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Brief Report

Clinical Phenotype and Outcomes of Indo-Asian Patients with ANCA-Associated Glomerulonephritis in the North West, UK

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Abstract: ANCA-associated vasculitides (AAV) are rare, autoimmune conditions associated with end-stage kidney disease (ESKD) and mortality. Data have predominately been from White populations of European ancestry although geographical differences are well documented. Few studies have looked at the incidence, phenotype and clinical outcomes of ethnic minority patients, in particular Indo-Asian populations. A two-center, retrospective cohort study was conducted of patients with ANCA-associated glomerulonephritis (AAGN), self-identifying as Indo-Asian in the North West, UK between 2009 and 2023. A control group of White patients was identified from the same databases and recruited consecutively in relation to the original cohort of Indo-Asian patients. A total of 66 patients were included, 24 patients of Indo-Asian ethnicity and a control cohort of 42 patients of White ethnicity. Indo-Asian patients had a lower median age at diagnosis (53.0 vs. 57.5 years, $p = 0.15$) and there was an increased prevalence of diabetes mellitus (33.3% vs. 4.8%, $p = 0.002$) and a higher incidence of previous TB exposure (12.5% vs. 0%, $p = 0.019$). Outcomes including relapse, ESKD and mortality were similar. We demonstrated an increased crude incidence of AAGN in Indo-Asian patients in the UK compared to similar epidemiological studies. Consideration needs to be given to epidemiological and genetic research, achieved by collaboration and broader recruitment in clinical trials.

Keywords: ANCA; vasculitis; glomerulonephritis; ethnicity; epidemiology

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1. Introduction

Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) is a multisystem, autoimmune condition encompassing three main clinical phenotypes: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (eGPA) [1]. ANCA is central to disease pathogenesis, binding to auto-antigens of either perinuclear myeloperoxidase (MPO) or cytoplasmic proteinase 3 (PR3) expressed on the neutrophil cell surface [2]. MPO ANCA is more commonly associated with MPA and eGPA phenotypes, whereas PR3 ANCA is seen typically but not exclusively in those with GPA phenotypes [3].

AAV can present at any age, but tends to be a disease of older age, with a peak incidence in those aged 65–74 years [4,5]. Kidney involvement with ANCA-associated glomerulonephritis (AAGN) occurs in more than half of patients with a diagnosis of AAV and can lead to end-stage kidney disease (ESKD) and increased risk of death [1]. Across the United Kingdom (UK) and Europe, historical data identified an annual incidence

of AAV of 18–19/million/year [4,6], although more recent epidemiological studies have shown that the global incidence of AAV is rising [5,6]. Data on patients with AAV have been predominately in White populations of European ancestry; however, the available literature indicates that there are geographical variations in the clinical phenotype and disease characteristics [7–9]. Genetic, epigenetic and environmental factors have all been identified as contributory factors to the pathogenesis of AAV [8,10,11]. Genetic studies have revealed distinct genetic factors contributing to disease susceptibility, such as HLA alleles and non-HLA genotypes [12–15].

AAV exhibits geographical variability in its phenotype and manifestation worldwide (Figure 1). GPA, for example, is seen more commonly in Northern European countries at higher latitudes with less UV exposure [16]. In contrast, MPA is seen more frequently in Japanese, Chinese and Southern European populations [7,9,17]. Variations in AAV phenotype have been noted across Asia [9,18]; in China and Japan, MPO ANCA positivity is more prevalent, while Indian and Korean patients show a higher incidence of PR3 ANCA positivity [18]. Comparatively few studies have looked at the incidence, phenotype and outcomes in ethnic minority patients, in particular patients from continents such as Oceania and Africa as well as Indo-Asian populations [19].

US and European studies looking at ethnic minority AAV patients demonstrated that AAV occurs much less commonly in non-White Europeans [20,21], with African Americans, Hispanics and Asians together making up only 1–4% of all AAV patients [9,22,23]. Comparative studies have shown Black patients (Black sub-Saharans, African-Caribbeans and North Africans) have more severe granulomatous manifestations and shorter time to relapse [20], while Japanese populations have less ENT and respiratory involvement compared to UK patients [22]. We aimed to look at the phenotypes and clinical outcomes of Indo-Asian patients with AAGN from two centers in the North West, UK.

