Received: 20 May 2022 | Accepted: 15 June 2022

DOI: 10.1111/bjh.18337

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

ORIGINAL PAPER

# Peripheral-blood cytopenia, an early indicator of inborn errors of immunity

**Helena M. Cornelissen**[1,2] | **Ernest M. Musekwa**[1,2] | **Richard H. Glashoff**[2,3] | **Monika Esser**[2,3,4] | **Moleen Zunza**[5] | **Deepthi R. Abraham**[4] | **Zivanai C. Chapanduka**[1,2]

[1]Department of Haematology, National Health Laboratory Service, Tygerberg Hospital, Cape Town, South Africa

[2]Faculty of Medicine and Health Sciences, University of Stellenbosch, Cape Town, South Africa

[3]Department of Medical Microbiology and Immunology, National Health Laboratory Service, Johannesburg, South Africa

[4]Division of Paediatric Rheumatology and Immunology, Department of Paediatrics and Child Health, Tygerberg Hospital, Cape Town, South Africa

[5]Division of Epidemiology and Biostatistics, Department of Global Health, University of Stellenbosch, Cape Town, South Africa

**Correspondence**
Helena M. Cornelissen, Department of Haematology, National Health Laboratory Service, Tygerberg Hospital, Cape Town, South Africa.
Email: hcornelissen@sun.ac.za

**Summary**

Inborn errors of immunity (IEI) are inherited monogenic disorders resulting in defective immune response. Non-infectious presentations are increasingly more apparent. Widely available, cost-effective early indicators are needed. Peripheral-blood cytopenia may be a presenting laboratory feature or an observed secondary phenomenon. This retrospective review of the South African Primary Immunodeficiency Registry (SAPIDR) aimed to assess the haematological indices at presentation and their association with the International Union of Immunological Societies (IUIS) 2019 IEI classification and mortality. Of 396 patients on the SAPIDR, 66% ($n = 257$) had available haematological results. Sixty percent were males and 85% under 18 years. A majority (53%) had predominantly antibody deficiency. At presentation, infection was prominent (86%) followed by cytopenia (62%). Neutropenia was associated with IUIS III [odds ratio (OR) 3.65, confidence interval (CI) 1.44–9.25], thrombocytopenia with IUIS II (OR 14.39, CI 2.89–71.57), lymphopenia with IUIS I (OR 12.16, CI 2.75–53.73) and pancytopenia with IUSI I (OR 12.24, CI 3.82–39.05) and IUIS II (OR 5.99, CI 2.80–12.76). Cytopenia showed shorter overall survival (OR 2.81, CI 1.288–4.16). Cytopenias that are severe, persistent, unusual and/or recurrent should prompt further investigation for IEI. The full blood count and leucocyte differential may facilitate earlier identification and serve as an adjunct to definitive molecular classification.

**KEYWORDS**
cytopenia, early indicators, inborn errors of immunity (IEI), non-infectious manifestations, primary immunodeficiency

## INTRODUCTION

Inborn errors of immunity are inherited monogenic defects resulting in dysregulation of the innate and/or adaptive immune response.[1–4] The current prevalence is estimated at 4 to 10 per 100 000 live births per year with few studies describing the epidemiological features in Africa, less so in South Africa.[5–8] Phenotypic presentation is heterogeneous and early recognition can be difficult.[3–5] Both the International Union of Immunological Societies (IUIS) 2019 classification

of IEI and the European Society for Immunodeficiency (ESID) have provided a clinical framework for classifying and understanding disease presentation.[4,9]

Although severe, unusual or recurrent infections are the most common presentation, up to 25% of IEI cases may be missed if clinical focus is on infection alone.[10] Non-infectious manifestations are becoming increasingly more apparent.[10–14] Severe, persistent and/or recurrent peripheral-blood cytopenia, the reduction of one or more mature blood cell lines, that is otherwise unexplained or unusual, may be a presenting laboratory feature or an observed secondary phenomenon.[2,10,15,16] The recent IUIS 2019 addition of bone-marrow failure highlights the relevance of haematological manifestations in IEI.[4]

The pathogenic mechanisms of cytopenia in IEI are multifactorial. They are commonly attributed to cell-mediated and humoral immune dysfunction or dysregulation, driving autoimmunity and autoinflammation. However, non-immune causes should also be considered.[2,15–17] B- and T-cell responses have a complex interdependent relationship, primary defects resulting in altered maturation and regulation with subsequent decreased number and function.[2,15,18] Haemophagocytosis is an important cause of cytopenia, particularly in the paediatric population, and may herald an underlying primary aetiology.[19,20] Secondary factors such as splenic sequestration and bone-marrow infiltration by malignancy or infection are non-immune causes that should not be overlooked (Figure 1).[17,21–23]

Inborn errors of immunity are increasingly more common than previously thought and require early identification for life-changing and/or lifesaving intervention.[6,17,24] Understanding the non-infectious manifestations of IEI is important, to improve awareness of the wide diagnostic spectrum and facilitate precision drug targets.[10] Definitive diagnostic investigations serve little purpose if the disease is not entertained at the outset. Identifying abnormalities of laboratory parameters that already form part of routine diagnostics, are readily available and that may facilitate earlier case identification, are paramount. The widely available full blood count (FBC) and leucocyte differential (DIFF), forming part of first-line investigation for suspected IEI, may facilitate earlier identification. This retrospective review of the South African Primary Immunodeficiency Registry (SAPIDR) aimed to assess the haematological indices at presentation; their association with IUIS 2019 classification for IEI; and mortality.

# METHODOLOGY

## Study design

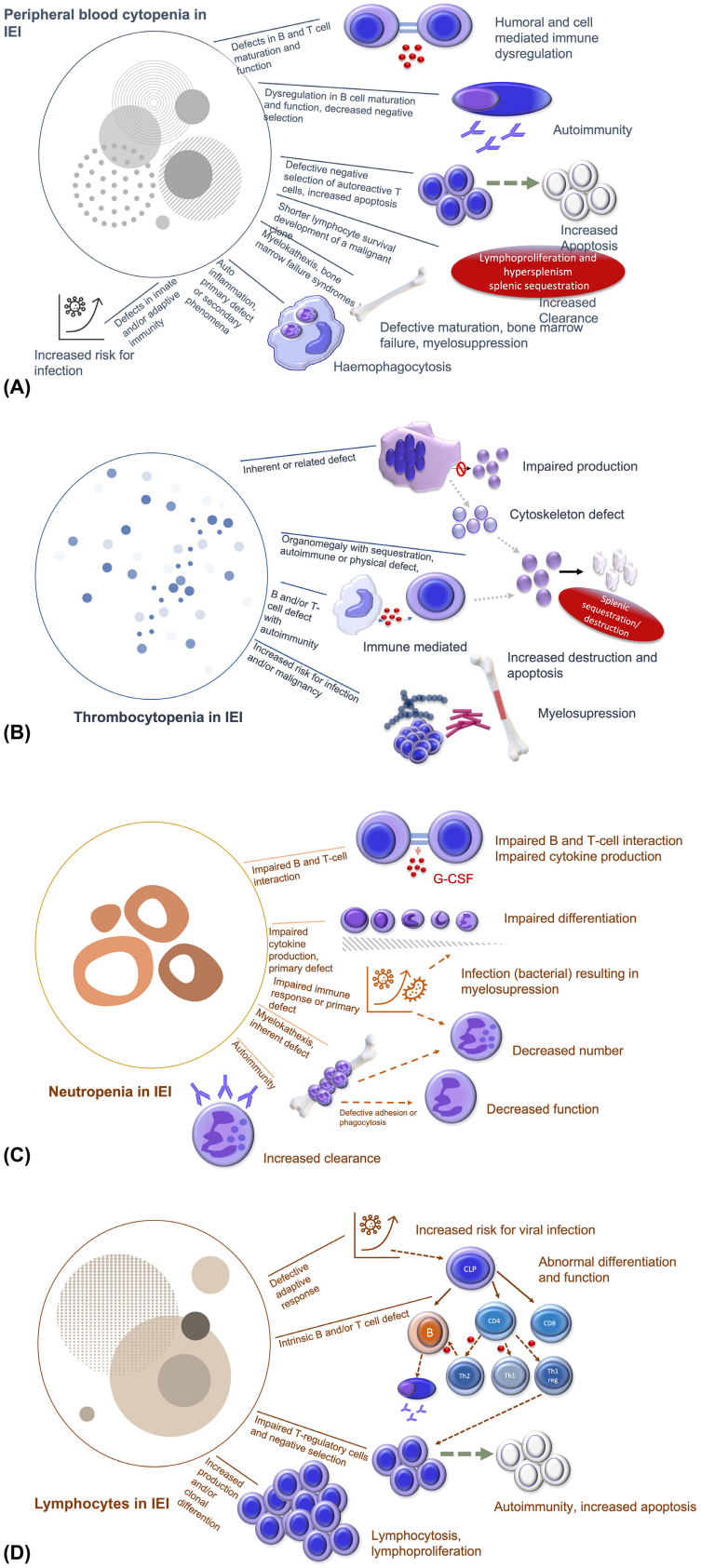
This retrospective cross-sectional descriptive study spanning 2013 to 2020, was conducted in a tertiary state care facility in South Africa, utilising SAPIDR data. The IUIS 2019 IEI classification was applied and haematological parameters, at or within one month of diagnosing IEI, were assessed. SAPIDR patients undergo rigorous investigation to exclude secondary causes of immunodeficiency and have pre-existing signed informed consent. Data collection was granted by custodians. Ethical approval and waiver of consent was given by the Health Research Ethics Committee (S20/03/082).

