Paediatric-onset Takayasu's arteritis associates with worse survival than adult-onset Takayasu's arteritis. A matched retrospective cohort study

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Abstract

Objective

A subset of Takayasu's arteritis (TAK) begins in the paediatric age group (≤18 years). Differences in prognosis between paediatric-onset and adult-onset TAK are unclear. We compared the differences in the presentation and survival between paediatric-onset and adult-onset TAK in our cohort of TAK.

Methods

From a retrospective cohort of TAK, clinical presentation, angiographic features, treatments received, disease activity, and survival were compared between paediatric-onset and adult-onset TAK. Multivariable-adjusted logistic regression models were used to compute adjusted odds ratio (aOR) with 95% confidence intervals (95%CI) for paediatric-onset vs. adult-onset TAK. Hazard ratios (HR, with 95%CI) for mortality with paediatric-onset vs adult-onset TAK (crude, adjusted for prognostic covariates or differences in presentation) and propensity score-matched survival analyses were estimated.

Results

Among 56 paediatric-onset and 135 adult-onset TAK, chest pain (aOR 3.21, 95%CI 1.06-9.74), heart failure (aOR 3.16, 95%CI 1.05-9.53), headache (aOR 2.60, 95%CI 1.01-6.74), ascending aorta (aOR 3.02, 95%CI 1.04-8.80) and left renal artery involvement (aOR 2.45, 95%CI 1.04-5.80) were more frequent in paediatric-onset TAK. Despite similar longitudinal patterns of disease activity and glucocorticoid or disease-modifying anti-rheumatic drug (DMARD) use, mortality was higher for paediatric-onset TAK (HR, unadjusted 6.13, 95%CI 1.51-24.91; adjusted for prognostic covariates gender, diagnostic delay, baseline disease activity, number of conventional and biologic/targeted synthetic DMARDs used, 4.97, 95%CI 1.20-20.58; adjusted for differences between groups 5.54, 95%CI 1.22-25.09; after propensity-score matching for prognostic covariates, 54 pairs, log-rank p-value 0.026).

Conclusion

Considering the greater mortality risk, greater vigilance is required while managing paediatric-onset TAK.

Key words

aortitis syndrome, childhood onset, paediatric onset, paediatric vasculitis, Takayasu's arteritis

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Introduction

Takayasu's arteritis (TAK), a rare granulomatous large-vessel vasculitis (LVV), predominantly affects young females and is more common in Asian countries. Large-vessel pathology in TAK often begins insidiously, becoming apparent months to years later after vascular occlusion has set in (1, 2). The onset of TAK can occur in the paediatric (≤18 years) or adult age group (2-4). Different classification or diagnostic criteria or definitions are used for paediatric-onset TAK (5) and adult-onset TAK (6, 7).

Paediatric-onset TAK is less common, accounting for about one-fifth of TAK (8). A recent systematic review with meta-analysis compared 263 patients with paediatric-onset TAK and 981 with TAK starting in adulthood from seven different cohorts (8-15). Constitutional features (fever, weight loss), hypertension, cardiac involvement, bowel angina, and renal failure were more frequent in childhood-onset TAK, as opposed to upper limb claudication, pulse asymmetry, or pulse loss in adult-onset TAK. Hata's angiographic subtype type IV was more common in childhood-onset TAK and type I in adult-onset TAK. The use of biologic disease-modifying anti-rheumatic drugs (DMARDs) appeared to be more frequent in paediatric-onset TAK. The risk of mortality and remission were similar between paediatric-onset and adult-onset TAK. An important limitation of the studies identified in this systematic review was that none of the cohorts of pediatric-onset and adult-onset TAK had been matched for important prognostic factors (8). Moreover, only one study with small numbers of patients (17 paediatric-onset and 45 adult-onset TAK) had reported similar mortality rates (14). The largest series of 119 patients with paediatric-onset TAK compared with 483 adult-onset TAK made no mention of mortality (10). Therefore, differences in prognosis between paediatric-onset and adult-onset TAK remain unclear.

In this study, we analyse the presenting features, angiographic subtypes, disease activity at baseline and follow-up, and treatments used from a retrospective cohort comprising paediatric-onset and adult-onset TAK from a dedicated vasculitis clinic in North India (16, 17). Furthermore, we compare mortality rates and survival (unadjusted and adjusted/ propensity score-matched) between paediatric-onset and adult-onset TAK.