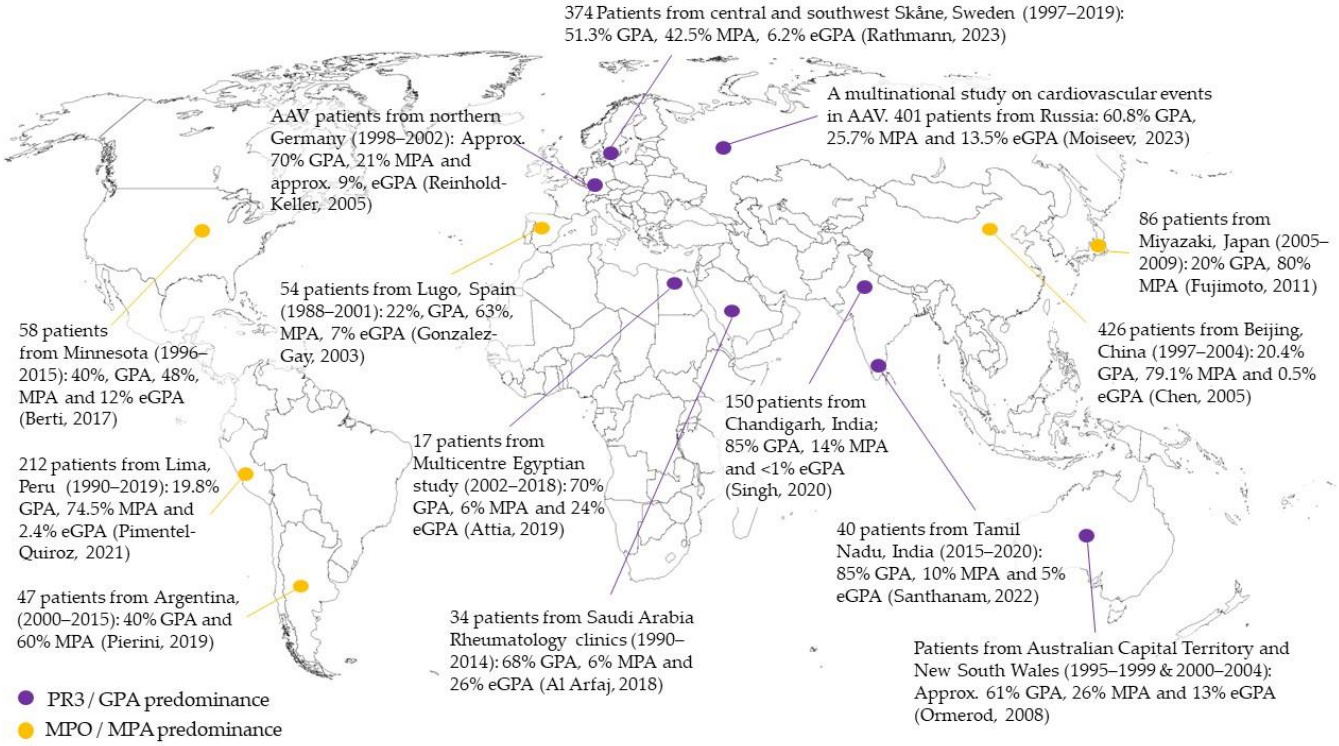


Figure 1. Global epidemiology of MPO (yellow) and PR3 (purple) predominance of ANCA-associated vasculitis [15,17,22,24–34]. Adapted from Watts et al. [35] and Kitching et al. [36].

2. Materials and Methods

2.1. Patient Selection and Data Collection

This was a twin-center, retrospective cohort study involving patients with AAV from the following ethnic groups: Indian, British Indian, Pakistani, British Pakistani, Bangladeshi, British Bangladeshi, Asian or Asian British. The study included patients treated in two regional renal centers in the North West of the UK (Royal Preston Hospital and Salford Royal Hospital) between 2009 and 2023. Patients were identified based on each center's biopsy database and electronic patient record (EPR). All included patients had a diagnosis of AAGN, which was confirmed either on renal biopsy or AAV-related increase in serum creatinine and/or associated proteinuria, hematuria and active urine sediment suggesting glomerular involvement. Exclusions included those aged <18 years and patients with secondary ANCA positivity as a result of infection, drugs or malignancy. Using data from the census available from the Office of National Statistics, denominator populations were obtained [37].

A control group of White patients was identified from the same databases and recruited consecutively in relation to the original cohort of Indo-Asian patients. Data collection for each patient included baseline demographics, ANCA status, clinical presentation, organ involvement, baseline laboratory values, renal histology and requirement for kidney replacement therapy (KRT) at presentation. Comorbidities of interest were similar to those used in the Charlson comorbidity index and included a history of diabetes mellitus, hypertension and ischemic heart disease, as well as previous tuberculosis (TB) exposure [38]. Outcomes included relapse, progression to ESKD and mortality. Patients were stratified by ANCA status from the time of diagnosis.

2.2. Statistical Analysis

For continuous variables, results are expressed as median and interquartile range (IQR) if normally distributed or mean ± standard deviation (±SD) if non-normally distributed. The Indo-Asian group was compared with the control White group. The *p*-value was generated by the chi-squared test for categorical variables and by Mann–Whitney U test for continuous variables. Analysis was performed using SPSS (IBM Corp. 2022. Armonk, NY, USA). In statistical analysis, $p < 0.05$ was considered significant. Kaplan–Meier curves were generated to determine overall survival, freedom from KRT and relapse-free survival for the 2 groups. Crude incidence rates were calculated from denominator populations and presented as per million person-years and stratified by ethnicity.

This study complied with the declaration of Helsinki and, as indicated by the NHS Health Research Authority tool, was not considered research requiring ethics committee review. The need for individual patient consent was waived by the research and innovation committee of the Northern Care Alliance NHS Group. The committee granted study approval and registered the study (Ref: 23HIP22).

3. Results

A total of 66 patients diagnosed between 2009 and 2023 were included in the study: 24 patients of Indo-Asian ethnicity and a control cohort of 42 patients of White ethnicity. Using data from the 2021 census [37], the combined total population of the two centers was 2,790,253. The majority identified as White (84.9%), followed by Asian/Asian British (10.9%). Black/African/Caribbean/Black British made up 1.8% of the population and mixed/multiple ethnic groups and other ethnic groups made up 2.4%. The isolated 2021 incidence of AAGN in the Indo-Asian population was 18.1 per million Indo-Asian person years across the two North West centers. This is higher than the 2011 annual incidence in Indo-Asian patients, which was 11.7 per million Indo-Asian person years.

3.1. Clinical Characteristics

The overall mean age was 55.6 ± 16.6 years. The Indo-Asian patients had a younger mean age of 51.5 ± 17.4 years compared to 57.9 ± 15.9 years for the White cohort, although

this was not statistically significant, $p = 0.15$ (Table 1). Sex difference was similar, 58.3% female in the Indo-Asian group and 52.4% female in the White group ($p = 0.64$). PR3 ANCA and MPO ANCA positivity across the groups are presented in Table 1. There was a higher number of ANCA-negative patients in the White control group; 9.5% vs. 4.2%. A total of 36 patients were tested for concurrent anti-glomerular basement membrane antibodies (9 Indo-Asian patients and 27 white patients) and only 1 was positive. There was no difference in AAV clinical subtype between the two groups (GPA observed in 54.2% of the Indo-Asian group and 57.1% in the White group and MPA in 45.8% of the Indo-Asian group and 33.3% of the White group ($p = 0.482$)). Four patients in the White control group had an unclassifiable clinical phenotype. There were also no differences with respect to the type of organ involvement seen clinically (Table 2). There was a significantly higher prevalence of diabetes mellitus in the Indo-Asian group (33.3% vs. 4.8%, $p = 0.002$) as well as a higher incidence of previous TB exposure (12.5% vs. 0%, $p = 0.019$).

