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The Incidence and Prevalence of Patients with Paroxysmal Nocturnal Haemoglobinuria and Aplastic Anaemia PNH syndrome: A retrospective analysis of the UK's population-based Haematological Malignancy Research Network 2004 – 2018.

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Running Title

Incidence and Prevalence of Paroxysmal Nocturnal Haemoglobinuria

Key Words

Paroxysmal Nocturnal Haemoglobinuria, Incidence, Prevalence, Aplastic Anaemia

Summary Statements

Novelty Statement: This is the first population-based study on the incidence and prevalence of patients with PNH and associated disorders.

Findings: The overall incidence rate was estimated at 0.35 cases per 100,000 people per year. This equates to 220 cases newly diagnosed in the United Kingdom each year. The overall prevalence rate was 3.81 per 100,000, this equates to an estimated 2,400 prevalent cases in the UK.

Clinical Relevance of the work: Assist strategic planning for rare disease services given the high cost of treatments for classical PNH.

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Abstract

Objectives: A retrospective population-based study to determine the incidence and prevalence of patients with the rare blood disease paroxysmal nocturnal haemoglobinuria (PNH).

Methods: All patients were identified by flow cytometric detection of blood cells deficient in glycosylphosphatidylinositol (GPI) linked proteins at a single diagnostic reference laboratory that serves the Yorkshire based, Haematological Malignancy Research Network (HMRN) with a population of 3.8 million.

Results. 197 patients with detectable PNH clones at a level of >0.01% in at least 2 lineages of cells (neutrophils, monocytes and/or red cells) were identified over a 15-year period (2004 – 2018). Of these, 88% had aplastic anaemia (AA), 8% classical PNH and 3% myelodysplastic syndrome. The overall incidence rate was estimated at 0.35 cases per 100,000 people per year. This equates to 220 cases newly diagnosed in the United Kingdom each year. The overall prevalence rate was 3.81 per 100,000, this equates to an estimated 2,400 prevalent cases in the UK. The overall and relative 5-year survival rates were 72% and 82.7% respectively.

Conclusions. This study showed that classical haemolytic PNH is a rare disease and represents only a small proportion overall of patients with detectable PNH cells, the majority of which have aplastic anaemia.

1 Introduction

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare form of acquired haemolytic anaemia that has a close relationship to immune mediated bone marrow failure (1, 2). Laboratory diagnosis of PNH is centred on demonstrating the presence of peripheral blood cells that show deficiency of glycosyl phosphatidylinositol-linked antigens (GPI) by flow cytometry (3, 4). The size and phenotype of these GPI deficient cells or PNH clones correlates with disease type: large PNH clones are typically associated with classical haemolytic PNH, and smaller clones with aplastic/cytopenic types, though there is a degree of overlap and disease evolution in some patients (5, 6, 7). Rare cases of PNH are also associated with a concomitant diagnosis of myelodysplastic syndrome or myeloproliferative disorders (7) with variable PNH clone sizes at presentation. Furthermore, a small proportion of patients can go on to develop a secondary myeloid malignancy such as acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS) (8).

Although much is understood about the biology of PNH, its incidence and prevalence has so far been poorly defined, with estimates of prevalence ranging between 5-10 per million population to as high as 20 per 1,000,000 (9, 10). In this retrospective analysis we set out to more accurately define incidence and prevalence of patients with detectable PNH clones in the peripheral blood within the Yorkshire based Haematological Malignancy Research Network (HMRN) (www.hmrn.org). An important feature of this cohort of patients was that from the start date of 2004, all new diagnoses of classical PNH that were eligible for complement blockade therapy with Eculizumab (Soliris®; Alexion Pharmaceuticals, Inc., Boston, MA, USA) received this treatment if indicated. The profound positive effect of this on survival has already been described and will clearly have a major influence on contemporaneous studies of disease prevalence (11, 12).

2 Methods

2.1 Identification of Patients

Patient samples were referred to the Haematological Malignancy Diagnostic Service (HMDS) for PNH screening with a range of clinical indications including PNH, aplastic anaemia (suspected or confirmed), myelodysplastic syndrome, unexplained cytopenias, unexplained thrombosis or haemolysis. Patients were not identified from routine population screening of individuals. HMDS

is a central diagnostic laboratory that serves all 14 hospitals and a population 3.8 million within the HMRN. Testing for PNH is not undertaken at any other laboratory within this network. We included all patients in which populations of GPI negative cells were detected by flow cytometry at a level of >0.01% in at least two lineages of peripheral blood cells that included any combination of red cells, neutrophils and/or monocytes as previously described (13, 14).