Materials and methods

Study population

Information was retrieved from a retrospective cohort of patients with angiographically-proven TAK from 1996 to 2022 (all of whom had clinic visits after 2017) attending a dedicated vasculitis clinic at a large tertiary care referral and training centre in North India. The diagnosis of TAK was confirmed by two Rheumatologists (DPM, VA). Paediatric-onset TAK (onset ≤18 years) fulfilled the 2008 European Alliance of Associations for Rheumatology (EULAR)/ Paediatric Rheumatology European Society/Paediatric Rheumatology International Trials Organization classification criteria (5). Adult-onset TAK fulfilled the 1990 American College of Rheumatology (ACR) classification criteria for TAK (6) or the 2012 Chapel Hill Consensus Conference definition for TAK (7).

Data items

Information was collected on predesigned case record proformas in the vasculitis clinic to capture demographic characteristics (gender, age at disease onset, delay to diagnosis, age at cohort entry), comorbid conditions at baseline, and other coexistent autoimmune diseases. Disease activity at baseline was assessed using the Indian TAK Clinical Activity Score (ITAS2010) (18), the Disease Extent Index in TAK (DEI.TAK) (19), and physician global assessment (PGA; active or inactive). Disease activity at 6 months, 12 months, and 24 months of follow-up was recorded using ITAS2010, DEI.TAK, PGA, and National Institutes of Health (NIH) disease activity criteria (20). ITAS2010, DEI.TAK, and NIH scores had either been recorded at the clinic visit or were calculated retrospectively. Clinical features in the cardiovascular, neuro-

Table I. Characteristics of the cohort.

Variable	Paediatric-onset TAK (n=56)	Adult-onset TAK (n=135)	*p*-value*
Demographic characteristics			
Age at disease onset (years, Mean ± SD)	14.48 ± 2.89	29.98 ± 8.66	**<0.001**
Age at cohort entry (years, Mean ± SD)	20.64 ± 11.65	33.77 ± 9.96	**<0.001**
Sex distribution (Female:Male)	39:17	103:32	0.338[a]
Diagnostic delay (years, mean ± SD)	3.38 ± 3.61	2.86 ± 4.10 (n=133)	0.414
Duration from disease onset to cohort entry (years, mean ± SD)	5.61 ± 8.00	3.79 ± 4.58	0.050
Duration of follow-up (months, mean ± SD)	35.53 ± 34.89	50.57 ± 55.32	0.062
Prevalence of comorbidities [n (%)]			
Diabetes mellitus	0 (0)	6 (4.44)	0.183[b]
Smoking	0 (0)	2 (1.48)	>0.999[b]
Other autoimmune diseases	0 (0)	3 (2.22)	0.557[b]
Details	-	Systemic sclerosis (n=1) Statin-induced myositis (n=1) Crohn's disease (n=1)	-
Other comorbidities	2 (3.57)	11 (8.15%)	0.093[b]
Details	Hypothyroidism (n=2)	Hypothyroidism (n=8) Osteoporosis (n=1) Epilepsy (n=1) Rheumatic heart disease (n=1)	-
Mortality [n (%)]	6 (10.71%)[$]	4 (2.96%)[&]	0.066[b]

*Independent samples Student's t test for continuous variables, Chi squared[a]/Fisher's exact[b] for categorical variables.
DEI.TAK: disease Extent Index in Takayasu arteritis; ITAS2010: Indian Takayasu arteritis Clinical Activity Score; SD: standard deviation.
[$]Five deaths occurred within 8 years of follow-up: sepsis (n=1), stroke (n=1), intractable heart failure (n=1), recurrent myocardial infarction (n=1), cause unclear (?) stroke (n=1). One death occurred after 8 years of follow-up due to intractable heart failure.
[&]Three deaths occurred within 8 years of follow-up: sepsis (n=1), recurrent stroke (n=1), intractable heart failure (n=1). One death occurred after 8 years of follow-up due to suspected myocardial infarction or aortic dissection.
p-values <0.05 are highlighted in bold.

logical, systemic, and other domains, and acute-phase reactants erythrocyte sedimentation rate (ESR, mm/hour), C-reactive protein (CRP, mg/L), and neutrophil: lymphocyte ratio at presentation were noted. Imaging modalities used at the initial assessment, viz., conventional angiography, computerised tomography (CT) angiography, magnetic resonance (MR) angiography, 18-fluorodeoxyglucose positron emission tomography (PET)-CT, and ultrasound, were recorded. More than one of these modalities could have been used. The involvement of individual vessels and angiographic classification according to Hata's system (21) was noted. Proportions of patients treated with glucocorticoids, conventional DMARDs, biologic or targeted synthetic DMARDs, antihypertensive drugs, aspirin, clopidogrel, statins, and duration of treatment with immunosuppressants were recorded. The first and second-line DMARDs utilised were tabulated. The total number of conventional synthetic DMARDs and biologic/targeted synthetic DMARDs utilised for each patient was calculated. Open surgical or endovascular procedures related to TAK or its complications were noted. Dates of the first and last follow-up (whether in-person or telephonic) were used for survival analyses. Mortality recorded in hospital or out-of-hospital were noted.

