to unavailability of data on full text and on the prevalence of Sickle Cell Disease, 139 records were removed and 45 article records were included.

PREVALENCE OF SICKLE CELL DISEASE IN THE WORLD

Estimation of the prevalence, incidence and burden of disease remains Challenging. About 5% of the world's population carries genes responsible for haemoglobinopathies (Banu Aygun 2012). It is estimated that around 85% of births affected with SCD occur in Africa. Each year about 300, 000 infants are born with major haemoglobin disorders – including more than 200, 000 cases of sickle-cell anaemia in Africa (World Health Organisation 2006). Up to 3% of all Children are born with this condition in some Sub- Sahara African regions (Scott D Grosse 2011). The prevalence of the sickle-cell trait ranges between 20% - 30% in 40 Countries in region and in 23 countries of West and Central Africa. Even if more than 40 countries are affected much of data available are only hospital based and not population based. When the prevalence of SCT exceeds 20%, SCD is estimated to be at least 2%. In West African countries such as Ghana and Nigeria, the frequency of the trait is 15% to 30% whereas in Uganda it shows marked tribal variations, reaching 45% among the Baamba tribe in the West of the country (World Health Organisation 2010). Frequencies of the carrier state determine the prevalence of sickle-cell anaemia at birth. For example, in Nigeria, by far the most populous country in the sub region, 24% of the population are carriers of the mutant gene and the prevalence of sickle-cell anaemia is about 20 per 1000 births. This means that in Nigeria alone, about 150, 000 children are born annually with sickle-cell anaemia (World Health Organisation 2006). This distribution reflects the fact that sickle-cell trait confers a survival advantage against malaria and that selection pressure due to malaria has resulted in high frequencies of the

mutant gene especially in areas of high malarial transmission. Sickle-cell anaemia contributes the equivalent of 5% of under-five deaths on the African continent, more than 9% of such deaths in West Africa, and up to 16% of under-five deaths in individual West African countries (Banu Aygun 2012).

In United States the exact number of people living with SCD is unknown but it is estimated that SCD affects approximately 100,000 Americans. SCD occurs among about 1 out of every 365 Black or African-American births. SCD occurs among about 1 out of every 16, 300 Hispanic-American births. About 1 in 13 Black or African-American babies is born with sickle cell trait (SCT) (Centers for Disease Control and Prevention 2021).

The lack of proper epidemiological data on SCD, mortality data in particular in the areas of high prevalence has lead to an obscure view and uncertain reliability on the current number of all- age individuals affected by it globally.

PREVALENCE OF SICKLE CELL DISEASE IN STATES OF INDIA

India has around eighteen million people with sickle cell trait and 1.4 million patients with sickle cell disease. Chhattisgarh, West Bengal, Uttar Pradesh, Maharashtra, Madhya Pradesh, Jharkhand, Gujarat, Odisha, Kerala and Rajasthan show a notably higher prevalence of SCD than the average for the country and hence known as Sickle Cell Belt. The disease is more common among three socioeconomically disadvantaged ethnic groups of scheduled caste, scheduled tribe and other backward classes in Central, Western and in Southern India. However, due to migration SCD is becoming more common. Extensive studies conducted by the Anthropological Survey of India have documented the distribution and frequency of the sickle cell trait reaches levels as high as 35% in some communities the rise in prevalence of inherited haemoglobin disorders in India can be attributed to various evolutionary forces such as natural selection & social behaviour like endogamy (Prasanta Purohit 2014).

According to estimates from the Global Burden of Disease (GBD)—a global research programme published Estimation of prevalence at state level which suggested that the highest prevalence of sickle cell disease is found in Chhattisgarh, Bihar and Uttar Pradesh. However, some stakeholders in India consider the GBD to have underestimated prevalence of the condition (Anil Khatri 2020).

In Maharashtra, the sickle cell gene is widespread in all the eastern districts, also known as the Vidarbha region, in the Satpura ranges in the north and in some parts of Marathawada. The prevalence of sickle cell carriers in different tribes varies from 0 to 35%. The tribal groups with a high prevalence of HbS (20-35 %) include the Bhils, Madias, Pawaras, Pardhans and Otkars. It has also been estimated that Gadchiroli, Chandrapur, Nagpur, Bhandara, Yoetmal and Nandurbar districts would have more than 5000 cases of sickle cell anaemia. From a state level study conducted in Maharashtra among non-tribal infants of maternal carriers, the total numbers of 2134 individuals were screened from which 113 individuals are affected with SCD. This indicates the prevalence of Sickle cell disease as 5.30 % (Patel 2017).

In Chhattisgarh state level study to evaluate feasibility of systematic neonatal screening for sickle cell disease conducted in which 1,158 neonates screened, 628 were boys (54.2%) and 530 were girls (45.8%) among tribal and non-tribal infants. On reinvestigation 6 of them found to have Sickle Cell Disease indicating 0.52% of prevalence in the state (Sumanta Panigrahi 2012).

There are reports on haemoglobin (Hb) variants identified in the tribal and non-tribal populations of Tripura State in north-eastern India. Of 2400 cord blood samples screened, 225 (9.3%) were HbE heterozygotes, 80 (3.3%) were Hb E homozygotes and one carried HbE -β-thalassemia. Other abnormalities were also detected including 15 HbS heterozygotes, two HbD-Punjab heterozygotes and two compound heterozygotes for HbD-Punjab and HbE. Of the 80 homozygous HbE babies, four were non-tribal and 76 babies were tribal, and 225 patients carried HbE trait, 141 were tribal, while 84 were non-tribal. But the prevalence for homozygous HbS was 0 (Dipti Upadhye 2018).

In Tamil Nadu 9,646 individuals (60.4%) under the age of 30 of a population of 25,000 individuals were screened. 111 active patients of Sickle cell disease were detected in the remote aboriginal tribal population in southern India (Vivek Nimgaonkar 2013).

The of study clinical and haematological profile of the patients with sickle cell disease (HbSS)and the prevalence of sickle cell anaemia among scheduled tribe (Garasia) of Sirohi district in Rajasthan state was conducted. In this prospective cross-sectional study, 1676 Garasia tribals attending the hospital or the mobile clinic were screened for sickle cell anaemia. Prevalence of sickle cell anaemia was found to be 9.2% (155/1676) of which 0.8% (14/1676) were homozygous (disease, Hb SS) whereas 8.4% were heterozygous (carrier, Hb AS) (Sanjay Mandot 2009).

