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Research Article

Age-adjusted reference intervals for serum ceruloplasmin levels: Insights from a hospital data-based study

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Abstract

Objectives: Ceruloplasmin (Cp), a plasma protein that acts as a copper transporter, plays a crucial role in the screening process for Wilson's disease. Measuring the serum Cp level serves as the initial step in this screening procedure. However, serum Cp reference limits can vary over age, sex, and using of different measurement methods. In reference interval (RIs) studies, the utilization of hospital data is considered an accepted approach, especially in situations where achieving strict standardization is challenging, such as in pediatric age group. Our study aimed to determine the RIs for Cp levels from 1 to 80 years of age using laboratory data, providing valuable guidance for clinicians and researchers in interpreting Cp test results across different age groups.

Methods: Forty-seven thousand five hundred and fifty-six (47,544) Cp data points were collected between July 2010 and 2020 from Acıbadem Labmed Laboratories. To determine the RIs, both common RIs and sex-specific RIs were calculated using the Bhattacharya indirect method.

Results: The RIs for serum Cp levels in children are as follows: 1–5 years: 23–48.2 mg/L, 5–10 years: 23–38.2 mg/L, and 10–15 years: 20.5–36.3 mg/L, respectively. For women, the RIs for serum Cp levels are as follows: 15–20 years: 19–33.5 mg/dL, 20–40 years: 19.6–36.8 mg/dL, 40–60 years: 20.4–42 mg/dL, and 60–80 years: 23.5–45 mg/dL, respectively. For male, the RIs for serum Cp levels are as follows: 15–20 years: 17.0–31.3 mg/dL, 20–40 years: 17.8–34.5 mg/dL, 40–60 years: 18.6–38.0, and 60–80 years: 23.0–40.5 mg/dL, respectively.

Conclusion: This study has demonstrated a significant and independent association between age and gender concerning Cp concentrations. Although our methodology provided only approximate RIs for Cp, our results emphasize the significance of age adjustment when determining RIs. Taking age and gender into account is crucial for accurately establishing appropriate reference ranges for Cp in clinical settings.

Keywords: Bhattacharya analysis, ceruloplasmin, reference interval

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Ceruloplasmin (Cp) is responsible for binding approximately 90% of copper in the serum and exhibits ferroxidase enzyme activity, which plays a crucial role in iron metabolism [1]. It is the primary diagnostic test for Wilson's disease (WD). A concentration less than the lower reference limit (0.20 g/L) has been considered as the conventional diagnostic cutoff for WD [2]. In addition to WD, serum Cp levels are lower than the normal in some diseases such as, Menkes disease, copper deficiency, liver disease, and malnutrition. However, inflammation, infection, estrogen therapy (e.g., oral contraceptives), and pregnancy can lead to serum Cp elevation [3]. In addition, serum Cp reference limits can vary over age, sex, and using of different measurement methods. Therefore, these factors should be considered when determining the reference ranges for the Cp test [4]. Accurately determined reference intervals (RI) are of critical importance in the evaluation of laboratory test results and the clinical decision-making

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process. According to the clinical and laboratory standards institute EP28-A3C guide to establish population-based RIs, individuals can be collected from a healthy population using either the direct sampling technique or selected through data mining techniques, also known as the indirect sampling technique [5].

Using healthy individuals' data is a preferred approach in RI studies [6]. However, in situations where standardizing pre-analytical conditions, such as in the pediatric age group, is challenging, using hospital data for RI studies is an accepted approach [7]. The Bhattacharya is an indirect method using unselected big laboratory data to calculate RIs of laboratory tests. According to this method, the majority of patients admitted to the hospital are considered to be non-patient. This method aims to separate healthy data from pathological data using some statistical methods [8, 9].

The Bhattacharya method is a statistical technique used to identify possible Gaussian distributions in data. This technique is used in calculating RIs for tests based on large laboratory data. The linear portion of the obtained graph (R^2 >0.99) includes the data that will be used for RI calculation and data between the lower and upper limits that form the curve are used for RI calculation [10].

For the clinical evaluation of the Cp test results, it is necessary for the reference ranges of this test to be accurately determined based on age groups and the specific instrument and method that is used. There is a limited number of published reference range studies for the Cp test that stratified the RI by age and gender in the healthy population. We aimed to calculate the RIs for the Cp test results measured by the nephelometric method on the BN-Prospect Systems Siemens using the Bhattacharya method in this study.