Once PNH cells were detected, patients were classified based on a combination of clinical features and extensive routine and follow up laboratory investigations. Patients were then assigned as classical haemolytic PNH, myelodysplastic syndrome (MDS), myeloproliferative neoplasm (NPM), pure thrombotic PNH, haemolytic/thrombotic PNH and aplastic anaemia as previously described (7). Conventional world health organisation (WHO) diagnostic criteria were used for assigning patients to the MDS and MPN categories (15). Diagnoses of aplastic anaemia were established using conventional criteria (16, 17).

All blood samples were obtained following informed consent and referred to HMDS for diagnostic purposes. No additional, non-routine investigations were undertaken. The study itself does not meet the criteria used to define 'Research' as used by the NHS Health Research Authority/Medical Research Council on-line assessment tool (http://www.hra-decisiontools.org.uk/ethics/). All patients were followed up at regular intervals with routine laboratory and clinical assessments.

2.2 Statistical Analysis

Analyses were conducted using standard methods in the statistical package Stata v16. Incidence rates and their 95% Confidence Intervals (CIs) were estimated by Poisson regression. Prevalence calculations included all patients even if they were considered "cured" as is standard practice in calculating cancer/disease prevalence.

3 Results

3.1 Descriptive Data

Between 2004 and 2018, 197 patients were identified with PNH clones detected by flow cytometry in at least two lineages of peripheral blood cells. The baseline clinical and laboratory characteristics of these presentation cases are shown in Table 1. The largest group of patients were those with aplastic anaemia, comprising over 88% of all patients. Over the study period of 15 years, only 15 patients were identified that could be classified as classical PNH, highlighting that

patients with large PNH clones and typical PNH features were relatively rare (8% of all cases). As expected, PNH clones were significantly larger in those patients with classical haemolytic PNH compared with those with aplastic anaemia (Table 1). Clear differences were also evident for lactate dehydrogenase (LDH) levels and reticulocyte counts, reflecting the haemolytic anaemia seen in classical PNH. Rare presentations were also identified: a single patient with pure thrombotic PNH was identified in 15 years of study. Similarly, a single patient with a JAK2 (V617F) mutated myeloproliferative neoplasm (MPN) was identified. Both these very rare cases had large PNH clones detectable at presentation and markedly elevated LDH levels.

Further analysis of the patient group with aplastic anaemia showed a distinct bimodal age distribution, consistent with previous findings in a much larger series of patients (7). A more detailed analysis of this cohort was made on patients <40 years old versus those >40 years old at presentation (Table 2). The only notable statistical difference between the two groups in terms of laboratory parameters was a lower mean platelet count in the older age group ($P = 0.01$).

3.2 Incidence and Prevalence

The overall incidence rate of patients with detectable PNH clones was estimated to be 0.35 cases per 100,000 people per year or 3.5 per million per year. This equates to 220 cases newly diagnosed in the United Kingdom each year. The overall prevalence rate was 3.81 per 100,000, this equates to an estimated 2,400 prevalent cases in the UK. Too few cases of haemolytic PNH were identified for incidence and prevalence calculations to be undertaken.

3.3 Disease Progression, Clinical Course and Survival

Of the 197 patients included in this study, 12 patients showed disease evolution (Table 3). Seven patients developed symptomatic haemolytic PNH and one patient developed thrombotic disease associated with increasing type II or partially GPI-deficient PNH cells. The development of secondary acute myeloid leukaemia or myelodysplastic syndrome was seen in four patients and associated with an adverse outcome. Cases showing disease evolution were predominantly in the >40 years old cohort.

For patients with aplastic anaemia, conventional immunosuppressive therapies were used initially, with 62% receiving ciclosporin, 41% receiving anti-thymocyte globulin and 6% of cases were given Tacrolimus. Disease recovery, as defined by improved blood counts with or without

reduction in PNH clone size, differed between the two age groups with aplastic anaemia. 24% of the <40 years old age group underwent successful allogeneic haematopoietic stem cell transplant (HSCT) with consequent loss of PNH clones. Even taking this into consideration, the >40 years old cohort showed only 16.6% of patients with evidence of disease recovery, compared to 67% for the <40 years age group. No patients with concurrent MDS and PNH clones showed disease recovery. Of the patients that presented with classical haemolytic PNH, none developed a haematological malignancy. Two patients showed a sustained fall in PNH clones, normalisation of blood counts associated with reduction in haemolytic symptoms and eventual cessation of complement blockade therapy. The single patient with JAK2 (V617F) mutated MPN and large PNH clones had a very poor prognosis and survived only 4 months following diagnosis. Cases with a similar phenotype have previously been reported and also showed a poor clinical course (18).