In Madhya Pradesh a hospital based a cross-sectional study showed 12.26% prevalence of hemoglobinopathies among 416 pregnant women, the sickle cell trait being 7.45%, followed by β-thalassemia trait (2.89%), haemoglobin E trait (0.24%), and sickle cell disease (1.68%). About 88% of the pregnant women were found free of hemoglobinopathies. Of the 9.13% pregnant women included in the study were suffering from sickle cell disorders (Balgir 2015).

While there isn't a consensus on which provides the most accurate estimates but these screening programmes shows a range of estimates of prevalence of Sickle cell disease in India (Anil Khatri 2020)

PREVALENCE OF SICKLE CELL DISEASE WITHIN DISTRICTS OF ODISHA

In the state of Odisha, 22.1% of the total populationis constituted by tribes and they are 9.7% of the total tribal population of India. There is no population based cross sectional prevalence study of this disorder from the state of Odisha. The sickle gene is highly prevalent in western districts of Odisha with a frequency of 21%. In a few tribes studied, the frequency of sickle gene was found to be 8%. As a component of Odisha Sickle Cell Project, field studies are carried out in western districts of Odisha to estimate the prevalence of inherited

haemoglobin disorders. The Kalahandi district is also under Janani Suraksha Yojana program of the Government of India (Prasanta Purohit 2014) (Sujata Dixit 2015).

Selection of study area Kalahandi District for SCD for two reasons: Kalahandi is a tribal dominated district with area-specific variation in marriage practices and the district hospital is located at Bhawanipatna town which is the center of Kalahandi district and gets delivery cases of invariable proportions from 13 different areas of the district. Out of 761 cases, 83.44 % (n=635) without any abnormal Hb,14.71 % (n=112) heterozygous, and 1.7 % (n=13) homozygous for sickle cell gene were observed among those neonates delivered at Kalahandi District Hospital. Kalahandi district is surrounded by 13 areas, out of which maximum deliveries were from Bhawanipatna area where the hospital is situate followed by Jhunagarh. Ksinga, Narla, and Madanpur Rampur (also known as M.Rampur) was found to have almost equal number of heterozygous cases; however, unlike M. Rampur, there was no case of homozygous SCD in Ksinga and Narla. Homozygous for sickle cell gene was found in three (Bhawanipatna, Jhunagarh,M. Rampur) out of 13 areas studied, and the prevalence was highest in M. Rampur (10.52 %) . The Prevalence of SCD in different areas of Kalahandi district varies from 1.71 to 10.52 % (Sujata Dixit 2015).

Another cross sectional prevalence study was carried outas a component of Odisha Sickle Cell Project, under which field studies are carried out in western districts of Odisha to estimate the prevalence of inherited haemoglobin disorders. From three tribal dominated villages two of villages were situated in Bargarh district and the other one in Kalahandi. Sickle gene was found in four out of the five tribes studied. In this study the prevalence of sickle allele was 13.1% with an allelic frequency of 0.08. The prevalence was highest (31.0%) in Gond with an allelic frequency of 0.17. Sahara tribe constituted the majority of the population (42.4%) and the prevalence of sickle allele was 14.3% in them which is higher than the earlier report of in 1991. Kandha was the largest tribe in the district of Kalahandi. The prevalence of sickle allele was found to be 9.0% in Kandha of Odisha state which is similar to earlier report in 1985. For the first time the Kuda (Mirdhas) tribe of western Odisha was studied and the prevalence of sickle allele was lowest (8.51%) with an allelic frequency of 0.05. Sickle allele was not found in Oraon tribe. Similar finding has been reported by (M. Kaur 2013).The lack of sickle allele in the Oraon tribe could be due to recent migration of the Oraon population with founder effect. In this study this population constituted of only 2% of the total subjects studied and were localized to one village. Majority of the Sahara were found in the district of Bargarh (94.4%). Kandha and Oraon were found in Kalahandi district and Gond and Kuda in Bargarh district (Prasanta Purohit 2014).

The high prevalence of sickle gene (in heterozygous or homozygous state) in tribal population in this region is probably due to selection pressure of endemic malaria in this part of India. These results serve as a good source to identify the local hotspots for Sickle Cell Disease and other epidemiological studies in future (Prasanta Purohit 2014) (Sujata Dixit 2015) .

DISCUSSION

SCD is a complex, multisystem condition characterized by acute and chronic complications. Advances in general medical care, early diagnosis and comprehensive treatment have led to substantial improvements in the life expectancy of individuals with SCA in high-income countries. The clinical severity of sickle cell disease varies considerably. There are therapies that have been useful for pain relief and disease free survival of patients (Kato 2018) (Shruti Mishra 2018).

For some acute situations, such as severe anaemia and acute chest syndrome, and also to prevent some chronic complications, such as cerebrovascular disease blood transfusion is established as an important treatment to relieve vaso-occlusion as during painful crisis, The availability of blood transfusion varies widely across South Asia, as only a few patients have access to a safe and reliable supply of blood. Most blood is supplied by private blood banks in Bangladesh, India and Pakistan even though there are State-run blood transfusion services in Sri Lanka, Bhutan and the Maldives. As per a modelling study, India is estimated to have the biggest unmet need for blood units in the world. with important implications for the treatment of Sickle Cell Disease. Making reliable blood transfusion services available would improve the standard of care for patients with SCD and facilitate the development of curative treatments, including gene therapy and bone marrow transplantation (Valentine Brousse 2021).

Hydroxyurea (HU) as the first licensed disease-Modified therapy there with proven effectiveness in the reduction of acute painful episode and chronic complications. It has shown consistent evidence of benefit. The drug significantly reduces the incidence of SCA vaso-occlusive crises, transfusion requirements, hospitalizations and mortality in high-income countries. This is used as a treatment in the US and Europe for more than 25 years. The benefit/risk ratio of HU in SCD argues very strongly for its wider use. Strong evidence-based guidelines in India could reassure primary attending physicians and increase the knowledge on the beneficial effect of HU in SCD (Kato 2018) (Valentine Brousse 2021).

