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Demographics and baseline disease characteristics of UK patients within the global aHUS registry

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Abstract

Atypical haemolytic uraemic syndrome (aHUS) is a rare kidney disease characterized by thrombotic microangiopathy. This study presents the first analysis of UK patients enrolled in the Global aHUS Registry, focusing on patient characteristics and disease natural history prior to treatment initiation ($n=172$; 74 paediatric, 98 adult). Mean age at first aHUS manifestation was 23.6 years overall (4.9 years for paediatric patients, 37.8 years for adults). Additional thrombotic microangiopathy events occurred in 57.0% of patients between initial clinical suspicion and registry enrolment. Potential precipitating factors were recorded in 14.0% of patients. Of 115 patients at active sites, 90.4% had genetic data recorded, with 73.8% undergoing "complete" genetic testing (results entered for *C3*, *CD46*, *CFH*, *CFB* and *CFI*, as a minimum). Of those with genetic data available, 52.9% had an identified pathogenic variant. Gastrointestinal involvement was the most common extra-renal manifestation, presenting in 22.2% of patients. End-stage kidney disease (ESKD) was present in 8.7% at baseline. ESKD-free survival probability at five years was 0.80 for paediatric patients and 0.57 for adults. ESKD-free survival was negatively influenced by *CFH*, *C3*, or *CFI* variants. This study highlights the historically poor prognosis for untreated patients with aHUS. The UK population of the Global aHUS Registry represents a valuable research cohort with comprehensive demographic data and high genetic characterization. These findings underscore the importance of early aHUS identification and intervention to prevent ESKD and improve patient outcomes.

Keywords Atypical haemolytic-uraemic syndrome (aHUS), Registry, Genetics, Prognosis

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Introduction

Atypical haemolytic uraemic syndrome (aHUS) is an ultra-rare kidney disease characterised by thrombotic microangiopathy (TMA) [1], affecting approximately 0.5 per million people per year [2, 3]. The reported incidence and prevalence of aHUS vary across studies, due to differences in case definitions and the potential underdiagnosis of the disease, which complicates accurate epidemiological characterization [4].

In aHUS, complement dysregulation predominantly involves uncontrolled activation of the alternative pathway in the solid phase, and is characterized by defective regulation of complement proteins bound to host cell surfaces [2, 5, 6]. Patients present with a triad of microangiopathic haemolytic anaemia, thrombocytopenia and end-organ damage, principally affecting the kidney [1].

The clinical presentation of aHUS closely resembles other TMAs, including Shiga toxin-producing *Escherichia coli* (STEC)-HUS and thrombotic thrombocytopenic purpura (TTP), as part of the differential diagnoses. Once microangiopathic haemolysis and thrombocytopenia have been identified, the clinical diagnosis of aHUS is one of exclusion, made only after ruling out other TMA conditions. TTP is distinguished from aHUS by measuring ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity, which are severely reduced (less than 10% of normal activity) in TTP. Given the clinical severity of TTP, this test should be performed as a priority in any patient with a TMA, before initiating plasma therapy; [3, 5] STEC-HUS can be identified through Shiga toxin testing via PCR or by stool culture [7], although a negative test result does not fully exclude STEC infection.

In the UK, the terminal complement (C5) inhibitor eculizumab received a NICE recommendation for funding for the treatment of aHUS in 2015 [8]. Prior to this, around half of patients diagnosed with aHUS would progress to end-stage kidney disease (ESKD) [9], consistent with an international study in 2010 showing that up to 50% of patients with aHUS would develop ESKD [10].

The pathogenesis of aHUS is believed to be driven by interplay between a number of factors, including genetic variants and environmental triggers. As noted, the diagnosis of aHUS is one of exclusion and there is currently active debate around the use of the terms "secondary HUS" versus "primary aHUS". It can be challenging to differentiate whether the TMA is being driven by a triggering (or "secondary") condition, or whether the disease is being driven by genetic or autoimmune defects in complement regulatory proteins causing chronic complement dysregulation [11–13].

It is estimated that at least 50% of patients with aHUS have an underlying inherited and/or acquired complement abnormality, which leads to dysregulated activity of the alternative complement pathway [2]. In a study of 214 children and adults with aHUS in France between 2000 and 2008, complement gene variants were identified in 60% of patients [14]. aHUS is understood to have incomplete genetic penetrance [15], and a significant proportion of patients with aHUS have no identified genetic variant, suggesting that some patients either develop the disease without a predisposing factor or have a presently unidentified genetic variation. Even in individuals with a genetic predisposition to aHUS, a 'second hit' (a trigger or precipitating factor) is often required for disease development [16]. In 2010 it was estimated that around 70% of aHUS patients had at least one triggering factor [10]; however, more recent analyses report a lower rate of precipitating factors (14–30%) [9, 17]. The most common environmental triggers include gastroenteritis and upper respiratory tract infections [5, 10, 18]. Other proposed triggers include autoimmune conditions, metabolic conditions, malignancy and malignant hypertension, though in these cases it is often unclear whether the condition is a true trigger of aHUS or is itself the driver of the TMA [19].

aHUS can also lead to acute and chronic extra-renal manifestations (peripheral and central nervous, gastrointestinal, cardiovascular, integumentary, pulmonary and ocular) and organ failure in both adults and children, which are associated with significant morbidity and mortality [20–22].

