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Sickle cell disease: A global health concern; pathophysiology, epidemiology and advances in point of care diagnostics

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Abstract

Sickle cell disease (SCD) is the most critical “hemoglobinopathy” worldwide in terms of frequency, and social impact. Recently, it is recognized as global health concern by World Health Organization (WHO). SCD affects approximately 5% of the world population with a various estimate in different continents. Deaths from SCD are evitable by cost effective diagnosis and efficient health interventions for management.

Our comprehensive review focuses mainly on the prevalence of SCD, its associated clinical features including crisis, pulmonary pathobiology, muscular, neurological, hepatobiliary and ophthalmological complications along with frequent sepsis and priapism. Further, the present scenario of SCD diagnosis and confirmation requires sophisticated equipment, reagents and adequately trained laboratory persons, also there is unmet requirement for advance methods, to diagnose and monitor SCD that are both inexpensive and accessible. As new diagnostic methods are delayed in clinical trials and more are in pipeline, the purpose of this review is also provides an overview on emerging point of care (POC) techniques offering hope for detection and management of this unfortunate disease.

Keywords: SCD (Sickle Cell Disease); POC (Point of Care Techniques); SCD Complications; SCD Management; SCD Prevalence; SCD Diagnosis

1. Introduction

Sickle cell disease (SCD) is an umbrella term for a group of hemoglobinopathies, which is defined as homozygosity for the sickle hemoglobin (HbS) gene (Hb S: [β 6, (A3), Glu→Val, GAG>GTG]). Among the other haemoglobinopathies, SCD is the prevalent genetic public health issue, because of abnormal hemoglobin polymerization, in case of homozygous (HbSS) persons (SCD affected) will suffer from lifelong acute, and chronic complications [1]. Sickle shape of RBCs causes hemolysis and leads to vaso-occlusive crisis (VOC); primary life-threatening risk factor with pathophysiological effects of end organ ischemia, and infarction. VOC also leads to acute chest syndrome (ACS); by triggering different factors including pulmonary hypertension (hypoventilation), it is one of the most serious pulmonary infectious diseases in adults. The pulmonary hypertension estimated 6% and is more frequently described in patients with venous ulcers and higher levels of chronic hemolysis [2]. After observing the serious problems involved with SCD, on 63rd world health assembly in 2010, management and prevention of birth defect adopted a resolution, for SCD and enabled haemoglobinopathies to include in the most recent global burden of diseases [1].

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Worldwide, every year approximately 330,000 babies born with hemoglobinopathies [3] this number could reach to 400,000 by 2050, both in high-income and lower-income countries [4]. In this, prevalence of disease almost 80% burden is from in Sub-Saharan Africa and out of it half belongs to mainly to three countries Nigeria, Democratic republic of Congo, and India [5]. India alone has 15% of world neonates with SCD [6], and previous studies suggested that Madhya Pradesh is expected to have the greatest number of births with SCA in 2020, followed by Tamil Nadu, Maharashtra, Gujarat, Odisha, and Chhattisgarh [7,8]. Approximate, 50-90% of SCD children die before they attain the age of five because of lacking diagnosis and care [9]. However, pervasive fast and accurate testing procedures still need to be implemented. Although, many techniques used for the diagnosis of SCD at primarily level, one of them is solubility test. However, solubility test cannot distinguish between sickle cell trait (SCT) and SCD; therefore, it needs further confirmation tests such as, hemoglobin electrophoresis, isoelectric focusing (IEF), and high-performance liquid chromatography (HPLC) [10]. Further, these methods require specialized equipment and are not feasible in low income countries. Thus, the development of portable and cost-effective methods is indispensable. Few advances in screening methods emerged in the past couple of years, with their pros and cons. The new screening methods includes paper-based solubility test, density-based separation, lateral flow immunoassay, and digital mode detection. These advance techniques are user friendly and cost effective. Though, these techniques have their own limits in terms of detection, such as high fetal hemoglobin (HbF), and fabrication issue. Given the implications of SCD, World Health Organizations (WHO) had a call for the design and implementation of programs for the prevention and management of SCD, which includes monitoring and screening programs in countries where SCD is a public health issue. In this review we discuss about prevalence of SCD in continent like Africa, UK, US, and India with clinical manifestation and point of care technique (POC) along with their advantages and pitfalls.

