Multidisciplinary approaches to study anaemia with special mention on aplastic anaemia (Review)

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Abstract. Anaemia is a common health problem worldwide that disproportionately affects vulnerable groups, such as children and expectant mothers. It has a variety of underlying causes, some of which are genetic. A comprehensive strategy combining physical examination, laboratory testing (for example, a complete blood count), and molecular tools for accurate identification is required for diagnosis. With nearly 400 varieties of anaemia, accurate diagnosis remains a challenging task. Red blood cell abnormalities are largely caused by genetic factors, which means that a thorough understanding requires interpretation at the molecular level. As a result, precision medicine has become a key paradigm, utilising artificial intelligence (AI) techniques, such as deep learning and machine learning, to improve prognostic evaluation, treatment prediction, and diagnostic accuracy. Furthermore, exploring the immunomodulatory role of vitamin D along with biomarker-based molecular techniques offers promising avenues for insight into anaemia's pathophysiology. The intricacy of aplastic anaemia makes it particularly noteworthy as a topic deserving of concentrated molecular research. Given the complexity of anaemia, an integrated strategy integrating clinical, laboratory, molecular, and AI techniques shows a great deal of promise. Such an approach holds promise for enhancing global anaemia management options in addition to advancing our understanding of the illness.

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Abbreviations: AA, aplastic anaemia; IAA, immune AA; AAA, acquired AA; RAA, refractory AA; MSCs, mesenchymal stem cells; ATG, anti-thymocyte globulin; MDS, myelodysplastic syndrome; AML, acute myeloid leukaemia; NORD, National Organization of Rare Diseases

Key words: anaemia, genetic disorders, precision medicine, artificial intelligence techniques, molecular research, vulnerable groups

Contents

1. Introduction

Anaemia is a condition in which the body does not have enough healthy red blood cells (RBCs) to carry adequate oxygen to the body tissues. RBCs provide oxygen to body tissues, and insufficient oxygen levels can lead to sensations of fatigue or weakness. According to the World Health Organization (WHO), anaemia is a serious global public health problem that particularly affects young children, menstruating adolescent girls, and women, pregnant and postpartum women. It is estimated that 500 million women between the ages of 15 and 49 years and 269 million children between the ages of 6 and 59 months are affected worldwide. Globally, (1 May 2023) it is estimated that 40% of all children aged 6-59 months, 37% of pregnant women, and 30% of women 15-49 years of age are affected by anaemia (sourced from https://www.who.int/news-room/fact-sheets/detail/anaemia#). Similarly, it also states that ~37% (32 million) of pregnant women were also affected by anaemia in 2019. In the world, African and South-East Asian individuals are the most affected with an estimated 106 million women and 103 million in African and 244 million women and 83 million children in South-East Asian regions. The contributing reasons can be malnutrition, poverty, infections, inflammations, and gynaecological and obstetric conditions. According to a survey in India by National Family Health Survey (NFHS-5) in 2019-2021, 25.0% of men (15-49 years), and 57.0% of women (15-49 years), 31.1% in adolescent boys (15-19 years), 59.1% in adolescent girls, 52.2% in pregnant women (15-49 years) and 67.1% in children (6-59 months) were found anaemic, which was a drastic change from the NFHS-4, where the prevalence of anaemia was ~50.3% totally (1,2). Anaemia is a syndrome of an underlying illness of

various conditions such as cancer, rheumatoid arthritis, chronic renal disease, etc., rather than a disease in and of itself (3,4). Anaemia can be caused by a combination of several factors, such as chronic diseases, nutritional deficiencies, bone marrow disease, and blood disorders. In some cases, it can be due to a combination of factors, and thus identification and classification may help in further treatment.

2. Anaemia and its types

The term anaemia is generalised and is used to refer to all diverse types/subtypes of anaemia. According to the WHO, anaemia is identified by haemoglobin (Hb) levels and is further classified into three types based on severity: mild anaemia (9 to 10.9 g/dl), moderate anaemia (7-8.9 g/dl) and severe anaemia (less than 7 g/dl). It has been stated that it is classified into six types, roughly based on Hb levels, RBC morphology, physiological abnormality, aetiology, category and RBC indices; anaemia can be classified based on its pathogenic behaviour and morphology (5,6). In its morphology of RBCs and blood cell indices, it is further classified into microcytic hypochromic, normocytic normochromic, macrocytic, and dimorphic anaemia. Meanwhile, the pathogenic classification is regenerative and hypo-regenerative. There are >400 types of anaemia, and it is further classified into three types, namely: Anaemia caused by blood loss, anaemia caused by decreased or faulty RBCs' production, and anaemia caused by the destruction of RBCs (7). Thus, based on the aforementioned surveys, anaemia can be also classified broadly into three types based on: i) nutritional deficiencies; ii) genetic changes such as mutations and autoimmune conditions; and iii) chronic disorders, (Fig. 1). In the present review, focus was addressed on anaemia which is caused by genetic conditions such as mutations, autoimmune conditions, and inheritance. Apart from genetic conditions, anaemia can also be caused by other factors such as overuse of drugs, viral infections and overexposure to chemicals. The several types of anaemia caused by genetic factors are haemolytic anaemia, sickle cell anaemia, thalassemia, aplastic anaemia (AA), Diamond-Blackfan anaemia (DBA), Fanconi anaemia (FA) and sideroblastic anaemia.

Haemolytic anaemia. Haemolytic anaemia is a condition characterised by the early destruction of premature RBCs before their life span. It can be caused by a range of factors, such as autoimmune disorders, genetic defects, infections and toxins. Haemolytic anaemia has two distinct types, namely, inherited and acquired. Inheritance is caused by genetic conditions like a mutation in the PKLR, SPTA1, ANK1, SPTB, SLC4A1 and AK1 genes (8,9). Apart from the mentioned genes, numerous genes are involved depending on the type and underlying conditions. Inherited haemolytic anaemia is classified into numerous forms depending on the abnormalities in the structure or function of RBCs. Acquired haemolytic anaemia is caused by specific conditions and their types (10).

Sickle cell anaemia. It is an inherited blood disorder where the RBCs are crescent in shape rather than round, which makes them rigid and sticky. This was caused by mutation in the Hb beta gene (HBB), a point mutation at chromosome 11p15.5. This point mutation leads to the production of abnormal RBCs. Thus, this type of anaemia is known as sickle cell anaemia. The sickle-shaped cells will last only for 10-20 days, leading to a shortage of RBCs in the body. Apart from this, the sickle shape can block or slow down the blood flow. It is the most common genetic disorder in the United States, affecting 1 in 500 African Americans (11).

Thalassemia. Thalassemia is a genetic disorder caused by mutation or deletion of the Hb genes. Hb is the protein that carries oxygen throughout the body. It is also an inherited disorder, as it transfers from one of the parents or the parent acts as a carrier. In normal human Hb, six globin chains (α, β, γ, δ, ε, ζ) are found at various stages of development (12). Among the six globin chains, alpha (HBA1 and HBA2) and beta (HBB) globin chains play a vital role in the ability of Hb to bind and release oxygen as it travels throughout the body. In the case of thalassemia, mutation or deletion in either alpha globin or beta globin can induce an excess of other types of globin chains. This provokes an instability that inclines to affect the production of Hb which paves the way for anaemia and other complications. There are two types of thalassemia, namely alpha thalassemia and beta thalassemia, which are further categorised into various subtypes such as α-thalassemia silent carriers, α-thalassemia treat, α-thalassemia major with Hb, β-thalassemia minor, β-thalassemia intermediate and β-thalassemia major which is also known as Cooley's anaemia (12,13).

AA. AA, as the name suggests, refers to the lack of bone marrow cells, which is the primary source of RBCs' production. Depletion or insufficient bone marrow cells can lead to a lack of erythrocytes as well as other components of the blood. It is an autoimmune disorder that is caused by assorted reasons, such as exposure to chemicals, over-intake of drugs, some viral infections, and in some rare pregnancy cases. AA is classified into two types, namely inherited and acquired. T-cells are found to play a leading role in the onset of the disease in both inherited and acquired cases. Apart from these types, idiopathic AA is one of them, where the cause of the disease and the relationship are unknown (14).

DBA. DBA is a rare genetic disorder caused by mutation in any one of numerous genes, including RPL5, RPL11, RPL35A, RPS10, RPS17, RPS19, RPS24 and RPS26. These genes provide instructions for making ribosomal proteins. Mutations in these genes lead to defects in ribosome biogenesis and function, impairing the production of erythrocytes, especially in their development and maturation. DBA is characterised by red blood aplasia, which means that the bone marrow does not produce enough RBCs (15). Apart from ribosomal protein, the GATA1 gene has been involved in DBA, because it is a haematopoietic transcription factor that is required for normal erythropoiesis. Mutations in this particular gene can also favour this disease (16).

