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Reference Distributions for the Negative Acute-Phase Proteins, Albumin, Transferrin, and Transthyretin: A Comparison of a Large Cohort to the World's Literature

Robert F. Ritchie,* Glenn E. Palomaki, Louis M. Neveux, and Olga Navolotskaia

Foundation for Blood Research, Scarborough, Maine

Clinical interpretation of the acute-phase proteins—albumin, transferrin, and transthyretin—has been hampered by the lack of accurate and precise methods for quantifying the levels and a stable and respected reference material. Now that these issues have been addressed, the community is faced with the need for credible age- and gender-specific reference values. The number of publications that address this issue, even for an analyte as familiar as albumin, is small and, in most cases, such publications lack the relevant data that would allow a combined experience to be created. We have identified 40 studies that meet our criteria: a description of the study participants' health status, of the statistical methodology, and of the laboratory technique and/or reference material used. Few of these studies reported values stratified by gender. A summary of the published median levels by age is presented for the three analytes, along with our own age- and gender-specific medians based on a large cohort. Ten of the studies presented a 95 percent reference range, in close agreement with ours where selection was based upon reported diagnosis rather than upon determination of individual health status. This meta-analysis provides support for the reliability of our recently published methodology and reference data for the clinical interpretation of individual albumin, transferrin, and transthyretin values. As with most laboratory measurements, clinical interpretation requires that other laboratory and clinical factors be considered. J. Clin. Lab. Anal. 13:280–286, 1999.

Key words: serum proteins; acute-phase proteins; meta-analysis; CRM 470/RPPHS

INTRODUCTION

The acute-phase proteins, a complex family of about 30 different moieties, have been traditionally viewed as markers of overt inflammation, infection, tissue necrosis, or malignancy. However, their clinical application has been hampered by uncertainty in the appropriate reference ranges for a given patient. This is particularly evident in very young individuals where significant inflammation may be accompanied by elevations in the acute-phase proteins that fall well within the adult reference ranges, but would be considered high were reference ranges to be available for children and infants. The three proteins examined in this study represent the major negative acute-phase proteins (APP) whose synthesis is downregulated by the same cytokines, IL-1 and IL-6, that drive the acute-phase response (APR). This study, like its predecessor (1), aims to identify publications from 1961 to the present that report reference data for albumin, transferrin, and transthyretin (prealbumin) and that satisfy minimal acceptable criteria. All results were standardized against CRM 470/RPPHS (2,3) before comparison.

MATERIAL AND METHODS

Identification of Published Reference Data

The methods used to search for relevant publication was the same as for the previous study (1) with the addition of searching PubMed (http://www.ncbi.nlm.nih.gov/PubMed) online for the same key headings as were used for MEDLINE CD-ROM (OVID Technologies, New York, NY) searches. Briefly, the literature was searched by direct review of the Cumulative Index Medicus published compendia and the computerized MEDLINE CD-ROM. Articles were considered acceptable if they: (1) identified the assay method and reference material; (2) provided details of the study population such as age; and (3) provided the information required for statistical analysis (4–102). Studies that were exclusively methodological or reported measurements only in individuals with known disease were removed from consideration.

*Correspondence to: Robert F. Ritchie, M.D., Foundation for Blood Research, Scarborough, Maine, 04074. E-mail: ritchie@fbr.org

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Estimating the Central Estimate and Reference Range From Published Studies

For each study, either the mean, median, or geometric mean was used as the estimate of the center of the distribution. If these estimates were not directly available, they were computed using observed or smoothed centiles (e.g., the 2.5th and 97.5th centile) If none of these were available, the study was excluded from all analyses. Observed 95 percent ranges were used for the reference interval analysis. If the range was estimated from parameters or was other than the 95 percent range, the study was excluded from the reference interval analysis.

Conversion of Reported Results to a Single Reference Material

Results were standardized against CRM 470/RPPHS by conversion from package insert data from the period of the study as previously described (1). This material was released by the International Federation of Clinical Chemists (IFCC), the Community Bureau of Reference (BCR) in Brussels, and the College of American Pathologists (CAP) in the United States (the latter being labeled Reference Preparation for Proteins in Human Serum [RPPHS]).