Given the rarity of the disease and small patient population, the multi-site, multi-national, non-interventional Global aHUS Registry (NCT01522183) was initiated in 2012 to collect retrospective and prospective data on demographics, disease characteristics and natural history, along with continued treatment outcome and safety data, in people presenting with aHUS both before and after the availability of eculizumab [23].

To date, regional data from the Global aHUS Registry have been released from Australia [24], Canada [25], Germany [26], and Italy [27]. The Global aHUS Registry has also been used to investigate pregnancy-triggered disease [28] and patient-reported outcomes [29], as well as inviting input from patient representatives to inform future analyses [30].

In the UK, the management of patients with aHUS is primarily coordinated by the National Renal Complement Therapeutics Centre (NRCTC), a specialist multidisciplinary unit who liaise directly with local clinicians as part of a nationwide shared-care initiative. The NRCTC has overseen the National aHUS Service since it was commissioned by NHS England in May 2016 [31], contributing to the consistent collection of data from UK patients for inclusion in the Global aHUS Registry.

This is the first report of UK patients enrolled in the Global aHUS Registry. Patient characteristics and disease natural history are reported prior to treatment initiation.

Methods

Patients of all ages with a clinical diagnosis of aHUS were eligible for enrolment in the Global aHUS Registry (NCT01522183), which was initiated on 30 April 2012. Patients with or without an identified complement pathogenic variant or anti-complement factor H (CFH) antibody were included, and patients with evidence of Shiga toxin-producing bacterial infection or a disintegrin and metalloproteinase with a thrombospondin type 1 motif-13 (ADAMTS13) activity level of 5% or lower, were excluded as previously reported [23]. During Registry enrolment and every six months thereafter, data are collected, as available, on patient demographics, medical and disease history, symptomatology, laboratory parameters (including genetic test results), TMA complications and efficacy and safety findings following treatment initiation [23]. Change in signs and symptoms of organ involvement were assessed for the central nervous system (CNS), renal, gastrointestinal, cardiovascular and pulmonary organ systems. The Registry study was established, and is conducted, in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki. All patients provided written Informed Consent before participation.

Data cut-off for this UK analysis was 25 December 2023, with eligibility dependent on availability of dates of first aHUS presentation and registry enrolment, date of birth and sex. Only patient data prior to initiation of treatment with eculizumab have been included in this analysis, which focuses on patient characteristics and demographics. Baseline was defined as the earliest clinical suspicion of aHUS being recorded, up to and not beyond treatment initiation. ESKD was defined as a report of chronic dialysis (dialysis lasting > 3 months) or kidney transplant.

In the analysis of the UK Registry genetic data, it was noted that some patients had undergone historical testing that would not be considered "complete" by current standards, for example those who had undergone testing for variants in a single gene. For the purpose of this analysis, patients were considered to have undergone "complete testing" if results had been entered for *C3*, *CD46*, *CFH*, *CFB and CFI*, as a minimum [3]. Those without complete testing were still included in the analysis and were classified as "incomplete testing" or "absent data/unknown".

On review of the registry genetic data, a number of site entries were incomplete. In an effort to generate a more complete data set for analysis, study sites that were still actively recording were contacted, by the study and Registry sponsor, on behalf of the authors, to ensure that their historical data had been entered fully into the registry. This follow-up provided a more complete data set for active sites but was not feasible for sites that had either closed or ceased data collection. As a result, the genetic data provided by active sites has a higher degree of completion. For the purposes of the genetic analysis only, we have therefore conducted a subgroup analysis of patients from active sites only (excluding genetic data from inactive sites).

Results

Patient demographics and clinical characteristics at baseline

At the data cut-off timepoint, 172 people from the UK had been entered into the Global aHUS Registry and were eligible for inclusion in this analysis. The earliest recorded onset of aHUS in this analysis was in March 1978. Based on age at the time of initial aHUS presentation, 74 (43.0%) were categorised as paediatric patients (i.e. age at onset < 18 years) and 98 (57.0%) were adults (age at onset ≥ 18 years). Baseline demographics and clinical characteristics are summarised in Table 1. Ninety-eight (57.0%) patients were female (52.7% of paediatric patients and 60.2% of adults). Patients were mostly white (80.8%, 73.0% and 86.7% in the overall, paediatric and adult populations, respectively). There was a known family history of aHUS in 30/172 (17.4%) of patients, seventeen (56.7%) of whom had only first-degree relatives affected. Of the patients who reported a family history, paediatric patients were more likely to report a first-degree relative with aHUS (12/16; 75.0%) compared with adults (5/14; 35.7%).