FA. FA is a rare genetic disorder caused by mutations in at least 23 genes, known as FA genes, comprising FANC genes (A, B, C, D1, D2, E, F, G, I, J, L, M, N, O, P, Q, R, S, T, U, V, W, Y) that result in an impaired response to DNA damage. Due to mutations in these genes, there is a disruption in the

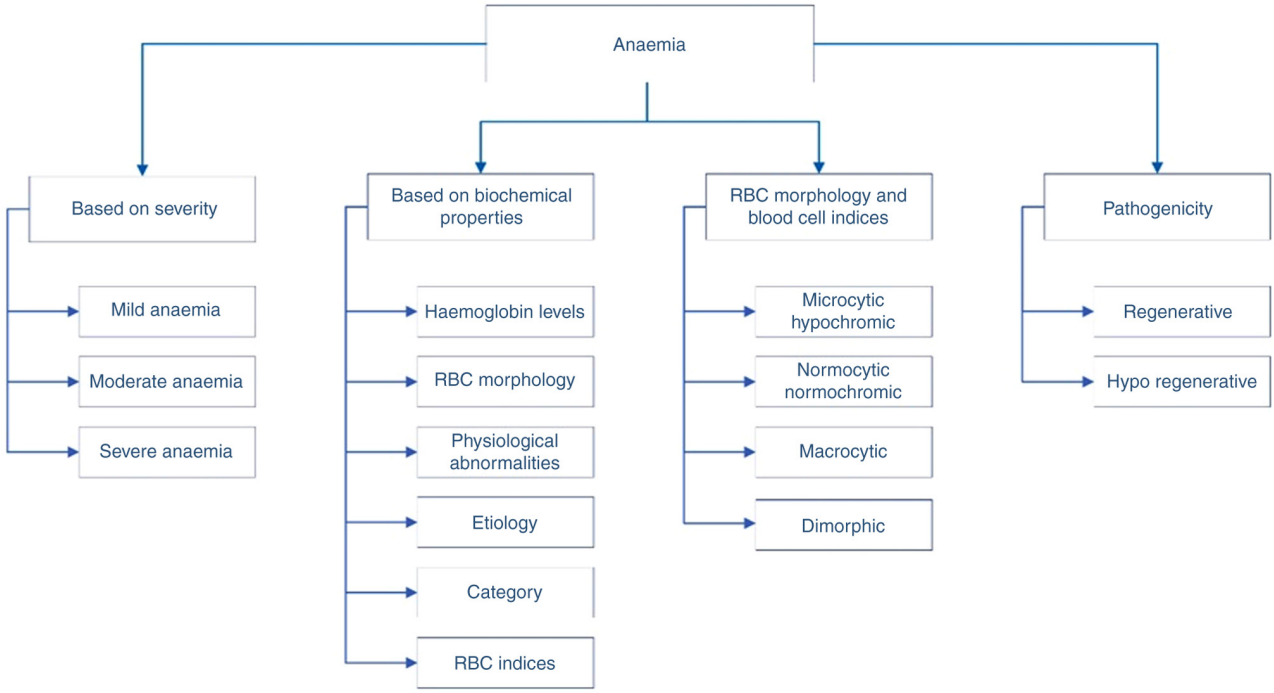

Figure 1. Classification of different types of anaemia.

normal function of FA genes, which results in bone marrow failure, physical abnormalities, and an increased risk of developing cancer. This type of anaemia is also associated with birth defects and affects almost all organs of the body (17).

Sideroblastic anaemia. Sideroblastic anaemia is a rare blood disorder caused by a mutation of genes involved in heme biosynthesis, iron-sulphur cluster biogenesis, and mitochondrial metabolism. In this type of anaemia, the bone marrow produces ring sideroblasts (immature RBCs with nuclei surrounded by rings of iron). It is classified into two types, namely inherited and acquired, in which inherited is classified into two forms, namely X-linked sideroblastic anaemia (mutation in ALAS2) and autosomal recessive congenital sideroblastic anaemia (mutation in various genes, including TRNT1, PUS1, LARS2, YARS2, FECH, GLRX5 and HSPA9). Similarly, acquired sideroblastic anaemia has two forms, namely primary and secondary. The primary is associated with myelodysplastic anaemia and the secondary is associated with exposure to certain chemicals, medications, and toxicity (18,19). Several types of anaemia and the features associated with them are consolidated in Table I.

3. Diagnosis of anaemia

The process of diagnosing diverse types of anaemia encompasses a multifaceted process that integrates clinical evaluation, laboratory techniques, in some instances molecular techniques, and in recent days prognosis and classification using artificial intelligence (AI) methods, as illustrated in Fig. 2.

Physical examination. When we consult a physician, a comprehensive physical examination is conducted, entailing the assessment of the retina of the eye, nails, tongue, and skin. Additionally, the patient's age and past medical history are gathered. The tips of the nails are examined for signs of weakening Hb levels, such as brittleness and spoon-shaped malformations. Pallor or glossitis are checked for on the tongue, and any colour, texture, or nutritional deficiency indicators are noted. The examination of the skin involves noting any pallor in the conjunctiva, nail beds, or palms; jaundice, which indicates potential haemolysis or liver failure, is also noted. A detailed examination of the retina is also carried out in order to find any vascular abnormalities or alterations in blood vessels associated with anaemia, as well as any potential indications of retinopathy. This information is crucial for a proper diagnosis.

Typically, most anaemia share common symptoms including dizziness, fatigue, paleness, loss of appetite, brittle nails, an increase in heartbeat and frequent infections. Apart from the above symptoms, they may vary depending on the type of anaemia. In the case of genetic disorders, it may affect the nervous system, muscle contraction, eye problems, neutropenia, heart problems, hypospadias and physical abnormalities. Consequently, the range and severity of symptoms are contingent on the underlying type of anaemia.

Biochemical analysis. Biochemical parameters are essential in assessing the body's physiological state since they provide important information on a range of health and illness-related topics. These characteristics, which are quantifiable indicators present in biological samples like blood, urine, or tissues, offer crucial details regarding the operation of organs, metabolic processes, and the existence of particular compounds. A complete blood count (CBC) test will be followed, which measures numerous different parts and features of blood, such as RBCs, white blood cells (WBCs), Platelets (PLT), Hb, haematocrit, Mean Corpuscles Volume (MCV) and Mean

Table I. Different types of anaemia, its features and involved genes.

S. no.	types	causes	Features	Genes involved	(Refs.)
1	Haemolytic anaemia	Autoimmune/mutation	Abnormality in the structure of RBC	PKLR, SPTA1, ANK1, SPTB, SLC4A1, AK1	(8,9)
2	Sickle cell anaemia	Inherited blood disorder/point mutation	RBC crescent shape	HBB - 11p15.5	(11)
3	Thalassaemia	genetic disorder	Microcytic RBCs	HBA1, HBA2 and HBB	(12,13)
4	Aplastic anaemia	Autoimmune/ acquired/genetic	Depletion of bone marrow cells	TERT, PIGA, FANCA, FANCC, DNMT3A, FANCGs	(14)
5	Diamond-Blackfan anaemia	Genetic disorder/ mutation	Impairment in the development of erythrocytes	RPL5, RPL11, RPL35A, RPS10, RPS17, RPS19, RPS24 and RPS26 genes	(15,16)
6	Fanconi anaemia	Genetic	Bone marrow failure	FANC (A, B, C, D1, D2, E, F, G, I, J, L, M, N, O, P, Q, R, S, T, U, V, W, Y)	(17)
7	Sideroblastic anaemia	Mutation	Immature RBCs with nuclei surrounded by rings of iron	TRNT1, PUS1, LARS2, YARS2, FECH, GLRX5 and HSPA9	(18,19)

RBCs, red blood cells.

Corpuscles Haemoglobin (MCH). Furthermore, it is recommended assessing serum 25-hydroxyvitamin D levels in the diagnosis of anaemia, as vitamin D deficiency can contribute to various anaemia and serves as a potential risk factor for underlying conditions (20).

Immunomodulatory role in anaemia. Vitamin D is essential for our bone strength and supports our immune system and its function. Deficiency in vitamin D is primarily associated with skeletal health and calcium metabolism; however, vitamin D is indirectly intertwined with anaemia (21). According to a previous study, calcitriol (1,25-dihydroxy vitamin D) which is an active form of vitamin D, increases erythropoietin-receptor expression and synergistically stimulates proliferation along with erythropoietin (22). Erythropoietin is a hormone that is responsible for stimulating the production of RBCs in the bone marrow. A deficiency in vitamin D may impair this process and potentially contribute to anaemia. Chronic kidney disease or malabsorption disorders are associated with vitamin D deficiency and can lead to anaemia through various unrelated mechanisms related to vitamin D deficiency itself. The relationship between anaemia and vitamin D is as follows: i) Several observational studies (23-25) have indicated the reverse relationship between vitamin D levels and anaemia in adults; ii) it was found that vitamin D was associated with the prevention of chronic diseases, modulation of immunity, regulation of cellular growth, and differentiation and induction of erythropoiesis in bone marrow cells (22,23); iii) low levels of vitamin D may affect the body's ability to produce new erythrocytes, which may lead to anaemia (26,27); and iv) deficiency of vitamin D is associated with a greater prevalence of anaemia, especially in children and adolescents (25,26).