Overall and relative survival rates are show in Table 3 and Figures 1a and b. For the whole cohort of patients, the overall five-year survival rate was 72% (Confidence Intervals 64.5 – 78.2). The relative survival was 82.7% (CI 75.0 – 88.2). For the aplastic anaemia patients, the overall five-year survival rate was 70.6% (CI 62.6 – 77.3) and the relative survival was 80.9% (73.0 – 86.6). A more specific analysis of survival based on age, showed a five-year relative survival of 97.8% for patients under the age of 40. The five-year survival became progressively shorter for patients within the 40-59 years and in >60 years age categories (Table 3 and Figures 2a & 2b). These findings for aplastic patients with small PNH clones were similar to those reported by other groups for aplastic anaemia patients in whom PNH analysis had not been undertaken (19, 20). For haemolytic PNH patients, overall survival at 5 years was 100%, though there were insufficient case numbers to estimate relative survival. Similarly, only 5-year overall survival (64%) could be calculated for the MDS cohort of 7 patients. Of note, two of the patients with haemolytic PNH died 81 months and 169 months after the original diagnosis.

4 Discussion

PNH is a rare and complex haematological disorder. Obtaining definitive data on incidence and prevalence of the disease is challenging due to several factors. Firstly, as a rare disorder delay in diagnosis is a frequent occurrence. One large study showed that 10 months was the median time to definitive diagnosis, though it can be as long as 5 years before a diagnosis is made (21). Secondly,

flow cytometric testing is not only required to confirm a suspected diagnosis but is also essential for identifying those patients with small PNH clones. The test may not be accessible to all requesting physicians. Thirdly, disease course is variable. For some patients it can be a lifelong condition whilst others can undergo disease progression, spontaneous recovery or develop a secondary myeloid malignancy.

In this unique, retrospective analysis we identified a population-based cohort of 197 patients with PNH cells detected by flow cytometry over a 15-year period at a central reference laboratory used by all hospitals within a defined clinical network and distinct geographical area. This approach to analysing real-world data has been successfully used by HMRN to define incidence and prevalence data for a range of haematological malignancies (22, 23). Importantly, only a small number of presentation cases of classical haemolytic PNH were identified, with most patients falling into the categories of either i) PNH in the setting of another specified bone marrow disorder or ii) Subclinical PNH (PNH-sc) (3). Whether these latter two categories should be classified as clinical PNH is contentious, as in reality they behave much like immune mediated aplastic anaemia, and the small populations of PNH cells probably arise due to immune escape (24) or reflect underlying clonal haematopoiesis. Nevertheless, it is accepted that these cases form part of the spectrum of disease associated with PNH. The incidence of aplastic anaemia is about 2.34/million in Europe and the United States and has the two age peaks of incidence (young adults and elderly) similar to the results obtained in this study (19). A significant feature of these cases is that a small proportion can progress to classical, symptomatic PNH or develop a secondary myeloid malignancy such as MDS or AML (8) with the ensuing implications for changes to therapy or the adverse outcome for the patient respectively. In this current series it was patients in the aplastic >40 years old category that most frequently showed disease evolution (8.3% of cases).

All patients with PNH clones identified in this study were new diagnoses and importantly from a distinct, geographically defined, population. Data analysis showed an estimated overall incidence rate to be 0.35 cases per 100,000 people per year or 3.5 per million per year. This equates to 220 newly diagnosed cases for the whole of the UK per year. The overall prevalence rate was 3.81 per 100,000, this equates to an estimated 2,400 prevalent cases in the UK, Given the relatively low numbers of presentation haemolytic PNH cases we identified, together with the small number of aplastic PNH cases that evolved to haemolytic PNH, we can conclude that the disease in its classical form is extremely rare. The patients with aplastic PNH showed many similar

characteristics to conventional aplastic anaemia. This is not altogether unexpected as up to 60% of aplastic anaemia patients reportedly have PNH clones at presentation (6, 25). Given the differences in incidence rates of aplastic anaemia between Europe/America and Asia it is likely that the findings in this current study may not be directly applicable to Asian countries where the incidence of aplastic anaemia is much higher (19). Other studies have also highlighted a series of differences in baseline clinical characteristics between Asian and non-Asian patients with PNH (26, 27).