RESULTS

Number of Studies Available for Analysis

We identified 71 publications that contained information on albumin in nondiseased individuals (4–9,12–16,18,19,21–26,28,29,32,33,35,36,45,46,54–56,58–60,62–70,72–91,94–102). Thirty-one of these studies did not include adequate information about assay methodology and/or the reference material used (9,12,14–16,22,23,25,26,29,33,35,58,60,62–64,72,76,77,79,85–90,95,99,100,102). Five studies did not include information about the age of the study subjects (8,18,19,75,94). The remaining 35 studies (4–7,13,21,24, 28,32,36,45,46,54–56,59,65–70,73,74,78,80–84,91,96–98,101) were considered acceptable for the analysis of albumin measurements.

We identified 30 publications that contained information on transferrin in nondiseased individuals (4–7,9–11,18–20,26,28,37–39,47–49,53,54,56,59,62,63,69–71,76,83,84). Eleven studies did not include adequate information about assay methodology and/or the reference maternal used (11,26,39,47,48,53,62,63,71,76,84). Two studies did not include information about the age of study subjects (10,18). The remaining 17 studies (4–7,9,19,20,28,37,38,49,54, 56,59,69,70,83) were considered acceptable for the analysis of transferrin measurements.

A total of 42 publications were identified which contained information on transthyretin in nondiseased individuals (5–8,17,18,22,27,28,30,31,34,36,40–44,46,49–53,56,57,61–63,65,69–71,73,76,78,83,92,93,98,99,101). Twenty-five studies did not include adequate information about assay methodology and/or the reference material used (17,22, 27,30,31,34,36,40,41,43,44,50,51,53,57,62,63,65,71,76, 78,92,93,98,99). Two studies did not include age (8,18). The remaining 15 studies (5–7,28,42,46,49,52,56,61,69,70,73, 83,101) were considered acceptable for transthyretin measurements.

For the analysis of reference range width, ten studies provided adequate information for at least one of the proteins (6,24,32,54,56,70,73,80,83,101).

Comparison of the Central Estimates

Figure 1 shows the central estimates from the published studies of albumin (a), transferrin (b), and transthyretin (c). The reported mean (or median) age of the study population is shown on the logarithmic horizontal axis versus the reported mean or median analyte level on the logarithmic vertical axis over a fourfold range in values. Each observation is shown as a circle with the smallest and darkest circles representing estimates based on over 100 observations, median sized circles representing between 50 and 99 observations, and the largest circles representing between 10 and 49 observations. If a published observation was based on less than 10 observations, it was combined with an adjacent age group from the same publication. For purposes of comparison, the solid and dashed lines represent the median levels found for males and females, respectively, in our companion study (3).

Figure 1 shows the reported albumin median values from the 35 published studies considered acceptable. Most data are for adults over age 30. Our median levels for albumin are identical to the large number of published estimates for subjects over age 60. Our estimates are somewhat lower than, but consistent with, the estimates for younger adults. The figure shows that little reliable data has been published for children under age 10, but our estimates are consistent with that which does exist. There are far fewer published median levels of transferrin than for albumin and the spread of the estimates is greater. Our median levels for adults are near the middle of the range of published estimates. The few estimates available for young children, however, are considerably lower than ours. However, five of the six published estimates under age 10 are from two studies (56,83). The estimates of our median albumin and transferrin levels (Fig. 1a,b) are remarkably consistent with published studies of single age- and gender-specific consensus values generated soon after CRM 470 was released (103,104). The published median estimates for transthyretin are similar to our estimates over the entire range of ages (Fig. 1c).

Comparison of the Reference Ranges

The reference ranges reported in the studies used in the above analyses were generally based on a small number of observations; half were based on 489 observations or less.