2. Global scenario of sickle cell disease

SCD is a monogenic hemoglobinopathy affecting approximately 5 % of world population, and over 7% of pregnant women are carriers of hemoglobinopathy. In every year 33, 00,000 new babies are born with hemoglobinopathy, and 2, 75,000 born affected with SCD [5]. In this almost 80% of SCD patient born in sub-Saharan Africa and in that half were born mainly on three countries; democratic republic of Congo, Nigeria, and India [6]. With 15% of all SCD neonates born worldwide in India, the disease is quite prevalent in this country [7].

2.1. Prevalence of SCD in Africa

The prevalence of the SCD is high throughout large areas in sub-Saharan Africa, every year 240,000 babies born with SCD and leads a low quality of life, lower life expectancy and higher infant mortality [7]. It is estimated that 50 -90% babies born with SCA in Africa were died at preschooler's age [11]. From Africa, Uganda was the first country documented large burden of SCD; from testing programs in Uganda, they had tested 10,000 infants in 112 districts, and the prevalence was noted in peak in the mid northern and east central regions. SCT prevalence was 13.3 percent nationwide, while it was over 20 percent in eight districts. The lowest prevalence was in the South Western area, with less than 5% in nine districts and less than 3% in two districts. Eight districts showed prevalence rates of more than 20 percent, with Alebtong having the highest rate at 23.9 percent. This suggests that at least 15,000 kids are born with SCD in Uganda each year [12].

The prevalence percentage of sickle cell trait (SCT) in various parts of Africa 10-45%, SCD affects 2 to 3 % of Nigerian population. The carrier prevalence of sickle cell in Nigeria 20-30%. Nearly 150,000 babies born sickle cell anemia in Nigeria annually [13]. From Africa, four main haplotypes were reported and named as Senegal, Benin, Bantu and Cameroon haplotypes which were characterized and believed to originate in these regions. The high prevalence of SCD in sub-Saharan Africa has an advantage which conferred the resistance to plasmodium falciparum infection by the SCT [14].

2.2. Prevalence of SCD in United States

The sickle gene was transferred to Latino population of the western hemisphere mainly through migration occur in endings of 1800s. The largest number of Africans under duress taken to America was distributed to the Caribbean and the U.S., Brazil. It estimates that 2-3 million "Americans" and 1-2 million Brazilians are SCT carriers [15]. Table no.1 shows population affected in various states of United States, the estimated number of SCD affected population from USA is given in Table.1.

Table 1 SCD population in United States

Country name	SCD population
United states	89,079
Hispanics	8,928
New york (total)	8,308
Hispanics	1,338
California (total)	5,100
Hispanics	408
Brazil	30,000
Cost rica	<500
Venezuela	2,500-3,200

2.3. Prevalence of SCD in Europe

SCD is the most common hereditary disorder and its frequency has been steadily increasing in the European population from past few decades. In Europe it is mainly present in Italy, France and UK. In 2018, France has reported more than 26,000 SCD cases and the country has high prevalence followed by UK. The cases are transfers from one area to another depending on the distribution of risk communities. The prevalence rate of, 5-7% increasing each year since 2000. There are around 1,275 people with SCD residing in Italy, according to 2019 statistics from the National Registry of Thalassemia and 128 haemoglobinopathies. In 1998, 129 researchers from the University of Catania's Department of Hematology and Pediatric Oncology conducted a survey that was then circulated to 130 paediatric and haematology clinics throughout Italy. It was discovered that, of the 673 SCD patients with known places of residency, 60% lived in Sicily, 20% in Southern Italy, 6% in Central Italy, and 13% in Northern Italy. When the poll was updated in 2003, the percentage of SCD patients in northern Italy had climbed to 20%, whereas the percentage in Sicily had declined to 53% [16].