Table 1. A comparison of demographics, baseline laboratory values, histological and clinical outcomes in Indo-Asian and White patients.

		Total (N = 66)	**Indo-Asian (n = 24)**	**White (n = 42)**	***p*-Value**
Demographics					
Age, years (SD)		55.6 ± 16.6	51.5 ± 17.4	57.9 ± 15.9	0.150
Female %		36 (54.5)	14 (58.3)	22 (52.4)	0.640
Diabetes %		10 (15.2)	8 (33.3)	2 (4.8)	0.002
Previous history of TB %		3 (4.5)	3 (12.5)	0 (0)	0.019
GPA %		37 (56.1)	13 (54.2)	24 (57.1)	0.482
MPA %		25 (37.9)	11 (45.8)	14 (33.3)	0.482
eGPA %		0 (0)	0 (0)	0 (0)	1.0
PR3 ANCA %		30 (45.5)	12 (50)	18 (42.9)	0.553
MPO ANCA %		31 (47.0)	11 (45.8)	20 (47.6)	0.445
Negative %		5 (7.5)	1 (4.2)	4 (9.5)	0.218
KRT at presentation %		11 (16.7)	5 (20.8)	6 (14.3)	0.492
Baseline laboratory values					
Creatinine, µmol/L		219 (115–346)	180 (114–258)	243 (125–389)	0.233
eGFR, ml/min/1.73 m^2		24 (12.5–55.5)	32.5 (17–68)	18.5 (11–48)	0.242
Urine protein creatinine ratio, g/mol		109 (32–274)	115 (28–230)	104 (32–270)	0.793
Berden's classification and renal risk score					
Berden's classification [a]	Focal %	16 (35.6)	3 (21.4)	13 (41.9)	0.183
	Mixed %	9 (20.0)	4 (28.6)	5 (16.1)	0.334
	Crescentic %	9 (20.0)	5 (35.7)	4 (12.9)	0.077
	Sclerotic %	11 (24.4)	2 (14.3)	9 (29)	0.287
Renal risk score [a], %	Low	19 (42.2)	4 (28.6)	15 (48.4)	0.213
	Med	15 (33.3)	8 (57.1)	7 (22.6)	0.023
	High	11 (24.4)	2 (14.3)	9 (29)	0.287

Table 1. *Cont.*

		Total (N = 66)	Indo-Asian (n = 24)	White (n = 42)	*p*-Value
Outcomes					
Relapse %		11 (16.7)	4 (16.7)	7 (16.7)	0.382
Progression to ESKD		13 (19.7)	5 (20.8)	8 (19.0)	0.861
Mortality %	Overall	17 (25.8)	7 (29.2)	10 (23.8)	0.632
	1-year	2 (3.1)	1 (4.2)	1 (2.4)	0.697
	5-year	8 (12.1)	5 (20.8)	3 (7.1)	0.101

[a] Available for total of 45/66 patients, ANCA, Anti-neutrophil cytoplasmic autoantibody; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; eGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; KRT, kidney replacement therapy; MPA, microscopic polyangiitis; MPO; perinuclear myeloperoxidase; PR3, cytoplasmic proteinase 3; SD, standard deviation; TB, tuberculosis.

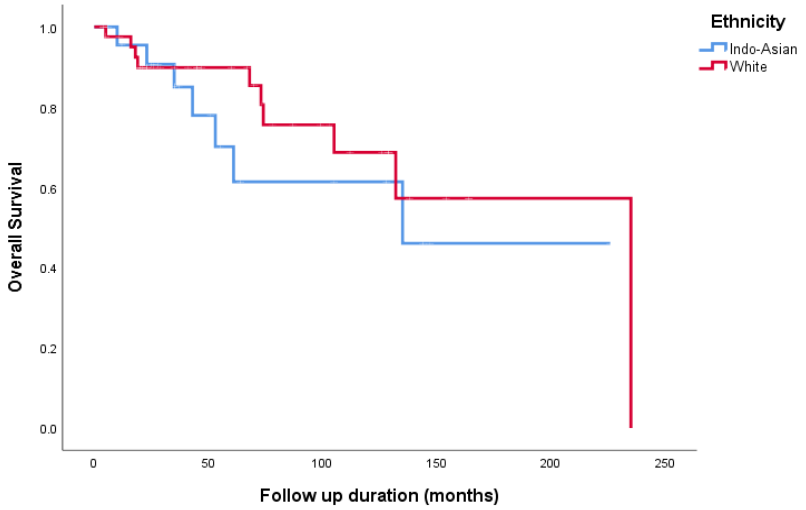
Table 2. A comparison of organ involvement between Indo-Asian and White patients.

	Total (N = 66)	Indo-Asian (n = 24)	White (n = 42)	*p*-Value
General %	27 (40.9)	10 (41.7)	17 (40.5)	0.925
Joint/cutaneous %	24 (36.4)	8 (33.3)	16 (38.1)	0.699
Mucocutaneous/ ophthalmic %	10 (15.2)	4 (16.7)	6 (14.3)	0.795
Ear, nose, and throat %	21 (31.8)	8 (33.3)	13 (31)	0.842
Chest %	28 (42.4)	11 (45.8)	17 (40.5)	0.672
Cardiovascular %	1 (1.5)	0 (0)	1 (2.4)	0.446
Gastrointestinal %	1 (1.5)	0 (0)	1 (2.4)	0.446
Neurological %	6 (9.1)	3 (12.5)	3 (7.1)	0.466
Renal limited %	11 (16.7)	2 (8.3)	9 (21.4)	0.170