## Study procedures and measurements

Both state and private-sector laboratories must be accredited with the South African National Accreditation System (SANAS) and adhere to International Standards Organisation (ISO) ISO15189 requirements for medical laboratory quality. Molecular diagnosis was confirmed using Sanger Sequencing or next-generation sequencing (NGS) either through a focused IEI panel, whole-exome or whole-genome sequencing and results interpreted though multidisciplinary discussion. Data were supplemented from the National Health Laboratory Service (NHLS) Laboratory Information System and hospital electronic clinical management database (Electronic Content Management). Information was captured on a Research Electronic Data Capture (REDCap®) form.[25] Those without haematological indices available were excluded. The evaluated parameters included patient demographics and laboratory indices, namely FBC, DIFF and other relevant haematological or immunological results.

Age-appropriate NHLS reference ranges were used for interpretation.[26] Severe cytopenia was defined as; anaemia (haemoglobin) less than –2SD below age-appropriate reference range, thrombocytopenia less than $100 \times 10^9$/l, neutropenia less than $1.5 \times 10^9$/l and lymphopenia less than $3 \times 10^9$/l, persistent cytopenia lasting more than one month despite optimal management, unusual cytopenia with an otherwise unexplainable cause and recurrent or refractory

**FIGURE 1** Mechanisms contributing to cytopenia in inborn errors of immunity (IEI). (A) The pathogenic mechanisms of cytopenia are multifactorial and include: humoral and cell-mediated immune dysfunction and/or dysregulation, haemophagocytosis, splenic sequestration (secondary to abnormal lymphoproliferation), bone-marrow dysfunction including ineffective maturation, myelodysplasia, primary bone-marrow failure and myelosuppression due to secondary infections and bone-marrow infiltration.[2,16] (B) Cytoskeletal dysfunction with megakaryocyte dysfunction, increased apoptosis and splenic platelet destruction. Contributory causes of non-immune thrombocytopenia in IEI include: increased clearance and apoptosis; myelosuppression by infections, myelofibrosis/bone-marrow malignancy, cytotoxic drugs or transplant are also contributory.[2,16,28] (C) Defective myeloid cell differentiation or release of granulocytes from the bone marrow, enhanced apoptosis and increased destruction of peripheral-blood granulocytes are the main physiological mechanisms underlying chronic severe or intermittent neutropenia in primary immunodeficiency patients.[2,26,27] (D) Lymphopenia driven by B- and T-cell-intrinsic defect with abnormal maturation and defective function, negative selection of autoreactive T lymphocytes in the thymus as well as defects in the number or function of regulatory T-cells, impaired apoptosis of autoreactive lymphocytes, loss or breakage of tolerance, increased lymphoid production and cytokine secretion which likely also drives the immune dysregulation and associated autoimmune cytopenia.[2,25] [Colour figure can be viewed at wileyonlinelibrary.com]


Peripheral blood cytopenia in IEI
Defects in B and T cell maturation and function
Humoral and cell mediated immune dysregulation
Dysregulation in B cell maturation and function, decreased negative selection
Autoimmunity
Defective negative selection of autoreactive T cells, increased apoptosis
Increased Apoptosis
Shorter lymphocyte survival
development of a malignant clone
Myelokathexis, bone marrow failure syndromes
Lymphoproliferation and hypersplenism splenic sequestration
Increased Clearance
Auto inflammation, primary defect or secondary phenomena
Defects in innate and/or adaptive immunity
Increased risk for infection
Defective maturation, bone marrow failure, myelosuppression
Haemophagocytosis
(A)
Inherent or related defect
Impaired production
Cytoskeleton defect
Organomegaly with sequestration, autoimmune or physical defect,
Splenic sequestration/ destruction
B and/or T-cell defect with autoimmunity
Immune mediated
Increased destruction and apoptosis
Increased risk for infection and/or malignancy
Myelosupression
Thrombocytopenia in IEI
(B)
Impaired B and T-cell interaction
Impaired B and T-cell interaction
Impaired cytokine production
G-CSF
Impaired differentiation
Impaired cytokine production, primary defect
Impaired immune response or primary defect
Infection (bacterial) resulting in myelosupression
Myelokathexis Inherent defect
Decreased number
Autoimmunity
Neutropenia in IEI
Defective adhesion or phagocytosis
Decreased function
Increased clearance
(C)
Increased risk for viral infection
Defective adaptive response
CLP
Abnormal differentiation and function
Intrinsic B and/or T cell defect
B
CD4
CD8
Th2
Th1
Th1 Hi
Impaired T-regulatory cells and negative selection
Increased production and/or clonal differention
Lymphocytes in IEI
Autoimmunity, increased apoptosis
Lymphocytosis, lymphoproliferation
(D)

cytopenia as persistent despite optimal management.[16,18,27,28] Pancytopenia was defined as absolute white cell count less than $4 \times 10^9$/l, haemoglobin less than 100 g/l and thrombocytopenia less than $150 \times 10^9$/l.[29–31]

## Statistical analysis

STATA 17 (College Station, Texas 77845, USA) was used for analysis. Descriptive statistics were performed on demographic and laboratory parameters, in relation to IUIS 2019 classification. Empirical diagnostic cut-off points that maximised sensitivity and specificity were determined for the neutrophil-to-lymphocyte ratio (NLR) using receiver operating characteristic (ROC) curves. Association between FBC parameters and IUIS classification was tested using the chi-squared test, or Fishers exact test. Odds ratios (OR) were reported as measures of association with the corresponding 95% confidence intervals (CI). The Kaplan–Meier method was used to analyse time until death from diagnosis, and comparisons were made with the log-rank test. Statistical significance was considered as $p < 0.05$.

# RESULTS

## Cohort characteristics

The SAPIDR includes both children and adults. Two thirds (65%, $n = 257$) of patients on the SAPIDR ($n = 396$) had available haematological indices, 34% ($n = 136$) without haematological indices were excluded from the analysis. A molecular diagnosis with a pathological variant was identified in 30% ($n = 77$) (Figure 2A). Those younger than 18 years made up majority (84%; $n = 217$) of the cohort, of which 49% ($n = 123$) were younger than five years while the remainder (16%; $n = 40$) were older than 18 years. The median age at diagnosis was 76 months (range from birth to 420 months) with a median delay in diagnosis of 75 months (IQR = 30–174 months). Nineteen percent ($n = 48$) presented within the first 12 months of life and 47% ($n = 121$) below 60 months. Majority (54%, $n = 138$) had a predominantly antibody deficiency (IUIS III). (Figure 2A) Those with cellular and humoral immune deficiency (IUIS I) and combined immunodeficiency (IUIS IIa) presented younger whilst those with IUIS III and complement deficiency (IUIS VIII) presented later in life (Table S1a). Presentation with cytopenia and age at diagnosis had a bimodal distribution, younger age (below 12 months) and older age most significant (Table S1a,b). The majority were of male sex (60%, $n = 154$). Male sex was significantly associated with a molecular diagnosis ($p = 0.004$) (Table S2).

Most (86% $n = 223$) presented with severe, persistent, unusual and/or recurrent infection, 62% ($n = 161$) were cytopenic at presentation and 27% ($n = 71$) had a known family history of IEI, none were from a consanguineous relationship (Figure 2B). Haematological malignancy was observed in three cases, all with B-cell lymphoma; one with combined immunodeficiency (CID), one a hyper-IgM like syndrome and the other an undefined hypogammaglobulinaemia. Autoimmunity was seen in seven patients (3%), two cases had undefined hypogammaglobulinaemia, Aicardi Goutieres syndrome ($n = 2$), IgA deficiency ($n = 1$) and one a C6 deficiency ($n = 1$). Only one patient with a complement deficiency (IUIS VIII) had documented haemolysis (Figure 2B).