2.4. Prevalence of SCD in Asia

2.4.1 Prevalence of SCD in India

The sickle cell gene is primarily observed within tribal populations in India. It contributes 15% of world neonates with SCD born every year. The prevalence of SCA is very common in the tribal belt of southern and central India. It has been stated that the SCA in India being linked to the Arab Indian haplotype has a mild clinical presentation. In India the prevalence rate of SCD varies from 1-40% in the tribal population. It is estimated that almost 10 million children by 2050 have SCD [7].

With an estimated population of 9, 61,492 sickle heterozygotes and 67,861 sickle homozygotes, Madhya Pradesh has the largest load. It's also common in south Gujarat, Maharashtra, Chhattisgarh, and western Odisha, with a smaller distribution in Andhra Pradesh, Karnataka, northern Tamil Nadu, and Kerala in the south India. SCD is commonly found among tribes that are thought to be the original inhabitants [17].

2.4.2 Prevalence of SCD in Saudi Arabia

The population of Saudi Arabia is 23.98 million. The adult population's prevalence of the sickle cell gene was evaluated by the Saudi government's premarital screening programme, which found 4.2 percent for SCT and 0.26 percent for SCD, with the highest incidence recorded in the eastern province (nearly 17 percent for sickle-cell trait and 1.2 percent for SCD). Prevalence for SCD in the eastern province over a 9-year period was 2.6 percent in a local with neonatal screening, compared to 17 percent and 1.2 percent, respectively, from premarital screening. Up to 1.4 percent of people in some locations had SCD, while the heterozygote status ranged from 2 to 27 percent [18].

3. Clinical manifestations of sickle cell disease

Clinical presentation of SCD in India is relatively softer than in African patients and it is extremely variable within different tribal and nontribal population [19]. There are many clinical complications of SCD i.e., early mortality,

anemia, painful crisis, and widespread organ damage. Three types of pain of sickle cell include chronic tenderness syndromes, acute recurring painful crises, and neuropathic pain. Inflammation associated with each acute painful episode that worsens with recurrent episodes often terminate in serious problem and organ damage, such as acute chest syndrome, multi-organ failure, neuropathic pain and unexpected death.

3.1. Vaso-occlusive crises

Sickle shape of RBC causes hemolysis leads to VOC, primary life-threatening risk factor with pathophysiological effects of end organ ischemia, and infarction. These acute changes convert to chronic vasculopathy and immune dysregulation. Key hallmarks of SCD pathophysiology is hemolytic anemia, Vaso-occlusion, and vasculopathy [20]. Complications such as acute-on-chronic, Acute, and chronic, contribute to end-organ damage and badly affects quantity and quality of life [21]. Three types of pain of sickle cell include chronic tenderness syndromes, acute recurring painful crisis, and neuropathic pain. The hallmark of the disease is acute painful crisis needs hospitalization and emergency treatment in the hospital. Inflammation associated with each acute painful episode that worsens with recurrent episodes [22]. Within one month and one week after discharge most of the patient with acute painful episodes were readmitted and pain score was recorded, showed significantly decreased during first four days of hospital admission. The parameter included for readmission is recurrence of new acute painful episodes accompanying high mortality. Admitted and discharged patient seeks careful monitoring at hospital and home [23].