Another important aspect of this study was that all patients that presented with haemolytic PNH commenced treatment immediately with eculizumab if indicated. As reported previously, the use of complement blockade therapy has a significant impact on survival for PNH patients. Prior to the availability of eculizumab, the 5-year survival rate was 67%, which is significantly worse than the 5-year survival rate of 96% for patients treated with Eculizumab (11). This dramatic improvement in outcome will clearly influence the prevalence of classical haemolytic PNH, as the treatment blocks haemolysis but does not cure the underlying PNH. It was also evident from overall survival figures that patients with MDS and patients >40 years old with aplastic anaemia had poorer survival than those with classical PNH or were <40 years old with aplastic anaemia. Clearly, a much larger number of MDS patients would be required to confirm these observations.

Long term follow-up of two of the 12 patients that presented with classical haemolytic PNH showed a slow but sustained fall in PNH clone sizes over a period of 10 years. Both were initially treated with Eculizumab. One patient showed normalization of blood counts and is no longer receiving complement blockade therapy and the second patient is now mildly cytopenic but remains on Eculizumab and erythropoietin treatment. Although drawing definitive conclusions about disease course was not possible due to the low number of patients with classical PNH identified in this study, we are currently analysing a much larger cohort of non-HMRN patients referred into the Leeds National PNH service (www.pnhleeds.co.uk). This should provide more definitive data on disease progression, spontaneous remissions and the frequency of development secondary MDS and AML. For all patients identified in this study 36% show significant changes in terms of disease course resolution (therapeutic or otherwise) or disease progression to haemolytic or secondary myeloid malignancy. Clearly collecting and analysing high quality epidemiological data is central to improving both understanding and therapeutic approaches to rare diseases.

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Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authorship

SJR wrote the manuscript. Laboratory investigations were performed by SJR, AJD and DP. Clinical assessments were performed by AH, RK, TM, MG, PH, LA, PM and AP. Statistical analysis was performed by DP, AS and ER. Data collection was undertaken by LA, CM, RJ and DN. All authors reviewed and approved the submitted version of the manuscript.

Data Availability Statement

Due to the nature of this research, participants of this retrospective study did not consent for their data to be shared publicly, so supporting data is not available.

References

1. Griscelli-Bennaceur A, Gluckman E, Scrobohaci ML, Jonveaux P, Vu T, Bazarbachi A, Carosella ED, Sigaux F, Socié, G. Aplastic anemia and paroxysmal nocturnal hemoglobinuria: search for a pathogenetic link. Blood 1995; 85: 1354-1363.

2. Hillmen P, Lewis SM, Bessler M, Luzzatto L, & Dacie JV Natural history of paroxysmal nocturnal hemoglobinuria. N Engl J Med 1995; 333: 1253-1258.

3. Parker C, Omine M, Richards S, Nishimura J, Bessler M, Ware R, Hillmen P, Luzzatto L, Young N, Kinoshita T, Rosse W, Socié G. International PNH Interest Group. Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood 2005; 106: 3699-3709.

4. Richards SJ, Rawstron AC, Hillmen P. The Application Of Flow Cytometry To The Diagnosis Of Paroxysmal Nocturnal Hemoglobinuria. Cytometry (CCC) 2000; 42: 223-233.

5. Moyo VM, Mukhina GL, Garrett ES, Brodsky RA. Natural history of paroxysmal nocturnal haemoglobinuria using modern diagnostic assays. Br J Haematol 2004; 126: 133-138.

6. Scheinberg P, Marte M, Nunez O, Young NS. Paroxysmal nocturnal hemoglobinuria clones in severe aplastic anemia patients treated with horse anti-thymocyte globulin plus cyclosporine. Haematologica, 2010; 95: 1075-1080.

7 Richards SJ, Dickinson AJ, Cullen MJ, Griffin M, Munir T, McKinley C, Mitchell LD, Newton DJ, Arnold L, Hill A, Hillmen P. Presentation clinical, haematological and immunophenotypic features of 1081 patients with GPI-deficient (paroxysmal nocturnal haemoglobinuria) cells detected by flow cytometry. Br J Haematol 2020; 189: 954-966.