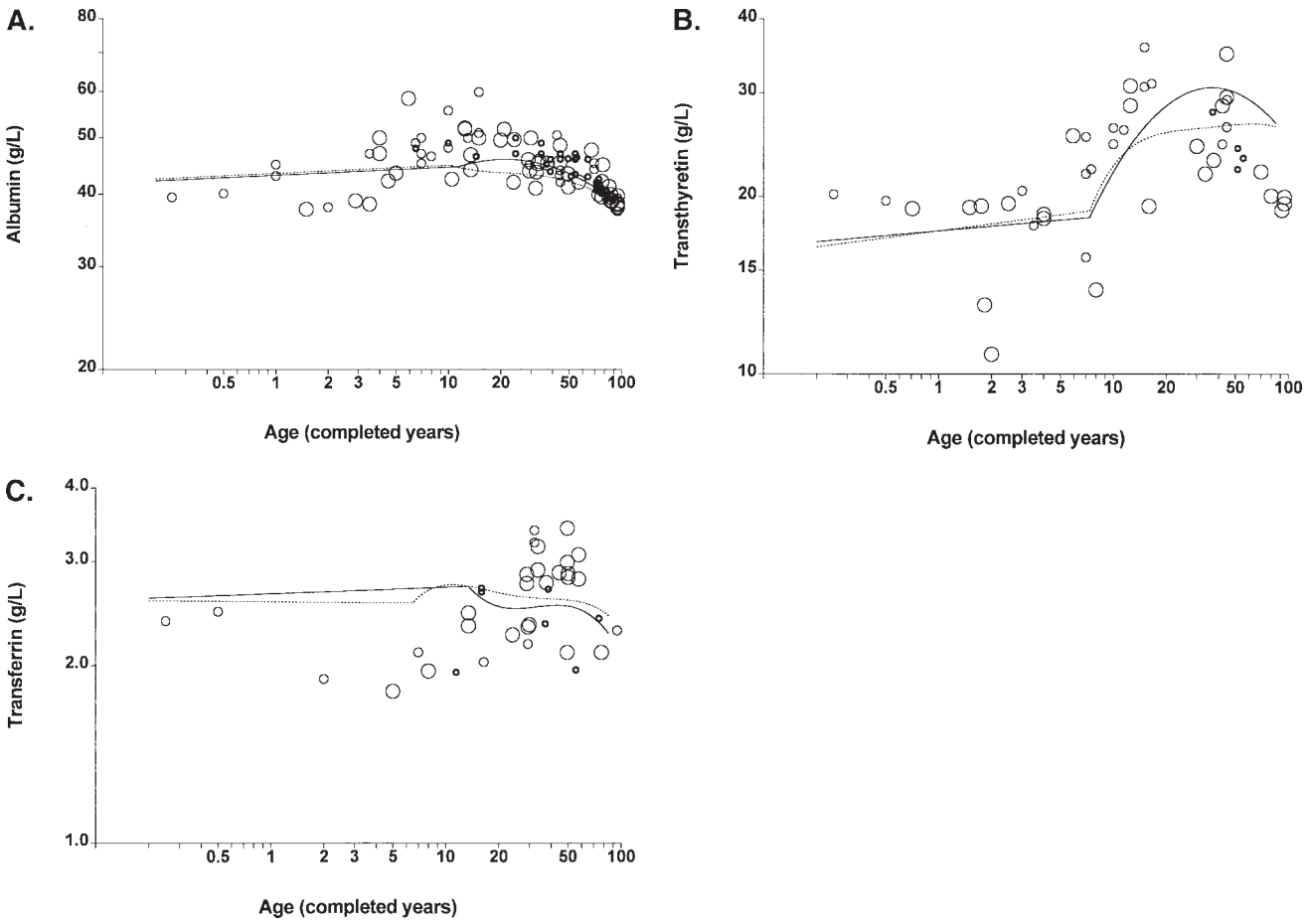

Fig. 1. A summary of published acute phase protein median reference values. The published median (or geometric mean) levels for albumin (**A**), transferrin (**B**) and transthyretin (**C**) levels are displayed on the logarithmic vertical axis (spanning a factor of four) versus the mean (or median) age on the logarithmic horizontal axis. The three symbol sizes represent the number of observations in each group (small, medium and large circles representing over 100, 50 to 99 and 10 to 49. The solid (males) and dashed (females) lines are the regressed median levels from our large cohort study (3).