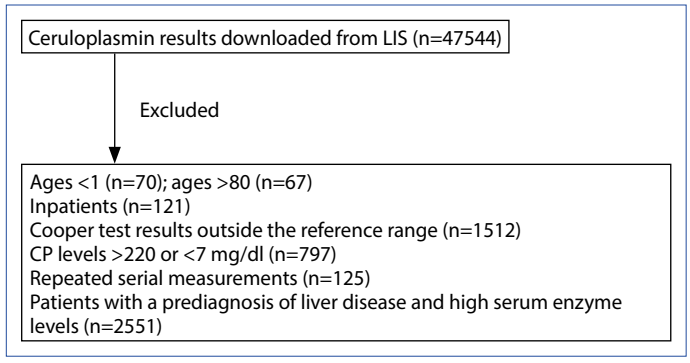

Figure 1. The exclusion criteria for ceruloplasmin results.
LIS: Laboratory information system; CP: Ceruloplasmin.

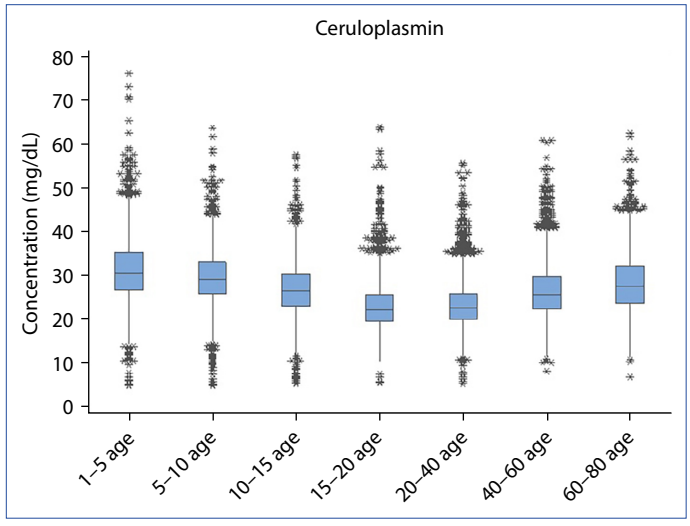

Figure 2. Boxplot graphic for ceruloplasmin test shows the range of data from the 25th to the 75th percentile, while the bar in the middle of each box plot value represents the median value. Asterisks indicate outliers.

Materials and Methods

Population selection

In our study, we utilized laboratory raw data registered in the LIS system between 2010 and 2019 from Acıbadem Labmed Laboratories to calculate the reference range for Cp based on hospital data. (n=47544). The study was not designed with preselected patients, but certain exclusion criteria were applied for patients included in the study [7]. Data were only included from 1 to 80 years old participants. Patients under 1 year and over 80 years of age were excluded from the study due to insufficient laboratory data (n=137). Patients with concomitant Cp and copper test orders and copper test results outside the reference range (n=1512); patients with a pre-diagnosis of liver disease and high serum enzyme levels (n=2551); inpatients (n=121); and follow-up patients (n=125) were excluded from the study. In addition, data exceeding the detection limits of the assay methods (Cp levels >220 or <7 mg/dl) were excluded from the study without any statistical analysis (n=797) (Fig. 1).

Laboratory analysis

Cp measurements were performed on automated BN-Prospect Systems Siemens using nephelometric method and no modifications were made to the analytical procedures throughout the study period. The analytical measuring range was 7–220 mg/dL; the within-run coefficient of variation (CV) was 2.4% at 24.6 mg/dL; the between-run CV was 4.1% at 24.6 mg/dL and 5.5% at 37.3 mg/dL for Cp. Cp is a routine test conducted in our laboratory, and before analyzing patient samples, we perform internal quality control testing using two samples with levels of known specific Cp concentrations. We also actively participated in the Reference Institute for Bioanalytics (RfB; Germany) periodic external quality control assessment program for Cp. Our performance in this program has consistently demonstrated minimal changes over time, indicating a stable and reliable performance.