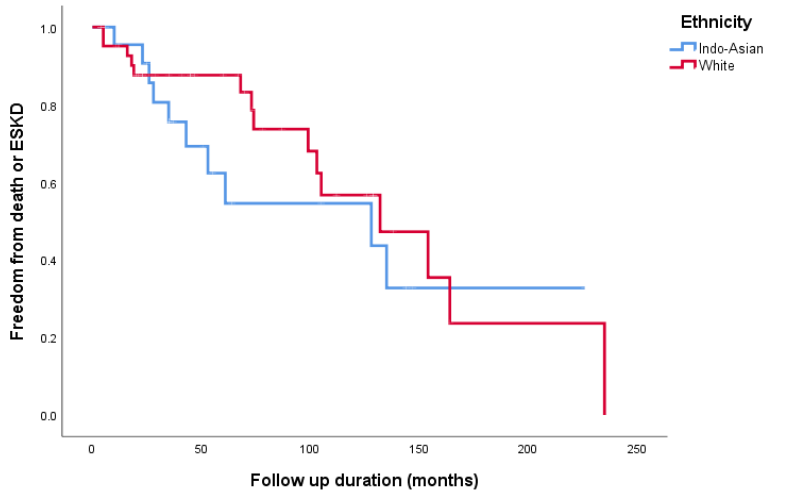
A similar proportion of patients in the Indo-Asian and White patient groups required KRT at presentation (n = 5, 20.8% vs. n = 6, 14.3%, respectively, $p = 0.492$). Forty-five patients had a renal biopsy of which there was a comparable split across the four subtypes in the Berden classification [39], with no significant difference seen between the two groups. The percentage of normal glomeruli in the Indo-Asian group was lower, and there was a trend towards a higher proportion of the crescentic subclass in comparison to the White control group (33.9% vs. 39.7% and 35.7% vs. 12.9%, respectively), but this was not statistically significant; $p = 0.533$ and $p = 0.077$. The renal risk score (RRS) [40] was also determined for each patient and categorized as either low, medium or high-risk. There was a higher percentage of White patients in the high-risk groups compared to Indo-Asian patients (29% vs. 14.3%, $p = 0.287$) who had predominately low or medium risk scores (Table 1).

3.2. Clinical Outcomes

Outcomes including relapse, progression to ESKD and mortality were determined. There were no significant differences between the two groups and any of these outcomes (Figure 2A–C). Relapse occurred in 16.7% in each group ($p = 0.382$), progression to ESKD occurred in 20.8% of the Indo-Asian group and 19% of the White group ($p = 0.861$) and mortality occurred in 29.2% of the Indo-Asian group and 23.8% of the White group ($p = 0.632$). There was also no significant difference between one- and five-year mortality.



(**A**)



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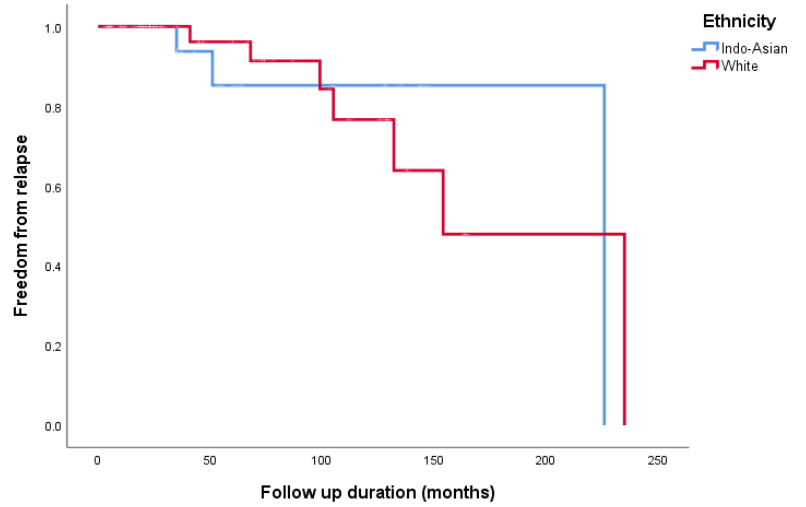

(**C**)

Figure 2. (**A**) Kaplan–Meier curve comparing overall survival of Indo-Asian and White patients with ANCA-associated glomerulonephritis. Log rank $p = 0.395$. (**B**) Kaplan–Meier curve comparing overall and kidney survival of Indo-Asian and White patients with ANCA-associated glomerulonephritis. Log rank $p = 0.384$. (**C**) Kaplan–Meier curve comparing relapse rate of Indo-Asian and White patients with ANCA-associated glomerulonephritis. Log rank $p = 0.988$.

3.3. Treatment

With the exception of two patients, one in each cohort, all received remission-induction therapy. The majority (n = 38, 59.4%) received cyclophosphamide alongside glucocorticoids as induction treatment with a near equal split across the two groups, as shown in Table 3. Rituximab alongside glucocorticoids was used in five patients in each cohort and there was a larger number of patients in the White control group that received combination therapy with low-dose cyclophosphamide and rituximab (22% vs. 8.7%). One patient in each group was treated with prednisolone monotherapy and azathioprine. One patient in the White control group received mycophenolate mofetil (MMF) as initial immunosuppressive therapy. Glucocorticoids were used in all those treated. The use of intravenous methylprednisolone with doses ranging from 250 mg to 3 g was similar across the groups (65.2% vs. 65.9%). In contrast, plasma exchange was used more often in the Indo-Asian group (17.4% vs. 12.2%).

Table 3. A comparison of remission-induction treatment between Indo-Asian and White patients.

	Total (N = 64)	**Indo-Asian (n = 23)**	**White (n = 41)**
CYC and GCs %	38 (59.4)	14 (60.9)	24 (58.5)
RTX and GCs %	10 (15.6)	5 (21.7)	5 (12.2)
CYC and RTX and GCs %	11 (17.2)	2 (8.7)	9 (22.0)
Other %	5 (7.8)	2 (8.7)	3 (7.3)
PLEX %	9 (14.1)	4 (17.4)	5 (12.2)

CYC, cyclophosphamide; GCs, glucocorticoids; RTX, rituximab; PLEX, plasma exchange.

