

Natural history of cow's milk allergy: a prospective study in children aged 6 to 12 years

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July 27, 2023

Abstract

Background: Approximately 50–90% of children with immediate-type cow's milk allergy (CMA) acquire tolerance by pre-school age. We aimed to investigate the tolerance acquisition rate of CMA in children aged 6–12 years. **Methods:** Children with CMA that persisted until 6 years of age were included. Tolerance acquisition was defined as either passing an oral food challenge with 200 mL of unheated cow's milk (CM) or consuming CM of any quantity without symptoms. Persistent CMA was defined as fulfilling neither of these criteria by 12 years of age. Children undergoing oral immunotherapy were defined as having persistent CMA. Risk factors associated with persistent CMA were assessed using Cox regression analysis. **Results:** Of the 123 children analyzed, 60 (49%) had previous CM anaphylaxis, 82 (67%) eliminated CM from their diet, and the median CM-specific immunoglobulin E (sIgE) level was 23.3 kU_A/L at 6 years of age. Twenty-five children (20%) acquired tolerance by 9 years of age, and 46 (37%) by age 12. At baseline, higher CM-sIgE levels (hazard ratio: 2.58 [95% confidence interval: 1.62–4.12], optimal cutoff level: 34.4 kU_A/L), previous CM anaphylaxis (2.42 [1.24–4.69]), and complete CM elimination (5.18 [2.45–10.99]) were associated with persistent CMA. None of the children with CMA who had all three risk factors (n = 26) acquired tolerance. **Conclusion:** At least one-third of the children with CMA at 6 years of age acquired tolerance by 12 years of age. Children with CMA who have the risk factors are less likely to acquire tolerance.

Introduction

Cow's milk allergy (CMA) is one of the most common food allergies in infants, with a global prevalence of 2–3%.^{1–6} In Japan, cow's milk (CM) is the second major food allergen, with a proportion of 21.8% of causative foods.⁷

Previous studies have reported that approximately 50–90% of children with CMA acquire tolerance by pre-school age.^{8–10} Regarding the natural history of CMA beyond school age, a CMA resolution rate of 97% by the age of 15 years was reported in a birth-cohort study from Denmark.¹¹ A longitudinal study in the USA reported that the CMA resolution rate was 42%, 64%, and 79% by 8, 12, and 16 years of age, respectively.⁹ However, these studies started follow-up in infancy, and there are no studies on the natural history of CMA that persist beyond school age.

Higher levels of CM-specific immunoglobulin E (sIgE), larger wheal sizes in skin prick tests, the presence of anaphylaxis, more severe atopic dermatitis, and coexisting bronchial asthma and allergic rhinitis have been reported as risk factors for the persistence of CMA in infants.^{8–10, 12–14} However, these factors were based on the results of studies in which follow-up started in infancy; thus, the risk factors associated with CMA that persists beyond school age are unknown.

Therefore, we aimed to investigate the tolerance acquisition rate in children with CMA persisting from the age of 6 years until the age of 12 years, as well as the factors affecting its persistence.

Methods

Study design and subjects

This is a single-center prospective review of the clinical records of patients registered in the iAnet database (UMIN000013561), designed with the cooperation of Hitachi Solutions Create.¹⁶

Participants who were born between January 2002 and December 2005, and first visited National Hospital Organization, Sagamihara National Hospital before the age of 6 years with IgE-mediated CMA were included. Patients who tolerated CM or underwent CM-OIT before the age of 6 years, who refused to participate in this study, or who had missing clinical information were excluded. All participants had confirmed sensitization to CM with CM-sIgE levels $> 0.35 \text{ kU}_A/\text{L}$ using ImmunoCAPTM (Thermo Fisher Scientific/Phadia, Uppsala, Sweden).

Definitions

IgE-mediated CMA was diagnosed by either sensitization to CM and a history of a convincing immediate-type allergic reaction to CM or failure in a CM oral food challenge (OFC). Tolerance acquisition was defined as either passing an OFC of consuming 200 mL of unheated CM or CM of any quantity without allergic symptoms. Persistent CMA was defined as fulfilling neither of these criteria by the age of 12 years. Partial elimination was defined as being able to consume $< 200 \text{ mL}$ of CM without allergic symptoms. Children with CMA who were enrolled in CM oral immunotherapy (OIT) after 6 years of age were defined as having persistent CMA.

Follow-up

Children with CMA were annually assessed using CM-sIgE and CM OFC. According to the Japanese guidelines for food allergies, we performed stepwise OFC.^{7, 16} When a child passed an OFC, we instructed them to consume the amount of CM that was confirmed by the OFC to be tolerated. Children with complete CM elimination were usually requested to undergo OFCs. Children who were lost to follow-up between the ages of 6 and 12 years were considered dropouts.

Detailed methods and eligibility criteria for enrollment in OIT at our institution are described in the Supplementary information.

Outcomes

The primary outcome was the rate of CM tolerance acquisition by 12 years of age when we defined children who enrolled in OIT after the age of 6 years as having persistent CMA. Secondary outcomes were the risk factors associated with persistent CMA among the children's characteristics at the age of 6 years, as well as immunological changes between 6 and 12 years of age. We also calculated the optimal cutoff values for laboratory parameters associated with persistent CMA. In sub-analysis, we estimated the rate of CM tolerance acquisition by either defining children who enrolled in OIT after the age of 6 years as dropouts or by factoring in the OIT results.