3.2. Pulmonary Pathobiology

SCA with pulmonary complications represent approximately 2-20% of mortality that includes acute and chronic events. VOC proceeds an acute lung injury as acute chest syndrome (ACS) by triggering different factors including pulmonary hypertension (hypoventilation) most serious, pulmonary infectious disease and vascular occlusions. In adult patients, the pulmonary hypertension estimated 6% and is more often depicted in patients with higher levels of chronic hemolysis and venous ulcers [24]. Graham et al, reported higher rate of chronic and acute sickle cell related lung damage i.e, pulmonary hypertension (33.3%) and fat embolism (33.3%), with right ventricular hypertrophy (33.3%). Unpredictable, episodic and unbearable pain of SCD considered as cardinal, most affecting pain of human being. Microvascular occlusion of SCD caused by stimulation of nociceptive fibers of nerves that leads to pain crisis. Flowing of blood to the organ hindered by sickled red blood cells (sRBCs) that obstruct microcirculation and leads pain, necrosis, ischemia and organ damage [23]. Hand foot syndrome is cardinal feature in the first year because of vaso occlusion of post capillary vasculature resulting pain of the extremities in tissue and oedema [25]. Infants showed uneasiness by irritability and delay in tendencies of crawl, walk and of underweight. Any body part gets affected by vaso-occlusive crisis in adults and older children. The pain resolution is unpredictable, onset of pain is episodic and can convert from acute to chronic pain with no precipitating factors along with well-known triggers of dehydration, acidosis, fever, infection, sudden weather change including cold, rain, wind speed and air pollution. SCA is connected with several neurological complications; epileptic seizures, stroke and febrile seizures in children, sensory neuropathy in adolescents and adults, paraplegia and localized, headache in children and adolescents [26].

3.3. Hepatobiliary complications

Disorders of the hepatobiliary symptoms with multiple organ failure are common in SCD [27]. In addition, the forms found in the general population, a number of conditions arise that are specific to SCD. These conditions include the occurrence of gallstones [28], and intrahepatic cholestasis [29].

3.4. Frequent infection

A lot of the early death associated with SCD is attributed to increased threat of infections due to untimely loss of splenic function [30]. Defective red blood cells including (sRBC) removed by spleen is main function of the spleen, resulting in further hemolysis [31]. In spleen blood flow through the spleen get slow thus increasing polymerization in HbS and reducing the oxygen tension. As a result, the splenic vascular capillaries shrink, additional hypoxia ensues, and afflicted blood cells are trapped by RBC polymerization. The spleen grows as a result of a cycle of hypoxia, RBC polymerization, and decreased blood flow; this can happen suddenly, with blood collecting in the vascular bed, leading to shock and circulatory failure. Abdominal distension, increased thirst, abrupt weakness, tachycardia, and tachypnea may result from this rapidly growing spleen tumour. Splenic sequestration crisis is an emergency because, if untreated, it can cause circulatory failure and result in death in 1–2 hours. [32].

3.5. Skeletal system/Muscular complications

Muscular and skeletal manifestations, with top incidence during the first 6-12 months of life. Dactylitis considers earliest muskoskeletol manifestation of SCD in infant and very young children [33]. Occurrence rates of dactylitis are

approximately 45% before age 2 years. It occurs more frequently in cold seasons and is coupled with a lower fetal hemoglobin and higher reticulocyte counts. Ischemia/infarction of the bone-marrow is associated with enhanced erythropoiesis and bone marrow enlargement involving the hands and feet, as well as with soreness, redness, swelling, and warmth of the affected limb/digit, according to the joint study of SCD (CSSCD) study [34]. Prolonged ischemia and/or associated osteomyelitis may result in bony deterioration of the terminal phalanges and metacarpals. [35].

3.6. Neurological complications associated with sickle cell disease

Central nervous system (CNS) stated cerebrovascular accident (CVA) major complications of SCD with age specific prevalence and incidence rate in patient with SS homozygous genotype were incidence of CVA is lowest in sickle cell (SS) patient between age 20 to 29 years and higher in children and older patients [36]. Acute patient with SCD-SS genotype diagnosed with headache (common) problem, associated with CNS events compared to general pediatric population. Confirmatory imaging studies permit for transient ischemia attack, history of stroke, seizure, focal neurological exam, elevated platelet count and neurologic symptoms [37].

CNS is one of the often-affected organs by SCD that starts early on life and results to neurocognitive dysfunction, that approx. one-fourth to one- third of children with shortage in specific cognitive domains and academic difficulties [38]. Children between age group 6-12 years were identified with CNS abnormalities in MRI and CVA in SCD-SS patient found significantly in poorer performance of children with CVA history these children with silent infarcts or no abnormality in MRI is the majorly neuropsychological evaluation measures [39].