Vitamin D has been found to be associated with anaemia in various healthy and diseased populations. It has been revealed that vitamin D may have a positive impact on anaemia through its down regulatory effects on inflammatory cytokines and hepcidin (28). Therefore, its deficiency may lead to opposite effects, whose sequelae consist of depressed erythropoiesis and accentuation of the anaemia. Similarly, vitamin D and other calciotropic hormones, such as PTH and FGF33, have been found to establish their effect on iron metabolism and erythropoiesis. Polymorphisms in vitamin D receptors are associated with inducing anaemic conditions (29). Single nucleotide polymorphisms at the vitamin D receptor gene (ApaI; rs7975232, TaqI; rs731236, BsmI; rs1544410, FokI; rs10735810) might also contribute to anaemic conditions. It has been also stated that Jessica Cusato has proved the role of vitamin D receptor gene polymorphisms in ribavirin-induced anaemia in patients with HCV during the second and fourth weeks of medication. An increase in the intake of vitamin D-rich foods has

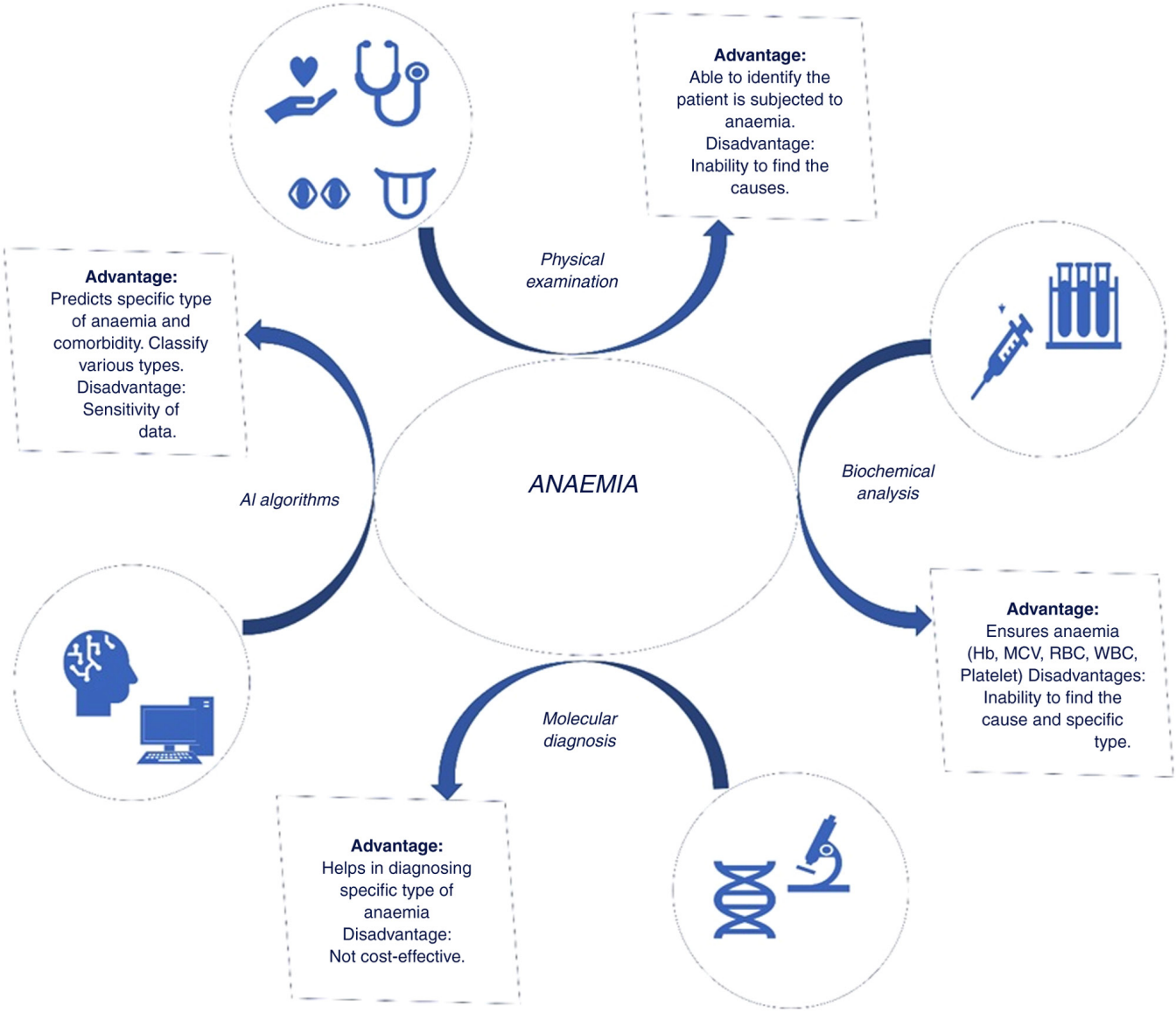

Figure 2. Different diagnostic methods.

been shown to improve Hb levels in patients with sickle cell anaemia as well as in anaemic individuals (30). In the aforementioned studies, it has been reported that calcitriol, which represents the active form of vitamin D, is involved in haematopoiesis.

Apart from the aforementioned relationships between anaemia and vitamin D, they were also found to play a significant role in AA. It has been previously found that decreased expression of vitamin D receptor (VDR) might contribute to the hyperimmune status of AA (31). Appropriate vitamin D supplements would partly rectify the immune dysfunction by strengthening signal transduction through VDR in patients with AA. A meta-analysis study, which includes 14 studies with 1,385 participants, showed a positive association between vitamin D deficiency and the incidence of anaemia (23). It also indicated that there is a possible reverse relationship, especially in adults. Vitamin D was found to be associated with the prevention of chronic diseases, modulation of immunity, regulation of cellular growth, differentiation and induction of erythropoiesis in bone marrow cells. As aforementioned, the importance of vitamin D in anaemic conditions and molecular biomarkers can also be used to detect this deficiency. Serum 25-hydroxyvitamin D can also be one of the best molecular biomarkers to identify its deficiency in its marginal levels as well as in its overt deficiency (21).

Even though vitamin D was considered a nutritional deficiency, it was found to play a significant role in managing certain genetic types of anaemia specific to impaired nutrient absorption. It was previously stated that vitamin D supplements were associated with an increase in Hb concentration in anaemic conditions (23,32). Vitamin D supplementation has demonstrated positive effects on transferrin saturation and iron status, and thus it has a cohort role in anaemia. Similarly, it was found that vitamin D has immunomodulatory properties, which may influence the immune system response, and deficiency in vitamin D might contribute to the dysregulation of anaemic conditions (33,34).

Table II. Molecular biomarkers associated with different types of anaemia.

S. no.	Anaemia type	Biomarkers	Description	(Refs.)
1	Haemolytic anaemia	LDH, Bilirubin, Reticulocytes	Combined haemolytic index assesses multiple markers of haemolysis. Elevated LDH and bilirubin indicate RBC destruction; increased reticulocytes indicate increased RBC turnover.	(32,36)
2	Sickle cell anaemia	Haemoglobin Electrophoresis, LDH, Bilirubin, Reticulocytes, Cytokines (IL-6, TNF-α), Chemokines (MCP-1)	Identifies abnormal haemoglobin (Hb S). Elevated LDH, bilirubin, reticulocytes, and inflammatory markers indicate vaso-occlusive crisis.	(37-39)
3	Thalassaemia	LDH, Bilirubin, Endocan-1, Lcn2, Genetic Testing (Gap-PCR), Plasma Proteome Profiling, Cytokines (IL-2, TNF-α), Chemokines (MCP-1, MIP-1β)	Endocan-1 and Lcn2 correlate with disease complications. Genetic mutations (α, β chains) via Gap-PCR. Plasma proteome profiling identifies dysregulated proteins.	(40-43)
4	Aplastic anaemia	Circulating microRNAs, Apolipoprotein-A, Anti-COX-2, Leucocyte Telomere Length, TERF2, GAS2L3, MK167, TMSB15 A, Flow Cytometry, Bone Marrow Biopsy	MicroRNAs monitor disease/treatment. Apolipoprotein-A/anti-COX-2 as novel biomarkers. Telomere length and other molecular markers for diagnosis	(14,44-47)
5	Diamond-Blackfan anaemia	Genetic Testing (Ribosomal Protein Genes), Erythrocyte Adenosine Deaminase Activity, GATA1, Apolipoprotein-A, Plasma microRNAs, anti-COX-2	Genetic mutations and elevated erythrocyte adenosine deaminase activity. GATA1 mutations and other novel biomarkers for diagnosis.	(44,48-50)
6	Fanconi anaemia	FANC Genes, Chromosomal Breakage Test, Microarray analysis	FANC gene mutations and chromosomal breakage test are primary diagnostics. Microarray analysis identifies gene expression patterns.	(16,17,51,52)
7	Sideroblastic anaemia	ALAS2, TRNT1, PUS1, LARS2, YARS2, FECH, GLRX5, HSPA9, SLC25A38, ABCB7, SF3B1	Genetic mutations in several genes indicate different forms. SF3B1 mutations differentiate clonal vs. non-clonal causes.	(48,53)

LDH, lactate dehydrogenase.

Molecular techniques. Biomarkers are specific molecules or genetic signatures that can be used to measure and analyse various biological samples such as blood, urine, saliva and tissue. Biomarkers can provide information about the presence, severity, or progression of a disease. Anaemia is a common disease that is generally detected with a blood test, which mentions the Hb content in them. As aforementioned about its type, the detection of specific types of anaemia is a tedious task. Hb concentration and hepcidin are the essential molecular biomarkers that are used for the detection of anaemia in general, which essentially do not classify its types (35). The use of molecular biomarkers varies for each type of anaemia (Table II).