Of the eight Indio-Asian patients with diabetes, all received hypoglycemic medications. Treatment with metformin alone or a combination with linagliptin and or sulphonylureas was used in six patients. Three patients received insulin therapy. In contrast, only two White patients had diabetes, one was treated with dietary modifications and one received metformin alone. Treatment data on those with TB history were limited. In two patients, the history of TB was known prior to their AAV diagnosis and treatment information was not available. In one patient, the diagnosis was made following the presentation with AAV; in this patient, standard initial phase therapy was commenced.

4. Discussion

Our findings suggest Indo-Asian patients tend to be younger and have a higher prevalence of preexisting diabetes and previous TB exposure. Similar rates of KRT at presentation, relapse, ESKD and mortality were observed when compared to White patients. These findings are similar to previously published work, which showed a younger mean age in Indo-Asian patients and no significant difference in clinical outcomes [18,41].

In 2016, Pearce et al. [21] conducted an epidemiological study looking at the incidence of ANCA vasculitis in the UK and found no significant difference between the incidence of AAV in a mixed ethnicity population. When compared to our cohort, which had an overlapping time period (2007–2013 versus our cohort from 2009–2023), Pearce et al. included only three Indo-Asian patients [21]. We found a similar crude incidence rate in 2011 but a higher rate in 2021 with a larger representation of Indo-Asians in our local population (10.9% versus 6.1% by Pearce et al.). This reflects that the global incidence and prevalence of AAV is rising and the impact of migration remains understudied [5]. Between 2001 and 2021, the percentage of the UK population which were from Asian ethnic groups has over doubled (4.4% in 2001 to 9.3% in 2021) [42]. Alongside this, improvements in diagnostic assays, clearer classification, improved treatments and increased clinician awareness are all contributing to the increased incidence and prevalence of AAV. With this

comes a need to consider service provisions and future planning to address the needs of individual patients.

When considering the clinical characteristics and phenotype of our cohort, we identified a higher incidence of GPA in Indo-Asian patients. Similar findings have been identified in studies from India, which showed a significantly higher incidence of PR3 ANCA positivity and patients presenting with GPA compared to MPA or eGPA [15,33]. This is in contrast to neighboring Asian counties such as China and Japan, which report higher prevalence of MPO ANCA positivity and MPA (Figure 1). The reasons for this are complex and multifactorial. Environmental associations with GPA have been identified but more recent work has identified potential genetic risk factors. HLA- DRB1/DQB1 and CTLA-4 + 49A/G have offered potential insights into the clinical and geographic disparities in those with PR3 and MPO ANCA positivity [14,15]. PR3 ANCA is frequently associated with HLA-DP, whereas MPO ANCA is more commonly linked to HLA-DQ [12]. These genetic associations might help explain the differences in AAV incidence; for example, Japanese and Chinese populations express less HLA-DP and have lower rates of GPA [9]. These alleles have also been associated with other autoimmune conditions and markers of disease severity, including ESKD [14,15]. Further research is needed but it suggests that MPO and PR3 AAV have unique genetic foundations that could potentially elucidate the global variations in clinical phenotype, alongside other contributory environmental factors such as pollution and immigration.

We found a significant increase in the number of Indo-Asian patients with a background of diabetes mellitus and previous history of TB. TB can present as infiltrates, cavitating lesions and nodules, all of which can also be seen in AAV, making the diagnosis and treatment challenging [43]. Some studies have suggested that up to 50% of GPA cases with pulmonary involvement in India were misdiagnosed as TB initially [14]. Immunosuppressive treatment can cause reactivation of TB, leading to complications in management, and therefore it is important that improved screening at diagnosis, prophylactic treatment and surveillance are considered when treating Indo-Asian patients with AAV. In addition, diabetes was more common in our cohort of Indo-Asian patients and is well known to be associated with poorer health outcomes. While relapse rates were comparable across our two groups, the risk of relapse in AAV patients can be >20% despite treatment, and repeated glucocorticoid dosing further adds to the risk of glucocorticoid-related toxicity [44,45]. Further work into the genetic predisposition of glucocorticoid-related toxicity is required to tailor healthcare for individuals.

Infection remains a leading cause of mortality in AAV patients and it is clear that different patient cohorts demand different treatment strategies in order to optimize outcomes [46]. We suggest that treatment should be stratified according to individual patient risks; for example, considering a steroid-sparing approach in the treatment of high-risk Indo-Asian patients where prolonged glucocorticoid exposure may cause additional adverse effects. AAV is a chronic and relapsing disease and the increased incidence in younger patients raises concerns about the service provisions in place to care for these complex patients over time. In addition, the impact of comorbidities such as diabetes and TB increases the need for clinical observation, monitoring and follow-up. Expansion of vasculitis services and an increased emphasis on multidisciplinary team input is required to optimize patient care.

While publications on the epidemiology of AAV from Europe, USA and Japan are widely available, fewer studies have been published from Indo-Asian countries. Berti et al. published a 20-year population-based cohort study on AAGN but this included only Caucasian patients [47]. The reasons for the limited studies of AAV in Indo-Asian patients may in part be due to the lack of registry data and few cohort studies limiting epidemiology studies. We hypothesize that the lack of published work on AAV in Indo-Asian patients may not necessarily reflect a reduced incidence but could be related to limited data collection, underdiagnosis and differences in access to healthcare [5]. Furthermore, recent landmark clinic trials in AAV have often failed to report the ethnicities of participants and none have included participating centers from India or Africa [48–51]. This is despite studies

suggesting more severe granulomatous manifestations, shorter time to relapse and more severe disease burden in some minority patients [20,48]. The reasons for these differences are not fully understood but may reflect a more significant pathogenic disease due to genetic variation, delays in access to healthcare and a high burden of chronic health issues at presentation, which can lead to worse outcomes. More work is needed to include ethnic minority patients in clinical trials.