Thus, it was possible to verify the health status of each individual. In contrast, our observed reference ranges were each based on over 50,000 observations and, therefore, it was not possible to verify the health status of each individual. Although the median levels derived in our study are in agreement with published ones, it is possible that our reference ranges may be wider than other smaller studies because we relied on the diagnosis provided on the laboratory slip (105). In order to determine whether this was the case, we re-analyzed the published reference ranges using our earlier finding (Fig. 1a,b,c) that the widths of the ranges are nearly completely independent of age and gender (3). Figure 2 shows the 10 previous studies for which it was possible to calculate a 2.5th to 97.5th centile range (after each study's reference limits were divided by their own population medians— conversion to multiples of the median). The reference numbers are shown on the horizontal axis, sorted by decreasing 95 percent reference-range width. The weighted average of the ranges reported in the literature (excluding those from our study) is shown by two thin horizontal dashed lines. The 95 percent reference ranges for our study (both observed and predicted from the population parameters) are represented as thick, dashed lines. Figure 2b,c shows a similar analysis for transferrin and transthyretin reference ranges, respectively. For all three analytes, our ranges are similar to the consensus estimate from the literature. Although there are a few extreme estimates that vary greatly from the consensus, the majority of the studies are consistent. Furthermore, the reference range widths for children (56,106), when compared to an elderly group (70), also are remarkably similar even though the median levels vary widely.

Ethnic Group-Specific Reference Ranges

A total of 25 studies included in the previous analyses reported the race or ethnic heritage of the study subjects. The majority, 19, reported measurements in Caucasian or mostly Caucasian populations (4,5,7,13,24,38,45,49,65,68,69,73, 78,82,83,91,96,97,101). Four studied only black Africans