Not much of a recourse has been spared in the field of curative therapy for SCD, hence replacement of the genetic defect in the haematopoietic stem cells is currently the only curative therapy. HSc transplant is so far the best treatment available. Here either an allogeneic HSc transplant from an HLA-matched sibling (with or without myeloablative condition) is done using a haplo-identical donor or auto-HSC transplant is done using gene therapy. HSc transplant ensures a disease free survival of the SCD patient once Engraftment has been done. The entire procedure revolves around the basic idea of replacement of the diseased marrow of the patient with that of a normal healthy marrow. Matched related or unrelated donors provide the stem cells required here. Peripheral blood by apheresis after adequate mobilization at present is the preferred method for stem cell collection.The availability of HSc transplant in high burden areas with comparatively low levels of income does not necessarily address the accessibility of curative therapies, in such areas. The most efficient way of easily

achieving an increase in the life expectancy of patients with SCD is improving the availability as well as accessibility of proven therapies like penicillin prophylaxis and HU. This apart from achieving its target of increased life expectancy also hits the target of enhanced quality of life (Valentine Brousse 2021).

There is an increasing number of pre-clinical and clinical drug trials registered every year. For the development of new SCD treatments in the United States, the FDA Division of Haematology Products decides to consider it as a top priority. SCD drug trials remains challenging due to low enrollment resulting early termination yet the recent completion of a series of large, multi-centre, multinational clinical trials resulted marketing in the community of patients with SCD and health care providers are interested to collaborate with the pharmaceutical industry to find effective new treatments. The prospects for new treatments in SCD have never looked better. Multi-drug approach would probably be the best for the SCD patients in low middle income countries as the present drug are unaffordable and inaccessible outside high income countries and have little efficacy (Kato 2018).

In India the Ministry of Health and Family Welfare of India drafted a policy on prevention and control of haemoglobinopathies in 2018, including sickle cell disease. The policy aims to provide evidence-based treatment for patients and reduce the number of new-born children with sickle cell disease through initiatives such as the Sickle Cell Anaemia Control Program, screening and prenatal diagnosis (Anil Khatri 2020).

Screening has already implemented a range of regional sickle cell programmes in high burden states, including Chhattisgarh, Gujarat, Maharashtra and Odisha. Programmes include prenatal, neonatal and premarital screening and counselling. The draft policy plans to push the screening programme out further (Anil Khatri 2020).

For the large scale data management the state, Chhattisgarh has implemented two main electronic systems: the State Wide Screening Data Interface (SWSDI) to manage data from screening programmes and the Sickle Cell Patients Temporal Data Management System (SCPTDMS) to handle patients' data at outpatient departments in 2014 the state produced a "Handbook on Sickle Cell Disease", setting out guidelines on recognition, management and counselling (Anil Khatri 2020).

Along with mass screening in 2006, the Sickle Cell Anaemia Control Programme initiated in five districts of South Gujarat under a public-private partnership strategy by the Department of Health and Family Welfare ongoing work of the Gujarat Sickle Cell Anaemia Control Society by SEWA Rural and the inclusion of sickle cell screening in annual "Mamta Divas", special immunisation days hosted in villages in tribal areas. Pneumococcal vaccine, monthly folic acid supplements, pain killers and blood transfusions were given to the patients for free (Anil Khatri 2020).

The potential of radical transformation of the sickle cell management system lies in these new innovations. Though the chances of any immediate impact of these on practice in India is thin, there availability will increase. Awareness of global trends & preparation of a practical plan on ensuring equitable & sustainable distribution of these new technologies is the need of the moment for healthcare systems in India.

CONCLUSION

Sickle cell disease is a major health issue that is both neglected and largely undocumented. Issues such as social stigma, rural isolation, staffing pressures and support for the poor has much more impact on the high prevalence of disease in socioeconomically backward and scheduled population. Even if the quality of life has considerably improved but the access to health care facilities is inequitable at all levels.Improvements in health policies are also needed, includingincreased funding for SCD programs, and establishment of comprehensive care programs encompassing nutrition, caregiver education, prevention and management of complications and proper treatment to assist the reduction of mortality and morbidity related to Sickle Cell Disease. Much of the suffer is avoidable if proper documentation and strategic interventions are followed especially in the areas of high burden.