In the paediatric and adult populations 5.4% and 12.2%, respectively, had received dialysis prior to baseline. Adults were significantly more likely to have received chronic dialysis (> 3 months duration) prior to baseline than paediatric patients (10.2% vs. 1.4%, respectively; $P = 0.02$). Plasma therapy (plasma exchange and plasmapheresis) prior to baseline was also more common in adult patients (11.2% vs. 4.1% in paediatric patients; not significant). Duration of plasma therapy was longer in paediatric patients (median [IQR] 1.0 [0.03–36.0] months) than in adults (median [IQR] 0.23 [0.03–2.0] months; not significant).

Fifteen patients (8.7%) had evidence of ESKD prior to baseline (three paediatric patients [4.1%] and 12 adults [12.2%]), and seven patients (4.1%) had undergone kidney transplantation (two paediatric patients [2.7%] and five adult patients [5.1%]). No patient had received more than one kidney transplant.

Complement genetics and anti-CFH antibodies

Of the 172 UK patients with aHUS enrolled in the Registry, 115 are at open sites that are actively recording data.

Table 1 Patient demographic and clinical characteristics of patients from the UK included in the global aHUS registry

Characteristic	All (*n* = 172)	Paediatric (*n* = 74)	Adult (*n* = 98)
Age at first aHUS manifestation, years, median (IQR)	21.8 (4.0–35.1)	2.7 (1.1–7.7)	33.1 (25.9–47.0)
Age at enrolment into the registry, years, median (IQR)	28.6 (11.4–41.9)	8.7 (3.9–16.1)	40.3 (31.0–49.0)
Female (%)	98 (57.0)	39 (52.7)	59 (60.2)
Race (%)	139 (80.8)	54 (73.0)	85 (86.7)
White	8 (4.7)	0 (0)	8 (8.2)
Black	13 (7.6)	10 (13.5)	3 (3.1)
Asian	12 (7.0)	10 (13.5)	2 (2.0)
Other			
Family history of aHUS (%)	30 (17.4)	16 (21.6)	14 (14.3)
Time from first aHUS manifestation to enrolment, years, median (IQR)	2.3 (0.4–7.6)	3.3 (0.6–8.8)	1.8 (0.2–7.3)
First aHUS manifestation within 6 months prior to enrolment (%)	77 (44.8)	32 (43.2)	45 (45.9)
Dialysis (%)			
Dialysis prior to or at baseline	16 (9.3)	4 (5.4)	12 (12.2)
Chronic dialysis (duration > 3 months)	11 (6.4)	1 (1.4)	10 (10.2)
Plasma exchange/infusion prior to or at baseline (%)	14 (8.1)	3 (4.1)	11 (11.2)
Plasma therapy type (%)[a]			
Plasmapheresis/plasma exchange	13/14 (92.8)	3/3 (100.0)	10/11 (90.9)
Infusion	1/14 (7.1)	0/3 (0)	1/11 (9.1)
Duration of plasma exchange/infusion, months, mean (SD)	3.3 (9.5)	12.4 (20.5)	0.8 (1.1)
Renal transplant prior to or at baseline (%)	7 (4.1)	2 (2.7)	5 (5.1)
ESKD prior to or at aHUS onset (%)	15 (8.7)	3 (4.1)	12 (12.2)

aHUS, atypical haemolytic syndrome; ESKD, end-stage kidney disease; IQR, interquartile range; SD, standard deviation

Values are median (interquartile range) or *n* (%)

[a] Presented as a percentage of patients who received plasma therapy

Table 2 Pathogenic variant status of patients at active sites - overall and by paediatric/adult age at aHUS onset

	All patients *N*	Paediatric *n* (%)	Adult *n* (%)
Testing performed			
Patients with at least "partial" testing[a]	104*	-	-
Patients with "complete" testing[b]	85	-	-
Patients tested for anti-CFH antibodies	94	-	-
Genotype			
Anti CFH antibody positive	16	9 (56.3)	7 (43.8)
CFH pathogenic variant	25	8 (32.0)	17 (68.0)
C3 pathogenic variant	9	6 (66.7)	3 (33.3)
CFB pathogenic variant	2	1 (50.0)	1 (50.0)
CFI pathogenic variant	12	5 (41.7)	7 (58.3)
CD46 (MCP) pathogenic variant	17	9 (52.9)	8 (47.1)
VUCS	7	2 (28.6)	5 (71.4)
Any pathogenic variant[c]	55	24 (43.6)	31 (56.4)
Either pathogenic variant or anti-CFH antibody positive[d]	62	29 (46.8)	33 (53.2)

C3, complement factor 3; *CFB*, complement factor B; *CFH*, complement factor H; *CFI*, complement factor I; MCP, membrane cofactor protein; VUCS, variant of unknown clinical significance

Genetic data are presented for patients at active sites only ()*n* = 115). This excludes patients at closed sites in the overall data set (*n* = 172)

Values are n (%); percentages based on the N count of each row

* One additional patient was tested only for anti-CFH antibodies and did not have genetic testing

[c] Patients who underwent genetic testing deemed "incomplete" vs (d)

[d] Patients were considered to have undergone "complete testing" if results had been entered for C3, CD46, CFH, CFB and CFI, as a minimum

[a] Not including VUCS or anti-CFH antibodies

[b] Including patients with *both* a pathogenic variant and anti-CFH antibodies (*n* = 9)

Of these patients, 90.4% (104/115) have had at least "partial" genetic testing, and 73.9% (85/115) had "complete" genetic testing.