Statistical analysis

Values are presented as the median (interquartile range [IQR]). To analyze the differences between the two groups, we used either the Mann–Whitney U test or Fisher's exact test (both two-tailed). Kaplan–Meier survival curves were generated to depict the acquisition rate of CMA tolerance. Hazard ratios (HRs) and 95% confidence intervals (CIs), comparing children with factors affecting persistent CMA, were determined based on a Cox proportional hazards model. We considered the number of children to be sufficient to confirm the occurrence of 10 or more tolerant events per explanatory variable.¹⁷ All statistical analyses were performed using SPSS (version 25.0; IBM Corp., Armonk, USA) and GraphPad Prism version 8.0.2 (www.graphpad.com). A p -value of 0.05 was considered significant. Specific IgE values to CM and casein $< 0.35 \text{ kU}_A/\text{L}$ were considered as $0.15 \text{ kU}_A/\text{L}$, and those $> 100 \text{ kU}_A/\text{L}$ were considered as $101 \text{ kU}_A/\text{L}$.

Ethical considerations

This study was approved by the Institutional Review Board of the National Hospital Organization Sagami-hara National Hospital (approval number: 2014031817). Written informed consent was obtained from the legal guardians of all participants in accordance with the Declaration of Helsinki.

Results

Patient enrollment

We enrolled 145 children who fulfilled the eligibility criteria. Children who were lost to follow-up between the ages of 6 and 12 years ($n = 22$) were also excluded; therefore, the 123 remaining children were analyzed in this study (Figure 1).

Of the 123 children, 82 (67%) were male, 60 (49%) had previous anaphylaxis due to CM, 82 (67%) had eliminated CM completely, and the median CM-, and casein-sIgE values were 23.3 (7.0-66.4) kU_A/L and 26.9 (5.8-72.0) kU_A/L , respectively (Table 1).

The estimated rates of tolerance acquisition of CMA in children

Twenty-five children (20%) acquired tolerance by 9 years of age, and 46 children (37%) by 12 years of age. Of the 77 remaining children (63%) who were considered to have persistent CMA, 20 (16%) had partially eliminated CM at the age of 12 years, 14 (11%) had completely eliminated CM at this age, and 34 (28%) were enrolled in CM OIT by the age of 12 years (Figure 2).

When we designated children who underwent OIT between the ages of 6 and 12 years as dropouts, the estimated rate of tolerance acquisition by the age of 12 years was 58%. When we defined tolerance acquisition as achieving short-term unresponsiveness to 200 mL of unheated CM for children who underwent OIT after the age of 6 years, the estimated rate of tolerance acquisition by the age of 12 years was 50% (Supplementary figure 1).

Risk factors for persistent CMA

In a comparison of baseline characteristics between the tolerant and persistent groups, statistically significant differences were observed for the presence of coexisting atopic dermatitis, anaphylaxis to CM before the age of 6 years, complete elimination of CM at the age of 6 years, and sIgE to CM and casein (Table 2). In both groups, the CM-sIgE level was the highest at ages 6–7 years and then decreased annually, except for ages 8 and 9 years in the tolerant group (Supplementary figure 2). At all ages between 6 and 12 years, the CM-sIgE levels were significantly higher in the persistent group than in the tolerant group.

The results of the Cox hazard model analysis are presented in Table 3. Using the significant risk factors identified by univariate analysis, the multivariate Cox regression analysis showed that previous anaphylaxis to CM (adjusted HR [95% CI]: 2.42 [1.24–4.69], $p = 0.01$), complete CM elimination at the age of 6 years (adjusted HR [95% CI]: 5.18 [2.45–10.99], $p < 0.001$), and higher CM-sIgE levels at the age of 6 years (adjusted HR [95% CI]: 2.58 per ten-fold increase [1.62–4.12], $p < 0.001$) were independent risk factors for persistent CMA.

The area under the curve for CM-sIgE levels was 0.83 (95% CI: 0.76–0.90), and the optimal cutoff level of CM-sIgE was 34.4 kU_A/L . Using this cutoff value, the sensitivity and specificity were 60% and 91%, respectively.

Although there was no statistical significance, these baseline characteristics tended to be higher in the persistent group with enrollment in OIT than in the persistent group without enrollment in OIT (Supplementary table 1).

Kaplan–Meier curves grouped by risk factors

Four of 50 children (8%) with a CM-sIgE level $\geq 34.4 \text{ kU}_A/\text{L}$ and 42 of 73 children (58%) with a CM-sIgE level $< 34.4 \text{ kU}_A/\text{L}$ acquired tolerance (Figure 3A). Twelve of 81 children (15%) with and 34 of 42 children

(81%) without complete CM elimination acquired tolerance (Figure 3B). Twelve of 59 children (20%) with and 34 of 64 children (53%) without previous anaphylaxis to CM acquired tolerance (Figure 3C).

Figure 3D shows the estimated rates of tolerance acquisition grouped by combining the two factors, CM complete elimination and previous anaphylaxis.