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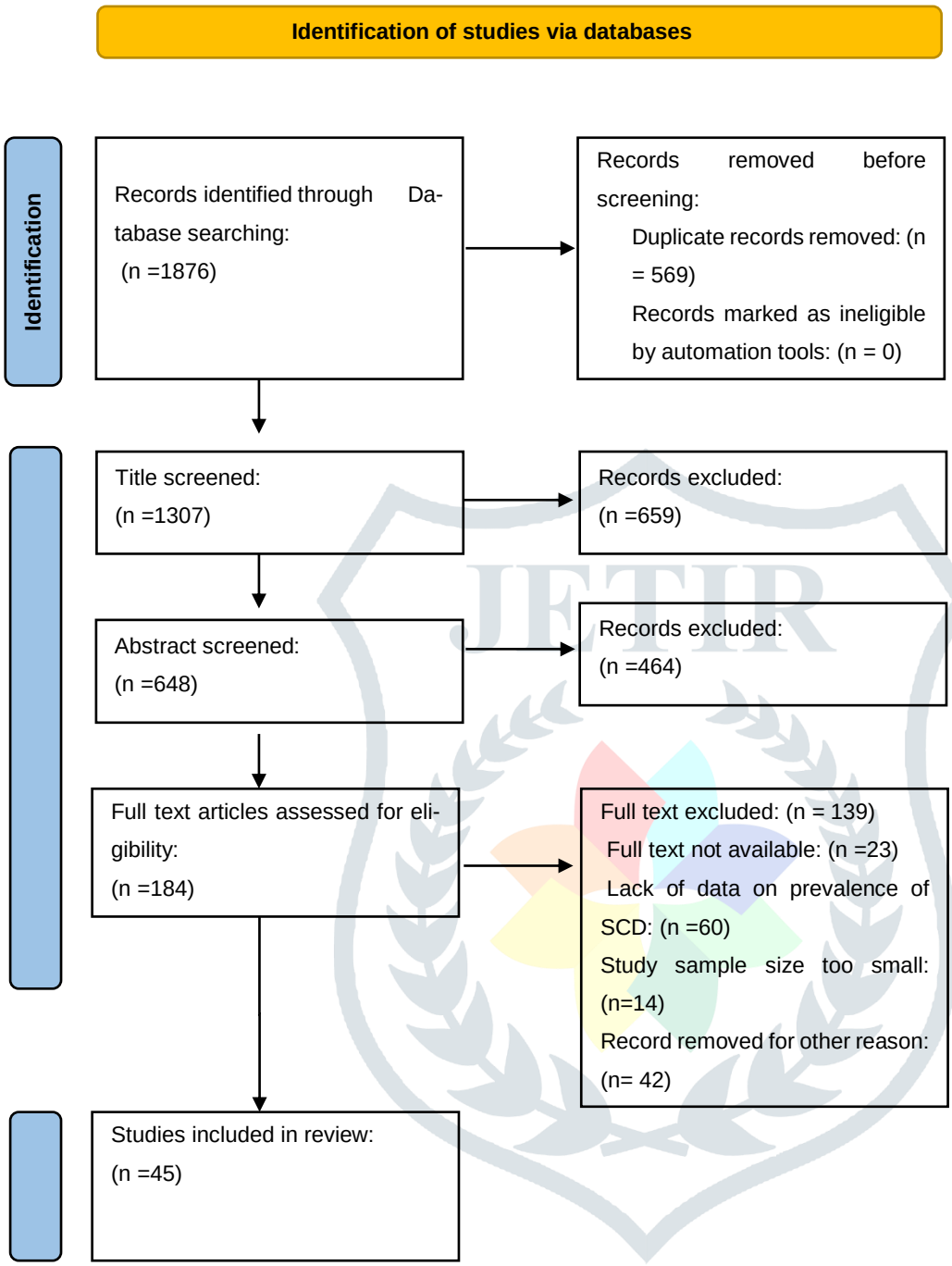
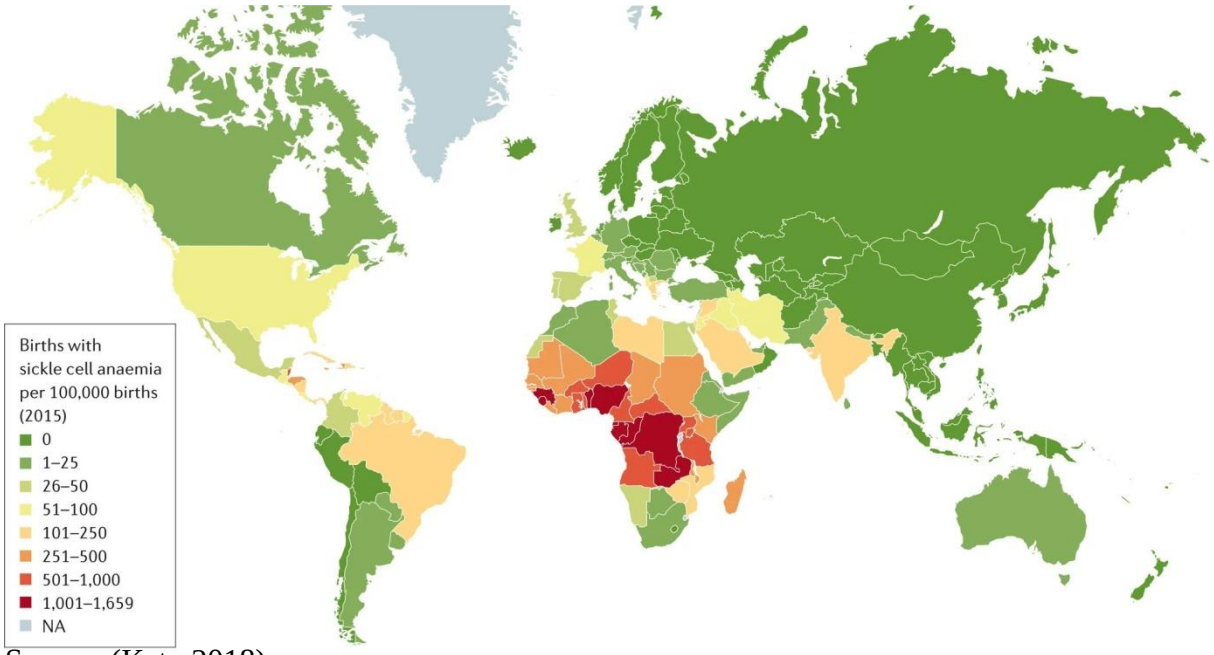


Figure 1. PRISMA flowchart detailing study selection



Source: (Kato 2018)