Table 2 presents the findings of the genetic subgroup analysis. A pathogenic variant, not including variants of unknown clinical significance (VUCS), was identified in 52.9% (55/104) of patients with at least "partial" testing, and 17% (16/94) tested positive for anti-CFH antibodies (43.8% of these were adults). One patient was tested for anti-CFH antibodies only. Over half of patients tested (59% [62/105]) had anti-CFH antibodies, pathogenic variants, or both, not including VUCS. In patients with complete genetic testing 8.2% (7/85) had VUCS, 71.4% of whom were adults; in four of these seven cases the VUCS was in *CD46* (MCP).

Overall, in those with at least "partial" testing, 64.8% (68/105) had a pathogenic variant, a VUCS or anti-CFH antibodies.

Age at initial disease manifestation

Mean (SD) age at first manifestation of aHUS was 23.6 (20.5) years in the overall population, 4.9 (5.0) years in paediatric patients and 37.8 (15.9) years in adults (Table 1). Median (IQR) age was 21.8 (4.0–35.1) years, 2.7 (1.1–7.7) years and 33.1 (25.9–47.0) years in the three patient groups, respectively. Mean (SD) age at initial aHUS manifestation was 24.7 (23.0) in male patients and 22.8 (18.5) years in female patients (median [IQR] age, 21.8 [3.0–39.4] and 22.1 [6.1–32.9], respectively).

In the sub analysis of patients with genetic data from active sites, mean (SD) age of onset was higher in patients with *CFH* pathogenic variants (23.1 [18.0] years) and *CFI* pathogenic variants (24.2 [24.5] years) and VUCS (29.3 [19.7] years) than in patients with other confirmed genetic variations (Supplementary Table 1).

Medical history and possible precipitating factors

The existence of potential precipitating factors prior to onset of aHUS was recorded, though these were not entered as confirmed triggering conditions. In most patients (148/172; 86.0%), no medical history of any of the preselected precipitating factors for aHUS was noted prior to diagnosis. A medical history of at least one potential precipitating factor was noted in 24 patients (six paediatric patients and 18 adults) (Table 3). Reported potential precipitating factors were: malignancy ($n=3$), kidney transplant ($n=2$) and autoimmune disease ($n=2$) in paediatric patients; and pregnancy ($n=7$), kidney transplant ($n=5$), malignancy, autoimmune disease and malignant hypertension (all $n=2$) in adults. The small number of patients with a history of potential precipitating factors found to have genetic or acquired defects in complement regulation precludes assessment of potential associations with specific pathogenic variants (Supplementary Table 2). Of patients with no reported potential precipitating factors, complement gene variants or anti-CFH antibodies were identified in 54.1% (53/98; data not shown), as assessed at active sites.

ESKD-free survival

Of the 46 patients with ESKD after aHUS onset, 33 (71.7%) presented before January 2015. The probability of ESKD-free survival at one and five years, respectively, was 0.88 and 0.80 in paediatric patients and 0.58 and 0.57 in adult patients (log-rank $P=0.0001$) (Fig. 1). ESKD-free survival probability at five years was 0.63 for females and 0.69 for males.

Multivariable Cox regression analysis showed a lower risk of ESKD in paediatric patients compared with adult patients (adjusted hazard ratio [HR], 0.29; 95% confidence interval [CI], 0.13–0.66) (Table 4). Compared with white patients, black patients appeared to be at the greatest increased risk of ESKD (adjusted hazard ratio [HR], 2.14; 95% confidence interval [CI], 0.67–6.83; Asian HR, 0.96; CI, 0.12–7.45; "Other" HR, 1.80; CI, 0.21–15.19); however, these findings were not statistically significant and should be interpreted with caution due to the low number of patients. No association with ESKD risk was seen for sex, family history of aHUS, time from onset of aHUS to diagnosis, and potential precipitating factors (Table 4). The probability of ESKD-free survival at one and five years was lower in patients with positive findings for anti-CFH antibodies and pathogenic *CFH* or *C3* variants than in those without (Supplementary Fig. 1). No patients with an identified pathogenic CD46 (MCP) variant progressed to ESKD in the observed timeframe for this study.