In the absence of the three risk factors, 23 of 26 children (88%) acquired tolerance, whereas in their presence, none of the children with CMA ($n = 26$) acquired tolerance (Supplementary figure 3).

Discussion

In this study, we investigated the natural history of IgE-mediated immediate-type CMA in children aged 6–12 years. Forty-six of the 123 (37%) children with persisting CMA until the age of 6 years acquired CM tolerance by the age of 12 years. Furthermore, we demonstrated that higher CM-sIgE levels, previous anaphylaxis to CM, and complete CM elimination from the diet were independent risk factors for persistent CMA.

It has been reported that most children with CMA acquire tolerance during the pre-school age.^{1, 8-12, 18-20} Half of Korean children with CMA develop tolerance by the age of 8.7 years.¹⁹ A Danish birth-cohort study showed that the tolerance acquisition rates in children with CMA, including non-IgE-mediated CMA, were 92% and 97% at 5 and 15 years of age, respectively.²⁰ However, all of these studies initiated follow-up in infancy, making it difficult to clarify the tolerance acquisition rate in children with CMA persisting beyond school age. Few studies on the natural history of CMA have focused on children beyond school age. Our data demonstrated that the tolerance acquisition rate in children with CMA between the ages of 6 and 12 years was 37%. This rate is obviously higher than that for peanut allergy; however, it seems to be lower than that for hen's egg allergy (HEA).^{21, 22} A previous study reported that the rate of tolerance acquisition for peanut allergy in children aged 4–20 years was 21.5%.²¹ Our institution reported a rate of tolerance acquisition for HEA of 60.5%.²² However, children with OIT were defined as dropouts in this previous study; therefore, their rate may be overestimated. When we defined children with OIT as dropouts, the tolerance acquisition rate was 58% (Supplementary figure 1), which was similar to the results of the previous HEA study.²² When we defined tolerance acquisition as achieving short-term unresponsiveness to 200 mL of unheated CM for children who underwent OIT after the age of 6 years, the tolerance acquisition rate was 50% (Supplementary figure 1); this is lower than the rate of 65.2% reported in the HEA study.²² This difference would result from the poor outcome of OIT to CMA compared to HEA.²² These findings indicate that the “real” tolerance acquisition rate in children aged 6–12 years with CMA might be between 37% and 50%. In many previous studies, CMA persistence was not confirmed in annual OFCs.^{8, 11, 12, 19} In our institution, children usually undergo blood tests and OFCs annually, providing a more accurate assessment of CMA tolerance.

In the present study, 88% of patients with CMA in the absence of the identified risk factors (higher CM-sIgE levels, previous anaphylaxis to CM, and complete CM elimination) acquired tolerance by the age of 12 years; therefore, these children should be proactively assessed by OFCs for their tolerance acquisition. In contrast, none of the children with CMA presenting all three risk factors acquired tolerance by the age of 12 years (Supplementary figure 3); therefore, these children should be considered for OIT. Previous anaphylaxis and higher CM-sIgE levels were common risk factors identified in the present and previous studies, and both factors contributed to difficulties in acquiring tolerance (Figure 3A and 3C). This is the first report showing that complete CM elimination from the diet is associated with CMA persistence. The immunomodulatory effects of consuming baked milk proteins may accelerate the progression to tolerance of non-baked milk.²³ In addition, continuous consumption of small amounts of heated milk has been suggested to increase the safely ingestible amount of CM.²⁴ These results suggest that continuous small-dose intakes of CM may induce immunological benefits for acquiring CM tolerance.

In the present study, CM-sIgE levels in the persistent group were significantly higher than those in the tolerant group at all ages from 6–12 years. Interestingly, CM-sIgE levels decreased annually, not only in the tolerant group, but also in the persistent group. In previous studies on the natural history of CMA, the CM-sIgE level in children with persistent allergy was reported to increase over the first 3–4 years of life,

followed by a plateau, and then a gradual decrease until the age of 18 years.^{9, 10} These findings indicate that decreasing CM-sIgE levels during school age may not be associated with CM tolerance acquisition.

This study has some limitations. First, we defined children undergoing OIT as having persistent CMA, not as dropouts. In children who received OIT, 95% of the children eliminated CM completely, two-thirds had previous anaphylaxis, and the median CM-sIgE level was 58.5 kU_A/L at the age of 6; these characteristics were higher than those in the persistent group who did not receive OIT (Supplementary table 1). Since children with OIT should have difficulty acquiring tolerance, we considered that children with OIT should be defined as having persistent CMA rather than as dropouts. Second, this study had a single-center design. Our facility is a tertiary center for food allergies, and children with food allergies tend to be more severely affected than the general population, which may have influenced the study outcomes.

In conclusion, at least one-third of patients who still had IgE-mediated CMA at the age of 6 years acquired tolerance by the age of 12 years. We demonstrated that children with CMA whose CM-sIgE levels were higher than the optimal cutoff value, who previously had anaphylaxis to CM, and who eliminated CM from their diet at the age of 6 years have difficulty acquiring tolerance by the age of 12 years. This study provides important insights into the natural history of CMA persisting into school age and identifies risk factors associated with persistent CMA.

Acknowledgements

We thank the pediatricians and nurses who were involved in the medical care at Sagami-hara National Hospital. We would like to thank Editage (www.editage.com) for assistance with English language editing.