8. Sun L, Babushok DV. Secondary myelodysplastic syndrome and leukemia in acquired aplastic anemia and paroxysmal nocturnal hemoglobinuria. Blood 2020; 136: 36–49.

9. Hill A, Platts PJ, Smith A, Richards SJ, Cullen MJ, Hill QA, Roman E, Hillmen P. The incidence and prevalence of paroxysmal nocturnal hemoglobinuria and survival of patients in Yorkshire. Blood 2006; 108: 985.

10. Jalbert JJ, Chaudhari U, Zhang H, Weyne J, Shammo JM. Epidemiology of PNH and Real-World Treatment Patterns Following an Incident PNH Diagnosis in the US. Blood 2019; 134 (S1): 3407.

11. Kelly RJ, Hill A, Arnold LM, Brooksbank GL, Richards SJ, Cullen M, Mitchell LD, Cohen DR, Gregory WM, Hillmen P. Long-term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival. Blood 2011; 117: 6786-6792.

12. Loschi M, Porcher R, Barraco F, Terriou L, Mohty M, de Guibert S, Mahe B, Lemal R, Dumas P-Y, Etienne G, Jardin F, Royer B, Bordessoule D, Rohrlich PS, Fornecker LM, Salanoubat C, Maury S, Cahn J-Y, Vincent L, Sene T, Rigaudeau S, Nguyen S, Lepretre A-C, Mary J-Y, Corront B, Socie G, Peffault de Latour R. Impact of eculizumab treatment on paroxysmal nocturnal hemoglobinuria: a treatment versus no-treatment study. Am J Hematol 2016; 91: 366-370.

13. Richards SJ, Hillmen P. Immunophenotypic analysis of PNH cells. Current Protocols in Cytometry 2002; 1: 6.11.1-6.11.16.

14. Sutherland DR., Illingworth A, Keeney M, Richards SJ. High-sensitivity detection of PNH red blood cells, red cell precursors, and white blood cells. Current Protocols in Cytometry 2015; 72: 6.37.1-6.37.29.

15. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, Bloomfield CD, Cazzola M, Vardiman JW. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016; 127: 2391-2406.

16. Guinan EC Diagnosis and Management of Aplastic Anemia. Hematology Am Soc Hematol Educ Program 2011; 1: 76–81.

17. Killick SB, Bown N, Cavenagh J, Dokal I, Foukaneli T, Hill A, Hillmen P, Ireland R, Kulasekararaj A, Mufti G, Snowden JA, Samarasinghe S, Wood A, Marsh JCW. Guidelines for the diagnosis and management of adult aplastic anaemia. Br J Haematol 2016; 172: 187-207.

18. Sugimori C, Padron E, Caceres G, Shain K, Sokol L, Zhang L, Tiu R, O'Keefe CL, Afable M, Clemente M, Lee JM, Maciejewski JP, List AF, Epling-Burnette PK, Araten DJ. Paroxysmal nocturnal hemoglobinuria and concurrent JAK2(V617F) mutation. Blood Cancer J 2012; 2: e63.

19. Young NS, Kaufman DW. The epidemiology of acquired aplastic anemia, Haematologica 2008; 93: 489-492.

20. Vaht K, Göransson M, Carlson K, Isaksson C, Lenhoff S, Sandstedt A, Uggla B, Winiarski J, Ljungman P, Brune M, Andersson P-O. Incidence and outcome of acquired aplastic anemia: real-world data from patients diagnosed in Sweden from 2000–2011. Haematologica 2017; 102: 1683-1690.

21. Petropoulou AD, Lamy T, Michallet M, Amoura Z, Peffault de Latour R, Socié G. ECLIPSE: a French Study Concerning the Diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH). Blood 2010; 116: 21.

22. Li J, Smith A, Crouch S, Oliver S, Roman E. Estimating the prevalence of hematological malignancies and precursor conditions using data from Haematological Malignancy Research Network (HMRN). Cancer Causes & Control 2016; 27: 1-8.

23. Roman E, Smith A, Appleton S, Crouch S, Kelly R, Kinsey S, Cargo C, Patmore R. Myeloid malignancies in the real-world: Occurrence, progression and survival in the UK's population-based Haematological Malignancy Research Network 2004–15 Cancer Epidemiology 2016; 42: 186-198.

24. Luzzatto L, Risitano AM. Advances in understanding the pathogenesis of acquired aplastic anaemia. Br J Haematol 2018; 182: 758-776.