Table 3 Disease characteristics according to preselected potential precipitating factors prior to aHUS onset, for patients at all sites

Parameter	Overall population *n*=172	None of the precipitating factors investigated *n*=148	Kidney transplant *n*=7	Pregnancy *n*=7	Malignancy *n*=5	Autoimmune disease *n*=4	Malignant hypertension *n*=2
Age at initial manifestation	74	68/74 (91.9)	2/74 (2.7)	0/74 (0)	3/74 (4.1)	2/74 (2.7)	0/74 (0)
<18 year (paediatric, %)	98	80/98 (81.6)	5/98 (5.1)	7/98 (7.1)[d]	2/98 (2.0)	2/98 (2.0)	2/98 (2.0)
≥18 year (adult, %)							
Any identified pathogenic variant or positive for anti-CFH antibodies[a] (%)	80	70/80 (87.5)	1/80 (1.3)	3/87 (3.4)	3/80 (3.8)	1/80 (1.3)	2/80 (2.5)
No identified pathogenic variant and negative for anti-CFH antibodies[b] (%)	47	36/47 (76.6)	6/47 (12.8)	4/47 (8.5)	0/47 (0)	2/47 (4.3)	0/47 (0)
No conclusive genetic or anti-CFH antibody information[c] (%)	45	42/45 (93.3)	0/45 (0)	0/45 (0)	2/45 (4.4)	1/45 (2.2)	0/45 (0)

C3, complement factor 3; CFB, complement factor B; CFH, complement factor H; CFI, complement factor I; MCP, membrane cofactor protein

Data from all sites in the Registry. This includes patients from closed sites, in addition to the active sites referenced in Table 2**and supplemental tables/figures** Values are *n* (%); percentages based on the *N* count of each row

The autoimmune disease group includes autoimmune disease, systemic lupus erythematosus, scleroderma and antiphospholipid syndrome

[a]Any identified pathogenic variant (*CFH*, *C3*, *CFB*, *CFI*, MCP), regardless of number of genes tested

[b]In patients tested for ≥ 5 genes

[c]In patients tested for < 5 genes. No conclusive information includes patients where no pathogenic variant was identified but not all genes were screened and therefore, no conclusion could be drawn, and patients tested for > 5 genes; however, their genetic report was ambiguous in the description of the abnormalities

[d]**Pregnancy was recorded in 7/52 (13.5%) of females of child-bearing age**, defined as age 15–49 years using the WHO definition

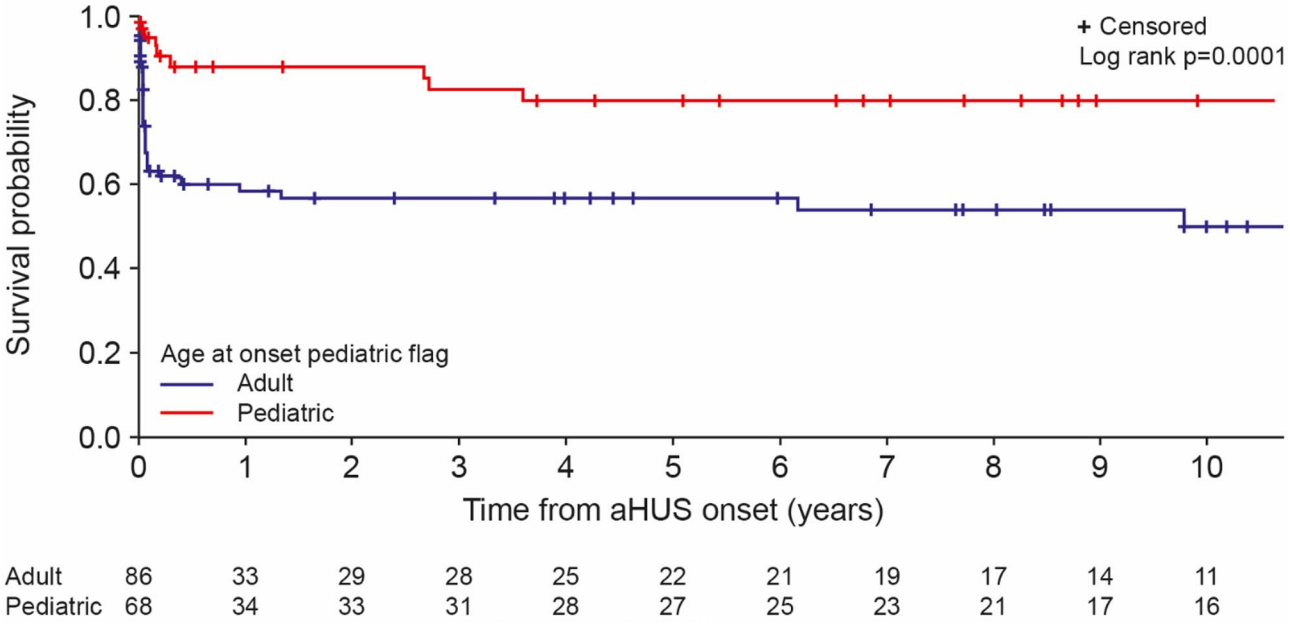

Fig. 1 Cumulative Kaplan–Meier estimates for ESKD-free survival according to age at initial presentation. Number of patients at risk shown for every year after initial aHUS presentation. Only data for untreated patients have been included in this analysis. aHUS, atypical haemolytic syndrome; ESKD, end-stage kidney disease

Post-baseline TMA manifestations

Ninety-eight of the 172 patients (57.0%) had experienced additional thrombotic microangiopathy (TMA) events post the first clinical suspicion of aHUS and before enrolment into the registry (44.9% and 55.1% of the paediatric and adult populations, respectively) (Table 5). 48/172 (28.0%) patients experienced ≥ 2 TMA relapses (17.6% of paediatric patients and 35.7% of adults). All patients were untreated when TMA relapse was reported.