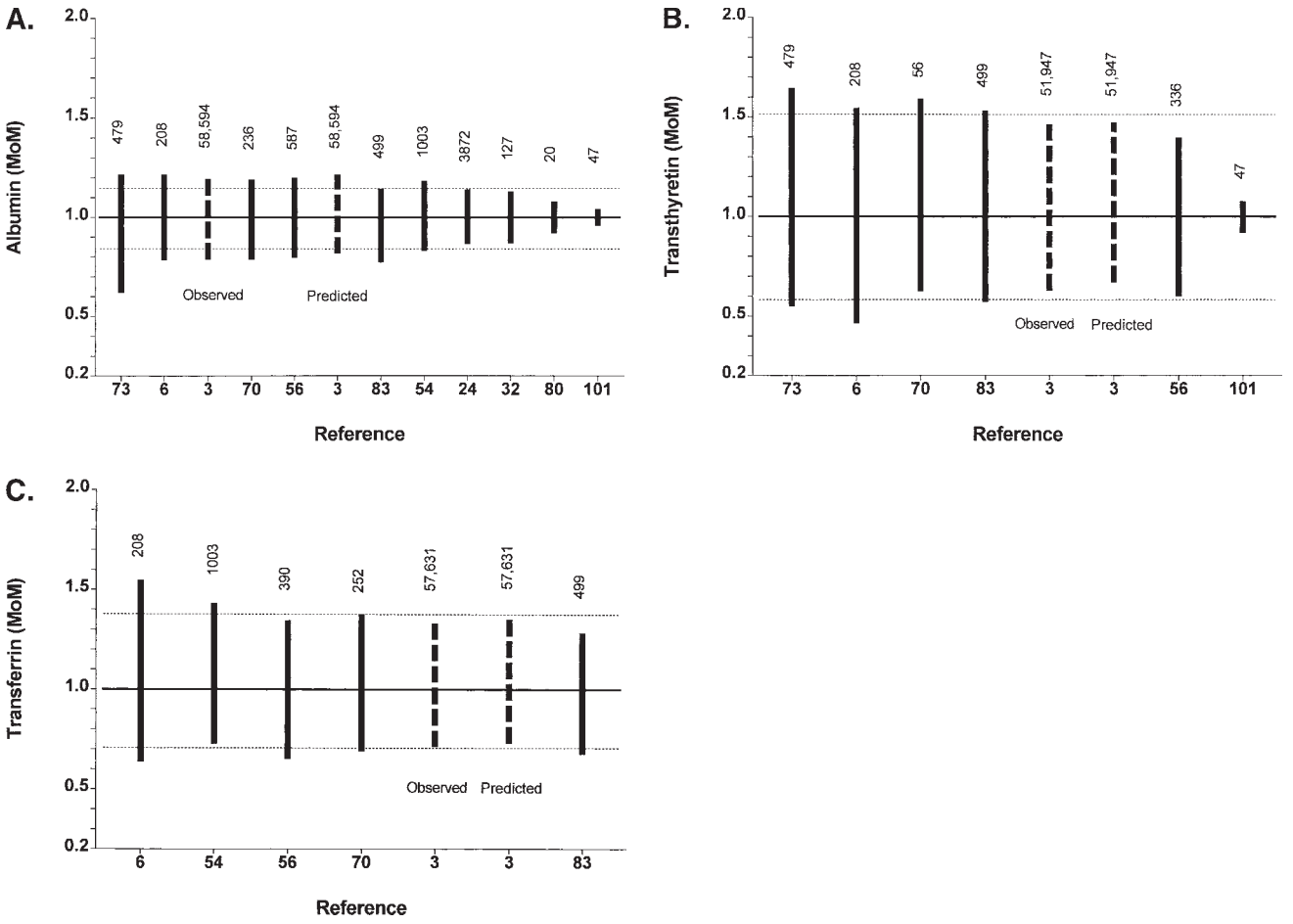

Fig. 2. Reference intervals from published studies**.** The bars represent the interval between the 2.5th and 97.5th centile for each study with the number of subjects above the bar. The horizontal axis shows the reference number for each study. The selected centiles have been presented as multiples of the median (MoM), compensating for age, gender and reference material differences between studies. Figure **2A**, 2**B** and 2**C** show the analyses for albumin, transferrin and transthyretin measurements, respectively, on identical logarithmic vertical axes. The horizontal dotted lines display the weighted consensus value at the 2.5th centile and the 97.5th centile for previously published studies. The broken bars represent the observed and predicted reference ranges from our large cohort study (3).

(42,80,81,98) and two studied only Asians (28,66). Of the 10 studies providing reference ranges displayed in Figure 2a (6,24,32,54,56,70,73,80,83,101), five did not provide information on race, four were based on Caucasians, and one was based on Blacks. Therefore, no claim for differences or similarities in reference-range widths between races can be made in this study.

DISCUSSION

With the considerable improvement in instrument performance (107) and the availability of a stable, widely accepted reference material (2), robust age- and gender-specific reference data have remained one of the last remaining barriers to improving clinical interpretation. Until now, reference ranges were based on relatively small numbers of study subjects but had the advantage of often documenting individual health status. Our companion study (3) reports reference data for albumin, transferrin, and transthyretin based on a much larger data set with less reliance on individual health status. The current study shows our reference data, in terms of both the median and reference interval width, to be on average, consistent with these smaller studies. The advantage of our larger study is that the reference data can now be specified for any age between 1 month and 85 years of age, for both males and females.

The establishment of a reliable set of reference data for males and females throughout life facilitates future reviews comparing serum protein levels in similar populations. Laboratories are being required to design and establish local reference ranges that can account for possible ethnic and geographic differences. Protocols have been developed to assist and guide laboratories in constructing and determining serum protein reference ranges in local cohorts (103,104).

This effort has been made easier with the completion of our two studies (3,105). These reference data for presumed healthy individuals also set the stage for estimating screening or diagnostic performance by establishing the distribution of analyte values in individuals with specific diseases. The importance of this knowledge is just becoming clear.

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