As the authors of the present review came across numerous types of biomarkers through a literature survey, an analysis has been done with all types of biomarkers in the Marker dB database (https://markerdb.ca/). It is an electronic database that has consolidated information on molecular biomarkers. The molecular biomarkers are categorised into four types: Chemical, protein, genetic (DNA) and karyotypic; and further four biomarkers are placed into categories such as diagnostic, predictive, prognostic and exposure. Currently, the database contains 142 protein biomarkers, 1,089 chemical biomarkers, 154 karyotype biomarkers, and 26,374 genetic markers. These are categorised into 25,560 diagnostic biomarkers, 102 prognostic biomarkers, 265 exposure biomarkers, and 6,746 predictive biomarkers or biomarker panels. Collectively, these markers can be used to detect, monitor, or predict 670 specific human conditions, which are grouped into 27 broad

condition categories (54). The biomarkers Coproporphyrin I (MDB00000206) and Coproporphyrin III (MDB00000191), which emerge as metabolites during heme synthesis, are used to identify sideroblastic anaemia (55,56). Important roles are played by pyridoxine (MDB00000117), pyridoxal (MDB00000335) and homocysteine (MDB00013433) in the conditions of sickle cell anaemia detection. Vitamin B6 in the form of pyridoxine helps produce RBCs and controls the proportion of sodium to potassium. Pyridoxal converts to pyridoxal phosphate, an essential coenzyme in the production of amino acids, sphingolipids, neurotransmitters, and aminolevulinic acid; low levels may indicate sickle cell anaemia. Methionine metabolism produces homocysteine, which is linked to endothelial dysfunction, a characteristic of sickle cell disease that exacerbates vaso-occlusive crises and causes tissue damage (57,58). A crucial part of energy synthesis is played by coenzyme Q8, sometimes referred to as ubiquinol 8 (MDB00000298). Genetic testing and Hb analysis are the main techniques used to determine the type and presence of beta-thalassemia, with ubiquinol 8 acting as a crucial biomarker for thalassemia diagnosis (59). The bile pigment bilirubin (MDB00000027), which is generated during heme breakdown, is important for diagnosing haemolytic anaemia. Increased bilirubin levels are an essential marker of the illness, emphasising their significance in the diagnostic procedure (60).

AI methods for anaemia detection. Computational prediction can be implemented for fast processes and time saving. Numerous machine learning and deep learning algorithms are recently used for the detection or prediction of anaemia in patients using their past health records and other details that can be obtained from electronic medical or health records, such as facial images, images of other parts of the body, electrocardiograms (ECG), electrohepatography (EHG), X-ray scans and magnetic resonance imaging (MRI) scans. The multitude of data types that can be used to train a machine model for accurate diagnosis makes it an efficient and cost-effective method to be explored. The elaborate usage of ECG and patient images for the detection of various types of anaemia has been previously shown (61). Other features such as age, CBC and other medical conditions of patients were also considered for further detection and analysis. Most of the machine learning and deep learning algorithms have used classification, identification, or predictive algorithms for detection. Some studies have shown the detection of iron-deficiency anaemia, thalassemia, and AA, which have been discussed below.

A previous study has predicted β-thalassemic carriers from CBC (62). The datasets were obtained from the Punjab Thalassemic Prevention and Program (PTPP) database (https://ptpp.punjab.gov.pk) and have 12 features, out of which 9 features have the details of CBC. The data imbalance was observed in the aforementioned dataset and was rectified with the Synthetic Minority Oversampling Technique and Adaptive Synthetic. The primary feature selection was done with principal component analysis and singular vector decomposition. Binary classification was their primary target, and supervised machine learning models including decision tree (DT), gradient boosting machine (GBM), support vector classifier, random forest (RF), extra tree classifier (ETC) and logistic regression (LR) were implemented to identify the best models. Among the aforementioned supervised models, ETC had the best performance with 0.96 accuracy and GBM with 0.89 accuracy. Similarly, in another study (63), the datasets were obtained from PTPP, which has data on 5,066 patients. A federated method was followed, and a global model was developed, which obtained an accuracy of 97.89%. The developed model has classified 2015 thalassemic patients and 3051 non-thalassemic patients from the dataset.

Extreme learning machine (ELM) models have been used in a four-class anaemic dataset, which has been used in the classification of iron-deficiency anaemia, β-thalassemia and HbE. The datasets were obtained from the clinical pathology laboratory in Indonesia, and the Department of Clinical Pathology and Laboratory, in Gadjah Mada. The datasets have been split into 67% for training and 33% for testing. A comparative study was conducted with other machine learning models such as RF, K-neighbour nearest (KNN), and support vector machine (SVM), in which the ELM model outperformed with 99.21% accuracy (64). A unique IDEAL-IQ was designed to distinguish AA and MDS. The IDEAL-IQ-based SVM classifier model was used for the quantification of bone marrow fat. The dataset collected has bone marrow biopsy and pelvic region of Magnetic Resonance Imaging (MRI), where the acetabulum is irregular in shape. The radiomic features of the biopsy samples were selected and some incomplete data was removed for curation. The model outperformed with 87.2% accuracy, and a comparative study was performed with LR and SVM (65).

The aforementioned studies deal with the detection of diverse types of anaemia. However, a previous study has mentioned a model for the treatment of the disease and the progression of recovery after the treatment with immunosuppressive therapy (IST) (66). The electronic medical records of 203 children affected with severe AA were collected from the Chinese Academy of Medical Sciences and Peking Union Medical College from 2000 to 2016 and classified based on the disease using LR, RF, multi-layer perceptron and SVM. The multi-layer perceptron has been used for the electroencephalogram dataset and SVM for pattern recognition. The model was built based on predictor sets of regular monitoring of the patient's remedy for IST. The receiving operating characteristic area under the curve (AUC) for binary classification has been achieved at around 0.962.

Researchers conducted a study focused on binary classification was outlined to distinguish Hb of haemolytic and sickle cell anaemia using various models such as the KNN the model, Naïve-Bayes model, DT and deep learning model with 7-fold cross-validation. Among the four models, the DT and deep learning model performed well with 0.99 accuracies in both models (67). By contrast, another study, built a deep neural network with sparse categorical cross entropy function as loss function and Adam optimizer and attained an accuracy of 0.897 with 8 features mapped to the model (68). The datasets were sourced from Guangzhou Medical University, China, and have two parts. The first part contains details such as RBC, RBC distribution width (RDW), MCV and age; while the other part has details of gene deletions and

17 β-globin point mutations. Because of this additional information, the model can be categorized into thalassemia and iron-deficiency anaemia. RDW was larger in iron deficiency anaemia than in thalassemia, a salient feature recognized in the study.

Bone marrow smears are employed in machine learning for the detection of AA. Apart from AA, they are also utilised in the detection of MDS and AML. The image datasets have existed in some clinics (432) and the ASH Image Bank (115). Two- and three-way classification methods were executed through the Resnet 50 algorithm (69). The two-way classification was performed, which initially classifies MDS and other samples but in three-way classification, they classified AA and AML from the sample. The model outperformed in the classification of bone marrow diseases with an accuracy of 0.926. Likewise, the detection of iron-deficiency anaemia was done through medical images such as images of the palm. The developed model has utilised CIE L*a*b colour space operation to identify the region of interest (ROI). A comparative study between various machine learning models was performed, and it was found that the naïve-Bayes algorithm outperformed and has an accuracy of 99.96%; Convolutional Neural Network and KNN have an accuracy of 99.92%, DT has an accuracy of 96.34%, and SVM has the least accuracy of 96.34%. A total of 1,520 anaemic patients were identified from the datasets (70). A previous study used facial images and deep learning technology to predict anaemia in patients in the emergency department (71). The video images of the patients are recorded live and then they are converted into readable images by GRAD-CAM. The five models have been used, namely Mobilenet, Resnet50, DenseNet121, Efficient NetB0, and Inception V3. In this model, Inception V3 outperformed well with 84.02%. Simultaneously, a comparative study with clinical assessment was performed, and the deep learning model (Inception V3) has higher accuracy when compared with clinical assessment. Digital image processing has also been used in the counting of RBCs from the blood smear in the detection of anaemia (72). Case-based reasoning (CBR) and the KNN algorithm were developed to predict anaemia severity using a machine learning algorithm. CBR is a technique that uses past experiences to derive results for new cases. It is a cyclic system and has four activities, namely retrieve, reuse, revise and retain. The experimental results have shown that the KNN models have 92% accuracy (73). Retinal fundus images also play an efficient role in the prediction of anaemia using a deep learning model. The datasets were obtained from UKBiobank, and the AUC for anaemia was 0.89 (74).

An ECG is usually used to record the electric signals from the heart to check for different heart diseases. A retrospective, multicentre study used deep learning algorithms for the detection of anaemia using ECGs (61). The real-time data was collected from Sejong General Hospital and Mediplex Sejong Hospital in South Korea, which has been classified into 12-lead, 6-lead and single-lead raw data. Additionally, they have other features such as the name, age and sex of the individuals. In total, they have used 57,435 ECGs from 31,898 patients. The DeLong method with the Sun & Su optimization method was used and obtained an AUROC (ROC-AUC) of 0.923 internally and 0.901 externally. Big data applications have been used in the classification of cancer by gene expression analysis (75). Similarly, it can also be applied to the classification of anaemia which requires further studies and investigation.

Genetic data can also be incorporated into text mining under the framework of classifying anaemia. Text mining can help extract pertinent genetic information from research publications, clinical notes and genetic databases. Genetic variables are important in numerous forms of anaemia. Finding certain genes linked to anaemia, comprehending genetic mutations or changes that can exacerbate the illness, and learning more about the inherited characteristics of anaemia subtypes are some examples of this. Treatment can be more individualised when genetic information is incorporated into the classification process, which improves the accuracy of diagnostic models. Healthcare practitioners can benefit from text mining techniques by using them to stay up-to-date on the most recent genetic markers and breakthroughs related to anaemia categorization, as they can help close the knowledge gap between genetic research discoveries and clinical applications. This full integration of textual data, which includes insights from literature, genetics, and clinical settings, advances our understanding of anaemia and facilitates its efficient classification (76,77).