## FBC parameters

In those with cytopenia at presentation ($n$=161), 17% ($n = 27/161$) were pancytopenic, 40% ($n = 64/161$) anaemic, 8% ($n = 13/161$) thrombocytopenic, 19% ($n = 30/161$) neutropenic and 62% ($n = 100/161$) lymphopenic (Figure 2B). Lowest median haemoglobin was seen in IUIS V and IUIS I, median platelet count was lowest in IUIS II, median lymphocyte count lowest in IUIS I and median neutrophil count lowest in IUIS III (Figure 3, Table S3). IUIS I diagnosis was significantly associated with cytopenia at presentation (OR 12.43, CI 3.82–39.05) namely; severe cytopenia (OR 3.96, CI 1.08–14.88), persistent cytopenia (OR 12.27, CI 3.75–39.95), and unusual cytopenia (OR 8.89, CI 3.04–25.86), namely; anaemia (OR 4.15, CI 1.58–10.90), leucopenia (OR 15.69, CI 1.86–132.29] and lymphopenia (OR 12.16, CI 2.75–53.73), where 52% (11/21) were anaemic, 38% (8/21) leucopenic and 90% lymphopenic (19/21). Cytopenia was associated with IUIS II (OR 5.99, CI 2.80–12.76) seen in 94% (31/33) namely; severe, persistent and/or unusual cytopenia (OR 3.58, CI 1.08–11.97), 3 (1.44–6.24) and 2.71 (1.32–5.60) respectively], 21% (7/33) were thrombocytopenic at presentation with significant association (OR 14.39, CI 2.89–71.57). Neutropenia was seen in 14% with IUIS III showing significant association (OR 3.65, CI 1.44–9.25) [Figure 4, Table S4]. Pancytopenia at presentation was most significantly associated with IUIS I (OR 4.21, CI 1.48–11.99) and a molecular diagnosis (OR 2.81, CI 1.23–6.42). Anaemia was the most prominent cytopenia in IUIS VIb. Class VII did not show marked cytopenia, although lymphocyte count was lower in IUIS VIIa than VIIb (Table S3). The neutrophil-to-lymphocyte ratio (NLR), with an optimal cut-off of 1.8, was associated with IUIS I (OR 2.72 CI 1.01–7.28) and molecular diagnosis, cut-off of 2.1 (OR 2.16, CI 1.19–3.92) with low positive predictive value but high negative predictive value (Table S5).

## Death outcome

At the time of last follow-up, 8% (n=20) were lost to follow-up and 11% ($n = 27$) had died. Infections predominated as the cause of death (33%, $n = 9$) followed by organ failure (22%, $n = 6$) with one patient succumbing to respiratory failure secondary to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. Male sex was significantly associated with death ($p < 0.001$). The highest mortality was seen in IUIS I, 21% ($n = 6$ of 21 IUIS I cases, none of whom had a bone-marrow transplant), followed by IUIS II 21% ($n = 7$ of 33), higher than in those with a molecular diagnosis 17% (13

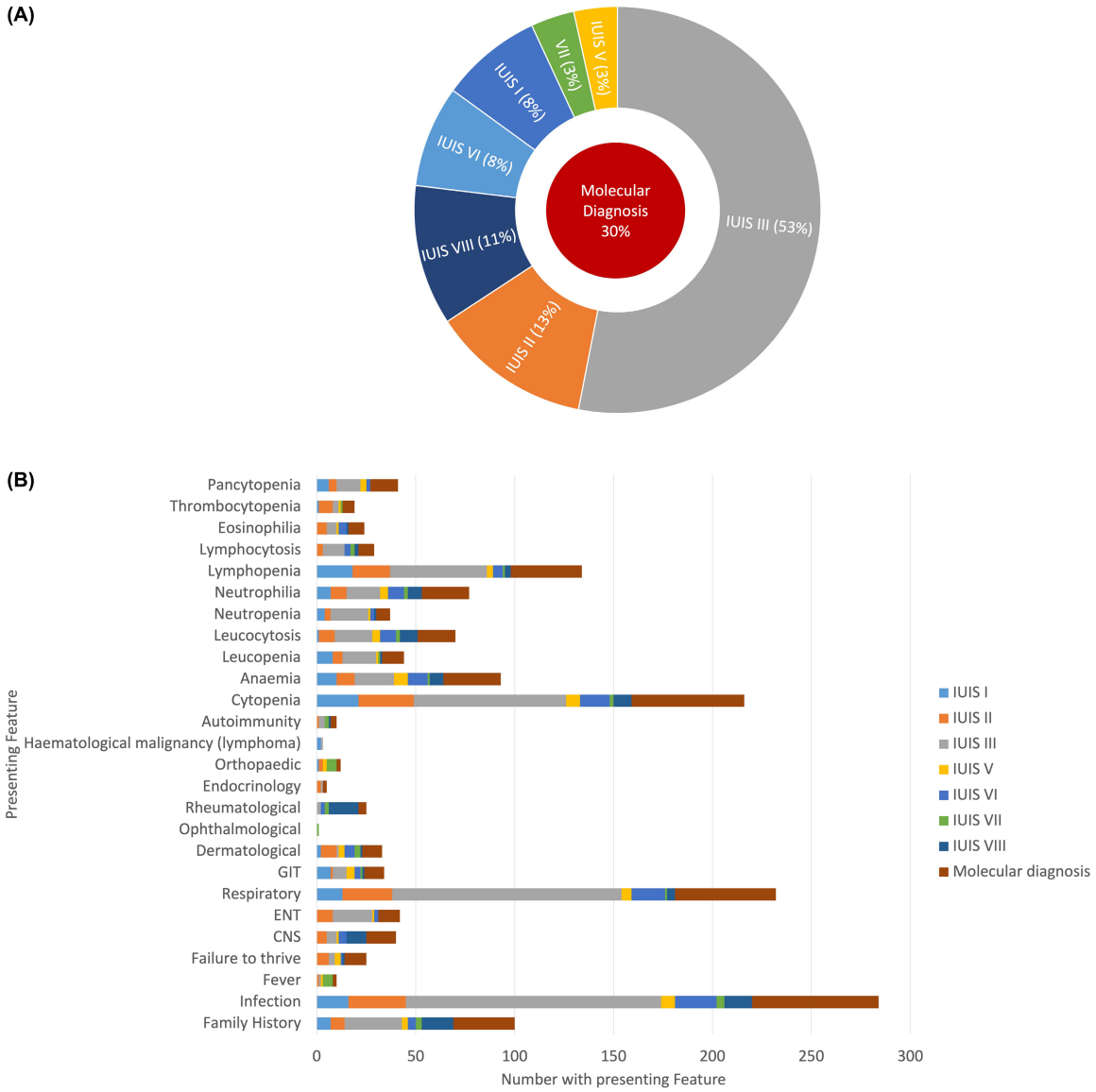



**FIGURE 2** Distribution of cases according to International Union of Immunological Societies (IUIS) 2019 classification, gender distribution, and clinical presentation. (A) A majority (53%) were classified as a predominantly antibody deficiency (IUISIII), 30% had a confirmed molecular diagnosis. (B) Infections were the most common presentation (86%) and peripheral-blood cytopenia was seen in 62%, 27% had a known family history of IEI (no history of consanguinity). See Table S2 for additional information. Only those IUIS diagnoses with sufficient cases are represented, as well as only the major classifications; subclassifications can be viewed in Table S2. International Union of Immunological Societies (IUIS) I, immunodeficiencies affecting cellular and humoral immunity; IUIS II, combined immunodeficiencies with associated or syndromic features; IUIS III, predominantly antibody deficiencies; IUIS IV, diseases of immune dysregulation; IUIS V, congenital defects of phagocyte number, function or both; IUIS VI, defects in intrinsic and innate immunity; IUIS VII, autoinflammatory disorders; IUIS VIII, complement deficiencies. [Colour figure can be viewed at wileyonlinelibrary.com]

of 77) (Figure S1). Extremes of age (2–12 and over 120 months) showed significant association with death ($p$ = 0.004 and <0.001; Table S5). Presentation with cytopenia was significantly associated with death (OR 2.81, CI 1.288–4.158), [$p$ = 0.005], namely; severe ($p$ = 0.003), and/or recurrent cytopenia ($p$ <0.001) (Table S6). Shorter overall survival was associated with pancytopenia ($p$ = 0.042), anaemia [$p$ <0.001] thrombocytopenia [$p$ <0.001], leucopenia [$p$ = 0.009] or neutropenia [$p$ <0.001] at presentation (Figure 5 and Table S6).

## DISCUSSION

In this retrospective review of the early haematological findings of IEI in a developing-world setting, cytopenia at presentation was found in 62% of cases. Association between presentation with peripheral-blood cytopenia and a molecular diagnosis of an IEI (OR 2.26 CI 1.42–3.59) and shorter overall survival (OR 2.81, CI 1.288–4.158) was shown.