Extrarenal symptoms

aHUS is known to be a multi-organ disease, thus the presence of extrarenal symptoms was also recorded. Only the concurrent presence of these symptoms is reported, and they are not necessarily confirmed manifestations of TMA driven by aHUS. Gastrointestinal symptoms were the most common, present in 22.1% of all patients (38/172) (Fig. 2). The prevalence was higher in adults (25.5% [25/98]) compared with paediatric patients (17.6% [13/74]). Cardiovascular symptoms were observed in 15.1% of all patients (26/172). The prevalence was slightly higher in adults (16.3% [16/98]) compared with paediatric patients (13.5% [10/74]). Pulmonary symptoms were less common, affecting 7.0% of the total population (12/172); the prevalence was similar between paediatric (6.8% [5/74]) and adult (7.1% [7/98]) populations. Overall, 11.0% of patients (19/172) exhibited CNS symptoms. However, there was a marked disparity between paediatric (2.7% [2/74]) and adult (17.3% [17/98]) populations.

Discussion

These data describe the baseline characteristics and burden of disease prior to treatment, providing insight into the natural history of aHUS in the UK. The UK data set is of particular interest because of a high degree of genetic characterisation in this aHUS population. Almost all patients enrolled in the UK aHUS registry data set have undergone some form of genetic testing and around three quarters have "complete" testing by current standards.

In this analysis, overall data for age and sex at the onset of aHUS in the UK were similar to findings in the global Registry, and to previous national findings in the UK and in Canada; however, Canadians were found to be older at adult presentation (50.8 years vs. 33.1 years) [9, 17, 25].

Potential precipitating factors were recorded in 14.0% of UK patients; this is in line with the proportion reported in the global data set [17]. It should be recognised that the absence of identified triggers does not necessarily imply their absence, and attention should be paid to this aspect as understanding of the disease evolves. It is also important to note that "potential precipitating factors" in this analysis were not confirmed as causative in the development of aHUS and were recorded as present or not present in the patient's medical history prior to their diagnosis of aHUS. These factors, or potential "triggers", were observed in a higher proportion of paediatric patients in the UK population compared with the global population (6/74 vs. 16/387), respectively) and a lower proportion of the adult population (18/98 vs. 105/464). Of the patients with an identified pathogenic variant

Table 4 Multivariable Cox regression analysis for the association of risk factors with ESKD

		Overall (*N* = 154)[a]	ESKD events, *n*	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Age at onset	Adult	86	35	1.00	1.00
	Paediatric	68	11	0.26 (0.13–0.55)	0.29 (0.13–0.66)
Gender	Female	90	25	1.00	1.00
	Male	64	21	0.84 (0.47–1.50)	0.82 (0.44–1.53)
Race	White	127	40	1.00	1.00
	Black	8	4	2.66 (0.94–7.51)	2.14 (0.67–6.83)
	Asian	10	1	0.45 (0.06–3.31)	0.96 (0.12–7.45)
	Other	9	1	0.49 (0.07–3.56)	1.80 (0.21–15.19)
Family history of aHUS	No	105	27	1.00	1.00
	Yes	25	8	1.12 (0.51–2.47)	1.41 (0.61–3.28)
	Unknown	23	10	1.68 (0.81–3.47)	1.32 (0.61–2.87)
Time from onset to diagnosis, days	0	30	10	1.00	1.00
	1–14	81	15	0.78 (0.34–1.77)	0.73 (0.31–1.73)
	15–30	16	7	1.90 (0.70–5.16)	1.81 (0.65–5.07)
	31–180	20	11	2.02 (0.84–4.86)	1.67 (0.66–4.23)
	> 180	7	3	1.07 (0.29–3.96)	0.68 (0.16–2.79)
Any precipitating factor	No	138	42	1.00	1.00
	Yes	6	4	1.54 (0.55–4.35)	0.98 (0.33–2.91)

aHUS, atypical haemolytic syndrome; CI, confidence interval; ESKD, end-stage kidney disease; HR, hazard ratio

[a] 18 patients were excluded due to negative or 0 values for time to ESKD

(excluding VUCS) or anti-CFH antibodies, 12.6% had a precipitating factor. Genetic variants are understood to be predisposing to, and not causative of, aHUS, and it is thought that in some cases an additional environmental trigger may be required before disease onset.