25. Wanachiwanawin W, Siripanyaphinyo U, Piyawattanasakul N, Kinoshita T. A cohort study of the nature of paroxysmal nocturnal hemoglobinuria clones and PIG-A mutations in patients with aplastic anemia. Eur J Haematol 2016; 76: 502-509.

26. Sakurai M, Jang JH, Chou WC, Kim JS, Wilson A, Nishimura JI, Chiou TJ, Kanakura Y, Lee JW, Okamoto S. Comparative study on baseline clinical characteristics of Asian versus non-Asian patients with paroxysmal nocturnal hemoglobinuria. Int J Hematol. 2019; 110:411-418.

27. Yu F, Du Y, Han B. A comparative analysis of clinical characteristics of patients with paroxysmal nocturnal hemoglobinuria between Asia and Europe/America. Int J Hematol. 2016;103: 649-654

Table 1: Age & sex demographics and laboratory findings for all patients studied.

			Disease Type †			
	Reference Ranges	**All Cases**	**Aplastic**	**Haemolytic**	**MDS**	**Other**
Patients: number and (%)		197 (100)	175 (88.8)	12 (6.1)	7 (3.6)	3 (1.5)
Age (years) at diagnosis: median and range		59 (5 - 91)	59 (5 - 91)	42 (20 - 86)	79 (58 - 87)	65 (49 - 78)
Sex (F/M): Number and (%)		91(46)/106(54)	81(46)/94(54)	6(50)/6(50)	2(29)/5(71)	2/1
Blood Count Parameters: mean & (standard deviation)						
WBC (x 10^9/L)	4.0 - 10.0	3.6 (1.8)	3.5 (1.7)	3.6 (1.6)	4.6 (3.5)	6.2 (2.1)
Neutrophils (x 10^9/L)	2.0 - 7.0	1.8 (1.5)	1.7 (1.3)	1.7 (1.2)	2.7 (3.3)	4.3 (1.9)
Lymphocytes (x 10^9/L)	1.0 - 3.0	1.6 (0.8)	1.6 (0.8)	1.4 (0.3)	1.4 (0.4)	1.0 (0.2)
Monocytes (x 10^9/L)	0.2 - 1.0	0.5 (1.7)	0.5 (1.9)	0.4 (0.2)	0.5 (0.2)	1.0 (0.2)
RBC (x 10^{12}/L)	3.8 - 5.5	2.8 (0.7)	2.8 (0.7)	2.9 (0.7)	2.4 (0.5)	3.56 (0.33)
Haemoglobin (g/L)	120 - 170	96.2 (21.5)	96.3 (21.7)	98.2 (22.9)	88.8 (17.9)	95.3 (2.9)
MCV (fL)	83 - 101	99.0 (8.2)	98.9 (8.0)	99.8 (10.1)	104.9 (6.8)	90.7 (6.2)
Platelets (x 10^9/L)	150 - 410	48 (55)	40 (44)	144 (84)	68 (65)	130 (20)

Flow Cytometry PNH clone:						
Neutrophil PNH clone (%). Median and IQR.		0.95 0.15 - 4.49	0.68 0.13 - 3.16	63.02 38.1 - 78.67	0.59 0.28 - 8.16	65 49 - 78
Monocyte PNH clone (%). Median and IQR.		1.12 0.15 - 5.69	0.82 0.13 - 2.93	72.13 45.78 - 88.52	0.90 0.26 - 49.52	80.94 83.2 - 95.9
Red cell PNH clone (%). Median and IQR.		0.11 0.02 - 0.72	0.09 0.02 - 0.43	29.33 18.84 - 44.91	0.16 0.05 - 4.91	63.37 24.1 - 89.9
Additional Laboratory Investigations:						
Reticulocyte Count (x 10^9/L) number, mean and SD	20 - 80	n = 110 61.48 (36.7)	n = 95 56.3 (31.6)	n = 8 104.4 (55.7)	n = 4 77.8 (49.9)	n = 3 59
Creatinine (µmol/L) number, mean and SD	70 - 100	n = 116 81.8 (27.0)	n = 101 81.5 (27.1)	n = 8 91 (20.7)	n = 4 96.5 (19.1)	n = 3 80
Lactate Dehydrogenase (IU/L) number, mean and SD	160 - 430	n = 108 574 (344)	n = 93 492 (232)	n = 8 1156 (356)	n = 4 627 (227)	n = 3 927

† Clinical disease types: Aplastic, Haemolytic, MDS (myelodysplastic syndrome). The 'Other' category comprised haemolytic/thrombotic (n = 1), thrombotic (n = 1) and myeloproliferative neoplasm (n = 1).

