DOI: 10.1111/all.15369

Tryptase reference ranges are age-dependent in a large population-based cohort

To the Editor,

Tryptase is a protease that is released during degranulation of mast cells and has several functions including promotion of vasodilatation and leukocyte recruitment, fibroblast proliferation and tissue repair.[1] Furthermore, tryptase concentrations in the circulation are thought to give a reflection of the mast cell burden. When elevated concentrations of tryptase are observed, it can be an indication for an underlying systemic mastocytosis or a systemic allergic reaction.[1] Tryptase concentrations may also be influenced by age, gender, adipose tissue, genetic variation, renal function, and time of day.

Currently, tryptase levels can only be measured on the ImmunoCAP platform (ThermoFisher Scientific; formerly known as Phadia).[2] Mean values and upper reference limits for serum tryptase concentration have been reported in three company-driven studies with a limited number of subjects.[3,4] The currently applied upper reference limit is based on the upper 95th percentile of the first study (11.4 μg/L)[3] whereas the 97.5th is considered the current standard. In this study, we determined tryptase reference ranges in a large population-based cohort in the Netherlands. Furthermore, we investigated the effect of age and gender.

All serum tryptase data obtained between December 2002 and January 2020 at the Maastricht UMC+, Maastricht, the Netherlands, were included ($N = 7003$). Subject data were anonymized, and tryptase concentrations were coupled to age and gender. Handling of data was in accordance with the code of conduct for responsible use in the Netherlands (www.federa.org). The database included patients suffering from mastocytosis, anaphylactic reactions and urticaria, meaning that several patients had multiple measurements. To determine the reference ranges, only a single value per patient was used. In principle, the first measurement of each patient was included. However, if the first measurement was elevated (e.g., in patients with anaphylaxis), the last measurement was included. A measurement was considered to be elevated if the value deviated >20% +2 μg/L in comparison with the most recent measurement.[5]

After excluding measurements as previously stated, the dataset was reduced to 5248 measurements (Figure S1). Because the data was skewed (Figure S2), data was normalized by logarithmic transformation before Bhattacharya analysis. This analysis is a frequently used method for determining reference ranges, enabling the identification of a mathematically distinct population within a study population based on the Gaussian distribution (see Appendix S1). It was performed using the option of Gaussian function in a home-made macroinstruction in an Excel spreadsheet (Microsoft Corporation), which was made available by Naus (personal communication). Reference ranges for female and male subjects were determined. For the calculation of reference ranges for different age categories, subjects were separated into groups per decade up until 70+ years of age. The subject's age ranged from 0 up until 102 years old and 60% were female (Table S1).

Bhattacharya analysis by age category showed a profoundly lower median tryptase concentration and upper reference limit in adolescents and adults compared with the currently used upper limit. Median tryptase concentrations showed a steady increase with the increase of age, with ages over 70 years having a higher upper reference limit than Phadia's 95th percentile of 11.4 μg/L (Table 1 and Figure 1). There was no significant gender-linked difference (Figure S3).

In conclusion, our robust new data clearly show that in a large population-based cohort, reference ranges are substantially lower in adults in comparison with the currently applied upper reference limit. These observations may also explain the published reports that show the risk of severe anaphylaxis is associated with tryptase levels >8 ng/ml.[6] We recommend implementing our age-based reference ranges in general practice to prevent under- or over-diagnosis of mastocytosis or systemic allergic reactions.

TABLE 1 Tryptase medians and reference ranges by age based on Bhattacharya analysis

Age category (years)	*N*	2.5th percentile	Median	97.5th percentile
0–9	186	1.74	3.92	8.74
10–19	279	1.52	3.33	7.28
20–29	545	1.48	3.31	7.44
30–39	582	1.52	3.71	8.35
40–49	866	1.72	3.80	8.40
50–59	1161	1.97	4.40	9.82
60–69	989	2.09	4.77	10.9
70+	640	2.12	5.37	13.6

Note: All values are expressed in μg/L.

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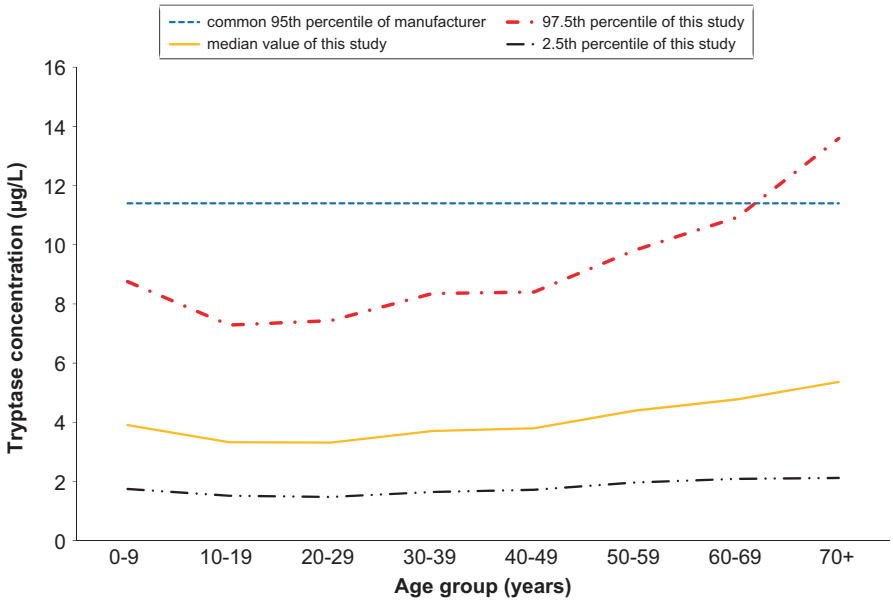

FIGURE 1 Tryptase median concentrations and lower and upper reference limit per age decade in comparison with current upper reference limit by manufacturer

CONFLICT OF INTEREST

The authors declare that they have no relevant conflicts of interest.

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