Figure 2 Map of Distribution of Sickle Cell Disease across the globe

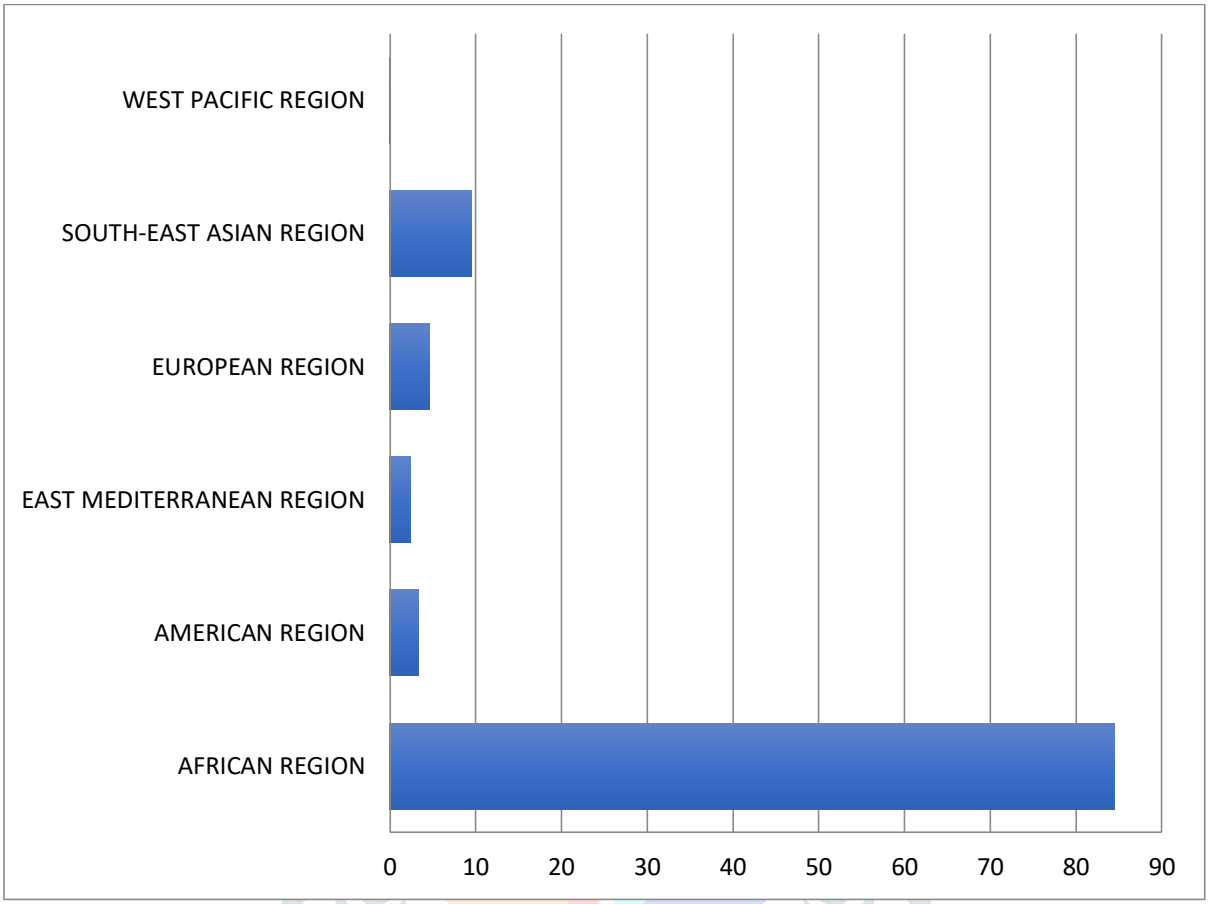
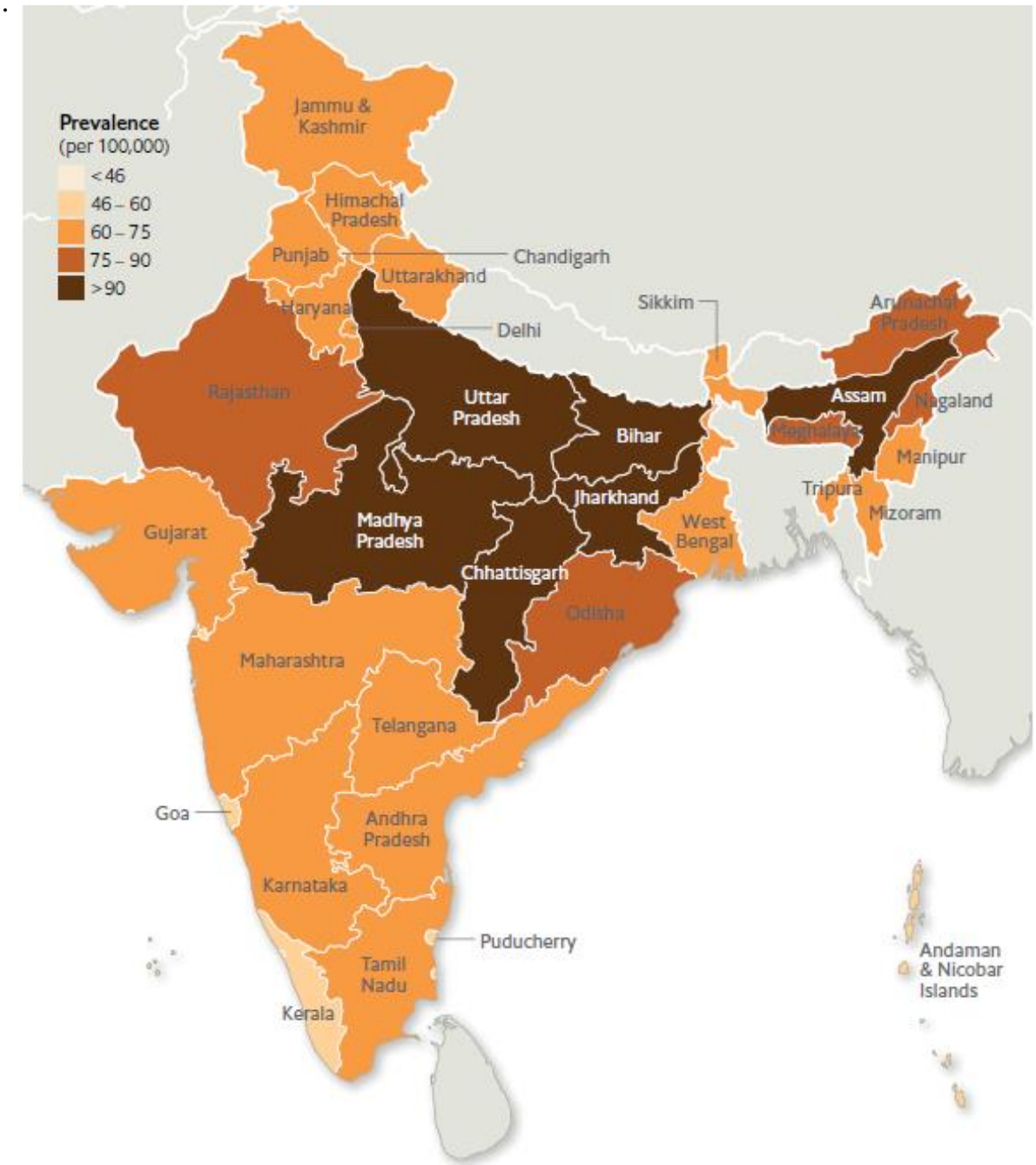


Figure 3 Bar graph representing prevalence of Sickle Cell Disease in the World



Source: Report by Economist Intelligence Unit (Anil Khatri 2020)