Statistical analysis and determination of RI

We initially employed a boxplot graph to examine the distribution of serum Cp levels in relation to age (Fig. 2). Subsequently, we utilized the Lahti algorithm to determine whether partitioning based on age and gender was necessary [11]. According to the Lahti algorithm, when the R-value is ≤1.5, the difference between the lower and upper limits

Table 1. Application of partitioning criteria to the ceruloplasmin test based on age and gender

Ceruloplasmin (mg/dl)	Data for subgroup distribution after box-cox transformation, (λ=0.001)		Lahti-distances partitioning criteria					
			Same age group		Different age group			
	Male	Female	D (s) (0.25–0.75)	Conclusion for one end	Male	Conclusion for one end	Female	Conclusion for one end
					D (s) (0.25–0.75)		D (s) (0.25–0.75)	
Group 1 (1–5 years)	n=1659	n=1233	M versus F		1 versus 2		1 versus 2	
Lower limit	3.3	3.31	0.06	Non-partitioning	0.35	Marginal	0.33	Marginal
Upper limit	3.56	3.57	0.06	Non-partitioning	0.47	Marginal	0.44	Marginal
Mean±SD	3.42±0.18	3.43±0.19						
Group 2 (5–10 years)	n=1086	n=1451	M versus F		2 versus 3		2 versus 3	
Lower limit	3.24	3.25	0.06	Non-partitioning	1.11	Partitioning	0.94	Partitioning
Upper limit	3.48	3.49	0.06	Non-partitioning	0.59	Marginal	0.65	Marginal
Mean±SD	3.37±0.17	3.37±0.18						
Group 3 (10–15 years)	n=2624	n=2032	M versus F		3 versus 4		3 versus 4	
Lower limit	3.05	3.09	0.24	Non-partitioning	0.70	Marginal	0.35	Marginal
Upper limit	3.38	3.38	0.0	Non-partitioning	1.23	Partitioning	0.47	Marginal
Mean±SD	3.2±0.17	3.2±0.17						
Group 4 (15–20 years)	n=2901	n=2259	M versus F		4 versus 5		4 versus 5	
Lower limit	2.93	3.03	0.59	Marginal	0.59	Marginal	0.72	Marginal
Upper limit	3.17	3.3	0.76	Partitioning	0.52	Marginal	0.77	Partitioning
Mean±SD	3.05±0.17	3.2±0.19						
Group 5 (20–40 years)	n=7853	n=5680	M versus F		5 versus 6		5 versus 6	
Lower limit	3.03	3.16	0.72	Marginal	0.36	Marginal	0.44	Marginal
Upper limit	3.26	3.44	1.0	Partitioning	0.36	Marginal	0.55	Marginal
Mean±SD	3.2±0.19	3.35±0.18						
Group 6 (40–60 years)	n=5007	n=7056	M versus F		6 versus 7		6 versus 7	
Lower limit	3.1	3.24	0.77	Partitioning	0.57	Marginal	0.33	Marginal
Upper limit	3.33	3.54	1.17	Partitioning	0.63	Marginal	0.66	Marginal
Mean±SD	3.2±0.19	3.35±0.18						
Group 7 (60–80 years)	n=2172	n=2957	M versus F					
Lower limit	3.21	3.30	0.47	Marginal				
Upper limit	3.45	3.66	1.1	Partitioning				
Mean±SD	3.3±0.19	3.4±0.19						

SD: Standard deviation; M: Male; F: Female.

of the subgroups is calculated. The distances between the lower and upper reference limits denoted as DL and DU, respectively, are determined for the subgroup distributions. The standard deviation of the narrower subgroup distribution is used as the scale unit (s) [12]. If the data does not follow a normal distribution at this stage, a Box-Cox transformation is applied to the data (λ=0.001).

If both DL and DU are <0.25s, partitioning is not recommended and categorized as "Non-partitioning."

If either DL or DU, or both, fall within the interval (0.25s, 0.75s), without exceeding 0.75s, the decision on partitioning must be made using considerations other than simple statistical measures. This category is labeled as "Marginal."

If either DL or DU, or both, equal or exceed 0.75s, partitioning is recommended and identified as "Partitioning."

According to the Lahti algorithm, the laboratory data were divided into the following age groups: 1–5 years, 5–10 years, 10–15 years, 15–25 years, 25–40 years, 40–60 years, and 60–80 years. In addition, for individuals aged 15 and above, partitioning based on gender was also performed (Table 1).

We performed Bhattacharya analysis using an Excel spreadsheet application to calculate the RIs for the Cp test. The data,

Table 2. The number and percentage of selected patients for statistical analysis using Bhattacharya method

Age group	Gender	Total number of lab raw data	Number of lab data selected for statistical analysis ($r^2 \geq 0.99$) (%)
1–5 years	Both	3555	2844 (80)
5–10 years	Both	3716	2564 (69)
10–15 years	Both	4861	3700 (76)
15–25 years	Female	3140	2669 (85)
15–25 years	Male	5399	4318 (80)
25–40 years	Female	5899	4070 (69)
25–40 years	Male	6126	4472 (73)
40–60 years	Female	7061	5357 (76)
40–60 years	Male	5359	3332 (62)
60–80 years	Female	2782	2262 (81)
60–80 years	Male	2786	2110 (76)

divided into subgroups, were sorted in ascending order with equal intervals. The total frequency of the data was then divided into 20 equally spaced classes, with a bin size of 2.0. We calculated the logarithm of the counts (represented as fi) and the Δlog (fi) values from one bin to another.