3.7. Ophthalmological complications

Sickle cell retinopathy (SCR) is the common complication of SCD [40], while susceptibility of vision loss due to retinopathy reported by [41]. Eye vascular beds including the conjunctiva, retina, anterior segment, choroids can be affected by vaso-occlusion with high risk of disturbing visual consequences, the disease need close monitoring of the ophthalmologic problem in SCD patients [42].

3.8. Priapism

Condition of persistent penile erection in the absence of sexual desires. Reported as a common (35%) but often understated complication in youth as well as adults with SCD. During normal erection the blood flow increases with increased oxygen extraction. In condition of hypoxia, it promotes sickling with congestion of the corpora, sludging, further injury of venous outflow and worsening hypoxia. From corpora venous outflow get reduced. During episode of priapism the blood aspirated from the corpora observed dark in color, low glucose level and low pO₂ [43]. The occurrence of priapism reported during the time of sleep with recurrent and changeable duration and minimum age of priapism reported in 7 years old and maximum 30 years [44]. It is a complicated condition of SCD that requires close awareness or attention due to its significant impact on the SCD patient life therefore should be further investigated.

4. Advanced techniques for SCD screening

Growing demand for population screening for the SCD, gives rise to a necessity for high pensive systems, which allow rapid, sensitive and profitable screening of clinically significant haemoglobinopathies. Traditional methods employed in the diagnosis of SCD involved the use of solubility test, electrophoresis, HPLC, and IEF. Cell solubility test is based on the principle of relative insolubility of HbS, and when coupled with sodium dithionite, a reducing agent, it is put through a qualitative test in which it is compared to other haemoglobin types. This technique is very well found, effective and shows a high specificity, and sensitivity. Electrophoresis totally relies on separating the different types of hemoglobin (Hb) via electrical charge, and can be used either liquid or dried blood samples. "Cellulose acetate membrane" is most commonly used for electrophoresis; other useful method is using electrophoresis along with citrate agar gel, which depends both on the charge of hemoglobin and its capability to merge with the agar gel mixture. HPLC is automated technique and hence, it is less laborious. But focus shifted to IEF gradually, which offers a higher resolution and is more cost effective. It is an equilibrium process in which hemoglobin (Hb) migrates within a pH gradient to a position of isoelectric point (pI) or zero net charge. However, HPLC has the ability to differentiate between different Hb variants and hence is more reliable but these methods are time consuming, laborious, expensive and difficult to perform.

The most recent technologies trending for SCD screening are (1) paper-based hemoglobin solubility assays, (2) lateral flow immunoassays, (3) density-based separation, (4) micro engineered electrophoresis and (5) digital mode detection. These laboratory techniques are briefly reviewed here with a focal point on complexity and specificity.

4.1. Hemoglobin solubility assay based on paper

A useful low-cost, rapid paper based SCD method is a tool for “screening” of adults and children with SCT and SCD; display its practicality in poor-resource clinical setup. Hemoglobin solubility buffer used for dilution of sample of blood and then drop of mixture is put onto chromatography paper. Because deoxy-HbS which is insoluble, is polymerized and cellular fragments are entangled by the paper fibers, left over within the original outline of the droplet on paper, while normal form of Hb is soluble and easily wicked laterally outwards by capillary action [45]. HbSS can be visually identified with sensitivity 94.2% and 97.7% specificity with validation results of this test in a resource-limited setup [46]. This paper-based assay gives the advantages of, cost-effectiveness, rapid, ease of use, uncomplicated fabrication, and minimal sample processing, as it requires only one step of mixing. Moreover, it uses the normal color of blood for detection without reinstate to complex color changes detection or labels. One more advantage of this, tests can be performed individually and no batching of sample is required.