Statistical analysis

Means (± standard deviations) were computed for continuous variables, and numbers (percentages) for categorical variables. Proportions were compared using the Chi-squared test (if there were at least five observations in each cell) or Fisher's exact test. Logistic regression analysis was used to compute unadjusted and multivariable-adjusted odds ratios (OR, with 95% confidence intervals – 95% CI) for paediatric-onset vs adult-onset TAK for categorical variables. Means with standard deviations were compared using the Student's *t*-test for independent samples. Where multivariable-adjusted analyses had not been performed, *p*-values were corrected for multiple testing using the Bonferroni-Sidak method. A sample size was not calculated for the study given the rarity of TAK.

Hazard ratios (with 95% CI) for mortality with paediatric-onset *versus* adult-onset TAK were estimated using Cox proportional hazards regression. Hazard ratios were adjusted for important covariates selected *a priori* which affect prognosis (delay to diagnosis, gender, active or inactive disease at baseline, number of conventional DMARDs used, number of biologic or targeted synthetic DMARDs used) (22-24). Hazard ratios for mortality were also calculated using separate Cox regression models adjusted for the observed differences in clinical features and vascular involvement between paediatric-onset and adult-onset TAK. The adequacy of the sample size of the regression models was ascertained if there were at least eight data points for each covariate (25). Propensity-score matching (PSM) was generated between these two groups for the *a priori* selected prognostic variables (with a tolerance level of PSM of 0.01). Kaplan-Meier curves were plotted for the unmatched and matched datasets (with propensity scores) and compared using the log-rank test. All analyses were conducted using STATA 16.1 I/C or Prism 9 for macOS [v. 9.4.1 (458)].

Propensity-score matched cohorts were generated using Statistical Package for Social Sciences (SPSS) v. 23. Statistical significance was set at a two-sided *p*-value of <0.05.

Ethical aspects

Retrospective retrieval of data for this study was approved by the Institutional Ethics Committee of Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow [document submission number 2021-165-IP-EXP-40, date of approval 16 July 2021] with a waiver of written informed consent given the retrospective chart review.

Results

Characteristics of the cohort

Of 191 TAK, 56 (29.3%) had disease onset in the paediatric age group (≤18 years) and 135 in adulthood. Both paediatric-onset and adult-onset TAK were more common in females. The follow-up duration was similar for both groups. While the delay to diagnosis was similar for both paediatric-onset and adult-onset TAK, paediatric-onset TAK appeared to have a longer duration from disease onset to cohort entry than adult-onset TAK (5.61±8.00 years *vs*. 3.79±4.58 years, *p*=0.05). Comorbid conditions or concomitant autoimmune diseases were more frequent in adult-onset than in paediatric-onset TAK, although the differences were not statistically significant (Table I). Similar DEI.TAK and ITAS2010 and similar proportions with active disease at baseline as per PGA were observed in both groups (Supplementary Fig. S1A-B).

Clinical presentation

Chest pain (OR 3.21), heart failure (OR 3.16), and headache (OR 2.60) were more often observed in paediatric-onset TAK (Table II). Acute-phase reactants were similar at baseline for paediatric-onset and adult-onset TAK (Suppl. Table S1).

Imaging modalities used for initial assessment and angiographic involvement at baseline

At the initial assessment, various angiographic imaging modalities had been used to a similar extent in paediatric-onset and adult-onset TAK. Overall, CT angiography was the most commonly used modality (Suppl. Table S2). Hata's type I was less common in paediatric-onset TAK (Table III). Among individual vessels, the ascending aorta and left renal artery were more commonly involved in paediatric-onset than in adult-onset TAK (Suppl. Table S3).

Medical treatments received

Glucocorticoids had been initiated in similar proportions of childhood-onset or adult-onset TAK, with similar duration of therapy and percentage reduction in glucocorticoid dose by the last visit (Suppl. Table S4). Methotrexate and tacrolimus were the most commonly prescribed first-line DMARD in both paediatric-onset and adult-onset TAK. Concerning second-line DMARD, methotrexate and mycophenolate had been used more commonly in paediatric-onset TAK, as opposed to mycophenolate and azathioprine in adult-onset TAK (Suppl. Table S5). The overall mean number of conventional DMARDs used was similar for paediatric-onset or adult-onset TAK. No significant differences were observed between usage and duration of treatment of paediatric-onset or adult-onset TAK with methotrexate, azathioprine, mycophenolate, or tacrolimus. Leflunomide and cyclophosphamide had only been used in adult-onset TAK. Biologic or targeted synthetic DMARDs had been used sparsely in our cohort (adalimumab - paediatric-onset TAK, n=1; tocilizumab - paediatric-onset TAK, n=1, adult-onset TAK, n=3; tofacitinib - adult-onset TAK, n=1). The use of anti-hypertensive drugs, aspirin, clopidogrel, or statins was similar between the two groups (Suppl. Table S4).