4. Bioinformatics approaches to anaemia

In recent years, bioinformatics has emerged as an irreplaceable tool, providing a comprehensive study of the intricate molecular mechanisms underlying various types of anaemia. It also plays a pivotal role in advancing the understanding and management of different types of anaemia, characterised by diverse genetic and phenotypic features.

A variety of bioinformatics techniques are being used for various anaemia forms, such as haemolytic, sickle cell, thalassemia, AA, DBA, FA and sideroblastic anaemia. Through the identification of genetic variants, sequence variations, and microdeletions, next-generation sequencing (NGS) approaches such as whole exome sequencing, targeted NGS and exome sequencing are essential in the diagnosis of various anaemia (48,51,78-86). In particular, genome-wide association studies provide valuable insights into the genetic pathways and variations related to sickle cell anaemia (79,87-89). Understanding molecular mechanisms, cellular composition, and heterogeneity can be gained through molecular profiling using RNA-Seq, proteomics, and single-cell genomics. Identification of microRNAs and meta-analyses using microarray technology aid in the discovery of hub genes, transcriptional regulation, and shared markers (90-92).

The development of possible treatment interventions is another benefit of bioinformatics techniques. Especially in the case of thalassemia (80), tiny compounds are evaluated using molecular docking for potential therapeutic uses. In numerous anaemias, including DBA and FA, the molecular targets for therapies are identified (93). To determine the functional properties of the proteins involved in haemolytic anaemia, machine learning-based predictions are conducted. Finding possible drugs is made easier with the use of bioinformatic analysis

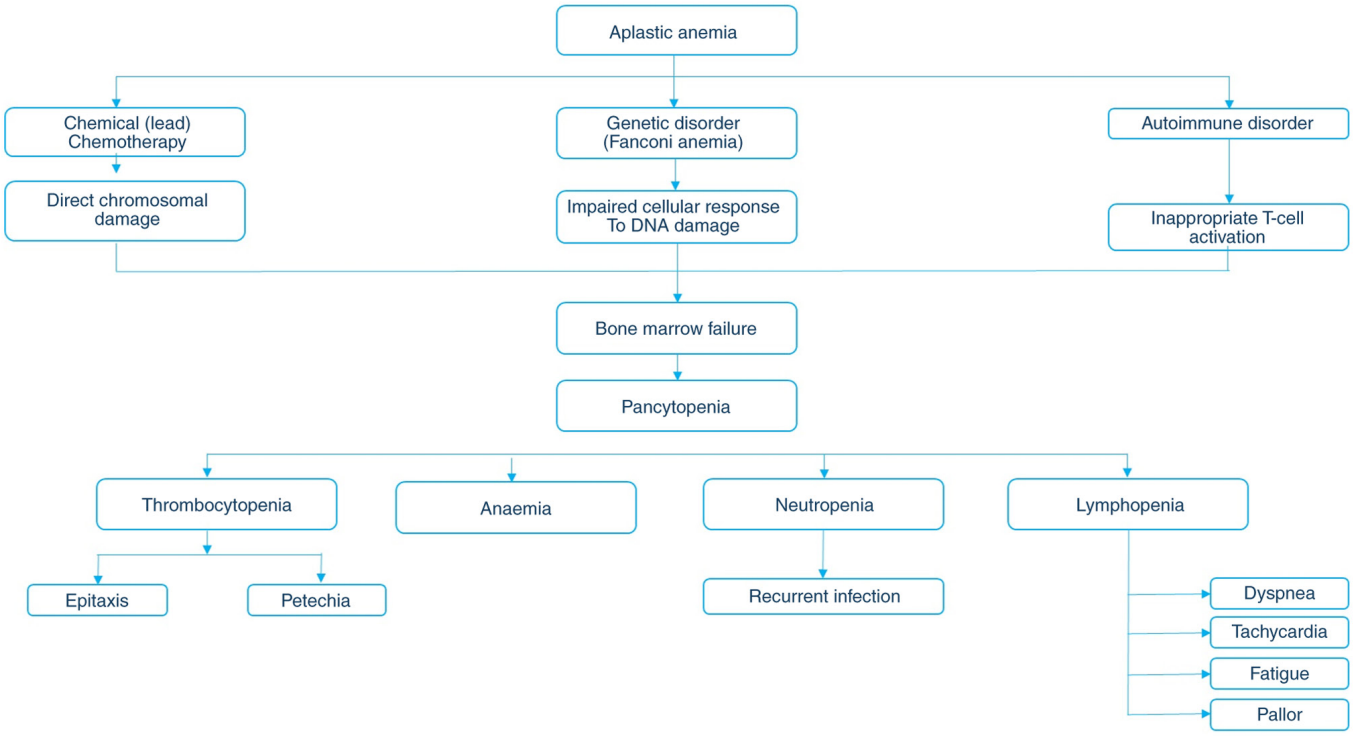

Figure 3. Overall cause and symptoms of the disease.

on proteomic and microarray datasets (94,95). Additionally, to close the gap between genetic discoveries and clinical practice-particularly in the case of sickle cell anaemia-efforts are being made to establish bioinformatics infrastructure in areas with high occurrences (89).

5. Aplastic pancytopenia

AA refers to an anaemic condition in an individual in which he or she cannot produce sufficient erythrocytes, WBCs and PLTs due to a lack of hematopoietic progenitor cells in them. The word 'aplastic' refers to the inability of the marrow to form blood, which might cause diverse pathogenic conditions, and anaemia refers to an anaemic condition. AA is also known as 'idiopathic' or 'idiopathic anaemia'. The first case of AA was reported by Paul Ehrlich in the year 1884 (14). AA is not specific to any age group. It is sparsely found in all age groups, from children to elderly individuals. AA is similar to FA and dyskeratosis congenita, which are genetic disorders caused by lack of DNA repair (14). AA can lead to other health concerns, such as an irregular heartbeat, an enlarged heart and heart failure. It can be caused by injury to blood stem cells due to exposure to certain drugs, chemotherapy, congenital disorders, drug therapy to suppress the immune system, pregnancy, radiation therapy, or toxins such as benzene or arsenic. The cause and symptoms of AA are described in Fig. 3.

AA can be classified into two types: These are immune AA (IAA) and acquired AA (AAA). IAA is an auto-immune disorder that can be transferred from one individual to another individual (for example, from the parents to their children). It is a very rare autoimmune disorder in which the T-cells act against the healthy cells. Functionally and phenotypically activated cytokine T-cells are skewed to produce type-1 cytokines. These cytokines induce apoptosis and cause cell destruction (96,97). Apart from cytokines, somatic mutations at the STAT3 signalling pathway and some histocompatibility antigens, such as human leukocyte antigen (HLA), are also responsible for the disease (98,99). It has been revealed that Treg cells are decreased in AA conditions, which further leads to hematologic processes (100). AAA is a disorder resulting from damage to progenitor cells by chemicals, exposure to ionising radiation, drugs, viral infections, constitutional genetic defects, or autoimmune destruction (101). AAA is a condition in which AA is attained due to some other factors apart from immunological reasons. Numerous factors are responsible for AA, such as chemoradiotherapy, viral hepatitis, overexposure to pesticides and insecticides, certain drugs, exposure to chemicals, and in some rare pregnancy cases. In all these conditions, the signalling pathway is still a mystery. Apart from these two types, AA is said to be idiopathic because there was no test to confirm a cause-and-effect relationship in most of the cases (102).

According to a previous survey, it was found that AA is higher in Asian regions when compared with Europe and North American regions. It was also identified that the incidence of the disease is higher in Asia when compared with the West (46,103). According to theNational Organization of Rare Diseases (NORD), AAA affects male and female patients in about equal numbers in most cases, as well as older children, teenagers, or young adults (104). The incidence rate is two or three times greater in Asia. The exact incidence rates that exist in the United States are unknown, although some sources report that approximately 500-1,000 new cases of AA are diagnosed each year. Similarly, NORD states that certain disorders share similar symptoms as AA, such as MDS and PNH. Apart from

Table III. Association of the genes with AA and its function.

S. no.	Gene	Functions	Relation with AA	(Refs.)
1	RAPGEF5	Regulation of RAS protein	Downregulated in AA	(103,105,106)
2	MANEA	Sialic acid production	Involved in adipogenesis regulation	(107)
3	TERF2	Telomere maintenance	Genetic changes connected to congenital dyskeratosis	(106,108,109)
4	TERT	Telomerase enzyme	Mutations linked to telomere shortening	(106,110)
5	AGT	Angiotensin regulation	Downregulated in bone marrow MSCs of AA patients	(107,111)
6	GAS2L3	Cytoskeletal dynamics	Role in controlling MSCs characteristics	(112)
7	MKI67	Proliferation marker	Identified as a proliferation marker in AA patients	(46,100)
8	TMSB15A	Thymosin beta family	Expression linked to better prognosis in paediatric AA	(108,109,113)
9	CAT	Catalase enzyme	Essential for reducing oxidative stress	(102,114,115)
10	GSH	Master antioxidant	Homozygous deletion linked to AA	(116)
11	SDF-1	Chemokine regulating BM	Altered expression in AA patients	(117)
12	SOD-2	Antioxidant enzyme	Presence in bone marrow of experimental AA	(118,119)
13	S100A8	Calcium-binding protein	Elevated in plasma of AA patients	(120,121)
14	RETN	Resistin hormone	Differentially expressed in haematopoietic cells	(46,111)
15	TNFAIP3	Negative regulator of NF-κB	Upregulated in T-cell differentiation of AA patients	(122,123)
16	JUN	AP-1 transcription factor	Differentially expressed in AA patients	(46,96,107,111)
17	IL1B	Proinflammatory cytokine	Elevated in patients with AA	(114)
18	FANC	Maintain genomic integrity	Pancytopenia caused by a hereditary disease resulting in defective DNA repair	(17,84)
19	GATA2	Transcription factor	Mutations linked to paediatric neutropenia, AA	(124)
20	CD	Cluster of differentiation	Immune cell markers | CD8+, CD38+ implicated in AA	(125,126)

AA, aplastic anaemia.

this, AA may also occur as part of an inherited disorder such as FA, telomere diseases, Shwachman-Diamond syndrome, ataxia-pancytopenia syndrome, and others.