Our study was limited by an unmatched control cohort and a small sample size, which is an inherent problem for studies in rare diseases, made even more challenging by analyzing data from a smaller sub-cohort of patients. For this reason, our findings may not be representative of all Indo-Asian patients and the role of genetics and environmental factors remains uncertain. The study investigated a small sample size and likely lacked power. Including more patients of Indio-Asian ethnicity in future epidemiology studies will potentially reveal statistically significant differences and assist in stratifying patients in ethnic-related risks. Furthermore, this study only included patients with AAGN and likely underrepresents the overall incidence of AAV in Indo-Asian patients when considering those with extra renal disease.

5. Conclusions

In conclusion, Indo-Asian patients tended to present younger and had more comorbidities, such as diabetes and TB, which may increase their long-term risk of morbidity and mortality. Future planning of healthcare services is required to meet the increasing needs of AAV patients. Further clinical, epidemiological and genetic research is essential to comprehend the incidence, prevalence and pathophysiology of AAV in Indo-Asian and other ethnic minority patients. International collaboration and more inclusive recruitment of patients into clinical trials is required in order to achieve this.

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References

1. Hunter, R.W.; Welsh, N.; Farrah, T.E.; Gallacher, P.J.; Dhaun, N. ANCA Associated Vasculitis. *BMJ* **2020**, *369*. [CrossRef] [PubMed]
2. Hagen, E.C.; Daha, M.R.; Hermans, J.; Andrassy, K.; Csernok, E.; Gaskin, G.; Lesavre, P.; Lüdemann, J.; Rasmussen, N.; Sinico, R.A.; et al. Diagnostic Value of Standardized Assays for Anti-Neutrophil Cytoplasmic Antibodies in Idiopathic Systemic Vasculitis. EC/BCR Project for ANCA Assay Standardization. *Kidney Int.* **1998**, *53*, 743–753. [CrossRef] [PubMed]
3. Jennette, J.C.; Falk, R.J. Small-Vessel Vasculitis. *N. Engl. J. Med.* **1997**, *337*, 1512–1523. [CrossRef] [PubMed]
4. Watts, R.A.; Lane, S.E.; Bentham, G.; Scott, D.G. Epidemiology of Systemic Vasculitis: A Ten-Year Study in the United Kingdom. *Arthritis Rheum.* **2000**, *43*, 414–419. [CrossRef]
5. Watts, R.A.; Hatemi, G.; Burns, J.C.; Mohammad, A.J. Global Epidemiology of Vasculitis. *Nat. Rev. Rheumatol.* **2022**, *18*, 22–34. [CrossRef]
6. Mohammad, A.J. An Update on the Epidemiology of ANCA-Associated Vasculitis. *Rheumatology* **2020**, *59*, iii42–iii50. [CrossRef]
7. Watts, R.A.; Gonzalez-Gay, M.A.; Lane, S.E.; Garcia-Porrua, C.; Bentham, G.; Scott, D.G.I. Geoepidemiology of Systemic Vasculitis: Comparison of the Incidence in Two Regions of Europe. *Ann. Rheum. Dis.* **2001**, *60*, 170–172. [CrossRef]
8. Austin, K.; Janagan, S.; Wells, M.; Crawshaw, H.; McAdoo, S.; Robson, J.C. ANCA Associated Vasculitis Subtypes: Recent Insights and Future Perspectives. *J. Inflamm. Res.* **2022**, *15*, 2567–2582. [CrossRef]
9. Pearce, F.A.; Craven, A.; Merkel, P.A.; Luqmani, R.A.; Watts, R.A. Global Ethnic and Geographic Differences in the Clinical Presentations of Anti-Neutrophil Cytoplasm Antibody–Associated Vasculitis. *Rheumatology* **2017**, *56*, 1962–1969. [CrossRef]