Key messages

At least one-third of the children who had immediate-type cow's milk allergy at the age of 6 years tolerated cow's milk by the age of 12 years. At 6 years of age, children with cow's milk allergy and higher cow's milk-specific immunoglobulin E, previous cow's milk anaphylaxis, and complete cow's milk elimination were less likely to tolerate cow's milk by the age of 12 years.

Author Contributions

KK: Conceptualization, data curation, formal analysis, investigation, and writing. NY: Conceptualization and supervision. YE: Conceptualization and supervision. SS: Conceptualization and supervision. ME: Conceptualization and supervision. KN: Conceptualization and supervision.

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Table 1. Patient characteristics at the age of 6 years

	n = 123
Male, n (%)	82 (67%)
Term delivery, n (%)	113 (97%)*
Breast-fed, n (%)	95 (79%)+
Age at the first visit to our hospital (years)	2.3 (0.9–4.1)
Atopic dermatitis, n (%)	96 (78%)
Bronchial asthma, n (%)	75 (61%)
Allergic rhinitis, n (%)	51 (41%)
Previous anaphylaxis to CM, n (%)	60 (49%)
Complete CM elimination, n (%)	82 (67%)
Number of food allergens, n	2 (2–4)
Total IgE (IU/mL)	1165 (661–1985)
CM-specific IgE (kU _A /L)	23.3 (7.0–66.4)
Casein-specific IgE (kU _A /L)	26.9 (5.8–72.0)++

CM, cow's milk. * Missing values: 7. + Missing values: 3. ++ Missing values: 22.

Table 2. Comparison of patient characteristics at the age of 6 years between the tolerant group and the persistent group

	Tolerant group (n = 46)	Persistent group (n = 77)	p value *
Male, n (%)	35 (76%)	46 (60%)	0.08
Term delivery, n (%)	41 (98%) ⁺	71 (96%) ⁺⁺	> 0.99
Breast-fed, n (%)	34 (77%) [§]	60 (79%) [#]	0.82
Age at the first visit to our hospital (years)	2.2 (0.8–4.3)	2.3 (1.0–4.1)	0.78
Atopic dermatitis, n (%)	41 (89%)	54 (70%)	0.02
Bronchial asthma, n (%)	26 (57%)	48 (62%)	0.57
Allergic rhinitis, n (%)	21 (46%)	29 (38%)	0.45
Previous CM anaphylaxis, n (%)	12 (26%)	47 (61%)	< 0.001
Complete CM elimination, n (%)	12 (26%)	69 (90%)	< 0.001
Number of eliminated foods, n	2.0 (2.0–3.0)	3.0 (2.0–4.0)	0.01
Total IgE (IU/mL)	1105 (734–2335)	1285 (617–1960)	0.59
CM-specific IgE (kU _A /L)	6.1 (2.3–17.7)	48.4 (13.1–94.5)	< 0.001
Casein-specific IgE (kU _A /L)	5.2 (1.4–22.1) ^{**}	50.9 (21.8–99.0) ⁺⁺	< 0.001

CM, cow's milk. * Mann-Whitney U test and Fisher's exact test (both two-tailed) were used to compare continuous and categorical data, respectively, between groups. +Missing values: 4. ++ Missing values: 3. § Missing values: 2. # Missing values: 1. ** Missing values: 9. ++Missing values: 13.

Table 3. Analysis of risk factors at the age of 6 years for persistent cow's milk allergy

	Crude HR ⁺ (95% CI)	p value	Adjusted HR ⁺⁺ (95% CI)	p value
Male, sex	1.86 (0.94–3.66)	0.07		
Term delivery	0.60 (0.08–4.37)	0.62		
Breast-fed	1.04 (0.51–2.10)	0.92		
Age at the first visit to our hospital	1.04 (0.88–1.22)	0.67		
Atopic dermatitis	0.35 (0.14–0.89)	0.03	0.55 (0.21–1.42)	0.22
Bronchial asthma	1.30 (0.73–2.33)	0.77		
Allergic rhinitis	0.78 (0.43–1.39)	0.39		
Previous CM anaphylaxis	3.22 (1.66–6.21)	< 0.001	2.42 (1.24–4.69)	0.01
Complete CM elimination	11.24 (5.71–21.74)	< 0.001	5.18 (2.45–10.99)	< 0.001
Number of eliminated foods	1.20 (1.00–1.43)	0.052		

	Crude HR ⁺ (95% CI)	<i>p</i> value	Adjusted HR ⁺⁺ (95% CI)	<i>p</i> value
Total IgE (IU/mL)	0.65 (3.11–1.38) [§]	0.27		
CM-specific IgE (kU _A /L)	4.52 (3.02–6.76) [§]	< 0.001	2.58 (1.62–4.12) [§]	< 0.001

CM, cow's milk; HR, hazard ratio; CI, confidence interval. Using Pearson's correlation analysis, the correlation coefficient between casein- and CM-sIgE levels exceeded 0.99; therefore, the casein-sIgE level was excluded from the Cox regression analysis. ⁺Univariate Cox regression analysis. ⁺⁺ Multivariate Cox regression analysis; adjusted for the significant items in the univariate analysis. [§] Hazard ratio per ten-fold increase in total IgE or cow's milk-specific IgE.