Figure 4 Map of Prevalence of Sickle Cell Disease in India

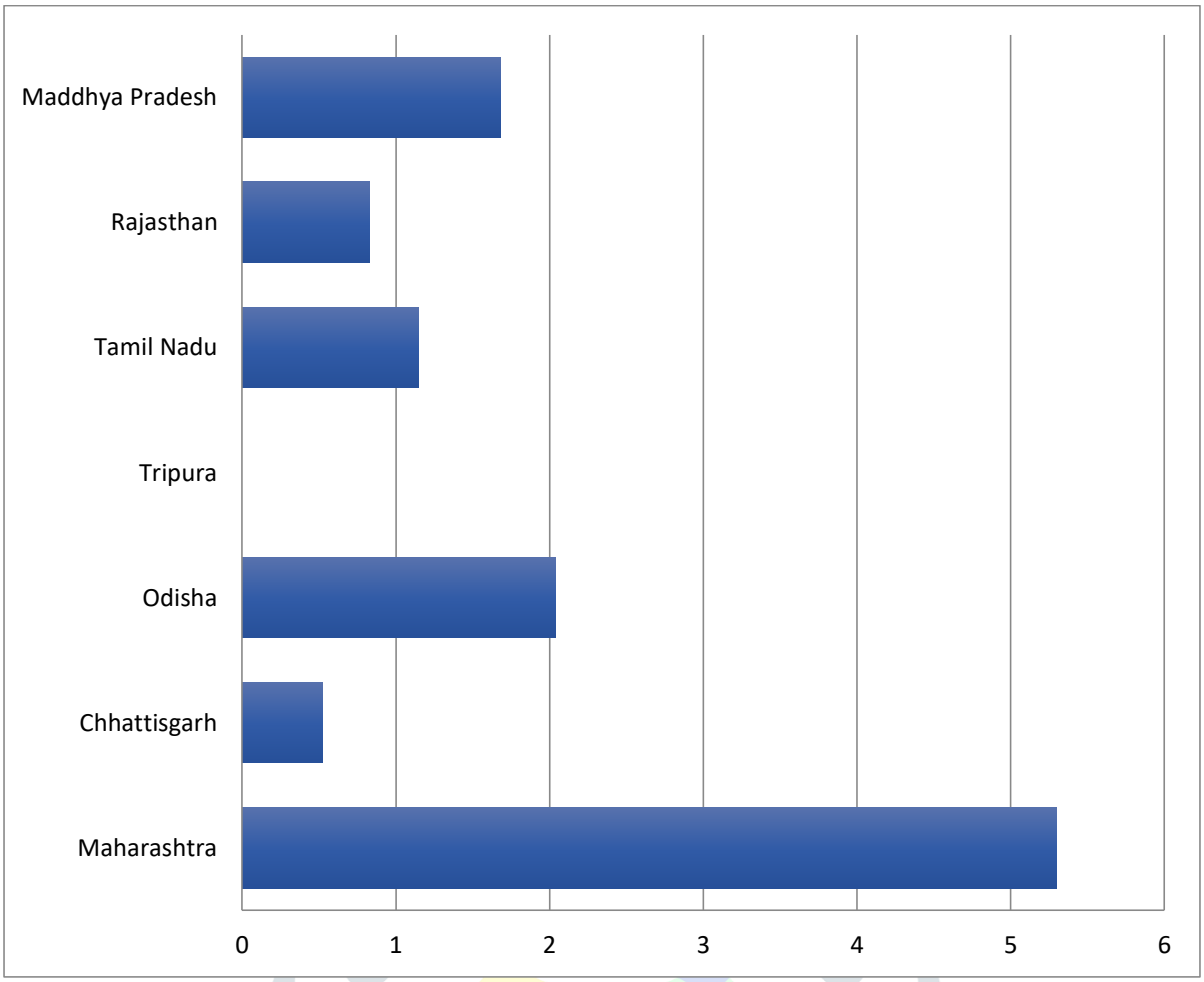
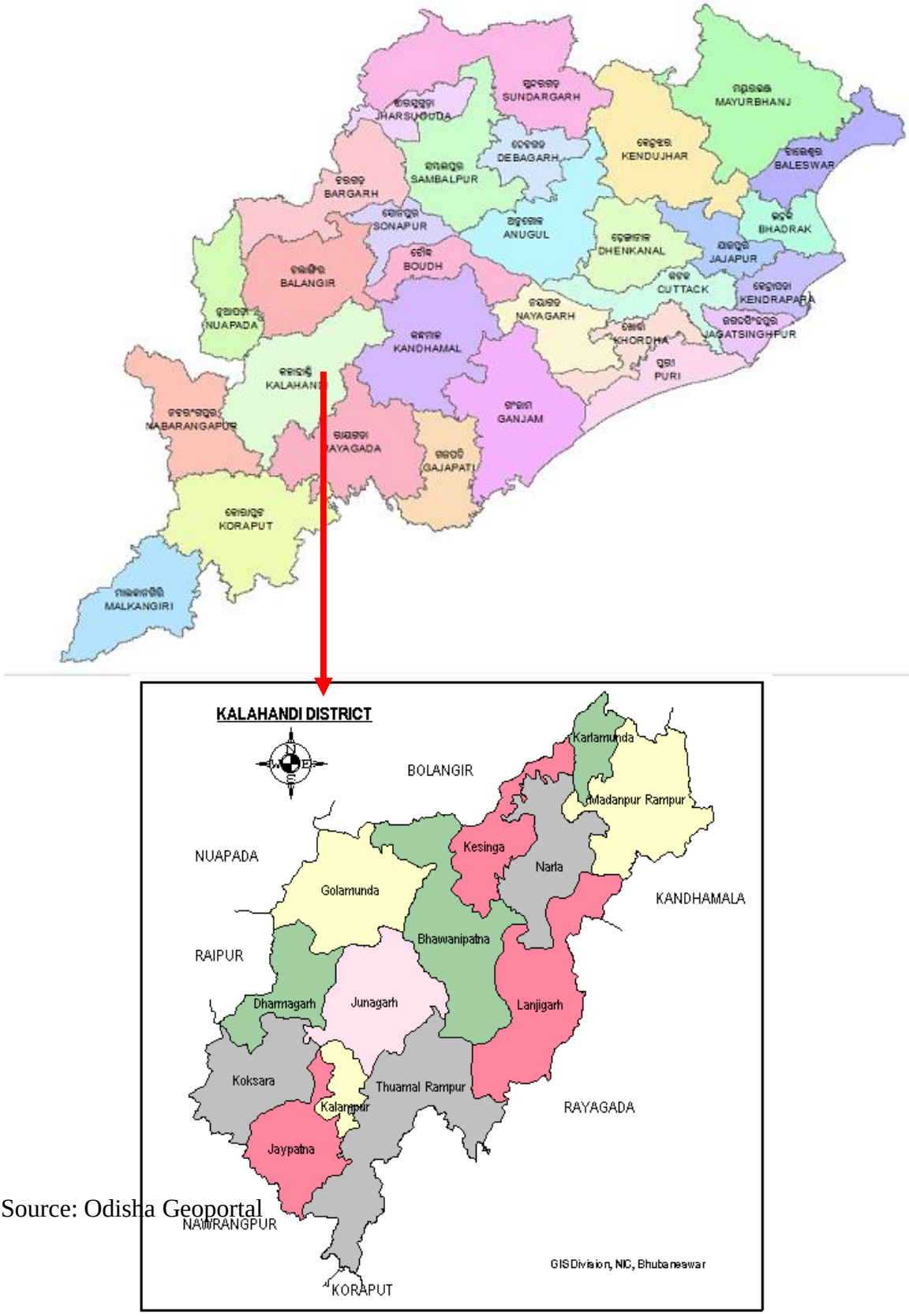