Endovascular or open surgical procedures

Sixteen procedures had been performed in paediatric-onset TAK in 14 patients (one procedure in 12, two procedures in 2). Thirty-two procedures had been performed in adult-onset TAK in 22 patients (one procedure in 16, two procedures in 3, three procedures in 2, and four procedures in 1). The proportion of patients undergoing procedures was similar for paediatric-onset and adult-onset TAK (OR paediatric-onset *vs*. adult-onset TAK 1.71, 95%CI 0.83 – 3.54, *p*= 0.161).

Major infections resulting in hospitalisation or death

Fifteen episodes of major infections were noted in paediatric-onset TAK in 12 patients (one episode in 9, two episodes in 3). Twenty-one episodes of major infections were noted in adult-onset TAK in 21 patients (one episode in 13, two episodes in 4). The proportion of patients developing major infections requiring hospitalisation or resulting in death was similar for paediatric-onset and adult-onset TAK (OR paediatric-onset *vs*. adult-onset TAK 1.89, 95%CI 0.80–4.08, *p*=0.121).

Disease activity on longitudinal follow-up

No significant differences were observed between paediatric-onset and adult-onset TAK for DEI.TAK, ITAS2010, or the number of items fulfilled on NIH disease activity scores at 6 months, 12 months, or 24 months of follow-up (Suppl. Fig. S1A). The proportions of patients with active TAK as per PGA also remained similar between the two groups at these time points (Suppl. Fig. S1B).

Survival analyses

Six deaths were observed in paediatric-onset TAK (sepsis, n=1; stroke, n=1; intractable heart failure, n=2; recurrent myocardial infarction, n=1; cause unclear – out-of-hospital death after neurological symptoms -possibly stroke, n=1) and four in adult-onset TAK (sepsis, n=1; recurrent stroke, n=1; intractable heart failure, n=1; chest pain followed by sudden death - suspected myocardial infarction or aortic dissection, n=1). Cardiac involvement or stroke were responsible for a majority of deaths (Table I). Paediatric-onset TAK had worse survival than adult-onset TAK on unadjusted analyses (log-rank test *p*-value =0.004; n=184 with at least one follow-up visit; 55 paediatric-onset TAK and 129 adult-onset TAK) (Fig. 1A). Paediatric-onset TAK had a greater risk of mortality than adult-onset TAK

Table II. Comparison of clinical features at presentation between adult-onset and paediatric-onset TAK.