Figure legends

Figure 1. Flow chart of study participant selection.

CMA, cow's milk allergy; CM-OIT, cow's milk oral immunotherapy

Figure 2. Kaplan–Meier analysis of the tolerance acquisition rate in children aged 6–12 years with CMA. Patients enrolled in oral immunotherapy after the age of 6 years were considered as having continued elimination of cow's milk.

CMA, cow's milk allergy

Figure 3. Kaplan–Meier curves showing CMA tolerance from ages 6–12 years. (A) Grouped by the optimal cutoff value of CM-sIgE levels, as determined by the receiver operating characteristic curve. (B) Grouped by complete elimination of CM by the age of 6 years. (C) Grouped by anaphylaxis to CM prior to the age of 6 years. (D) Grouped by combinations of the two factors, complete CM elimination from the diet and previous anaphylaxis to CM at the age of 6 years. Two of 45 children (4%) with complete CM elimination and previous anaphylaxis, 10 of 36 children (28%) with complete CM elimination but without previous anaphylaxis, 10 of 14 children (71%) with partial CM elimination and previous anaphylaxis, and 24 of 28 children (86%) with partial CM elimination but without previous anaphylaxis acquired tolerance (A-D) Groups are significantly different ($p < 0.001$, log-rank test).

CM, cow's milk; CM-sIgE, CM-specific immunoglobulin E; CMA, CM allergy

Figure 1

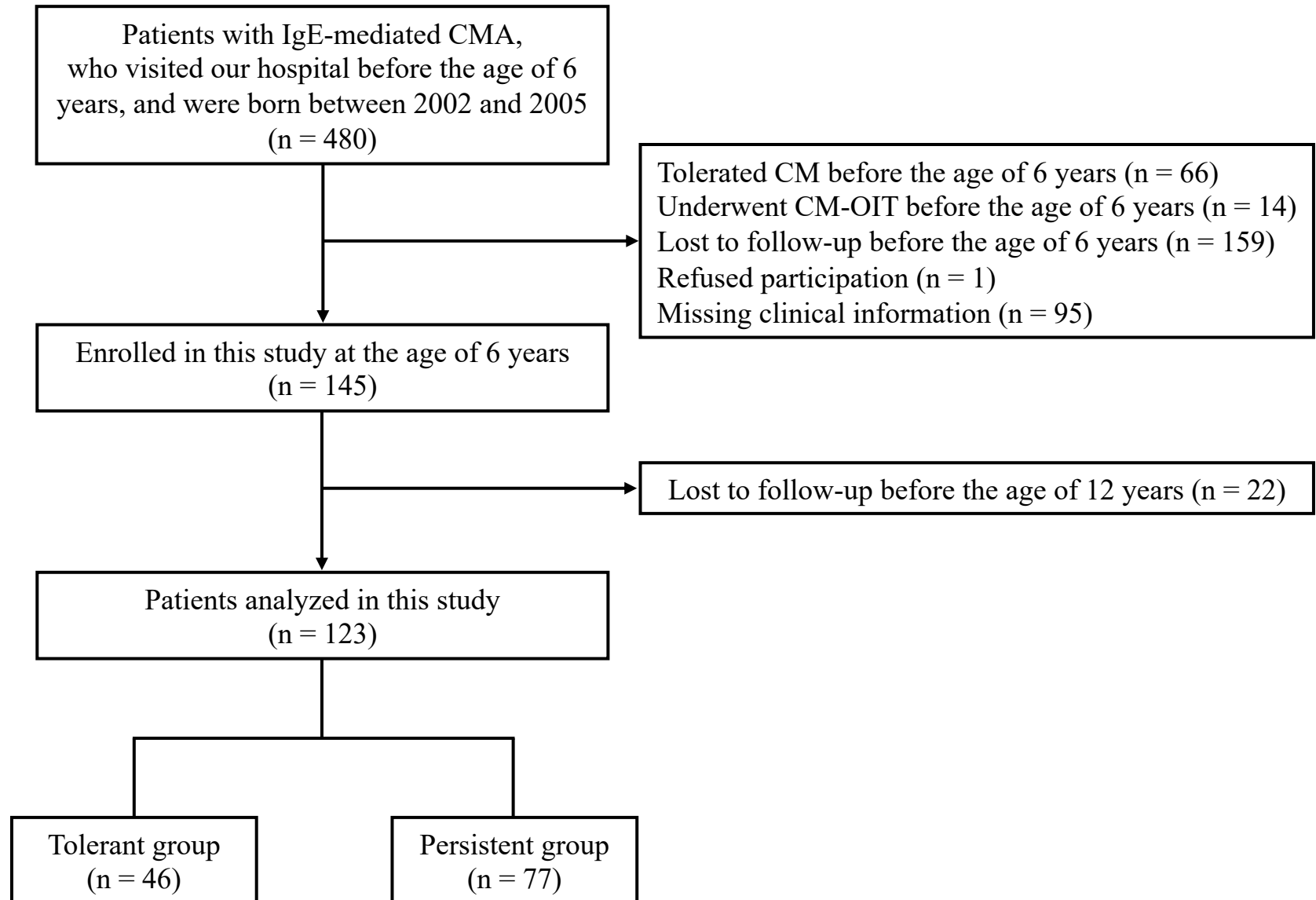


Figure 2

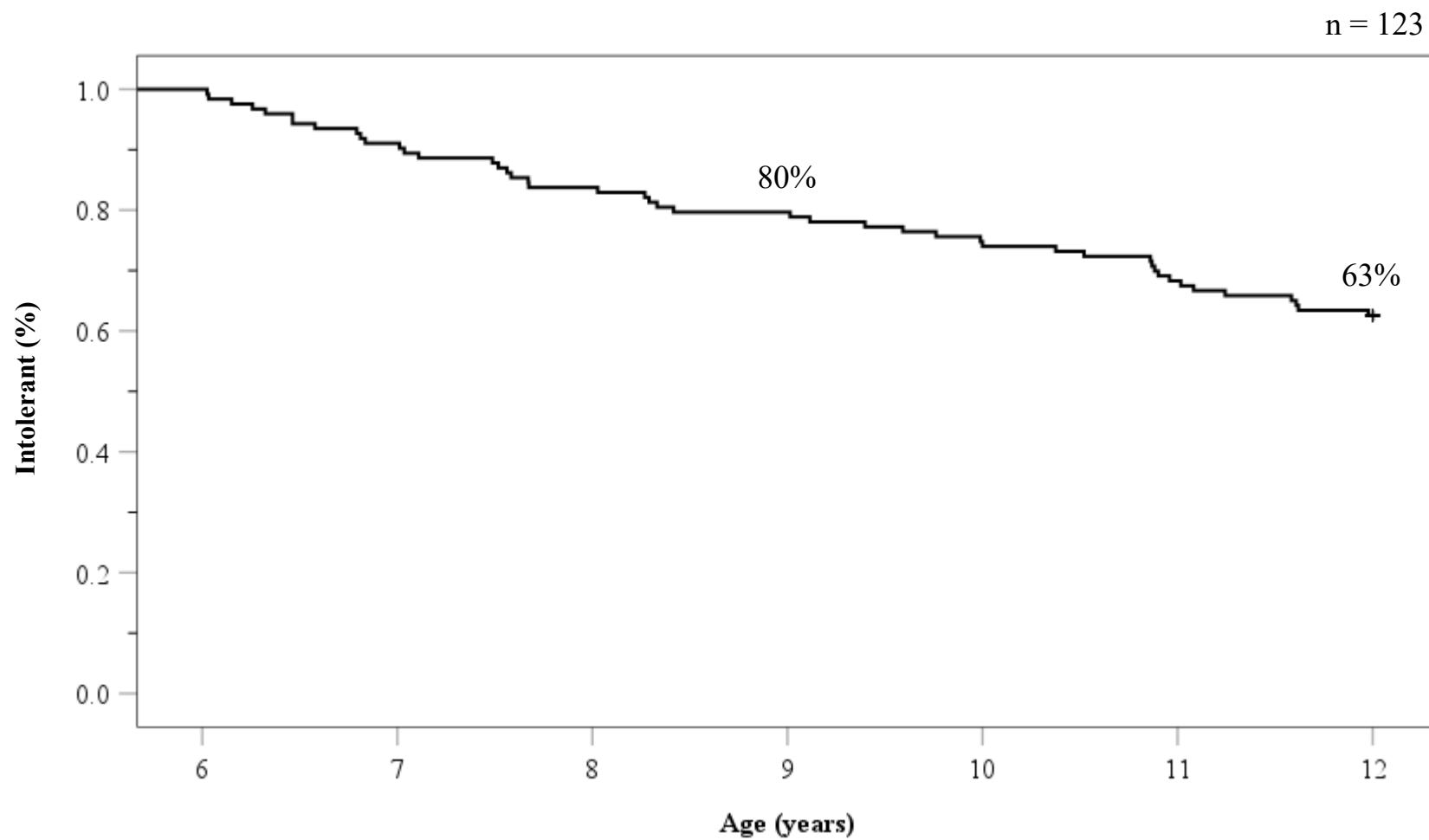
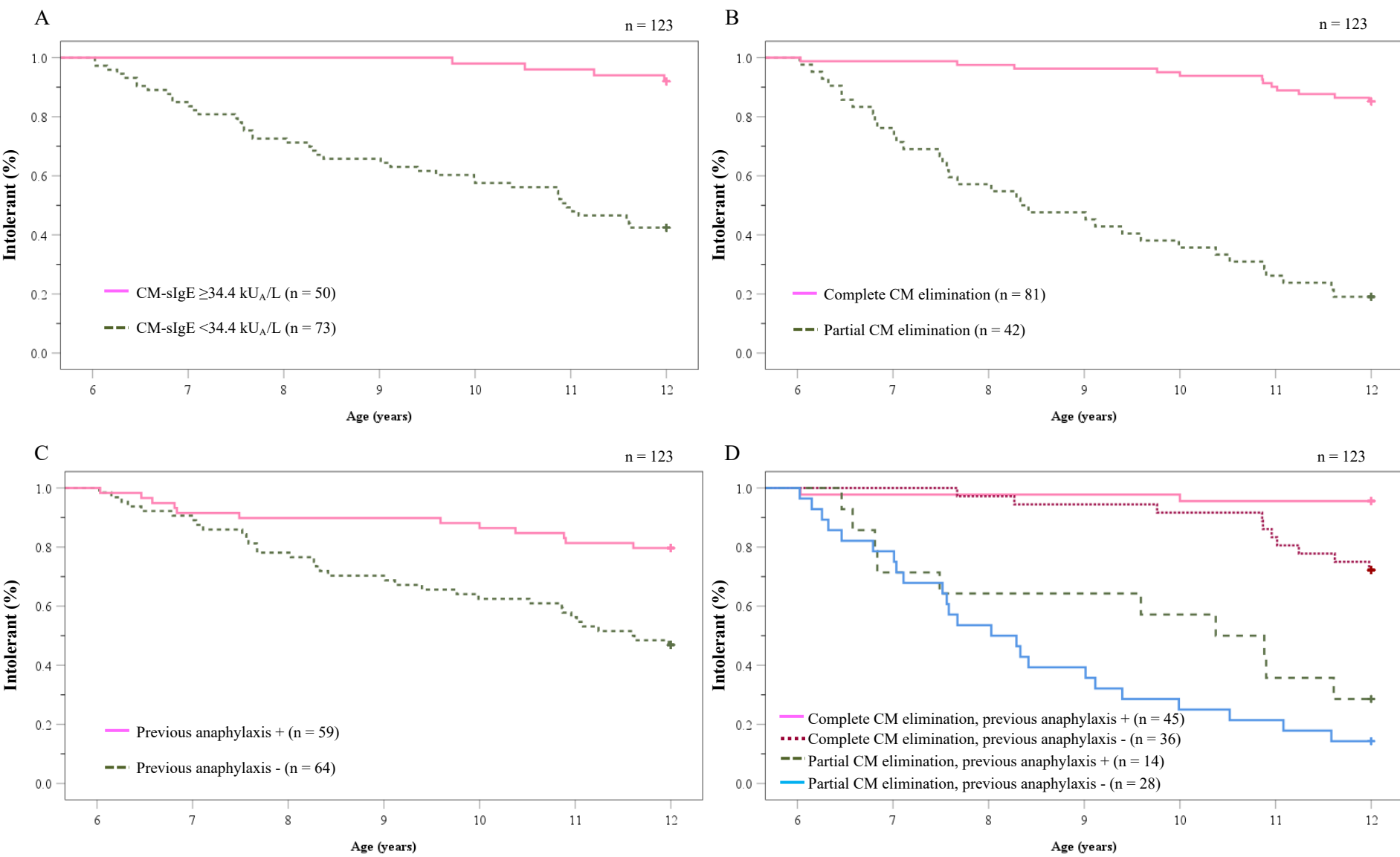
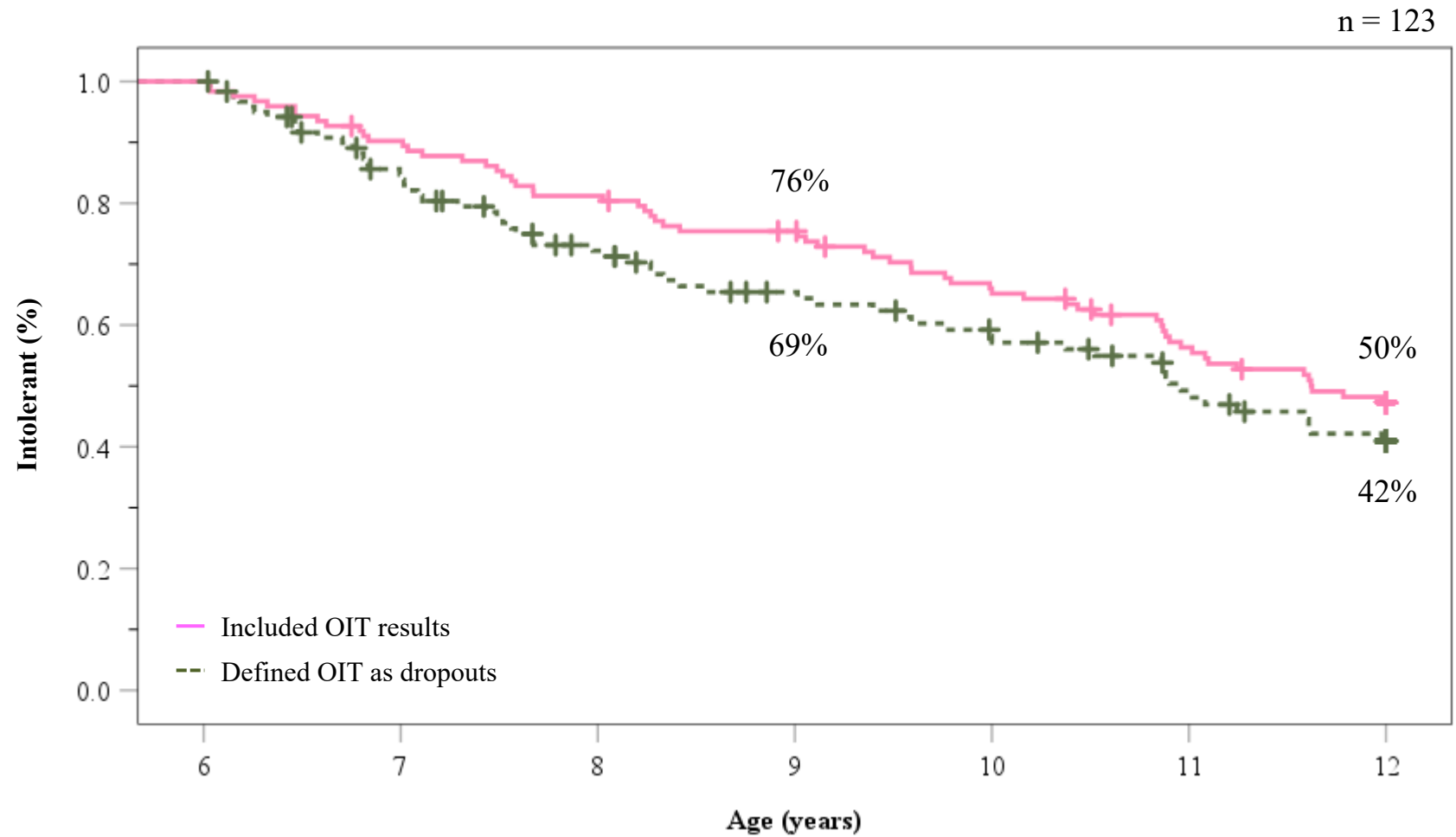