10. Gómez-Puerta, J.A.; Gedmintas, L.; Costenbader, K.H. The Association between Silica Exposure and Development of ANCA-Associated Vasculitis: Systematic Review and Meta-Analysis. *Autoimmun. Rev.* **2013**, *12*, 1129–1135. [CrossRef]
11. Willeke, P.; Schlüter, B.; Sauerland, C.; Becker, H.; Reuter, S.; Jacobi, A.; Schotte, H. Farm Exposure as a Differential Risk Factor in ANCA-Associated Vasculitis. *PLoS ONE* **2015**, *10*, e0137196. [CrossRef] [PubMed]
12. Lyons, P.A.; Rayner, T.F.; Trivedi, S.; Holle, J.U.; Watts, R.A.; Jayne, D.R.W.; Baslund, B.; Brenchley, P.; Bruchfeld, A.; Chaudhry, A.N.; et al. Genetically Distinct Subsets within ANCA-Associated Vasculitis. *N. Engl. J. Med.* **2012**, *367*, 214–223. [CrossRef] [PubMed]
13. Cao, Y.; Schmitz, J.L.; Yang, J.; Hogan, S.L.; Bunch, D.; Hu, Y.; Jennette, C.E.; Berg, E.A.; Arnett, F.C.J.; Jennette, J.C.; et al. DRB1*15 Allele Is a Risk Factor for PR3-ANCA Disease in African Americans. *J. Am. Soc. Nephrol.* **2011**, *22*, 1161–1167. [CrossRef] [PubMed]
14. Banerjee, P.; Jain, A.; Kumar, U.; Senapati, S. Epidemiology and Genetics of Granulomatosis with Polyangiitis. *Rheumatol. Int.* **2021**, *41*, 2069–2089. [CrossRef]
15. Singh, J.; Sharma, A.; Rani, L.; Kaur, N.; Anand, S.; Saikia, B.; Jha, S.; Nada, R.; Minz, R.W. Distinct HLA and Non-HLA Associations in Different Subtypes of ANCA-Associated Vasculitides in North India. *Int. J. Rheum. Dis.* **2020**, *23*, 958–965. [CrossRef]
16. Weiner, M.; Bjørneklett, R.; Hrušková, Z.; Mackinnon, B.; Poulton, C.J.; Sindelar, L.; Mohammad, A.J.; Eriksson, P.; Gesualdo, L.; Geetha, D.; et al. Proteinase-3 and Myeloperoxidase Serotype in Relation to Demographic Factors and Geographic Distribution in Anti-Neutrophil Cytoplasmic Antibody-Associated Glomerulonephritis. *Nephrol. Dial. Transplant.* **2019**, *34*, 301–308. [CrossRef]
17. Chen, M.; Yu, F.; Zhang, Y.; Zhao, M.H. Cinical and Pathological Characteristics of Chinese Patients with Antineutrophil Cytoplasmic Autoantibody Associated Systemic Vasculitides: A Study of 426 Patients from a Single Centre. *Postgrad. Med. J.* **2005**, *81*, 723–727. [CrossRef]
18. Naidu, G.S.R.S.N.K.; Misra, D.P.; Rathi, M.; Sharma, A. Is Granulomatosis with Polyangiitis in Asia Different from the West? *Int. J. Rheum. Dis.* **2019**, *22* (Suppl. S1), 90–94. [CrossRef]
19. Redondo-Rodriguez, R.; Mena-Vázquez, N.; Cabezas-Lucena, A.M.; Manrique-Arija, S.; Mucientes, A.; Fernández-Nebro, A. Systematic Review and Metaanalysis of Worldwide Incidence and Prevalence of Antineutrophil Cytoplasmic Antibody (ANCA) Associated Vasculitis. *J. Clin. Med.* **2022**, *11*, 2573. [CrossRef]
20. Terrier, B.; Dechartres, A.; Deligny, C.; Godmer, P.; Charles, P.; Hayem, G.; Dunogué, B.; de Bandt, M.; Cohen, P.; Puéchal, X.; et al. Granulomatosis with Polyangiitis According to Geographic Origin and Ethnicity: Clinical-Biological Presentation and Outcome in a French Population. *Rheumatology* **2017**, *56*, 445–450. [CrossRef]
21. Pearce, F.A.; Lanyon, P.C.; Grainge, M.J.; Shaunak, R.; Mahr, A.; Hubbard, R.B.; Watts, R.A. Incidence of ANCA-Associated Vasculitis in a UK Mixed Ethnicity Population. *Rheumatology* **2016**, *55*, 1656–1663. [CrossRef] [PubMed]
22. Fujimoto, S.; Watts, R.A.; Kobayashi, S.; Suzuki, K.; Jayne, D.R.W.; Scott, D.G.I.; Hashimoto, H.; Nunoi, H. Comparison of the Epidemiology of Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis between Japan and the UK. *Rheumatology* **2011**, *50*, 1916–1920. [CrossRef] [PubMed]
23. Hoffman, G.S.; Kerr, G.S.; Leavitt, R.Y.; Hallahan, C.W.; Lebovics, R.S.; Travis, W.D.; Rottem, M.; Fauci, A.S. Wegener Granulomatosis: An Analysis of 158 Patients. *Ann. Intern. Med.* **1992**, *116*, 488–498. [CrossRef] [PubMed]
24. Reinhold-Keller, E.; Herlyn, K.; Wagner-Bastmeyer, R.; Gross, W.L. Stable Incidence of Primary Systemic Vasculitides over Five Years: Results from the German Vasculitis Register. *Arthritis Rheum.* **2005**, *53*, 93–99. [CrossRef]
25. Rathmann, J.; Segelmark, M.; Englund, M.; Mohammad, A.J. Stable Incidence but Increase in Prevalence of ANCA-Associated Vasculitis in Southern Sweden: A 23-Year Study. *RMD Open* **2023**, *9*. [CrossRef]
26. Moiseev, S.; Bulanov, N.; Crnogorac, M.; Direskeneli, H.; Galesic, K.; Gazel, U.; Geetha, D.; Guillevin, L.; Hrušková, Z.; Little, M.A.; et al. Traditional and Disease-Specific Risk Factors for Cardiovascular Events in ANCA-Associated Vasculitis: A Multinational Retrospective Study. *J. Rheumatol.* **2023**, jrheum.220851. [CrossRef]
27. Gonzalez-Gay, M.A.; Garcia-Porrua, C.; Guerrero, J.; Rodriguez-Ledo, P.; Llorca, J. The Epidemiology of the Primary Systemic Vasculitides in Northwest Spain: Implications of the Chapel Hill Consensus Conference Definitions. *Arthritis Rheum.* **2003**, *49*, 388–393. [CrossRef]
28. Berti, A.; Cornec, D.; Crowson, C.S.; Specks, U.; Matteson, E.L. The Epidemiology of Antineutrophil Cytoplasmic Autoantibody–Associated Vasculitis in Olmsted County, Minnesota. *Arthritis Rheumatol.* **2017**, *69*, 2338–2350. [CrossRef]
29. Pimentel-Quiroz, V.R.; Sánchez-Torres, A.; Acevedo-Vásquez, E.; Gamboa-Cárdenas, R.V.; Reátegui-Sokolova, C.; Medina-Chinchón, M.; Zevallos, F.; Noriega-Zapata, E.; Alfaro-Lozano, J.; Cucho-Venegas, J.M.; et al. Demographic and Clinical Features of ANCA-Associated Vasculitides in a Peruvian Tertiary Center. *JCR J. Clin. Rheumatol.* **2021**, *27*. [CrossRef]
30. Pierini, F.S.; Scolnik, M.; Scaglioni, V.; Mollerach, F.; Soriano, E.R. Incidence and Prevalence of Granulomatosis with Polyangiitis and Microscopic Polyangiitis in Health Management Organization in Argentina: A 15-Year Study. *Clin. Rheumatol.* **2019**, *38*, 1935–1940. [CrossRef]
31. Attia, D.H.S.; Abdel Noor, R.A.; Salah, S. Shedding Light on Vasculitis in Egypt: A Multicenter Retrospective Cohort Study of Characteristics, Management, and Outcome. *Clin. Rheumatol.* **2019**, *38*, 1675–1684. [CrossRef] [PubMed]
32. Al Arfaj, A.S.; Khalil, N. ANCA Associated Vasculitis in Patients from Saudi Arabia. *Pakistan J. Med. Sci.* **2018**, *34*, 88–93. [CrossRef] [PubMed]
33. Santhanam, S.; Murugesan, H.; Mohanasundaram, K. Clinical Profile and Outcome of Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: A Retrospective Observational Study from South India. *Indian J. Rheumatol.* **2022**, *17*.