Variable	Paediatric-onset TAK (n=56) [n (%)]	Adult-onset TAK (n=135) [n (%)]	Odds ratio (95% CI) (paediatric-onset *vs*. adult-onset TAK)	Adjusted odds ratio (95% CI) (paediatric-onset *vs*. adult-onset TAK)	*p*-value*
Constitutional (fever, fatigue, weight loss, arthralgia/arthritis taken together)	26 (46.43%)	55 (40.74%)	1.26 (0.67 – 2.36)	1.11 (0.53 – 2.29)	0.784
Carotidynia	8 (14.29%)	13 (9.63%)	1.56 (0.61 – 4.01)	2.00 (0.67 – 5.98)	0.214
Headache	12 (21.43%)	17 (12.59%)	1.89 (0.84 – 4.28)	**2.60 (1.01 – 6.74)**	**0.048**
Syncope/dizziness/vertigo (taken together)	8 (14.29%)	29 (21.48%)	0.61 (0.26 – 1.43)	0.55 (0.20 – 1.51)	0.245
TIA/stroke (taken together)	4 (7.14%)	27 (20%)	0.31 (0.10 – 0.93)	0.32 (0.09 – 1.18)	0.086
Seizure	5 (8.93%)	4 (2.96%)	3.21 (0.83 – 12.44)	3.98 (0.79 – 20.06)	0.094
Blurring vision	8 (14.29%)	16 (11.85%)	1.24 (0.50 – 3.09)	1.35 (0.44 – 4.14)	0.601
Loss of vision	4 (7.27%)	6 (4.44%)	1.69 (0.46 – 6.22)	4.01 (0.86 – 18.61)	0.076
Documented TAK retinopathy	2 (3.57%)	0 (0%)	-	-	0.085[b]
Inflammatory ocular disease	2 (3.57%)	0 (0%)	-	-	0.085[b]
Pulse or BP inequality	25 (44.64%)	62 (45.93%)	0.95 (0.51 – 1.78)	0.79 (0.37 – 1.70)	0.551
Pulse loss	35 (62.5%)	87 (64.44%)	0.92 (0.48 – 1.75)	0.98 (0.44 – 2.16)	0.954
Vascular bruits	40 (71.43%)	95 (70.37%)	1.06 (0.53 – 2.12)	0.69 (0.31 – 1.53)	0.362
Upper limb claudication	14 (25%)	41 (30.37%)	0.76 (0.38 – 1.55)	0.41 (0.17 – 1.05)	0.062
Lower limb claudication	16 (28.57%)	24 (17.78%)	1.85 (0.89 – 3.83)	2.01 (0.81 – 5.00)	0.135
Claudication (upper or lower limb)	23 (41.07%)	52 (38.52%)	1.11 (0.59 – 2.10)	-	0.742[a]
Hypertension	47 (83.93%)	106 (78.52%)	1.43 (0.63 – 3.26)	1.70 (0.64 – 4.51)	0.284
Aortic regurgitation	5 (8.93%)	6 (4.44%)	2.11 (0.62 – 7.21)	2.84 (0.71 – 11.31)	0.139
Renal failure (acute or chronic)	3 (5.36%)	13 (9.63%)	0.53 (0.15 – 1.94)	0.35 (0.08 – 1.47)	0.151
Abdominal angina	4 (7.14%)	3 (2.22%)	3.38 (0.73 – 15.65)	3.55 (0.60 – 20.91)	0.162
Bowel infarcts	0 (0%)	1 (0.74%)	-	-	>0.999[b]
Chest pain	9 (16.07%)	8 (5.93%)	3.03 (1.11 – 8.34)	**3.21 (1.06 – 9.74)**	**0.039**
Acute coronary syndrome	0 (0%)	0 (0%)	-	-	-
Heart failure	11 (19.64%)	11 (8.15%)	2.76 (1.12 – 6.80)	**3.16 (1.05 – 9.53)**	**0.041**
Erythema nodosum	2 (3.57%)	0 (0%)	-	-	0.085[b]

**p* value for adjusted odds ratio; Chi squared[a]/Fisher's exact[b] for categorical variables where odds ratios could not be calculated
BP: blood pressure; 95% CI: 95% confidence interval; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SD: standard deviation; TAK: Takayasu's arteritis; TIA: transient ischaemic attack; NA: not assessable.
p-values <0.05 are highlighted in bold.

Table III. Comparison of angiographic subtypes at presentation between adult-onset and paediatric-onset TAK.

	Paediatric-onset TAK (n=56) [n (%)]	Adult-onset TAK (n=135) [n (%)]	Odds ratio (95% CI) (paediatric-onset *vs*. adult-onset TAK)	djusted odds ratio (95% CI) A (paediatric-onset *vs*. adult-onset TAK)	*p*-value
Angiographic subtype	(n=56)	(n=135)			
Hata I	2 (3.57%)	23 (17.04%)	0.18 (0.04 – 0.79)	**0.16 (0.04 – 0.73)**	**0.017**
Hata IIa	3 (5.36%)	6 (4.44%)	1.22 (0.29 – 5.05)	0.93 (0.22 – 3.94)	0.923
Hata IIb	3 (5.36%)	17 (12.59%)	0.39 (0.11 – 1.40)	0.33 (0.09 – 1.22)	0.098
Hata III	2 (3.57%)	8 (5.93%)	0.59 (0.12 – 2.86)	0.47 (0.09 – 2.33)	0.355
Hata IV	7 (12.50%)	8 (5.93%)	2.27 (0.78 – 6.59)	1.63 (0.55 – 4.85)	0.380
Hata V	39 (69.64%)	73 (54.07%)	1.95 (1.00 – 3.78)	-[#]	-
Hata P+	3 (5.36%)	8 (5.93%)	0.90 (0.23 – 3.52)	0.93 (0.08 – 1.61)	0.954
Hata C+	1 (1.79%)	2 (1.48%)	1.21 (0.11 – 13.61)	0.91 (0.17 – 4.89)	0.917

[#]Hata V was omitted from the logistic regression model due to collinearity.
95% CI: 95% confidence interval; C+: coronary involvement; CT: computerised tomography; PET: positron emission tomography; MRI: magnetic resonance imaging; P+: pulmonary involvement.
p-values <0.05 are highlighted in bold.