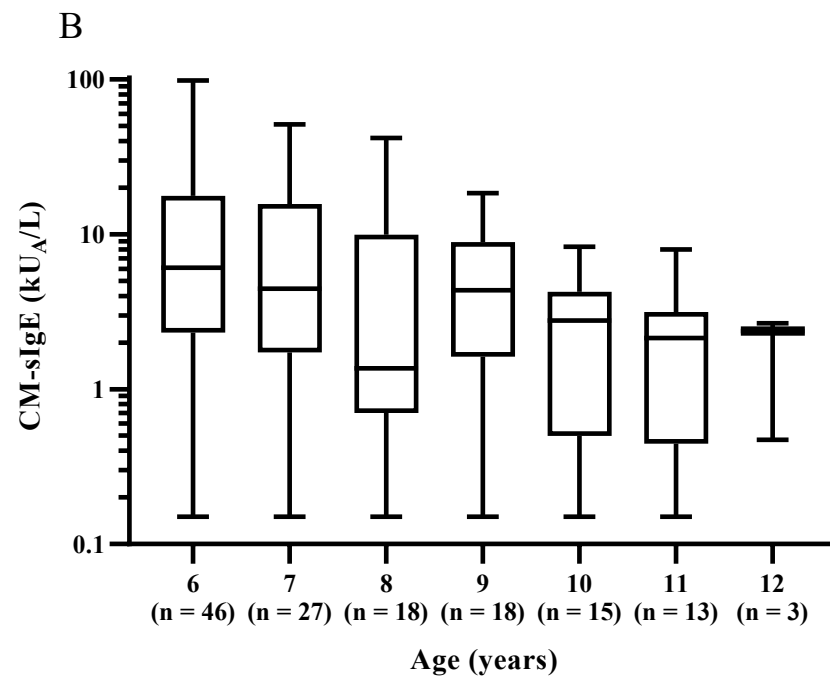
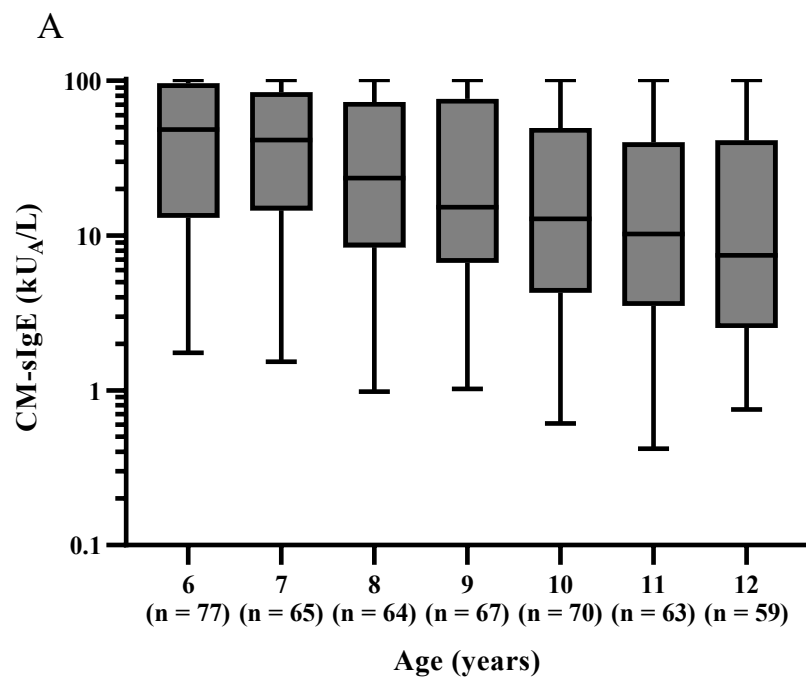
Figure 3



Supplementary figure 1



Supplementary figure 2



Supplementary figure 3