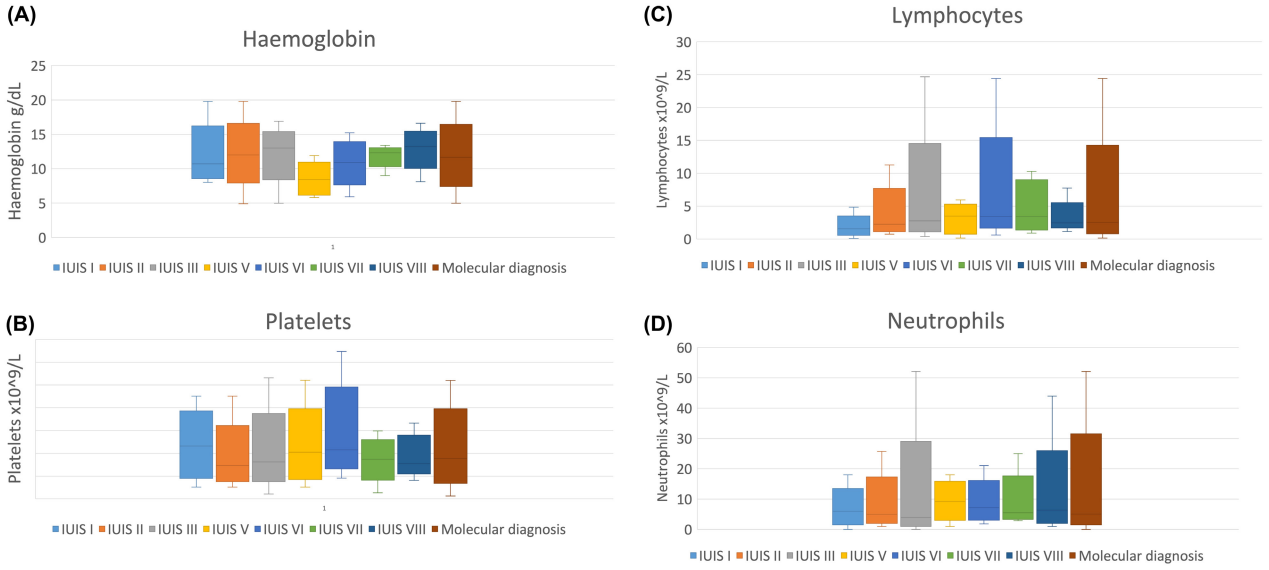



**FIGURE 3** Median and interquartile ranges of full blood count parameters according to International Union of Immunological Societies (IUIS) 2019 classification. (A) Low median haemoglobin in IUIS V and IUIS I diagnosis. (B) Platelet count was lower in IUIS II diagnosis. (C) and (D) Median lymphocyte count was lowest in IUIS I and median neutrophil count in IUIS III. Only those IUIS diagnoses with sufficient cases are represented, subclassifications can be viewed in Table S3. International Union of Immunological Societies (IUIS) I, immunodeficiencies affecting cellular and humoral immunity; IUIS II, combined immunodeficiencies with associated or syndromic features; IUIS III, predominantly antibody deficiencies; IUIS IV, diseases of immune dysregulation; IUIS V, congenital defects of phagocyte number, function or both; IUIS VI, defects in intrinsic and innate immunity; IUIS VII, autoinflammatory disorders; IUIS VIII, complement deficiencies. [Colour figure can be viewed at wileyonlinelibrary.com]

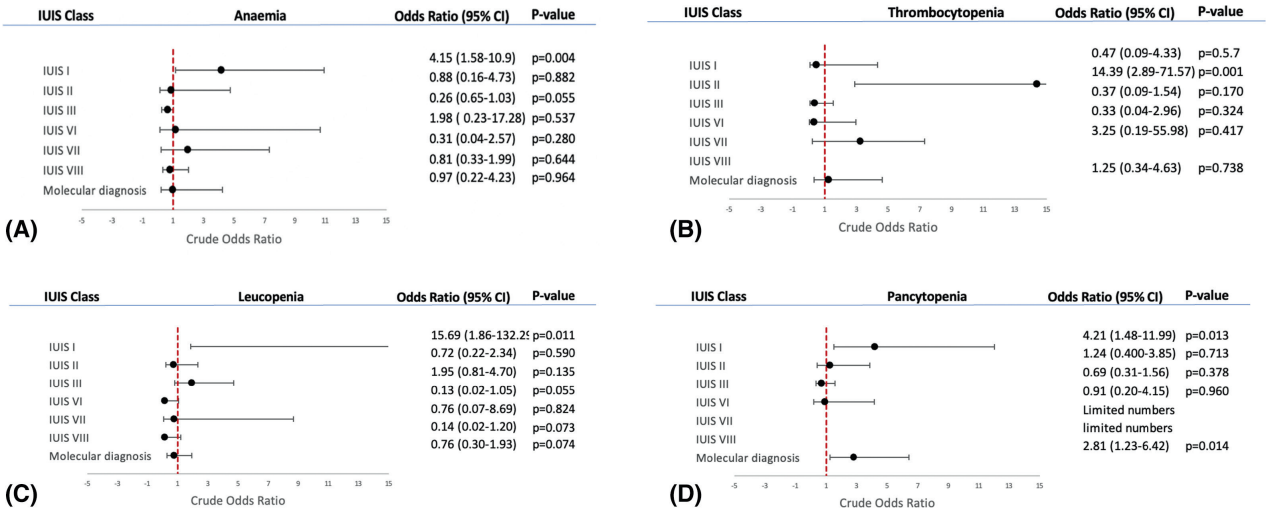



**FIGURE 4** Graphical presentation of the odds ratios and 95% confidence intervals showing association between peripheral-blood cytopenia and International Union of Immunological Societies (IUIS) 2019 classification. (A) Anaemia was associated with IUIS I. (B) Thrombocytopenia associated with IUIS II. (C) Leucopenia was significantly associated with IUIS I, neutropenia with IUIS III and lymphopenia with IUIS I (see Table S4). (D) Pancytopenia was associated with IUIS I and a molecular diagnosis. Only those IUIS diagnoses with sufficient cases are represented, subclassifications can be viewed in Table S4. International Union of Immunological Societies (IUIS) I, immunodeficiencies affecting cellular and humoral immunity; IUIS II, combined immunodeficiencies with associated or syndromic features; IUIS III, predominantly antibody deficiencies; IUIS IV, diseases of immune dysregulation; IUIS V, congenital defects of phagocyte number, function or both; IUIS VI, defects in intrinsic and innate immunity; IUIS VII, autoinflammatory disorders; IUIS VIII, complement deficiencies. [Colour figure can be viewed at wileyonlinelibrary.com]

## Cohort characteristics

Almost half were diagnosed within the first five years of life. Presentation with cytopenia was associated with a shorter delay in diagnosis. First-world settings report earlier presentation within the first year of life whilst later presentation is seen in the developing-world setting and reflected this cohort more closely.[10,32] Patients with IUIS I presented earlier and had a shorter delay in diagnosis; all were cytopenic at presentation namely anaemia, leucopenia and lymphopenia, of which 27% were pancytopenic (Figures 2B, 4D and Table S4). Due to the more severe