(hazard ratio 6.13, 95%CI 1.51–24.91 on unadjusted analyses). After adjustment for prognostic variables determined *a priori*, the excess mortality rate with paediatric-onset TAK when compared with adult-onset TAK persisted (hazard ratio 4.97, 95%CI 1.20–20.58). Paediatric-onset TAK appeared to have a longer duration to cohort entry from diagnosis when compared with adult-onset TAK in our cohort, which could also have adversely affected the prognosis of paediatric-onset TAK. However, even after adjustment of Cox proportional hazards model for duration to cohort entry from diagnosis instead of delay to diagnosis, the increased risk of mortality with paediatric-onset TAK when compared with adult-onset TAK still remained significant (hazard ratio 5.40, 95%CI 1.29–22.53). Cox regression models adjusted for differences in presenting features along with vascular involvement (hazard ratio 5.54, 95%CI

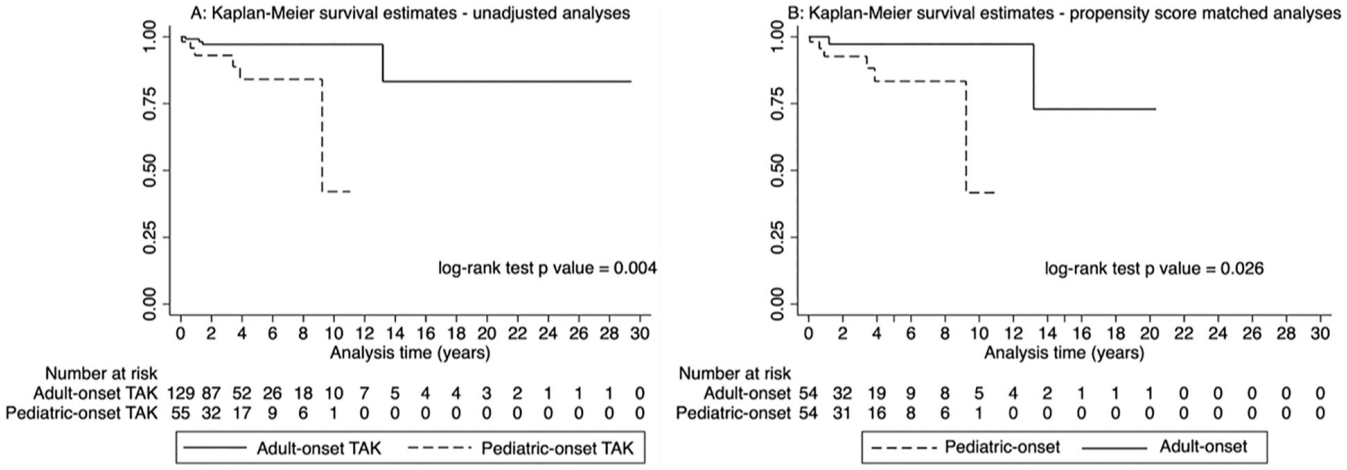

Fig. 1. Survival of patients with paediatric-onset and adult-onset TAK.
(**A**) Unadjusted analyses for the entire cohort (n=184). (**B**) Propensity scores matched analyses after matching for gender, delay to diagnosis, disease activity at baseline, number of conventional and biologic/ targeted synthetic disease-modifying anti-rheumatic drugs used during the period of observation (n=108, 54 each with paediatric-onset and adult-onset TAK). Comparisons were performed using log-rank test.

Table IV. Risk estimates for mortality with paediatric-onset TAK (vs adult-onset TAK).

Covariates adjusted for	Hazard ratio (95% confidence intervals)
Cox proportional hazards regression models based on prognostic variables chosen *a priori*	
None	6.13 (1.51 – 24.91)
Gender (male or female)	5.93 (1.46 – 24.08)
Gender (male or female), Delay to diagnosis	5.56 (1.36 – 22.67)
Gender (male or female), Delay to diagnosis, whether disease was active at baseline assessment or not	5.84 (1.45 – 23.50)
Gender (male or female), delay to diagnosis, whether disease was active at baseline assessment or not, number of conventional DMARDs used	5.70 (1.42 – 22.920
Gender (male or female), delay to diagnosis, whether disease was active at baseline assessment or not, number of conventional DMARDs used, number of biologic DMARDs used	4.97 (1.20 – 20.58)
Gender (male or female), delay from disease onset to cohort entry, whether disease was active at baseline assessment or not, number of conventional DMARDs used, number of biologic DMARDs used*	5.40 (1.29 – 22.53)
Cox proportional hazards regression models based on significantly different variables (clinical and vascular involvement/ angiographic subtype) between paediatric-onset and adult-onset TAK	
None	6.13 (1.51 – 24.91)
Headache	6.41 (1.57 – 26.06)
Headache, chest pain	6.19 (1.48 – 25.79)
Headache, chest pain, heart failure	5.43 (1.23 – 23.87)
Headache, chest pain, heart failure, ascending aorta	6.07 (1.39 – 26.62)
Headache, chest pain, heart failure, ascending aorta, left renal artery	5.54 (1.22- 25.09)
Headache, chest pain, heart failure, Hata's type I	5.34 (1.21 – 23.51)

For multivariable adjustment, Cox proportional hazards model was used. $p<0.05$ for all the hazard ratios.
*Since there was a difference in delay from disease onset to cohort entry between paediatric-onset and adult-onset TAK ($p=0.050$), the last model adjusted for delay from disease onset to cohort entry rather than delay to diagnosis. n=182 for all models.
DMARDs: disease-modifying anti-rheumatic drugs.