Abbreviations: WBC: White cell Count; RBC: Red blood cell count; MCV: Mean corpuscular volume; PNH: Paroxysmal Nocturnal Haemoglobinuria, MDS: Myelodysplastic syndrome, IQR interquartile range

Table 2: Statistical comparison of presentation laboratory and flow cytometric characteristics between patients with aplastic anaemia <40 years versus those ≥40 years of age.

		Patients with Aplastic Anaemia		
		Age at diagnosis (years)		
		<40	≥40	
	Reference Range			P value†
Age at Diagnosis (years)				
Median (range)		24 (5 – 39)	69 (40 – 91)	
Sex (number & %)				1.00‡
Male		30 (54.5)	64 (53.3)	
Female		25 (45.5)	56 (46.7)	
Blood Count Parameters: mean and (SD)				
WBC (x 10^9/L)	4.0 – 10.0	3.5 (1.9)	3.5 (1.7)	0.79
Neutrophils (x 10^9/L)	2.0 – 7.0	1.7 (1.4)	1.7 (1.3)	0.88
Lymphocytes (x 10^9/L)	1.0 – 3.0	1.8 (1.0)	1.5 (0.7)	0.13
Monocytes (x 10^9/L)	0.2 – 1.0	0.8 (3.4)	0.3 (0.3)	0.40
RBC (x 10^{12}/L)	3.8 – 5.5	2.9 (0.9)	2.8 (0.6)	0.78
Haemoglobin (g/L)	120 – 170	98.4 (27.9)	95.4 (18.3)	0.46
MCV (fL)	83 - 101	99.9 (8.0)	98.4 (8.1)	0.26
Platelets (x 10^9/L)	150 - 410	54.7 (58.1)	32.7 (34.6)	**0.01**
Flow Cytometry PNH clone: mean and (SD)				
Neutrophil PNH clone (%)		4.7 (12.2)	4.7 (13.5)	0.96
Monocyte PNH clone (%)		5.1 (13.6)	5.0 (14.2)	0.95
Red cell PNH clone (%)		1.0 (2.6)	1.1 (3.4)	0.85

Additional Parameters: Mean and (SD)				
Reticulocyte Count (x 10^9/L)	20 - 80	50.9 (26.5)	59.6 (34.1)	0.17
Creatinine (μmol/L)	70 - 100	77.7 (20.6)	83.7 (30.3)	0.24
Lactate Dehydrogenase (IU/L)	160 - 430	445 (125)	517 (271)	0.09

† P values derived from paired T Test (numeric data).

‡ Chi squared not significant for male/female distribution

Abbreviations: WBC: White cell Count; RBC: Red blood cell count; MCV: Mean corpuscular volume; PNH: Paroxysmal Nocturnal Haemoglobinuria; SD: Standard deviation.

Table 3: Disease evolution, overall and relative survival data, and disease recovery.

		Disease Type					
		All	**Aplastic (all ages)**	**Aplastic <40yrs**	**Aplastic >40yrs**	**Haemolytic †**	**MDS**
	n	197	175	55	120	14	7
Disease Evolution	n (%)	12 (6.1)	12 (6.8)	2 (3.6)	10 (8.3)	0 (0.0)	0 (0.0)
Haemolytic PNH	n (%)	7 (3.6)	7 (4.0)	1 (1.8)	6 (5.0)	0 (0.0)	0 (0.0)
Myelodysplastic Syndrome	n (%)	3 (1.5)	3 (1.7)	1 (1.8)	2 (1.6)	0 (0.0)	-
Acute Myeloid Leukaemia	n (%)	1 (0.5)	1 (0.6)	0 (0.0)	1(0.8)	0 (0.0)	0 (0.0)
Thrombotic PNH	n (%)	1 (0.5)	1 (0.6)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Disease Recovery ‡		59 (29.9)	57 (32.6)	37 (67.3)	20 (16.6)	2 (14.2)	0 (0.0)
HSCT	n (%)			13 (23.6)	2 (1.7)		
5-year overall survival §	% (95% CI)	72.0 (64.5 - 78.2)	70.6 (62.6 – 77.3)	97.9 (86.1 – 99.7)	57.4 (47.0 – 66.4)	100	63.6 (16.1 – 78.2)
5-year relative survival §	% (95% CI)	82.7 (75.0 – 88.2)	80.9 (73.0 – 86.6)	97.8 (84.1 – 99.7)	68.8 (58.1 – 77.3)	¶	¶