According to the literature review, the most commonly expressed genes are discussed in Table III. Certain genes were also found to be co-similar with other diseases, such as FA, and telomerase diseases. Likewise, most of the genes are involved in the inter and mitotic phases of cell division. Genes are subjected to network analysis using the STRING database (https://string-db.org). STRING is an online bioinformatics tool that provides information on protein-protein interaction, functional annotation, enrichment analysis, and network analysis. The specified genes are input into STRING with low confidence, allowing no more than five interactions in their configuration. The resulting network is visually represented in Fig. 4.

The network analysis has revealed a number of considerable enriched pathways and processes including IL-17 signalling pathway, TNF signalling pathway, Rheumatoid arthritis pathway, Chemokine signalling, inflammatory response, and immune system processes. A number of enriched terms are associated with the regulation of cell migration, proliferation, and apoptosis, indicating that the genes are involved in the regulation of these biological processes. Databases such as Kyoto Encyclopedia of Genes and Genomes (https://www.genome.jp/kegg/) pathways, Gene Ontology (https://geneontology.org/) terms, InterPro domains and UniProt keywords have shown enrichment, suggesting that the input gene collection is functionally diverse and engaged in a variety of biological processes. Ex aggravation of the diseased state is not clear and our future study emphasises on identification of specific pathways that can be targeted to modulate the immune response and for further treatment.

Treatment of AA. Hematopoietic growth factors such as erythropoietin and Neupogen are not effective in AA, but surprisingly Eltrombopag, a stimulator of PLT production, was effective in improving blood counts in refractory AA (RAA). In 2014, Promacta was approved to treat patients with severe AA who have had an insufficient response to IST and are not candidates for a hematopoietic stem cell transplant. When eltrombopag was combined with standard immunosuppression as first-line therapy, response and complete response rates were higher than with immunosuppression alone (104).

IST was given to the individuals affected with AA for 6 months. If it lacks response after a course, then it is known as RAA. Eltrombopag was found to be effective in refractory cases (14). Antithymocyte globulin (ATG) therapy and allogeneic stem transplantation were also found to be efficient in AA conditions (103). Apart from Eltrombopag, bone marrow transplantation was conducted in immune AA cases, but it was not successful in certain cases due to graft rejection. The survival of individuals is also reduced after transplantation. Later, umbilical cord transplantation was performed and it was found to be successful with 90% survival inpatients. Transplantation was done in severe cases of IAA and AAA. All these treatments depend upon the severity of the disease, age, and the initial treatment (14).

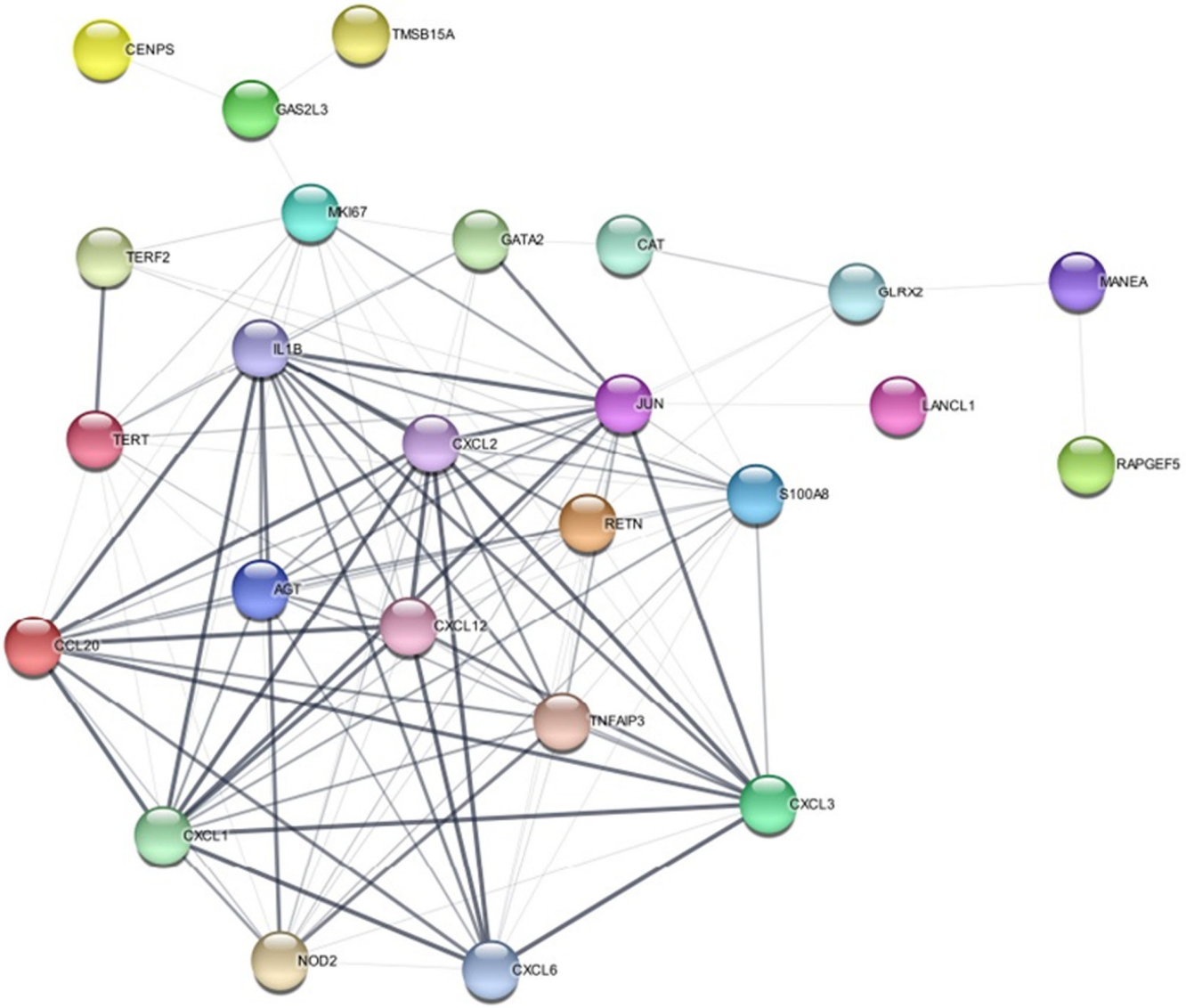

Figure 4. Network analysis of the genes using STRING database.

A new therapeutic intervention for AA in paediatric conditions was obtained through the telomere maintenance pathway and gene expression profiling of mesenchymal stem cells. Leukocyte telomere shortening was observed in individuals affected byAA. TERF2 gene was said to be involved in telomerase shortening. So, these genes can be focused on a therapeutic basis for AA-affected individuals in terms of molecular characterization (106,110).

Role of mesenchymal stem cells (MSCs) in AA treatment. (MSCs) are multipotent stem cells that are found in bone marrow for making and repairing skeletal tissues. Apart from this, they can also be found bounteous in the treatment of AA individuals. Previous studies found that the MSCs provide a specialised microenvironment for haematopoiesis (127,128). MSCs contribute to the organisation and function of the haematopoietic niche through their immunomodulatory properties. They were found to cause morphological, functional, and genetic alterations in both AA and MDS. They have also been shown to suppress T-cell proliferation and activation, which can help to reduce the autoimmune response in AA. However, some of the clinical manifestations of AA can be explained by mesenchymal dysfunction (129). This remains a query in the case of immune-related AA. Modulation of immune responses by secreting various cytokines and growth factors can promote the survival and proliferation of haematopoietic stem cells. These modulations are performed by MSCs, and thus these modifications can help in the further recovery of the disease (127). Previous studies have shown that MSC-derived extracellular vesicles can significantly reverse radiation damage to bone marrow, which could have implications for the treatment of AA (130,131). A combination of umbilical cord MSC and standard immunosuppressive drugs can effectively treat severe AA in paediatric patients.

Pathway analysis. Currently, there is no approved medication for AA. An in-depth analysis of the pathway could lead to a better understanding of the illness and potentially facilitate the development of target-specific medications. A total of

300 differentially expressed genes that were involved in apoptosis, adipogenesis and the immunological response were found in AA patients as compared with healthy individuals. Adipogenesis-cytokine signalling, chemotaxis, cell division, proliferation, the cell cycle, and hematopoietic cell lineage differentiation are among the other processes with which these genes are considered to be associated with. The cytokine genes are important in AA and also suggests that the disease may be caused by the deregulation of these genes. In addition to genes, chemical substances also play an indirect role in the pathway disruption. Lead has been shown to disrupt heme synthesis, which impacts erythrocyte development and function (102).