1.22–25.09) or Hata's angiographic subtype hazard ratio (5.34, 95%CI 1.21–23.51) also demonstrated excess mortality with paediatric-onset TAK (Table IV). The regression models were adequately powered (25).

Propensity-score matching was performed to balance *a priori* prognostic factors (gender, delay to diagnosis, disease activity at baseline, the number of conventional DMARDs and biologic/ targeted synthetic DMARDs used) between paediatric-onset and adult-onset TAK. With a tolerance of 0.01, 54 matched pairs of paediatric-onset and adult-onset TAK were identified. Even after matching, paediatric-onset TAK continued to have worse survival than adult-onset TAK (log-rank test *p*-value=0.026) (Fig. 1B).

Discussion

Chest pain, heart failure, and headache were more common at presentation in paediatric-onset TAK. Paediatric-onset TAK were more likely to have ascending aorta or left renal artery involvement, and less frequently had Hata's type I angiographic subtype. Patterns of DMARD and glucocorticoid use, disease activity at baseline and 6 months, 12 months, and 24 months of follow-up, proportions of patients undergoing procedures related to TAK, and proportions developing serious infections were similar for paediatric-

onset and adult-onset TAK. However, paediatric-onset TAK had a higher rate of mortality on unadjusted analyses, after adjustment for prognostic factors determined *a priori* or for differences in clinical features or angiography, as well as after propensity score matching for prognostic variables.

Akin to our observation of more frequent heart failure in paediatric-onset TAK, a previous study had also reported cardiomyopathy to be more common in paediatric-onset than in adult-onset TAK (10). A recent systematic review with meta-analysis reported a greater frequency of chest pain in paediatric-onset than in adult-onset TAK, similar to our observation. This systematic review reported more frequent hypertension in paediatric-onset than in adult-onset TAK on a meta-analysis of four studies from China, Europe, North America, and South America (8). However, in the present study, nearly 80% of patients had hypertension, without observed differences between paediatric-onset and adult-onset TAK. Hypertension has been reported more frequently (in 50-75% of patients) with TAK from Asia (10, 26, 27) than from Europe (21%) (23) or North America (38%) (28).

The recent meta-analysis reported a greater frequency of renal artery involvement in paediatric-onset TAK (similar to our findings) but not of ascending aorta involvement as we had observed. This meta-analysis reported that Hata's type I TAK (similar to our findings) was more frequent in adult-onset TAK and Hata's Type IV in paediatric-onset TAK (unlike our study) (8). CT angiography was the most commonly used imaging modality in our cohort for both paediatric-onset and adult-onset TAK. MR angiography has been recommended by the EULAR as the imaging modality of choice in TAK (29). However, pragmatic considerations related to access to this modality due to long procedure times for imaging the entire aortic tree coupled with prolonged waiting times limit the wider utilisation of MR angiography for vascular imaging in TAK in our setting. The use of CT angiography in some patients and MR angiography in others might have differently assessed the extent of disease, as MR angiography tends to overestimate stenotic lesions, particularly moderately stenotic lesions (30). However, the proportions of patients with paediatric-onset or adult-onset TAK who had undergone CT angiography or MR angiography were not significantly different in our cohort. PET-CT is emerging as a useful modality for imaging *in vivo* metabolic activity in large vessels in TAK (31). PET-CT in TAK identifies a subset of active vasculitis where traditional inflammatory markers like CRP might be normal (32). The data from our cohort revealed the use of PET-CT for disease activity assessment in about a third of our patients.

Most patients in our cohort (both paediatric-onset and adult-onset TAK) who had active disease at presentation had been treated with corticosteroids along with conventional DMARDs. Methotrexate, tacrolimus, mycophenolate, and azathioprine were the most frequently used DMARDs, used in similar proportions of paediatric-onset and adult-onset TAK. Heterogeneity in the choice of DMARDs relates to the poor evidence base for the management of TAK (33, 34). No drugs used in TAK have met the primary end-point in high-quality randomised controlled trials (34-36). There is also a lack of treatment recommendations for TAK from regional or national societies relevant to our setting (37, 38). A meta-analysis of previous studies comparing paediatric-onset and adult-onset TAK reported more frequent use of biologic DMARDs and cyclophosphamide in paediatric-onset than in adult-onset TAK (8). In our cohort, only four with adult-onset TAK (none with paediatric-onset TAK) had been treated with cyclophosphamide. Infrequent use of cyclophosphamide in our cohort relates to its limited effectiveness in TAK as opposed to other forms of vasculitis (34, 39). Despite evidence from observational studies to support the use of biologic DMARDs such as anti-tumour necrosis factor alpha agents and tocilizumab (34, 40), and emerging data to support the use of targeted synthetic DMARDs like tofacitinib in TAK (41), these drugs were used sparingly in our cohort. Cost constraints limit access to treatments such as biologic or targeted synthetic DMARDs in our setting.