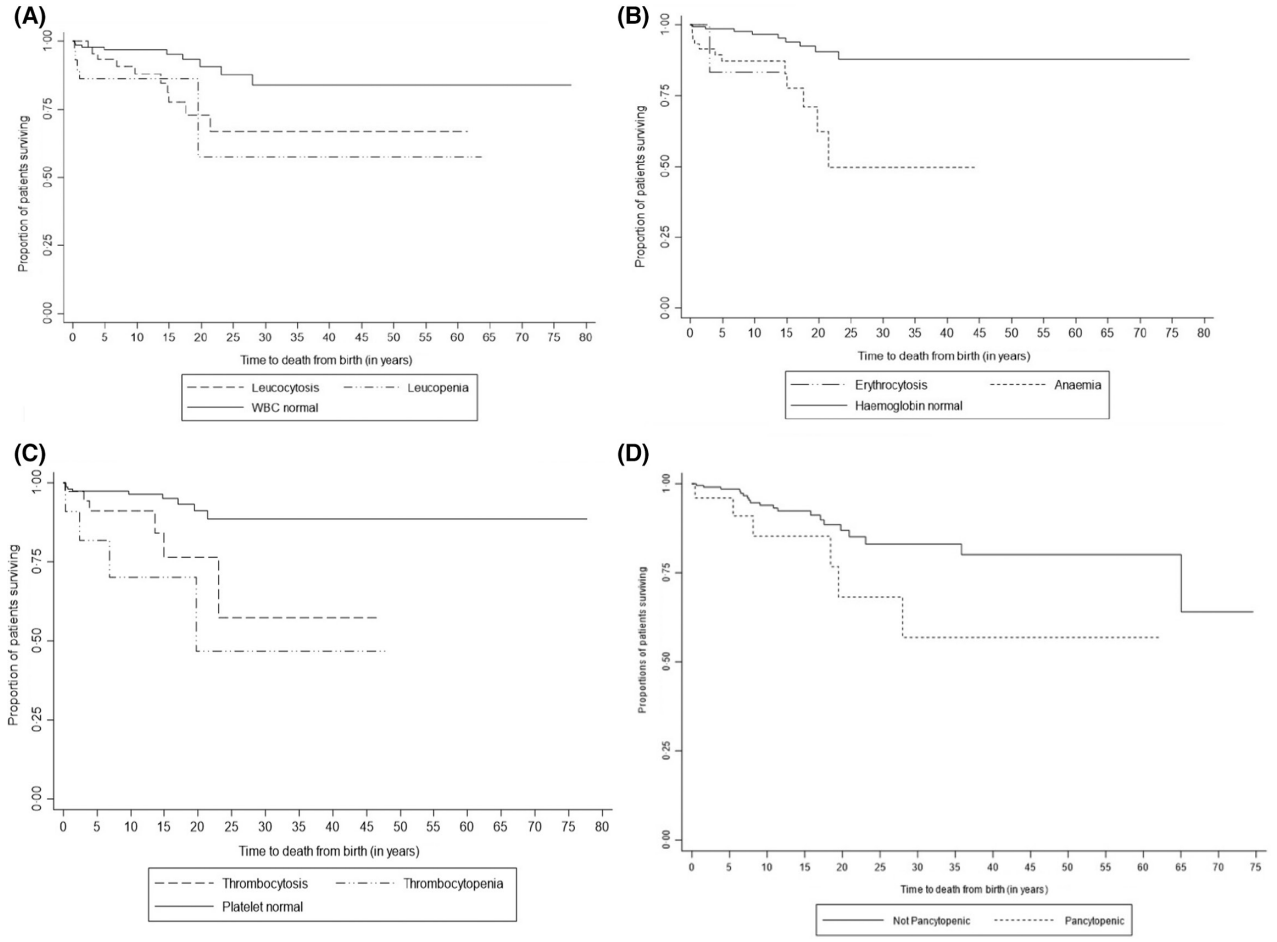



**FIGURE 5** Kaplan–Meier estimates of proportions of patients surviving according to full blood count parameters at presentation. Presentation with leucopenia, anaemia and thrombocytopenia was associated with shorter overall survival. Pancytopenia at presentation was associated with shorter overall survival, $p = 0.042$.

phenotype of IUIS I, classical presentation is typically within the first year of life with severe and/or recurrent bacterial infections as well as cytopenia (commonly lymphopenia, neutropenia and/or thrombocytopenia).[11,13] In European registries, B-cell disorders are the most common type of immunodeficiency, accounting for approximately 50%–60% of all IEI with most presenting in adulthood, in part due to a less severe phenotype.[10,12,13,33] Reflecting this, the majority (53%) were classified with a predominant antibody deficiency (IUIS III) where presentation with neutropenia showed significant association (Figures 2, 4). Interestingly, IUIS I and II are more common in populations with higher consanguinity.[11,34] As presentation with cytopenia was associated IUIS I and II diagnoses, the predictive value in cohorts with higher consanguinity may be of greater value.

## Cytopenia in IEI

Delineation of cytopenia determines whether the cause is increased loss, decreased production or decreased function of cells, namely immune or non-immune pathology.[2] A stepwise laboratory approach focuses on the often lengthy differential diagnosis. Exclusion of infection other than human immunodeficiency virus (HIV) may also be relevant, particularly Epstein–Barr virus (EBV), cytomegalovirus (CMV), parvovirus B19, other DNA viruses and bacterial infection.[2,35] The FBC, DIFF and peripheral-blood film direct the need for haemolytic screen (Coombs test, reticulocyte count, indirect bilirubin and haptoglobin), additional useful markers of cell lysis (lactate dehydrogenase, potassium, aspartate transaminase and uric acid) and haematinic studies (iron studies, B12 and folate).[2,18] Morphological findings of the peripheral-blood film may reveal salient features suggesting an IEI, such as giant azurophilic granules in Chediak–Higashi Syndrome (CHS), hypersegmented neutrophils with pyknotic nuclei and cytoplasmic vacuoles in Warts, Hypogammaglobulinemia, infections and Myelokathexis (WHIM) syndrome and abnormally small platelets in Wiscott–Aldrich syndrome (WAS)/X-linked thrombocytopenia (XLT).[27] The haematologist should be consulted early to guide decisions on flow cytometry and bone-marrow biopsy. Bone-marrow biopsy findings may help synchronise the differential such as myelodysplasia

in germline GATA2 (GATA binding protein 2) deficiency, myelokathexis in WHIM syndrome, promyelocyte arrest in ELANE (Elastase, neutrophil Expressed) gene mutation and characteristic vacuoles in myeloid precursors in vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic (VEXAS) syndrome (Table 1).[27,36,37] Pancytopenia, particularly in the child, may highlight underlying IEI such as diseases of immune dysregulation and bone marrow failure syndromes (BMFS).[15,35] One of the main diagnostic challenges in paediatric haematology is the correct diagnosis of patients with pancytopenia and a hypocellular bone marrow.[35] The BMFS often have overlapping morphology and therefore careful past medical, family history and physical examination, looking for syndromic features, is important.[2,35] (Further description of the BMFS can be seen in Table 1).

EuroFlow has developed standardised, accurate and highly sensitive flow cytometric tests for primary immunodeficiency. Although the molecular diagnosis delineates definitive classification in most cases; the cost, often long turnaround time and sometimes difficult interpretation are disadvantages, particularly in the developing setting. Flow cytometry, is already established in most major haematology laboratories, allows quick turnaround time to broadly classify IEI and may focus molecular investigation.[38] The immunologist will direct important immunologic investigation that may be influenced by immunoglobulin replacement or immune suppression which are used in the management of cytopenia, such as quantitative immunoglobulins, vaccine antibody tests, lymphocyte subsets and functional analysis.[2] Reflecting diagnostic yield of molecular testing in both international and local reports ranging from 30%–40%, a pathological variant was confirmed in 30%.[39–41] The molecular diagnosis is a cornerstone of IEI diagnostics, establishing the definitive classification.[4] Molecular analysis is however more expensive and less readily available in some settings and must be guided by clinical phenotype and focused immunological and/or haematological findings.[3,4]

Cytopenias in IEI are multifactorial, immune and/or non-immune aetiologies, often multilineage with a chronic or relapsing course and tendency towards treatment refractoriness.[16] Anaemia was associated with an overall shorter overall survival in this cohort (Figure 5). Only one patient, with a complement deficiency, presented with autoimmune haemolytic anaemia (AIHA). Haemolysis in complement deficiency is driven by the mutation or deficiency resulting in altered regulation with catastrophic activation.[42,43] Beyond immune cytopenia, the more common causes of red-cell loss, particularly in the context of severe infection, such as disseminated intravascular haemolysis (DIC) should be considered.[44] Ineffective red-cell production from haematinic deficiency or myelosuppression from immune dysregulation or secondary infection/malignancy may also be contributory.[2] Anaemia was seen in IUIS V and VI, of which Chronic Granulomatous Disease (CGD) and Mendelian Suceptibilty to Mycobacterial Disease (MSMD) fall into these categories respectively. Anaemia in CGD is probably attributable to decreased iron absorption or increased losses as a result of colitis as well as chronic disease.[45] Both CGD and MSMD carry an increased risk of tuberculosis (TB) infection. TB is associated with anaemia which is usually anaemia of chronic disease. Interestingly, anaemic patients may be at increased risk of TB infection.[46]

Lymphopenia in association with severe infections in infancy was described in early severe combined immunodeficiency (SCID) case reports and as a result has long been an early warning sign of immunodeficiency, incorporated into scoring systems for early identification of IEI. Severe ($<3\times10^9$/l) or persistent lymphopenia in an infant with a suggestive history should prompt immediate immunological investigation for IEI.[28] More than half (62%) of the cohort were lymphopenic at presentation. A raised NLR was predictive of IUIS I and a molecular diagnosis of an IEI, likely reflecting relative lymphopenia (Table S5). B- and T-cell immunodeficiencies commonly present with lymphopenia due to intrinsic cell defect, abnormal maturation and function and altered cytokine secretion (Figure 1D).[2,47,48] Closer investigation into the lymphocyte count with lymphocyte subsets will help focus the differential diagnosis and immunological investigation.[10,16]

Neutropenia is common in IEI, an absolute neutrophil count less than $1.5\times10^9$/l in patients over one year old or chronic neutropenia (lasting >3 months) a likely caveat.[27,49] The haematologists' early involvement is important as the peripheral-blood and bone-marrow findings along with careful clinical examination can guide the often lengthy differential (Table 1).[27] Non-immune causes such as severe infection common across all IEI groups, particularly in deficiencies of phagocyte number or function or bone-marrow infiltration, should also be considered (Figure 1C). The direct involvement of Bruton tyrosine kinase (BTK) in neutrophil development is unclear, but is thought to contribute to neutrophil differentiation resulting in neutropenia, likely explaining why neutropenia was predictive of hypogammaglobulinaemia in this cohort.[27,49] No clear association was seen with defects of phagocyte number or function to further divulge the association, likely attributable to the low numbe of cases in the cohort. One case however, with a confirmed ELANE mutation, did present with classical cyclic neutropenia.