Figure 5 Bar graph representing prevalence of Sickle Cell Disease in India



Source: Odisha Geoportal

Figure 6 Map of Kalahandi district in the States of India

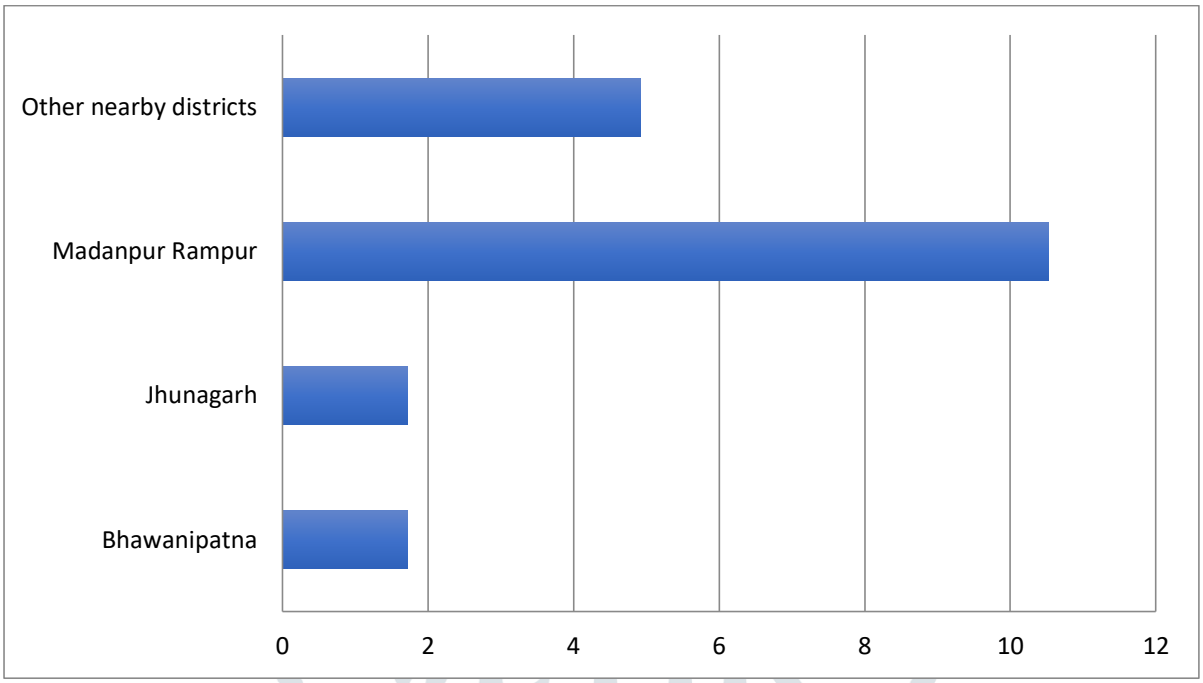


Figure 7 Bar graph presenting prevalence of Sickle Cell Disease in newborn at Kalahandi district

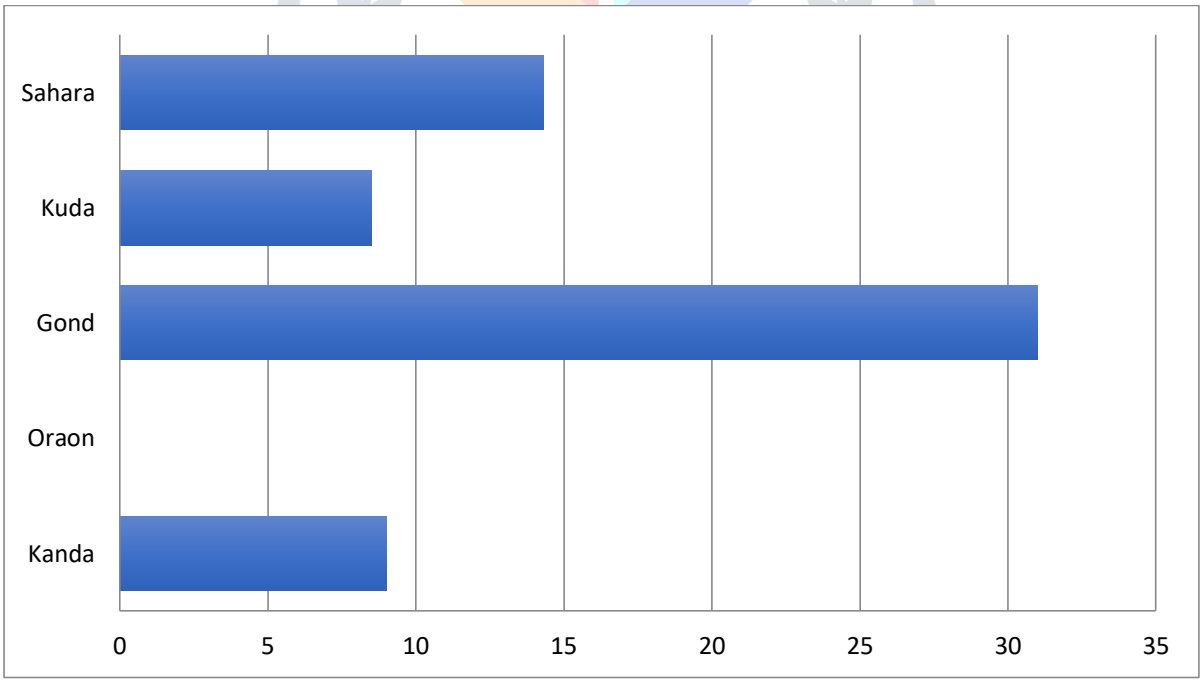


Figure 8 Bar graph presenting prevalence of Sickle allele in five tribal communities of Western Odisha