A disadvantage of this technique is, clotting of the blood samples may affects the results by which would prevent the wicking of the blood sample through the paper substrate. R. Kumar [47] from national institute of research in tribal health (NIRTH) studied and validate buffer in different storage condition, and for various time period and reveals results is that 100% sensitivity and 100% specificity for identification of HbSS and identification of all genotypes with 15% of metabisulphite, which is stored at 4 °C will give more accurate results. Stability of metabisulphite buffer at 4°C found up to 180 days. So, this can be used upto 6 month when stored at 4 °C, it will reduce labor from preparing daily fresh buffer [47]. This test cannot accurately distinguish between HbSC variant and HbAS variant is main disadvantage of test, even when used with automated image processing.

4.2. Lateral flow immunological assay

Key advantage of this technique is that, it distinguishes between SCD and SCT within 15 minutes, Sickle SCAN™ strips of this are equipped by using HbAA and HbSS taken from the donor of blood. Assay includes a test strip, with a polyclonal antibody (Ab) immobilized on four different test lines which is conjugated with colored nano-particles. Once in the test specimen when sample of blood is put on into the device, this solution diffuses to the test zones where the Hb is forming antibody–antigen complexes. In test strip have four lines corresponded to control and hemoglobin types, fourth line serve as control and other each one-line parallel with the three hemoglobin types to verify proper operation of the device. Consequently, blue line appearance indications the presence of targeted hemoglobin types [48]. Readout result can be found from the device in 2 min. The limit of detection (LOD) varies among different hemoglobin types. The specificity for HbSS is 98.4% and sensitivity of the test ranging from 95.2%-100% [49].

Another lateral flow immunoassay is HemoTypeSC™. The assay utilizes monoclonal Ab instead of polyclonal Ab specific to HbA, HbS, and HbC. It used membrane of nitrocellulose with Ab deposited on four different locations parallel to each of the three hemoglobin (Hb) types as well as a control. Distilled water used for blood sample dilution. When blood sample is put on the sample strip, and then this strip is dipped in a sample vial containing red-colored colloidal “gold nanoparticles” for rehydrated in assay buffer solution. This strip is allowed to the wick liquids only for 10 min before it is taken out of the vial. For test results analysis, red line absence on one or more of the four specific locations is a signal of the presence of the corresponding hemoglobin type. Within 20 min results are obtained from this assay. Sensitivity and specificity for detection of HbS, HbC, HbA, was reported to be achieved with 100%. As in the previous Sickle SCAN™ lateral flow immunoassay, quantification of the results is unable, and the processes involved in its fabrication are very complex. However, the assay is able to distinguish between HbSS, HbSC, HbAA, HbCC HbAS, and HbAC. But identification of other Hb types such as HbF and HbA2 is not possible [50].

4.3. Density-based separation method

The density-based test is quick and simple. The density of RBC variant is used for detection as HbSS RBC homozygous and heterozygous HbSC states greatest to intermediate density respectively, and it is lowest for non-sickling conditions. Cell density measurement via using aqueous multiphase systems (AMPS) detects sickles RBC. AMPS two and three-phase capable of distinguish normal cell among dense sickle RBC with sensitivity and specificity 90% and 97% respectively for the two-phase system, whereas sensitivity of three-phase system is 91% and with specificity of 88%. Estimated LOD for dense cells was 2.8%. This test requires aqueous polymeric solutions to be mixed with 5µL of blood. Mixture of sample is loaded into capillary tubes and centrifuged time is only 10 min. The dense RBC of SCD layer at the bottom of the tubes precipitated. Moreover, distinction between HbSS and HbSC improved via the use of greater centrifugation time and an optical reader. Further analysis of sediment layer would also allow for quantification dense cells fraction. Though, the use of a centrifuge raises the cost of the test and its use at the point of care (POC). Batching of sample to processed increase turn-around time. This technique is also not capable to differentiating between HbAA and heterozygous HbAS. On the other hand, this test might not be appropriate for detection of SCD in newborns babies since

blood of newborn is not as much dense due to high levels of HbF in the first 4–6 months of life. Moreover, treatment processes, many unhealth conditions, and prescribed medications, as well as genetic factors, influence the RBCs density and in turn edge the validity of the test [51].