Of note, 15 patients (8.7%) had ESKD at baseline, suggesting that in some cases the onset of aHUS may have pre-dated the available data. It is also recognised that there may be a delay in the diagnosis of aHUS, or very rapid progression of aHUS, which could further explain this loss of renal function prior to documented disease onset.

Table 5 Occurrence of TMA relapse between diagnosis and enrolment

Characteristic	All (*N* = 172)	Paediatric (*N* = 74)	Adult (*N* = 98)
Number of patients with TMA relapse between diagnosis and enrolment	98/172 (57.0%)	44/98 (44.9%)[a]	54/98 (55.1%)[a]
Number of TMAs between baseline and enrolment[b]			
1	50/172 (29.1%)	31/74 (41.9%)	19/98 (19.4%)
2	26/172 (15.1%)	9/74 (12.2%)	17/98 (17.3%)
≥3	22/172 (12.8%)	4/74 (5.4%)	18/98 (18.4%)

TMA, thrombotic microangiopathy

[a] Presented as a percentage of patients who experienced a TMA relapse

[b] Percentages of adult and paediatric patients that experienced TMA relapse between aHUS onset and enrolment are based on row total as described in (a), while the number of TMAs experienced are based on total numbers of patients in the registry (column total N)

Of the 46 cases of ESKD reported after aHUS onset, 72% were recorded prior to the NICE recommendation for funding of eculizumab for aHUS in the UK (i.e. before January 2015). In the UK registry, ESKD-free survival was 88% and 80% in paediatric patients and 58% and 57% in adult patients at one and five years, respectively, and multivariate Cox proportional hazard analysis confirmed initial presentation during adulthood to be an independent risk factor for ESKD; this highlights the considerable disease burden patients for patients with untreated aHUS. These data appear to vary slightly from the findings in the global dataset (79% and 73% in paediatric patients and 69% and 51% in adult patients at one and five years, respectively); however, it is important to note the differences in definition of baselines in the two studies. In the UK analysis, patient follow-up for the ESKD survival curves started at the point closest to aHUS diagnosis, whereas the global dataset analysis in 2018 used the enrolment date for untreated patients and treatment initiation date for treated patients. Therefore, the time-bound components of these analyses are not comparable. The observation that ESKD-free survival was not negatively affected by *CD46*/MCP pathogenic variant, but is negatively influenced by *CFH*, *C3* or *CFI* variant is consistent with previous findings [9, 32].

Limitations

This dataset includes those presenting both before and after the availability of eculizumab as a treatment option; therefore, only patients who survived long enough to be enrolled are included in this analysis. Only patient data prior to treatment initiation are included. Even

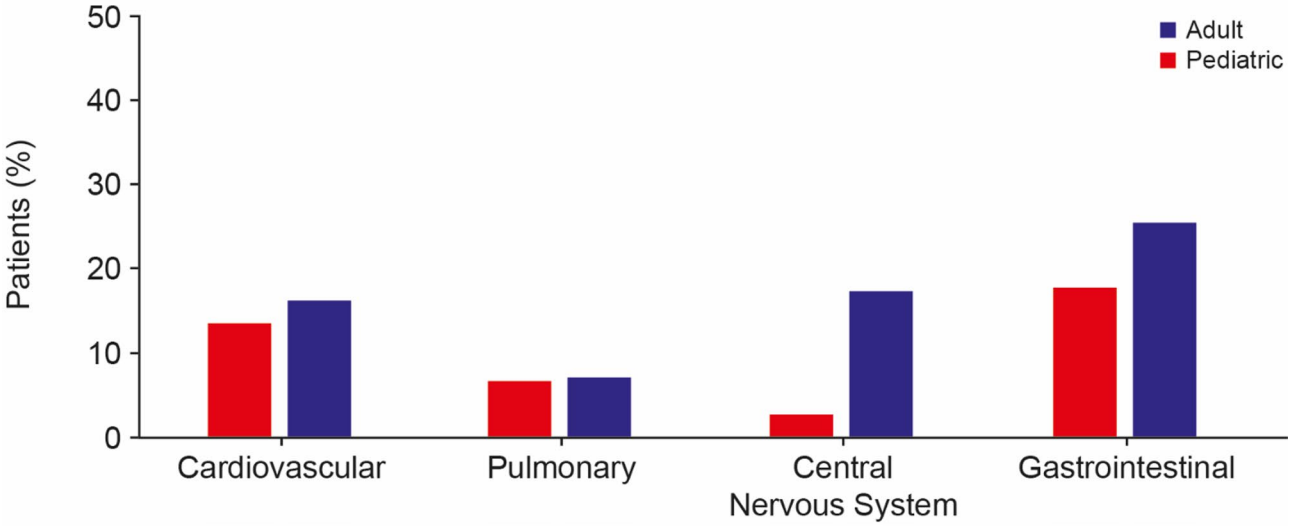

Fig. 2 Extrarenal vital organ symptoms preceding study entry. Values are presented as the percentage of the paediatric ($n=74$) and adult ($n=98$) populations. aHUS, atypical haemolytic syndrome

after eculizumab became more widely available in 2015, patients already with ESKD are less likely to have been treated and more of their data is therefore likely to be included (enriching this population). It is therefore plausible that the percentage of patients progressing to ESKD after 2015 has been over-represented. However, this is an observational study with no comparative-arm element, and confounding factors are not adjusted for. Data are presented as time-to-event points.