Table 1: Annually affected newborn with Sickle Cell Disease in WHO Regions

REGION	NUMBER	PERCENTAGE (%)
African Region	233, 289	84.47
American Region	9047	3.27
East Mediterranean Region	6491	2.35
European Region	1292	4.67
South East Asia	26037	9.42
West Pacific Region	13	0.004
World	**276, 168**	**83.68**

Source: Modified from (Banu Aygun 2012)

Table 2: Estimation of prevalence of Sickle Cell Disease through many state level studies in India

STATE	PROGRAMME	TOTAL SCREENED	SICKLE CELL DISEASE	%WITH SICKLE CELL DISEASE
Maharashtra	Non-tribal, infants of maternal carriers	2134	113	5.30
Chhattisgarh	Tribal and non-tribal infants	1158	6	0.52
Odisha	Tribal and non-tribal infants	1668	34	2.04
Tripura	Tribal and non-tribal infants	2400	0	0.00
Tamil Nadu	Tribal population under 30	9646	111	1.15
Rajasthan	Garasia tribals	1676	14	0.83
Madhya Pradesh	Pregnant women	416	7	1.68

Source: Modified from report of Economist Intelligence Unit (Anil Khatri 2020)

Table 3: Area wise prevalence of sickle Cell Disease in newborn at Kalahandi district, Odisha, India

AREA	TOTAL (n=761)	% WITH SICKLE CELL DISEASE (n=13)
Lanjigarh	8	
Bhawanipatna	292	1.71 (n=5)
Golmunda	42	
Jhunagarh	175	1.71 (n=3)
Kesinga	36	
Narla	27	
Dharmagarh	20	
Jaypatna	42	
Koksara	28	
Madanpur Rampur	19	10.52 (n=2)
Kalampur	2	
Thuamul Rampur	7	
Karlamunda	2	
Other nearby districts	61	4.916 (n=3)

Source: Modified from (Sujata Dixit 2015)

Table 4: Prevalence of Sickle allele in five tribal communities of Western Odisha

TRIBES	DISTRICTS	% WITH SICKLE CELL DISEASE
Sahara	Kalahandi and Bargarh	14.3
Kanda	Kalahandi	9.0
Oraon	Kalahandi	0.00
Gond	Bargarh	31.0
Kuda	Bargarh	8.51

Source: Modified from (Prasanta Purohit 2014)

Table 5: Emerging treatment approaches for sickle cell disease

Therapy (previous name)	**Advantages**	**Limitations**
FDA approved		
l-Glutamine	Oral formulation available; reduced the frequency of acute complications	Phase III trial results not yet published
Phase III study		
Rivipansel (GMI-1070)	Can reduce the duration of pain crises, shorten hospital stays and decrease the amount of opioid pain medication	Currently available only in intravenous formulation; phase III trial results not yet available
Hydroxycarbamide	Reduces frequency of acute pain events, acute chest syndrome and transfusions in infants and adults	Disproportionate perceptions of carcinogenicity, teratogenicity and reduced fertility
Prasugrel	Hypothesized to reduce the duration of vaso-occlusive crises; seems to be well tolerated at both therapeutical and supra-therapeutical doses	Phase III study results not significant
Vepoloxamer (MST-188)	Hypothesized to reduce the duration and severity of acute pain crises	Phase III study results showed no effect
l-Arginine	Significantly reduced the severity of vaso-occlusive crises in Phase II studies	Phase III trial results not yet available
***N*-Acetylcysteine**	Oral administration	Phase III study results showed no effect
Magnesium sulfate	Vasodilator, anti-inflammatory and pain reliever activities	Phase III study results showed no effect
Transfusions for silent cerebral infarcts	Significantly reduced the incidence of ischaemic stroke recurrence in children	Cumbersome to move into general practice
Transfusions for stroke prevention	Significantly reduced the incidence of first stroke in children with	Follow-up study showed that it was not safe to stop regular transfusions after 30 months

	high cerebral artery blood flow	
Transfusions changing to hydroxycarbamide	Efficacious for primary stroke prophylaxis	Not clearly superior to chronic transfusion for secondary stroke prophylaxis
GBT440	Well tolerated; proof of concept with improved oxy-gen delivery to tissues and marked reduction in circu-lating sickle erythrocytes	Phase III trial results not yet available
Phase II study		
Crizanlizumab (SelG1)	Reduced the incidence of acute complications by 45%–63%	Monthly intravenous infusions required
Inhaled NO	Provides NO to correct decreased bioavailability	Phase II trial showed no ef-fect on the duration or se-verity of vaso-occlusive pain crises
Sildenafil	FDA-approved for pulmonary hypertension and erectile dys-function	Phase II trial terminated early owing to increased frequency of acute pain events
Sanguinate	Hypothesized to prevent vaso-occlusive crises and leg ulcers	Limited data
Sevuparin (DF02)	Might decrease erythrocyte adhesion and favour normal blood flow and reduce the risk of vaso-occlusion	Limited data
Phase I study		
Pomalidomide	Well tolerated; increases HbF and total Hb levels; anti-in-flammatory effects	Limited data
IMR-687	Preclinical data indicate decreased sickling, Neutrophiladhesiveness and vaso-occlusion	Limited data
SCD-101	Natural product	Limited data
Gene insertion	Insertion of genes encoding anti-sickling engineered β-glo-bins	Unknown long-term risks; unclear whether curative or only ameliorative
Preclinical study		

Genome editing	Methods include zinc-finger nucleases, transcription activator-like effector nucleases and CRISPR–Cas9	Unknown long-term risks; potential cure or disease amelioration, depending on strategy

Source- Modified from (Kato 2018)

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