34. Ormerod, A.S.; Cook, M.C. Epidemiology of Primary Systemic Vasculitis in the Australian Capital Territory and South-Eastern New South Wales. *Intern. Med. J.* **2008**, *38*, 816–823. [CrossRef] [PubMed]
35. Watts, R.A.; Scott, D.G.I. ANCA Vasculitis: To Lump or Split? *Rheumatology* **2012**, *51*, 2115–2117. [CrossRef] [PubMed]
36. Kitching, A.R.; Anders, H.-J.; Basu, N.; Brouwer, E.; Gordon, J.; Jayne, D.R.; Kullman, J.; Lyons, P.A.; Merkel, P.A.; Savage, C.O.S.; et al. ANCA-Associated Vasculitis. *Nat. Rev. Dis. Prim.* **2020**, *6*, 71. [CrossRef]
37. Office for National Statistics. Nomis Official Labour Market Statistics. Available online: http://www.nomisweb.co.uk (accessed on 3 January 2023).
38. Ofer-Shiber, S.; Molad, Y. Association of the Charlson Comorbidity Index with Renal Outcome and All-Cause Mortality in Antineutrophil Cytoplasmatic Antibody-Associated Vasculitis. *Medicine* **2014**, *93*, e152. [CrossRef]
39. Berden, A.E.; Ferrario, F.; Hagen, E.C.; Jayne, D.R.; Jennette, J.C.; Joh, K.; Neumann, I.; Noël, L.-H.; Pusey, C.D.; Waldherr, R.; et al. Histopathologic Classification of ANCA-Associated Glomerulonephritis. *J. Am. Soc. Nephrol.* **2010**, *21*, 1628–1636. [CrossRef]
40. Brix, S.R.; Noriega, M.; Tennstedt, P.; Vettorazzi, E.; Busch, M.; Nitschke, M.; Jabs, W.J.; Özcan, F.; Wendt, R.; Hausberg, M.; et al. Development and Validation of a Renal Risk Score in ANCA-Associated Glomerulonephritis. *Kidney Int.* **2018**, *94*, 1177–1188. [CrossRef]
41. Rajappa, M. Assessment of Activity and Damage in ANCA-Associated Vasculitis in India. *Arthritis Res.* **2002**, *4*, 88. [CrossRef]
42. Office for National Statistics. Population of England and Wales. Available online: https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/population-of-england-and-wales/latest (accessed on 31 October 2023).
43. Dayal, L.; Choi, J.; Shammash, J. Distinguishing Vasculitis From TB: A Diagnostic Challenge in Differentiating Granulomatosis With Polyangiitis From TB. *Chest* **2016**, *150*, 1073A. [CrossRef]
44. Salama, A.D. Relapse in Anti-Neutrophil Cytoplasm Antibody (ANCA)–Associated Vasculitis. *Kidney Int. Reports* **2020**, *5*, 7–12. [CrossRef] [PubMed]
45. Floyd, L.; Morris, A.; Joshi, M.; Dhaygude, A. Glucocorticoid Therapy in ANCA Vasculitis: Using the Glucocorticoid Toxicity Index as an Outcome Measure. *Kidney360* **2021**, *2*, 1002–1010. [CrossRef] [PubMed]
46. Wallace, Z.S.; Fu, X.; Harkness, T.; Stone, J.H.; Zhang, Y.; Choi, H. All-Cause and Cause-Specific Mortality in ANCA-Associated Vasculitis: Overall and According to ANCA Type. *Rheumatology* **2020**, *59*, 2308–2315. [CrossRef] [PubMed]
47. Berti, A.; Cornec-Le Gall, E.; Cornec, D.; Casal Moura, M.; Matteson, E.L.; Crowson, C.S.; Ravindran, A.; Sethi, S.; Fervenza, F.C.; Specks, U. Incidence, Prevalence, Mortality and Chronic Renal Damage of Anti-Neutrophil Cytoplasmic Antibody-Associated Glomerulonephritis in a 20-Year Population-Based Cohort. *Nephrol. Dial. Transplant.* **2019**, *34*, 1508–1517. [CrossRef]
48. Loftis, C.E.; Dulgheru, E.C.; White, R. Disease Severity and Response to Induction Therapy in Hispanic Patients with Antineutrophilic Cytoplasmic Autoantibody-Associated Vasculitis-Related Diffuse Alveolar Hemorrhage. *Cureus* **2022**, *14*, e24470. [CrossRef]
49. Walsh, M.; Merkel, P.A.; Peh, C.-A.; Szpirt, W.M.; Puéchal, X.; Fujimoto, S.; Hawley, C.M.; Khalidi, N.; Floßmann, O.; Wald, R.; et al. Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis. *N. Engl. J. Med.* **2020**, *382*, 622–631. [CrossRef]
50. Jayne, D.R.W.; Gaskin, G.; Rasmussen, N.; Abramowicz, D.; Ferrario, F.; Guillevin, L.; Mirapeix, E.; Savage, C.O.S.; Sinico, R.A.; Stegeman, C.A.; et al. Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis. *J. Am. Soc. Nephrol.* **2007**, *18*, 2180–2188. [CrossRef]
51. Jayne, D.R.W.; Merkel, P.A.; Schall, T.J.; Bekker, P. Avacopan for the Treatment of ANCA-Associated Vasculitis. *N. Engl. J. Med.* **2021**, *384*, 599–609. [CrossRef]