Immune thrombocytopenic purpura (ITP) is common in IEI and may be associated with other immune cytopenias such as Evans syndrome (ES) (Figure 1B, Table 1).[2,15,44] In a child, ES should prompt investigation for a possible monogenic defect.[16] In this cohort thrombocytopenia was predictive of combined immunodeficiency (CID) with associated syndromic features (IUIS IIa) which includes WAS/XLT, the classical thrombocytopenic IEI with abnormally small platelets.

Inborn errors of immunity carry an increased risk for developing malignancy.[17,21–23,50] Haematological malignancy was seen in three cases, all with B-cell lymphoma. The development of malignant neoplasm is complex and related to the inherent impaired immunity, tumour immune

**TABLE 1** Haematological signs that should prompt a suspicion of inborn errors of immunity (IEI). The common haematological manifestations of IEI according to the International Union of Immunological Societies (IUIS) 2019 classification for IEI[2,15,17]

| **Haematological signs that should prompt further investigation for IEI** | | |
|---|---|---|
| In primary care[17] | | In the haematology clinic [17] |
| Adults and paediatrics: recurrent or severe neutropenia, persistent/refractory thrombocytopenia, persistent or severe lymphopenia, lymphoproliferation (lymphadenopathy and hepatosplenomegaly) | | Adults: Bone-marrow failure, aplasia, myelodysplasia and myelokathexis<br>Paediatrics: lymphocytopenia in infancy, persistent/refractory neutropenia bone-marrow failure with syndromic features |
| Pathophysiological mechanism | Associated Inborn Error of Immunity | Common haematological findings |
| Autoimmune-mediated cytopenia in IEI | CID, CVID | Immune cytopenia: potentially life threatening: AIHA and ITP, autoimmune neutropenia, Evans syndrome[2] |
| | ALPS, LRBA | Non-Immune cytopenia: thrombocytopenia<br>Lymphoproliferative disorders associated with viral infections[2,17] |
| | X-linked agammaglobulinemia (XLA) | Immune cytopenia, neutropenia (up to 10%–26%), decreased bone-marrow precursor, decreased myeloid maturation (BTK-related signal transduction)[27] |
| | SCID | Immune cytopenia, lymphopenia, eosinophilia, lymphocytosis in Omenn syndrome[2,17] |
| | CID, WAS, 22q11 deletion (DiGeorge Syndrome) | Immune cytopenia (refractory cytopenia of childhood), non-immune cytopenia — lymphopenia lymphoproliferation.[2] microthrombocytopenia [low mean platelet volume (MPV) in WAS] |
| | PI3KD | Lymphoproliferative disorders associated with viral infections |
| Immune dysregulation underlying cytopenia in IEI | IPEX and IPEX-like APECED | Immune cytopenia, lymphoproliferative disorders associated with viral infections, eosinophilia, lymphocytosis |
| | Familial haemophagocytic lymphohistiocytosis 1–5 (FHL) | Hyperferritinaemia, splenomegaly, cytopenias, haemophagocytosis |
| | Hermansky–Pudlak syndrome (HPS) | Bleeding diathesis normal platelet count and size: impaired secondary aggregation in platelet aggregometry, neutropenia[55] |
| | Chediak–Higashi Syndrome (CHS) | Normal platelet count and size, large azurophilic granules in lysozymes (neutrophils, eosinophils), neutropenia common, defective granulocyte mobilisation from bone marrow, increased turnover due to increased destruction[27] |
| | WHIM syndrome | Myelokathexis: retention of neutrophils in the bone marrow due to increased CXCL12 responsiveness thus peripheral neutropenia, hypercellular marrow[49] |
| | X-linked lymphoproliferative disease (XLP), IL-2-inducible T-cell kinase (ITK) deficiency, ALPS | Immune cytopenia — Evans syndrome, lymphoproliferative disorders associated with viral infections[2,44] |
| Phagocyte disorders | Schwachman–Diamond syndrome | Neutropenia, thrombocytopenia and anaemia may be severe, pancytopenia, maturation arrest myelopoiesis, hypocellular marrow, increased risk leukaemia[18,35] |
| | Elastase deficiency (ELANE mutation) | Cyclic neutropenia, promyelocytic arrest (exclude acute promyelocytic leukaemia)[27] |
| | GATA2 deficiency | Neutropenia common, neutrophil maturation preserved, monocytopenia myelodysplasia, atypical megakaryocytes, increased risk acute myeloid leukaemia[27] |
| | Chronic granulomatous disease (CGD), X-linked neutropenia | Neutrophilia, abnormal neutrophil function (commonly demonstrated with neutrophil oxidative burst assay), normal neutrophil morphology on peripheral blood film and/or bone marrow aspirate |
| Bone-marrow failure in IEI | Schimke syndrome<br>ALPS and FHL | Cytopenias, often pancytopenia. |
| | Dyskeratosis congenita (DKC) | Pancytopenia, increased risk: bone-marrow failure, myelodysplasia and acute myeloid leukaemia |
| | Cartilage hair hypoplasia (CHH) | Neutropenia, lymphopenia |
| | Reticular dysgenesis | Absence of neutrophils, bone-marrow failure |

(Continues)

**TABLE 1** (Continued)

| Haematological signs that should prompt further investigation for IEI | | |
|---|---|---|
| Secondary myelosuppression in IEI | Secondary states of immune suppression due to viral infections, toxic marrow damage from drugs used to treat IEI, bone-marrow infiltration secondary to malignancy | Pancytopenia, myelokathexis |
| | Secondary HLH | In SCID and CID: Epstein–Barr virus (EBV), cytomegalovirus and adenovirus<br>In CGD: *Burkholderia cepacia*, *Leishmania* species and fungi[19] |

Abbreviations: AIHA, autoimmune haemolytic anaemia; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; ALPS, autoimmune lymphoproliferative syndrome; BTK, Bruton tyrosine kinase; CGD, chronic granulomatous disease; CHS, chediak higashi syndrome; CID, combined immunodeficiency; CVID, common variable immunodeficiency; ELANE, elastase neutrohil expressed; FHL, familial haemophagocytic lymphohistiocytosis; GATA2, GATA binding protein 2; HLH, haemophgocytic lymphohistiocytosis; IEI, inborn errors of immunity; IPEX, immune dysregulation, polyendocrinopathy X-linked; ITP, immune thrombocytopenic purpura; LRBA, lipopolysaccharide responsive and beige-like anchor protein; PI3KD, PI3 kinase disease; SCID, severe combined immunodeficiency; WAS, Wiscott–Aldrich syndrome; WHIM, warts, hypogammaglobulinemia, infections, and myelokathexis.

surveillance as well as viral infections such as EBV.[50,51] The type of malignancy is closely associated to the underlying type of IEI, for example non-Hodgkin lymphoma frequent in common variable immunodeficiency (CVID) and acute myeloid leukaemia in WHIM syndrome.[23,50–52] Chronic infections, such as EBV, establish a persistent inflammatory stage creating tissue damage with subsequent malignant transformation.[53] Immunologists need to diagnose the malignancy and haematologists/oncologists the underlying immunodeficiency early to optimise management and outcome.[50]

Despite significant advances in diagnosis and treatment, many IEI patients still suffer unnecessary premature death.[14,54] X-linked IEI often display a more severe phenotype, males having a shorter overall survival, as reflected in this cohort. Severe and recurrent cytopenias were most significantly associated with death. Presentation with pancytopenia, anaemia, thrombocytopenia and leucopenia had a shorter overall survival (Table S6). This may reflect more advanced disease at presentation or severe phenotype that often has a shorter overall survival, especially with delayed intervention.

## Limitations

The retrospective nature of the study reflects only a window of time, at presentation, and patients may have developed immune cytopenias or malignancy over their disease course. Although greatest effort was made to delineate the nature of cytopenia based on laboratory history, clear aetiologies were not defined. Infectious manifestations are more widely known, and as case identification relied heavily on clinician identification, entry onto the SAPIDR may have been weighted toward infectious manifestations. The review of the literature has aimed to compensate for these limitations and attempted to provide an overview of both immune and non-immune mechanisms of cytopenia in IEI. Such limitations highlight the need for more prospective reviews with inclusion of age-matched controls.

# CONCLUSION

A high index of suspicion is imperative for early identification of patients with IEI. Both infectious and non-infectious manifestations must be considered.[10,12,13] Peripheral-blood cytopenia that is severe, persistent, unusual and/or recurrent (SPUR) should prompt further investigation for IEI in both children and adults. The cost-effective and universally available FBC and leucocyte differential could facilitate earlier case identification, serving as an adjunct to more costly definitive investigation. Although inconclusive in some, the molecular diagnosis is a cornerstone of IEI diagnostics, establishing definitive classification.