Patients with AA exhibit a Treg/Th17 imbalance, which is managed by MSCs via the production of exosomes. Sphingosine-1-phosphate (S1P), which is present in these exosomes, is enriched due to SphK1. MSCs use sphingosine 1-phosphate (S1P)-containing exosomes to produce and regulate the Treg/Th17 imbalance in AA. SphK1 rather than SphK2 is the source of S1P enrichment in MSCs-Exos. The exosomal S1P receptor S1PR1, which is expressed on $CD4^+$ T cells, mediates the exosomal S1P-induced increase in Treg production. *In vivo* experiments revealed that MSCs-Exos corrected the elevated Th17/Treg and prevented the advancement of AA in AA mice (130).

Oxidative stress. Oxidative stress alters several important signalling pathways and accelerates the ageing process of hematopoietic stem cells, according to (103). Oxidative stress reduces antioxidant activity, which results in the production of free radicals (132). The onset of AA could be caused by oncogenic Ras activating the mitogen-activated protein kinase (MAPK) pathway after oxidative damage. It was found that that the mechanism underlying the contraction of vascular smooth muscle may also apply to AA (103). This gene has been linked to the Treg phenotype associated with autoimmune diseases (103). Despite the fact that several genes exhibit differential expression in AA, it is unclear how exactly these genes relate to one another and the disease.

Apart from this, a lot of AA agents cause oxidative stress. The overuse of alkylating medications such as cyclophosphamide and busulfan resulted in a decrease in antioxidant agents such as SDF-1 and SOD-2 (105). Chemokine SDF-1 is involved in stem cell homing, angiogenesis and cell migration. One enzyme that contributes to the antioxidant defence system is SOD-2. Furthermore, the bone marrow's $CD150^+$ and C-Kit^+ cell counts decreased. According to flow cytometry investigations, there was a considerable decline in RUNX-2 and ALPH-1, which had an impact on the CD45-ve population. This decreased activity has shown that reactive oxygen species (ROS), which preceded the decline in antibodies such as STRO-1 and CFU-F, are involved.

Challenges in the classification of AA. There were numerous conflicts arising from the identification of AA in different illnesses. It was discovered that MDS and PNH had symptoms that were comparable to those of AA. They were also discovered to be associated with other illnesses, which further complicates the illness's diagnosis and analysis. A discussion of the diseases that were discovered to co-occur and be similar follows.

Complexity with similar diseases. The complex interactions among MDS, clonal haematopoiesis (CH), PNH, and AA are examined in detail. It draws attention to PNH is potentially fatal character, its possible emergence following coronavirus immunisation, and its diagnostic importance in figuring out the immune-mediated pathophysiology of AA's marrow aplasia. The higher risk of subsequent MDS or AML in patients with AA is examined, as well as the morphological parallels between AA and MDS. The following examines the recently developed notion of CH and its correlation with late clonal diseases following IST in AA, with a focus on the molecular aspects and its treatment and diagnostic implications.

PNH and AA. PNH is a rare, life-threatening disease of the blood. PNH is caused by somatic mutation in the phosphatidylinositol glycan class A (PIG-A). It is characterised by the destruction of erythrocytes, blood clots, and impaired bone marrow function and it is also closely related to AA (133). According to a previous study (134), individuals were subjected to AA after completion of two doses of vaccination for coronavirus which was observed in a 74-year-old man. A PNH clone was found in the blood sample which was developed after the vaccination and that specified clone might have caused AA. Similarly, PNH clones were observed in 63 patients who were affected by the disease in a case study (135). Patients with immune-mediated bone marrow failure frequently have PNH clones. PNH clones form in >50% of individuals with AAA, a T-cell-mediated autoimmune bone marrow failure illness. In AAA, it is considered that PNH cells can avoid the HSPC-directed autoimmune onslaught, which causes PNH cells to overrun wild-type cells and generate PNH clones. Patients with MDS and, less frequently, myeloproliferative neoplasms can also have PNH clones. Although immune-mediated bone marrow failure is the main risk factor for the emergence of PNH clones, patients might be given a diagnosis of classical PNH without having any history of cytopenia or a recognized diagnosis of bone marrow failure. Prior subclinical marrow failure is generally assumed in these situations, however subsequent proliferative mutations inside a PNH HSPC are another possibility (133).

A PNH clone can offer a critical diagnostic clue about the immune-mediated pathophysiology of marrow aplasia (133). The clonal growth of PNH cells is intimately linked to the HSPC-directed autoimmune onslaught in AA. Pancytopenia and hypocellular bone marrow are the presenting symptoms of AA; however, they are not always indicative of the disease. The rigorous exclusion of all potential causes of marrow failure, such as dietary deficiencies, infections, or toxins, is therefore necessary for the diagnosis of AA. The exclusion of inherited bone marrow failure disorders, a costly and time-consuming technique that might leave persistent diagnostic uncertainty, is especially crucial for children and young and middle-aged adults. PNH clones were found in 46% of patients with AA. This disease is found to have similar symptoms to AA as well as found comorbid with AA (136).

MDS and AA. As they cope with a shortage of bone marrow environment, AA and MDS exhibit substantial morphological similarities (124,137). Although the pathophysiology of AA and MDS differs, there are significant similarities. A clonal condition called MDS is defined by the build-up of genetic abnormalities in hematopoietic stem

cells, which results in defective blood cell formation and inefficient haematopoiesis (138). On the other hand, hematopoietic stem cells are destroyed by the immune system in AA, a non-clonal illness that results in pancytopenia. Acute myeloid leukaemia (AML) or MDS, however, may develop in certain AA instances. Although the precise processes that lead from AA to MDS or AML are not entirely understood, new genetic mutations or epigenetic modifications may be acquired (138).

There is an association between MDS and AA (139). Patients with AA have an increased risk of developing MDS and AML. In total, ~15-20% of patients with AA and 2-6% of patients with PNH were found to to develop secondary MDS/AML by 10 years of follow-up. The exact mechanisms underlying the progression from AA to MDS or AML are not fully understood, but they may involve the acquisition of additional genetic mutations or epigenetic changes.

CH and AA. Recent research has shown that CH is closely linked to the evolution of late clonal disorders, including PNH and MDS/AML, which are common complications after successful IST in AAA (140). The widespread discovery of somatic mutations that promote clonal evolution has shed light on the molecular component of CH in AA (134,135). Based on recent research, autoimmune destruction of early hematopoietic stem cells may be the cause of AAA, a rare condition that manifests as bone marrow failure syndrome and might be regarded as a clonal disorder of hematopoietic stem cells (136). Investigations on the prognostic importance of somatic mutations driving clonal evolution in AA are ongoing (134). Overall, new knowledge on CH in AA has shed light on the disease's pathophysiology and may have consequences for both diagnosis and treatment.

Comorbid nature of AA. The discussion below explores the causes of AA, with particular attention to telomere shortening, COVID-19 immunisation, AA caused by cancer, FA, and the relationship to chronic gut inflammation. It examines comorbidities, environmental factors, and genetic components related to AA, providing a comprehensive picture of the disease's pathogenesis. The genetic foundation of FA, COVID-19 vaccine-related instances, telomerase deficiency, and the relationship between severe AA and persistent gut inflammation are also addressed in the discussion.

Telomere shortening and AA. Telomerase is the end-part of the chromosomes. It is a hexanucleotide (TTAGGG) with tandem repeats of DNA. Telomerase is also known as the 'mitotic cycle' which has the record of a cell's proliferative history. Telomerase and its associated protein were known as 'Sheltrin'. The Telomerase region consists of genes such as TERT, TERC and Dyskerin. The diseases that are associated with telomerase shortening and deficiency are dyskeratosis congenita, Hoyerral Hreidarsson syndrome, and Revesz syndrome. Apart from the aforementioned disease telomerase shortening can take place due to ageing and ROS which were formed due to environmental toxins and irradiation (141). AA can also be caused due to somatic mutations at TERT and TERC genes which are the main proteins that are present in the telomerase region. In 10-20% of patients affected with AA, it is known as a clonal malignant disorder or premalignant disease (142).

Telomeropathy can cause damage to organs including the bone marrow, lungs and liver, which indirectly indicates that telomere shortening is observed in patients with AA. Adults with acute AA have been observed with base change in the TERT A 1062T variant which might be due to the environmental context. Likewise, the telomerase disease TERT gene was also accompanied by some clones of PNH (143). Similarly, telomerase shortening was observed in individuals who are affected with AA especially in children of the age group 3 to 15 (46).

COVID-19 and AA. A few case studies have been reported in recent days regarding the diagnosis of AA after COVID-19 vaccination. In all these case studies, the individuals do not have any past medical history of pancytopenia namely, thrombocytopenia, anaemia, neutropenia and lymphopenia. They were found to develop pancytopenia after vaccination. The first case of AA was reported in a 76-year-old man, who has been presented with severe AA with a PNH clone one month after the second dose of the Pfizer coronavirus vaccine. The individual could not survive because there were multifactorial reasons for it. However, his medical history does not show any pancytopenia symptoms (134). It was reported that the COVID-19 vaccination has led to the development of AA in the following cases (144). A 64-year-old woman has been found to develop AA after the first dose of Ad 26. Cov.2. S (Janssen vaccine). In the initial stages, the CBCs were found to be moderate neutropenia, thrombocytopenia, and anaemia. But later it exaggerated into severe conditions. The symptoms were petechiae and fever immediately after a week of vaccination.