The recent systematic review (8) reported a similar risk of dying with paediatric-onset or adult-onset TAK based on data from four studies (9, 11, 13, 14). However, mortality events (which were few – six in paediatric-onset TAK and fifteen in adult-onset TAK) but not the time duration of follow-up were considered for these analyses (8). Also, none of these cohorts of paediatric-onset or adult-onset TAK were matched for covariates that might affect the outcome (8). In our study, despite similar disease activity at baseline and on follow-up, similar proportions of patients undergoing vascular procedures related to TAK, and a similar number of serious infections, paediatric-onset TAK had worse survival than adult-onset TAK on unadjusted as well as adjusted analyses. A delay in diagnosis is associated with a worse prognosis in other inflammatory rheumatic diseases (22). Previous studies have shown a greater standardised mortality ratio in females with TAK than in males (23). Higher disease activity at baseline was associated with a greater risk of dying in TAK (24). Persistently active disease also associates with a worse prognosis in TAK (23, 24). Therefore, we pre-selected gender, delay to diagnosis, baseline disease activity, and the number of conventional or biologic/targeted synthetic DMARDs used on follow-up (as a surrogate for higher disease activity) as prognostic factors for adjustment in Cox regression analyses as well as on propensity score-matched analyses while assessing the risk of mortality with paediatric-onset *vs*. adult onset-TAK. Propensity score matching helps to reduce confounding in observational studies (42). However, recent literature has highlighted the limitations of propensity score matching (43). Therefore, we separately conducted Cox proportional hazards regression to adjust for the effects of the same confounding variables used in propensity score matching. We also undertook Cox regression to adjust for duration to cohort entry from diagnosis instead of delay

to diagnosis, differences in presenting features or angiographic involvement between paediatric-onset and adult-onset TAK. All the approaches used consistently revealed a higher risk of mortality in paediatric-onset than in adult-onset TAK. This leads us to hypothesise that factors intrinsic to paediatric-onset TAK possibly confer a worse prognosis than in adult-onset TAK.

The retrospective cohort design was a limitation of our study. However, the patients enrolled in the present cohort were following up at a dedicated tertiary-care referral and training centre for Rheumatology in a vasculitis clinic with uniform data collection proformas. The patients with paediatric-onset or adult-onset TAK were managed by the same Rheumatologists. Most patients had follow-up visits (whether in-person or telephonic) for survival analysis despite the interruptions in care due to the Coronavirus disease 19 pandemic. Missing data was minimal (less than 5%) for most items. Most of the studies comparing paediatric-onset with adult-onset TAK are retrospective cohort studies (9-13, 15), possibly related to the rarity of TAK. The retrospective nature of data retrieval did not permit the assessment of angiographic evolution or patient-reported outcomes (44), and their comparison between paediatric-onset and adult-onset TAK. We did not analyse the accrual of damage in our cohort, because different versions of the Vasculitis Damage Index are used in children (45) and adults(46), and these are not directly comparable. The lack of a published and validated damage index to assess the accrued damage in TAK is a lacuna that requires to be addressed in future studies of TAK (47, 48). Although we matched the patients with paediatric-onset and adult-onset TAK through propensity scores generated for important prognostic factors, the effect of unmeasured confounding cannot be excluded (49). Despite being a single-centre study, our analysis included a large number of patients with a rare large-vessel vasculitis. We were able to asses mortality rates rather than simply the risk of mortality which most studies comparing paediatric-onset and adult-onset TAK have done till now. A greater mortality rate in paediatric-onset TAK when compared with adult-onset TAK on unadjusted as well as adjusted analyses, confirmed even after matching patients with paediatric-onset and adult-onset TAK based on propensity scores lends greater credence to the observation of poorer survival in paediatric-onset TAK.

Conclusion

Paediatric-onset TAK was associated with a greater risk of dying when compared with adult-onset TAK in our cohort, even after multivariable-adjusted analyses. Clinicians should be more vigilant while managing paediatric-onset TAK because of the observed excess mortality associated with this subtype of TAK.

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