With the data available, it is not possible to correlate the presence of a precipitating factor to the risk of developing aHUS. There was no specific capture of *de novo* or recurrent events of the known precipitating factors, and only a medical history record stating the existence of these factors prior to diagnosis is available.

aHUS is a diagnosis of exclusion and insight into disease demographics and characteristics is challenging due to different understanding/disease nomenclature between centres and countries [33].

The field of aHUS genetics is highly specialist and complex and has evolved considerably over the time that the aHUS registry has been active. The data collected are therefore reflective of this and of variances in centres' understanding or interpretation, which may not fully capture the genetic variation or clinical significance. As an example, the Registry captures the presence ("yes/no") of CFHR1–3 but does not consistently capture gene sequences, copy number or homozygosity versus heterozygosity, which is required to determine any potential role in disease development.

As the findings presented are from an observational registry, they are also subject to the inherent limitations of such data sourcing, such as incomplete data entry, and validity and accuracy considerations, and can only include patients who consent to involvement.

Conclusions

The findings of this study highlight the historically poor prognosis for patients with newly diagnosed aHUS when untreated. Overall, 8.7% of patients in the UK Registry had ESKD and 4.1% had received a kidney transplant at baseline; furthermore, 56.9% had experienced TMA relapse between the first clinical suspicion of aHUS and enrolment in the Registry.

This study is broadly consistent with other national analyses of the aHUS Registry. The UK aHUS population represents a valuable research study cohort, with comprehensive demographic data and a high level of genetic characterisation, supported by a majority of patients undergoing complete genetic testing. Prior to the availability of effective treatments, UK aHUS patients faced a substantial disease burden, characterised by high rates of vital organ involvement and progression to ESKD. These findings underscore the importance of early aHUS identification and intervention to prevent ESKD and improve patient outcomes.

Abbreviations

ADAMTS13	A disintegrin and metalloproteinase with a thrombospondin type 1 motif: member 13
aHUS	Atypical haemolytic uraemic syndrome
C3	Complement factor 3
CD46	Membrane cofactor protein
CFB	Complement factor B
CFH	Complement factor H
CFHR	Complement factor H-related
CFI	Complement factor I
CI	Confidence interval
CNS	Central nervous system
ESKD	End-stage kidney disease

HR	Hazard ratio
IQR	Interquartile range
MCP	Membrane cofactor protein
NICE	National Institute for Health and Care Excellence
NRCTC	National Renal Complement Therapeutics Centre
PCR	Polymerase chain reaction
SD	Standard deviation
STEC	Shiga toxin-producing Escherichia coli
TMA	Thrombotic microangiopathy
TTP	Thrombotic thrombocytopenic purpura
VUCS	Variant of unknown clinical significance

Supplementary Information

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Supplementary Material 1

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Author contributions
RDG, DPG, SDM, SG, MSc, MSh, AW and NSS contributed data to the Registry. RDG, DPG, SDM, SG, MSc, MSh, AW and NSS and CB contributed to the initial conception of this manuscript and to interpretation of the data. TEC, IAD and NSS contributed to further data interpretation and to the analyses presented in this manuscript. All authors provided review and revision to the manuscript. All authors have approved this work for publication.

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Data availability
The datasets generated and/or analysed during the current study are not publicly available due to restrictions outlined in the informed consent forms (ICF), which do not permit the sharing of data beyond the research team. However, data may be available from the corresponding author on reasonable request and in accordance with applicable ethical guidelines.

Declarations

Human ethics and consent to participate
The aHUS Registry is approved through the Research Ethics Committee (REC) North East; Newcastle and North Tyneside 2, chaired by Professor Barry Hirst. The REC approvals are provided to the individual participating sites in the Registry. The Registry is conducted in accordance with International Conference on Harmonisation Good Clinical Practice Guidelines and the Declaration of Helsinki. Written informed consent was provided by patients or their parents or guardians, as deemed applicable by institutional review boards or the ethics committee.

Consent for publication
Not Applicable.

Competing interests
RDG has received several honoraria from Alexion for lectures on aHUS and serving on advisory boards. SDM and AW have no disclosures relating to this manuscript. MSc has received honoraria and a research grant from Alexion. DPG, SG, MSh and NSS have received honoraria from Alexion. CB and TEC are current employees of Alexion, AstraZeneca Rare Disease. IAD, at the time of writing and reviewing, was an employee of AstraZeneca Rare Disease.

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