## Recommendations

1. The FBC with leucocyte differential and peripheral-blood film is widely available and cheap. It should always form part of first-line investigation in suspected IEI.
2. Severe, persistent, unusual and/or recurrent (SPUR) cytopenia in the absence of secondary immunodeficiency should prompt further definitive investigation for IEI in children and adults.
3. Prospective review of patients presenting with SPUR cytopenia(s) prompting investigation for possible IEI with application of flow cytometry and molecular diagnostics to confirm diagnosis would provide further insight.

### AUTHOR CONTRIBUTIONS

H. M. Cornelissen, Z. C. Chapanduka and E. Musekwa conceptualised and designed the study. H. M. Cornelissen, Z. C. Chapanduka, E. Musekwa and R. H. Glashoff wrote the draft protocol and manuscript, H. M. Cornelissen facilitated data collection, statistical review, primary manuscript composure and the creation of figures with expert review and contribution from Z. C. Chapanduka, E. Musekwa, R. H. Glashoff, M. Esser, D. R. Abraham and M. Zunza. M. Zunza conducted the statistical analysis and contributed to manuscript review. M. Esser and D. R. Abraham contributed to

clinical history, manuscript review and expert clinical opinion.

## ACKNOWLEDGEMENTS

We thank the patients and their families who, by allowing case study, have facilitated further investigation and understanding in this field; the Primary Immunodeficiency Genetics Network (PIDDGEN) who tirelessly aim to further research into the area, in particular Prof Marlo Moller and Brigitte Glanzmann; Mrs Rina Nortjie who facilitates patient entry onto the registry and continued patient contact and the National Health Laboratory Service (NHLS) for the use of laboratory data; as well as the NHLS Tygerberg Hospital Department of Haematology who strive for optimised service delivery and thus patient care. Open access funding enabled and organized by ProjektDEAL.

## CONFLICT OF INTEREST

None to declare.

## DATA AVAILABILITY STATEMENT

Extensive supplementary data has been submitted. Additional data will be made available on request.

## ORCID

*Helena M. Cornelissen* https://orcid.org/0000-0002-1855-690X
*Ernest M. Musekwa* https://orcid.org/0000-0001-8080-3820
*Richard H. Glashoff* https://orcid.org/0000-0002-0100-0139
*Monika Esser* https://orcid.org/0000-0002-6835-859X
*Moleen Zunza* https://orcid.org/0000-0002-3270-8439
*Deepthi R. Abraham* https://orcid.org/0000-0001-6414-9128
*Zivanai C. Chapanduka* https://orcid.org/0000-0002-5489-8392

## REFERENCES

1. Picard C, Bobby Gaspar H, Al-Herz W, Bousfiha A, Casanova J-L, Chatila T, et al. International union of immunological societies: 2017 primary immunodeficiency diseases committee report on inborn errors of immunity. J Clin Immunol. 2018;38(1):96–128. https://doi.org/10.1007/s10875-017-0464-9
2. Seidel M. Autoimmune and other cytopenias in primary immunodeficiencies: pathomechanisms, novel differential diagnoses, and treatment. Blood. 2014;124(15):2337–44. https://doi.org/10.1182/blood-2014-06-583260
3. Seidel MG, Kindle G, Gathmann B, Quinti I, Buckland M, van Montfrans J, et al. The European Society for Immunodeficiencies (ESID) registry working definitions for the clinical diagnosis of inborn errors of immunity. J Aller Clin Immunol. 2019;7:1–8. https://doi.org/10.1016/j.jaip.2019.02.004
4. Bousfiha A, Jeddane L, Picard C, al-Herz W, Ailal F, Chatila T, et al. Human inborn errors of immunity: 2019 update of the IUIS phenotypical classification. J Clin Immunol. 2020;40(1):66–81. https://doi.org/10.1007/s10875-020-00758-x
5. Erjaee A, Bagherpour M, Van Rooyen C, et al. Primary immunodeficiency in Africa - a review. South Afr Med J. 2019;109(8):3–11. https://doi.org/10.7196/SAMJ.2019.v109i8b.13820
6. Bousfiha AA, Jeddane L, Ailal F, Benhsaien I, Mahlaoui N, Casanova JL, et al. Primary immunodeficiency diseases worldwide: more common than generally thought. J Clin Immunol. 2013;33(1):1–7. https://doi.org/10.1007/s10875-012-9751-7
7. Glanzmann B, Uren C, de Villiers N, van Coller A, Glashoff RH, Urban M, et al. Primary immunodeficiency diseases in a tuberculosis endemic region: challenges and opportunities. Genes Immun. 2018;20:447–54. https://doi.org/10.1038/s41435-018-0041-0
8. Eley B, Esser M. Investigation and management of primary immunodeficiency in south African children. S Afr Med J. 2014;104(11):1–4. https://doi.org/10.7196/SAMJ.8946
9. Bousfiha A, Jeddane L, Picard C, Ailal F. The 2017 IUIS phenotypic classification for primary immunodeficiencies. J Clin Immunol. 2017;38:129–43. https://doi.org/10.1007/s10875-020-00758-x
10. Thalhammer J, Kindle G, Nieters A, Rusch S, Seppänen MRJ, Fischer A, et al. Initial presenting manifestations in 16,486 patients with inborn errors of immunity include infections and noninfectious manifestations. J Allergy Clin Immunol. 2021;148(5):1332–41.e5. https://doi.org/10.1016/j.jaci.2021.04.015
11. Goudouris ES. Immunodeficiencies: non-infectious manifestations. J Pediatr (Rio J). 2021;97:S24–33. https://doi.org/10.1016/j.jped.2020.10.004
12. Costa-Carvalho BT, Grumach AS, Franco JL, Espinosa-Rosales FJ, Leiva LE, King A, et al. Attending to warning signs of primary immunodeficiency diseases across the range of clinical practice. J Clin Immunol. 2014;34(1):10–22. https://doi.org/10.1007/s10875-013-9954-6
13. McCusker C, Upton J, Warrington R. Primary immunodeficiency. Allergy Asthma Clin Immunol. 2018;14(S2):61. https://doi.org/10.1186/s13223-018-0290-5
14. Notarangelo LD, Bacchetta R, Casanova JL, Su HC. Human inborn errors of immunity: an expanding universe. Sci Immunol. 2020;5(49):eabb1662. https://doi.org/10.1126/sciimmunol.abb1662
15. Fischer A, Provot J, Jais JP, Alcais A, Mahlaoui N, Adoue D, et al. Autoimmune and inflammatory manifestations occur frequently in patients with primary immunodeficiencies. J Allergy Clin Immunol. 2017;140(5):1388–93.e8. https://doi.org/10.1016/j.jaci.2016.12.978
16. Zama D, Conti F, Moratti M, Cantarini ME, Facchini E, Rivalta B, et al. Immune cytopenias as a continuum in inborn errors of immunity: an in-depth clinical and immunological exploration. Immun Inflamm Dis. 2021;9(2):583–94. https://doi.org/10.1002/iid3.420
17. Sánchez-Ramón S, Bermúdez A, González-Granado LI, Rodríguez-Gallego C, Sastre A, Soler-Palacín P, et al. Primary and secondary immunodeficiency diseases in oncohaematology: warning signs, diagnosis, and management. Front Immunol. 2019;10(MAR):1–8. https://doi.org/10.3389/fimmu.2019.00586
18. Kaushansky K, editor. Williams Hematology. 9th ed. New York, NY: McGraw-Hill; 2016.
19. Canna SW, Marsh RA. Pediatric hemophagocytic lymphohistiocytosis. Blood. 2020;135(16):1332–43. https://doi.org/10.1182/blood.2019000936
20. Jordan MB, Allen CE, Greenberg J, Henry M, Hermiston ML, Kumar A, et al. Challenges in the diagnosis of hemophagocytic lymphohistiocytosis: recommendations from the north American consortium for histiocytosis (NACHO). Pediatr Blood Cancer. 2019;66(11):e27929. https://doi.org/10.1002/pbc.27929
21. Mortaz E, Tabarsi P, Mansouri D, Khosravi A, Garssen J, Velayati A, et al. Cancers related to immunodeficiencies: update and perspectives. Front Immunol. 2016;7(SEP):1–13. https://doi.org/10.3389/fimmu.2016.00365
22. Bomken S, van der Werff Ten Bosch J, Attarbaschi A, et al. Current understanding and future research priorities in malignancy associated with inborn errors of immunity and DNA repair disorders: the perspective of an interdisciplinary working group. Front Immunol. 2018;9(December):2912. https://doi.org/10.3389/fimmu.2018.02912
23. Mayor PC, Eng KH, Singel KL, Abrams SI, Odunsi K, Moysich KB, et al. Cancer in primary immunodeficiency diseases: cancer incidence in the United States immune deficiency network registry. J Allergy Clin Immunol. 2018;141(3):1028–35. https://doi.org/10.1016/j.jaci.2017.05.024
24. Elsink K, van Montfrans JM, van Gijn ME, Blom M, van Hagen PM, Kuijpers TW, et al. Cost and impact of early diagnosis in primary