4.4. Micro engineered electrophoresis (HemeChip)

HemeChip recently developed to analyze and measure hemoglobin types including HbS, HbF HbA, and HbC/A2, among others. HemeChip principles based on, current clinical standard electrophoresis method. It is made up with a microfabricated polymethyl methacrylate (PMMA) chamber lodging an electrophoresis paper strip of cellulose acetate, electric field applied for separate hemoglobin types. Objective and automated quantification of HemeChip for results at the POC application of mobile for image processing has also been developed [52]. For sample preparation lyse the cells and release Hb, then addition of blood sample with pure or deionized (DI) water and proceeded mixture solution is stamped onto the paper substrate inside the chip. The next step involves applying an electric field over integrated electrodes. Each type of haemoglobin will travel a different distance from the application point across the paper strip due to variances in haemoglobin mobility that different haemoglobin bands acquire. In less than 10 minutes, screening is completed, and test results are obtained with 90 percent sensitivity and 89 percent specificity in identifying HbC/A2 and HbS bands, and with 100 percent sensitivity and 86 percent specificity for differentiating between HbF and HbA. In bands, 89 percent sensitivity and 82 percent specificity are obtained in identifying HbS and HbF bands. [53]. HemeChip is rapid, low cost, accurate, and robust. Furthermore, laboratory-scale electrophoresis and routine HPLC tests yield reliable results for haemoglobin identification and quantification. Another benefit of this method is the potential for integration with mobile devices for more precise analysis. Additionally, the present HemeChip test configuration uses a bench-top power supply. Though, due to the low power requirement for the test, for real-world applications this power supply can be replaced by portable rechargeable batteries [54].

4.5. Digital mode detection of sickle cell disease (sickle cell tester)

Mobile is attracting increasing interest in global health to reduce resource disparities and optimize healthcare sector. Over the past few years, POC haemoglobin tests and POC ultrasonography have also been developed for use with mobile phones [55]. Sickle cell tester is an alternative portable test that relies on density approach, uses very little amount of blood for testing, and omits the utilisation of centrifugation equipment. To classify RBCs affected by SCD, a 3D printer attachment used optical lenses, light emitting diodes (LEDs), and magnets. Magnetic levitation used for this test is omits the need for a microscope to analyze the sickle shape directly and allows the use of smart phone imaging to examine, at a lower image resolution. RBCs are separated based on density. The densities of HbSS, RBCs vary, so it is possible to distinguish between control RBCs and relatively high-density SS RBCs using magnetic levitation, which may be seen as a change in the levitation of the cells in a magnetic field. As an oxygen scavenger used to produce the deoxygenated form of haemoglobin in order to improve RBC density, sodium metabisulfite can be used to counteract this effect using control RBCs. However, under these conditions, SS RBCs undergo an increase in density. A smart phone attachment device makes it portable and allows self-diagnosis. This platform eliminates the need of an internet connection and found label-free, sensitive, and specific detection of SCD. This device is portable compare to larger instrument, possible to transmit medical results obtain in various remote location for epidemiological analysis [56].

Table 2 Comparison between traditional and advanced SCD diagnostic techniques

Diagnosis specificity	Citrate agar electrophoresis	IEF	HPLC	HemoTypeSC™ (Lateral flow immunoassay)	Sickle Dx (paper-based test)	SCD-AMPS (Density based separation)	Sickle Cell Tester (digital mode)
Able to Diagnose SS from SCD in Newborns?	No	Yes	Yes	Yes	No	No	No
SS from AS	Yes	Yes	Yes	Yes	Yes	Yes	No
SS from AA	Yes	Yes	Yes	Yes	Yes	Yes	Yes
AA from AS	Yes	Yes	Yes	Yes	Yes	No	Unknown
Time required	Approx. 1 hour of labor for one gel (14 sample)	8 hrs	8 hrs	15 min	15 min.	<20 min.	<15 min.

Besides that, drawback of sickle tester is, it cannot detect SCT, is a major limitation of this technique and also the user may face accessibility issue and need additional research for accessible to add on different mobile sets as it only compatible with Samsung galaxy4, a comparative analysis between traditional and advanced SCD diagnostic techniques in given in Table.2.