Similarly, numerous case studies show that individuals were affected with AA after the completion of one or two doses of corona vaccination. It can be considered a drop in Hb, leading to haematological conditions in healthy individuals. Focus should be addressed on the aftermath of vaccines and this should be brought to light for the prevention of the disease (10,145-147). The correlation between these two diseases is still unclear and a detailed study between them should be performed for further medication and treatment.

Cancer and AA. Cancer is one of the deadliest diseases and it is incurable. The incidence rate of cancer increases every year. The primary cancer treatment is radiotherapy and chemotherapy. But chemotherapy can also lead to AA. Temozolomide is also known as 'Temodal', which is a type of chemotherapy used in the treatment of a type of brain tumour cells malignant gliomas. Malignant gliomas include glioblastoma multiforme and anaplastic astrocytoma (148). A 55-year-old female patient was detected with glioblastoma multiforme through MRI. The first cyclic dose of partial brain radiotherapy with Temozolomide (75 mg/m^2) for 6 weeks and 150 mg/m^2 afterward. After 19 sessions, there was bleeding from the infection sites on her thighs and bruises. The blood profile revealed that the individual was affected with pancytopenia (AA) with a reticulocyte count of 0.2 indicating a hypo-proliferative marrow. Bone marrow biopsy shows the hypocellularity with increased plasma cells. Immunosuppressive drugs did not apply to the patients as they are affected with malignancy and pulmonary embolism. Despite this condition, the affected female was given a trial of IV immunoglobulin, which did not show any response (149,150). AA can be caused due to numerous factors, in chemotherapy is one of the reasons for it.

According to the aforementioned studies, therapists should be aware that it should not cause any hematologic suppression or damage to the individuals under chemotherapy.

FA. FA is a rare genetic disorder in the bone marrow which leads to a decrease in the production of all types of blood cells. AA can be caused due to multiple factors and the mechanism of the disease remains a query. FA is caused due to mutation in the FANC gene and it can occur in any of 23 genes. It does not show any symptoms in childhood but has a high risk of developing cancer (17,104). AA and FA are two different disorders with similar features of pancytopenia. FA is characterised by chromosomal instability and congenital anomalies while AA has a diverse aetiology. A chromosome breakage test in the blood is the only diagnostic technique that can be used in the differentiation of FA from AA (151).

Patients with FA have a higher risk of developing AA than the general population. FA is one of the most prevalent causes of AA concerning genetic causes. The core complex of FA is produced by the FANCA gene, which is involved in the mutation and repair of DNA damage. This damage leads to the accumulation of ICLs (interstrand crosslinks) that can cause AA (17). Most of the patients with FA have at least one of the physical anomalies but it is not well characterised in patients with AA and not present in all cases (152). A previous study showed that the frequency of parental consanguinity among patients with AA was 73% and the parental consanguinity among patients with FA was also high (153). The aforementioned study also suggested that there may be a higher prevalence of comorbidity between AA and FA than in the general population. In this scenario of comorbidity, bone marrow transplants are the only treatment for patients with both AA and FA, but they are more complex (154).

Chronic gut inflammation. Chronic gut inflammation refers to a group of disorders that causes enduring inflammation of tissues in the digestive tract. The most common conditions of chronic gut inflammation are Crohn's disease and ulcerative colitis. AA and chronic gut inflammation were found to be comorbid in certain research studies. The individuals who are affected with severe AA conditions are found to suffer from long-lasting gut inflammation or vice-versa. Active chronic gut infections in the gut may sustain aberrant immune responses in AAA. The development of AAA conditions was due to the formation of polyps in the sigmoid of the colon and rectal regions in the mucosal membrane. These polyps were enlarged lymphoid follicles with infiltrated large numbers of lymphocytes and plasma cells. An excellent response of SAA to the treatment of gut inflammation was also reported (155). Patients with severe AA (SAA) frequently present with inflammatory episodes; during flared inflammatory episodes, haematopoietic cells in the bone marrow are replaced by adipocytes (156). Similarly, the plasma metabolomic and intestinal microbial profiles of patients with SAA were analyzed and it was found that the intestinal microbial composition of patients with SAA was significantly different from that of healthy controls (157).

6. Scope of the review

Anaemia is found to be associated with other diseases such as cancer, chronic kidney diseases, gastrointestinal disorder, inflammatory disorders, autoimmune disorders, endocrine disorders and so on (4,158-161). This network of links highlights the intricate interactions that exist between anaemia and more general health situations, indicating the need for a detailed investigation of these interconnections. Researchers are turning more to genetic analysis to identify the underlying genetic causes causing anaemia and associated comorbidities to gain deeper insights. This genomic research lays the groundwork for furthering our comprehension of the pathophysiology of anaemia.

Simultaneously, the healthcare landscape is changing and includes the idea of incorporating AI predictive modelling tools. Future research aims to use AI to create advanced prediction models for the early identification of anaemia and related disorders. Through the integration of genetic studies into these models, investigators hope to customise diagnostic methods more precisely, opening the door to proactive and individualised treatment approaches. In addition to enhancing early detection, this comprehensive and progressive strategy presents AI as a game-changing instrument that will revolutionise healthcare practices for haematological illnesses and eventually improve patient outcomes.

Another crucial thing we analysed was that the genetic types of anaemia such as AA, FA and DBA have some features which have certain concerns to aggravate MDS (117). This could require exigent and targeted personalised medicine to cease its further growth.

7. Conclusion

The present analysis highlights the varied classification of anaemia based on a range of characteristics, including aetiology, Hb levels, RBC morphology, and genetic factors, and the importance of identifying the type of anaemia. The paper explores the intricacies of numerous forms of anaemia, with a particular emphasis on those resulting from genetic diseases such as heredity, autoimmune disorders, and mutations. The genetic anaemias included in this study are haemolytic anaemia, thalassemia, sideroblastic anaemia, DBA, FA and AA. Each kind is distinguished by distinct physical properties of RBCs, pathogenic behaviours, and genetic factors. The roles that each kind's associated genes and mutations play have been clarified, offering a comprehensive grasp of the underlying genetic processes. The immunomodulatory role of vitamin D in anaemia is also examined in this work, with special attention to its connection to erythropoiesis and the potential impact of vitamin D deficiency on various forms of anaemia. The importance of considering dietary deficiencies, genetic changes, and chronic illnesses as potential causes of anaemia is emphasised throughout the study.

The use of biomarkers for identifying distinct forms of anaemia is highlighted, along with the diagnostic component of anaemia. The study identifies distinct molecular biomarkers linked to each kind, providing information on their possible use in the detection and tracking of anaemia. Even though machine learning and deep learning models have been used in the detection of various types of anaemia, there are numerous challenges associated with them. Medical data was the type of data that was used in the majority of cases. These data are extremely sensitive and subjected to strict privacy regulations.

The data are imbalanced, and restricted and have numerous ethical and legal concerns. Being limited, the biological data obtained from different individuals can vary significantly and thus it becomes a bigger challenge to create a universally applicable model. Apart from the data, there are numerous factors such as age, gender, locality, geographical region, and past medical history of individuals that should also be considered. Identification of relevant feature selection is the secondary challenge in these types of data. Inadequate feature selection may lead to suboptimal model performance and proper dimensionality reduction was required in processing and analysing the data. They deal with a lot of ethical and legal concerns in handling the data. The usage of EHR would be complex and requires a seamless integration of practical use as they require precise statistical and genetic analysis. Lack of domain expertise in understanding the intricacies of the diseases and further analysis in machine learning aspects. Anaemia is a disease which is dynamic and exhibits diverse and evolving characteristics. Machine learning and deep learning models should be continuously updated and adapted to handle new patterns and variations.

AA is a multifactorial and intricate illness typified by the bone marrow's incapacity to generate a sufficient quantity of RBCs. It can be caused by a number of things, including immunological-related conditions, exposure to chemicals, chemotherapy, genetic abnormalities, and in rare cases-such as the COVID-19 vaccine cases that have been reported recently-by particular immunisations. AA is difficult to classify because of its similarities to other disorders such FA, MDS and PNH. These diseases may require specialised testing, such as the chromosomal breakage test, due to their overlapping symptoms and comorbidities, which make diagnosis and distinction challenging. The kind and severity of an illness determine which AA treatment plan is best. Some immunomodulatory therapies have shown promise, such as ATG and allogeneic stem cell transplantation. Furthermore, it has been demonstrated that MSCs can regulate immune responses and offer a particular environment for the process of hemopoiesis. The association between AA and other conditions such as cancer, telomere shortening, clonal haematopoiesis, and chronic inflammatory bowel disease emphasises how complex the disease is and how important it is to fully understand its aetiology. For example, Alzheimer's disease has been associated with telomere shortening, and new discoveries regarding the genes associated with telomerase present new avenues for therapeutic methods. The sudden appearance of AA following COVID-19 vaccination raises serious questions about potential links between vaccinations and haematological disorders. Even though these incidents are uncommon, they serve as a reminder of the value of continuing observation and investigation to learn more about the possible adverse effects of immunisations.

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Authors' contributions

DS and IRO conceived the present study. DS developed methodology, conducted investigation, wrote the original draft. DS and IRO wrote, reviewed and edited the manuscript. IRO supervised the study. Both authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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