immunodeficiency disease: a literature review. Clin Immunol. 2020;213:108359. https://doi.org/10.1016/j.clim.2020.108359
25. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377–81. https://doi.org/10.1016/j.jbi.2008.08.010
26. Schmidt BM, Tameris M, Geldenhuys H, Luabeya A, Bunyasi E, Hawkridge T, et al. Comparison of haematology and biochemistry parameters in healthy south African infants with laboratory reference intervals. Trop Med Int Health. 2018;23(1):63–8. https://doi.org/10.1111/tmi.13009
27. Walkovich K, Connelly JA. Understanding neutropenia secondary to intrinsic or iatrogenic immune dysregulation. Hematology. 2021;2021(1):504–13. https://doi.org/10.1182/hematology.2021000285
28. Oliveira JB, Fleisher TA. Laboratory evaluation of primary immunodeficiencies. J Allergy Clin Immunol. 2010;125(2):S297–305. https://doi.org/10.1016/j.jaci.2009.08.043
29. Xanthou M. Leucocyte blood picture in healthy full-term and premature babies during neonatal period. Arch Dis Child. 1970;45(240):242–9. https://doi.org/10.1136/adc.45.240.242
30. Kardos G. Refractory anemia in childhood: a retrospective analysis of 67 patients with particular reference to monosomy 7. Blood. 2003;102(6):1997–2003. https://doi.org/10.1182/blood-2002-11-3444
31. Nell EM, Chapanduka ZC. Aetiology of pancytopenia: experience of a South African Tertiary Academic Centre. Afr J Lab Med. 2022;11(1):a1645. https://doi.org/10.4102/ajlm.v11i1.1645
32. Lashkari HP, Madkaikar M, Dalvi A, Gupta M, Bustamante J, Sharma M, et al. Clinical and genetic spectrum of inborn errors of immunity in a tertiary Care Center in Southern India. Indian J Pediatr. 2022;89(3):233–42. https://doi.org/10.1007/s12098-021-03936-w
33. Staels F, Collignon T, Betrains A, Gerbaux M, Willemsen M, Humblet-Baron S, et al. Monogenic adult-onset inborn errors of immunity. Front Immunol. 2021;12:753978. https://doi.org/10.3389/fimmu.2021.753978
34. Shendi HM, Al Kuwaiti AA, Al Dhaheri AD, Al-Hammadi S. The spectrum of inborn errors of immunity in The United Arab Emirates: 5 year experience in a tertiary center. Front Immunol. 2022;13:837243. https://doi.org/10.3389/fimmu.2022.837243
35. Erlacher M, Strahm B. Missing cells: pathophysiology, diagnosis, and management of (pan)cytopenia in childhood. Front Pediatr. 2015;3:64. https://doi.org/10.3389/fped.2015.00064
36. Beck DB, Ferrada MA, Sikora KA, Ombrello AK, Collins JC, Pei W, et al. Somatic mutations in *UBA1* and severe adult-onset autoinflammatory disease. N Engl J Med. 2020;383(27):2628–38. https://doi.org/10.1056/NEJMoa2026834
37. Wlodarski MW, Hirabayashi S, Pastor V, Starý J, Hasle H, Masetti R, et al. Prevalence, clinical characteristics, and prognosis of GATA2-related myelodysplastic syndromes in children and adolescents. Blood. 2016;127(11):1387–97. https://doi.org/10.1182/blood-2015-09-669937
38. van der Burg M, Kalina T, Perez-Andres M, Vlkova M, Lopez-Granados E, Blanco E, et al. The EuroFlow PID orientation tube for flow cytometric diagnostic screening of primary immunodeficiencies of the lymphoid system. Front Immunol. 2019;10:246. https://doi.org/10.3389/fimmu.2019.00246
39. Glanzmann B, de Villiers N, Möller M, Glashoff RH, Kinnear CJ, Franke A, et al. A primary immunodeficiency diseases odyssey – answer from the exome in a CASE with immunodeficiency and autoimmunity. Clin Immunol. 2017;30(4):7.
40. Engelbrecht C, Urban M, Schoeman M, Paarwater B, van Coller A, Abraham DR, et al. Clinical utility of whole exome sequencing and targeted panels for the identification of inborn errors of immunity in a resource-constrained setting. Front Immunol. 2021;12:665621. https://doi.org/10.3389/fimmu.2021.665621
41. Yska HAF, Elsink K, Kuijpers TW, Frederix GWJ, van Gijn ME, van Montfrans JM. Diagnostic yield of next generation sequencing in genetically undiagnosed patients with primary immunodeficiencies: a systematic review. J Clin Immunol. 2019;39(6):577–91. https://doi.org/10.1007/s10875-019-00656-x
42. Grumach AS, Kirschfink M. Are complement deficiencies really rare? Overview on prevalence, clinical importance and modern diagnostic approach. Mol Immunol. 2014;61(2):110–7. https://doi.org/10.1016/j.molimm.2014.06.030
43. El Sissy C, Rosain J, Vieira-Martins P, Bordereau P, Gruber A, Devriese M, et al. Clinical and genetic spectrum of a large cohort with total and sub-total complement deficiencies. Front Immunol. 2019;10:1936. https://doi.org/10.3389/fimmu.2019.01936
44. Rotz SJ, Ware RE, Kumar A. Diagnosis and management of chronic and refractory immune cytopenias in children, adolescents, and young adults. Pediatr Blood Cancer. 2018;65(10):e27260. https://doi.org/10.1002/pbc.27260
45. Leiding JW, Holland SM. Chronic Granulomatous Disease: 35.
46. Gelaw Y, Getaneh Z, Melku M. Anemia as a risk factor for tuberculosis: a systematic review and meta-analysis. Environ Health Prev Med. 2021;26(1):13. https://doi.org/10.1186/s12199-020-00931-z
47. Sogkas G, Atschekzei F, Adriawan IR, Dubrowinskaja N, Witte T, Schmidt RE. Cellular and molecular mechanisms breaking immune tolerance in inborn errors of immunity. Cell Mol Immunol. 2021;18(5):1122–40. https://doi.org/10.1038/s41423-020-00626-z
48. Yarmohammadi H, Estrella L, Doucette J, Cunningham-Rundles C. Recognizing primary immune deficiency in clinical practice. Clin Vaccine Immunol. 2006;13(3):329–32. https://doi.org/10.1128/CVI.13.3.329-332.2006
49. Edeer KN. Neutropenia in primary immunodeficiency diseases. In: Saxena K, Prakash H, editors. Innate Immunity in Health and Disease. London: IntechOpen; 2021. https://doi.org/10.5772/intechopen.97297
50. Kindler O, Quehenberger F, Benesch M, Seidel MG. The iceberg map of germline mutations in childhood cancer: focus on primary immunodeficiencies. Curr Opin Pediatr. 2018;30(6):855–63. https://doi.org/10.1097/MOP.0000000000000680
51. Hauck F, Voss R, Urban C, Seidel MG. Intrinsic and extrinsic causes of malignancies in patients with primary immunodeficiency disorders. J Allergy Clin Immunol. 2018;141(1):59–68.e4. https://doi.org/10.1016/j.jaci.2017.06.009
52. Duan L, Grunebaum E. Hematological malignancies associated with primary immunodeficiency disorders. Clin Immunol. 2018;194(June):46–59. https://doi.org/10.1016/j.clim.2018.06.011
53. Maffeis M, Notarangelo LD, Schumacher RF, Soncini E, Soresina A, Lanfranchi A, et al. Primary immunodeficiencies and oncological risk: the experience of the Children's Hospital of Brescia. Front Pediatr. 2019;7(MAY):1–8. https://doi.org/10.3389/fped.2019.00232
54. Al-Herz W, Moussa MAA. Survival and predictors of death among primary immunodeficient patients: a registry-based study. J Clin Immunol. 2012;32(3):467–73. https://doi.org/10.1007/s10875-011-9636-1
55. Velázquez-Díaz P, Nakajima E, Sorkhdini P, Hernandez-Gutierrez A, Eberle A, Yang D, et al. Hermansky-Pudlak syndrome and lung disease: pathogenesis and therapeutics. Front Pharmacol. 2021;12:644671. https://doi.org/10.3389/fphar.2021.644671

## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Cornelissen HM, Musekwa E, Glashoff RH, Esser M, Zunza M, Abraham DR, Peripheral-blood cytopenia, an early indicator of inborn errors of immunity. Br J Haematol. 2022;198:875–886. https://doi.org/10.1111/bjh.18337