5. Discussion

The aim of this article is to give an up-to-date prevalence, complicated clinical manifestations associated and advancement in diagnosis techniques of SCD. WHO has declared SCD is one of genetic disease of public health priority (1) as prevalence of SCD in Europe is mainly found in France, Italy, and UK. In Europe, every year more than 52,000 people are affected from SCD [16]. It is estimated that 73% of the people with the sickle cell gene in India are from the tribal population. SCD are projected to increase by 30% by 2050 in India (1). To prevent this, many countries have been implementing many programs like new born screening and pre-marital screening. SCD is widespread also in developing countries due to lack of proper health care facilities and socioeconomic issue. Clinical complication associated with SCD that affects SCD patient physically and psychologically, focuses on crisis (episodes of pain), that is frequent in SCD patient due to obstruction in blood flow caused by sickle shaped RBCs. Pulmonary pathobiology contributes approx. 2-20% of mortality with acute and chronic events. Adults' estimation of pulmonary hypertension is 6%, also includes venous ulcers and higher level of chronic hemolysis. Emphasis on the expression of uneasiness as irritability by infants [28]. Hepatic complications include stones [29], intrahepatic cholestasis, hepatic sequestration and recurrent hepatic ischemia and necrosis. Spleen of SCD patient dysfunction at early stage of life that contributes to the frequent infection [30]. Skeletal and muscular complications include dactylitis and ischemia/infarcts [35,36]. Headache frequent problem of SCD patient, CVA with higher prevalence in children and lower in 20-29 year age group [38].

Due to high mortality rate at early stage of life made requisite of SCD screening of neonates. In Africa, between 50 and 80 percent of newborns with SCD pass away before turning five. [11], due to a lack of diagnosis, basic therapy, supervision, and care, in developing nations like India and Africa, the diagnostic infrastructure is weak [57]. A better diagnosing facility is needed due to the rising demand for newborn screening. Many point of care techniques came in light with better specificity and sensitivity in low resource setup such as paper-based solubility test, density based separation, lateral flow immunoassay and SCD screening by digital mode. Despite the fact that HbF levels are high and have been shown to be difficult for all screening platforms, this is lowering the test's sensitivity and specificity. But throughout the first six months following birth, babies' HbF levels gradually decline, with an estimated 60% of that decline occurring at six weeks. Because it fits in nicely with the regular immunization regimens for children in poor nations, this time period is particularly advantageous for point-of-care screening. Insight about SCD prevalence, clinical manifestation and diagnosis technique helps us to improve screening technology expansion and disease management.

6. Conclusion

Recent literature demonstrates that clinical complications of SCD leads to high morbidity and low life expectancy. Clinical outcome of SCD is too complicated which leads death of patient. Global burden of SCD primarily affected in developing countries like Nigeria, Uganda, followed by India and then United States and others. Prevalence of SCD in these parts occurs largely in tribes; these populations are unaware of disease and not able to access government healthcare facilities. This not only demands training of health workers, spreading of knowledge, but also advancement in diagnosis and treatment. There is limited resource setup at point of care centers, SCD diagnosis became meagre in countries like African countries and India where the burden of SCD is high, they require good planning for monitoring, which can significantly reduce mortality. POC diagnostics for accurate SCD are feasible. However, many new techniques are in pipeline but it needs more research for cost effectiveness and reduce false positive results. Thus, it is hopeful that novel point-of-care testing for SCD screening/diagnosis will change the screening paradigm for some areas where central lab testing is not available.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no potential conflict of interest.

Authors' contributions

Sweta Gupta and Poornima Gautam contributed to the conceptualization, data curation, investigation, methodology, visualization, writing of manuscript with input from all the authors. Killamsetti Venkatramana, and Rishabh Paroha contributed to data curation, methodology, resources of the manuscript. Lokeswara Balakrishna Sunnam contributed to the supervision, review and editing of the manuscript. Parikipandla Sridevi contributed to the conceptualization, project administration, resources, supervision, review and editing of the original draft.

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