† Includes patients with haemolytic and haemolytic/thrombotic subtypes

‡ Disease recovery includes successful HSCT, loss or sustained decrease of PNH clone, and normalisation or sustained improvement in blood counts. PNH clones remain detectable at low levels in many of these patients

§ Four patients lost to follow up

¶ Number of cases too small to estimate relative survival

Abbreviations: CI = confidence interval; HSCT = Haematopoietic stem cell transplant; MDS = myelodysplastic syndrome

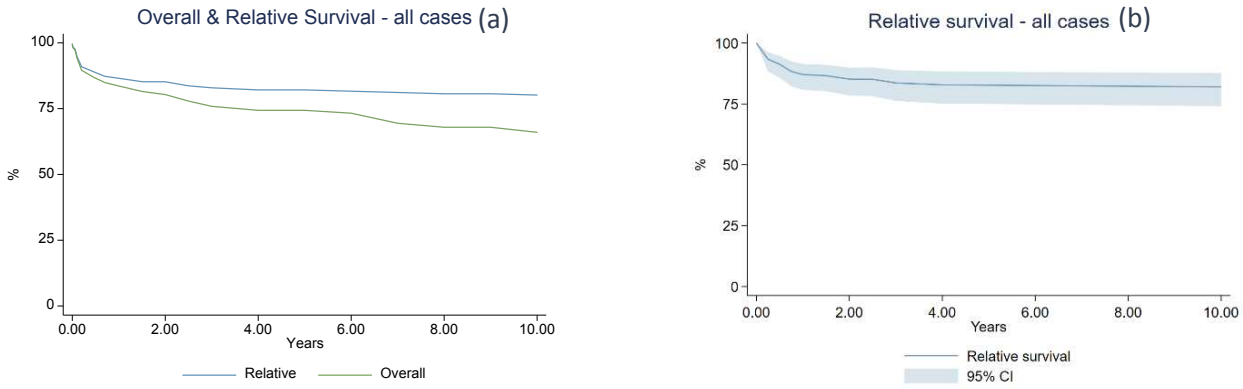

Figure 1: Overall (a) and relative survival (b) rates for all cases. The overall 5-year survival rate was 72% (Confidence intervals 64.5 – 78.2) and the relative survival rate was 82.7% (Confidence intervals 75.0 – 88.2).

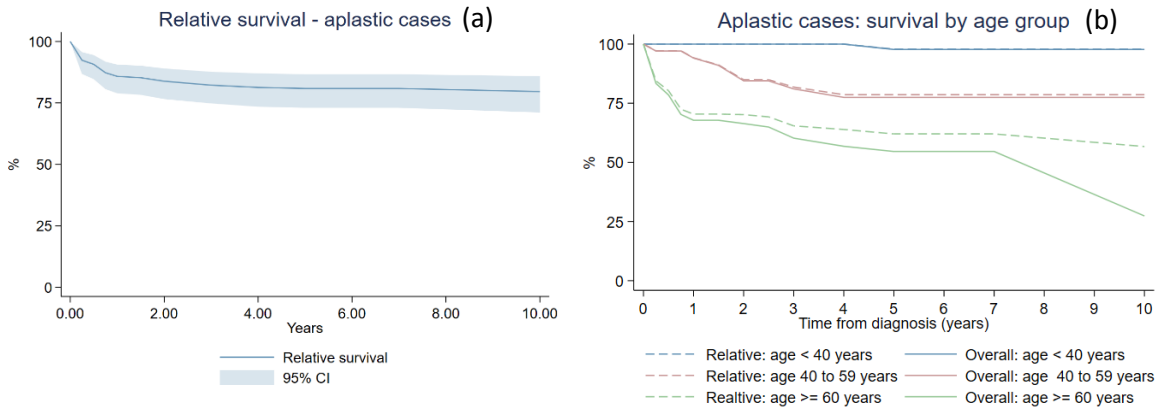

Figure 2: Relative survival for all patients with aplastic anaemia/PNH (plot a). Plot b shows falling overall survival for older age groups (40-59 years) and >60 years of age with most deaths occurring within the first year following diagnosis.