$y_i = \ln (f_{i+1}/f_i)$

f_i= number of results in class i

To minimize the influence of random fluctuations, the 5-point Savitzky-Golay smoothing procedure was utilized, resulting in a smoother curve [13]. Furthermore, following the suggestion of Oosterhuis et al., [14] a weighting factor was introduced to improve the precision of the Bhattacharya analysis.

Savitzky-Golay smoothing procedure:

$y_i = (-3(f_{i-2}) + 12(f_{i-1}) + 17(f_i) + 12(f_{i+1}) - 3(f_{i+2}))/35$

Weighting factor= $(f_i + f_{i+1})^2$

Following the plotting of the derivative of measured value frequency to concentration logarithms, we calculated the intercept (a) and slope (b) of the linear portion of the relationship, where the coefficient of determination (R^2) exceeded 0.99 (Table 2) [10]. If a good fit with the data was achieved, the analysis was performed without any transformation. However, if the fit was not satisfactory, a Box-Cox transformation was applied. The parameter λ for the transformation was selected based on the best fit to the data (Fig. 3).

Results

A total of 47,544 Cp results were downloaded from the LIS. After applying the inclusion/exclusion criteria (Fig. 1), 5243 data points were removed. The study included samples from 21,416 male and 20,895 female participants, ranging in age from 1 year to 80 years, to calculate the RIs for Cp. We calculated RIs for both sexes in the first 15 years and separately for men and women in the 15–80 age groups. The results are summarized in Table 1. The RIs for serum Cp levels in children are as follows: 1–5 years: 23–48.2 mg/dl, 5–10 years: 23–38.2 mg/dl, and 10–15 years: 20.5–36.3 mg/dl, respectively. For women, the RIs for serum Cp levels are as follows: 15–20 years: 19–33.5 mg/dl, 20–40 years: 19.6–36.8 mg/dl, 40–60 years: 20.4–42 mg/dl, and 60–80 years: 23.5–45 mg/dl, respectively. For male patients, the RIs for serum Cp levels are as follows: 15–20 years: 17.0–31.3 mg/dl, 20–40 years: 17.8–34.5 mg/dl, 40–60 years: 18.6–38.0 mg/dl, and 60–80 years: 23.0–40.5 mg/dl, respectively (Table 3).

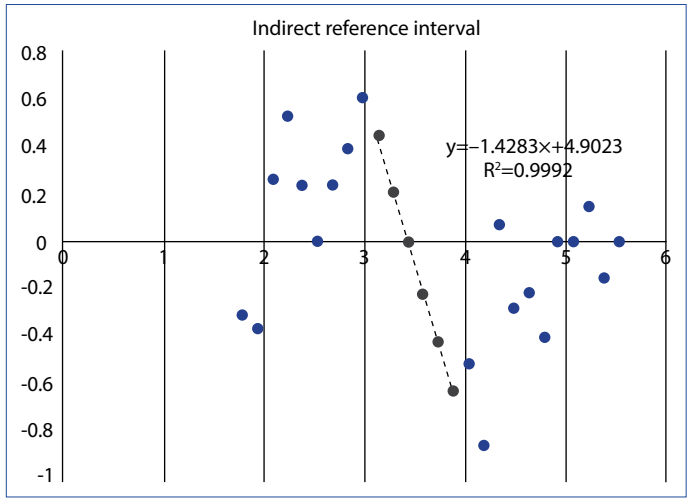

Figure 3. Bhattagram of dataset of 1–5 age groups. The mean and the standard deviation (SD) of the Gaussian component of the dataset calculated from the slope and y-intercept of the line of best fit of these data points.

Discussion

In WD and Menkes disease, impaired copper metabolism typically results in low Cp levels. Furthermore, conditions such as malnutrition and copper deficiency can also contribute to decreased Cp production, leading to low levels. It is important to consider these factors when evaluating Cp levels in individuals with suspected copper-related disorders. Conversely, conditions such as inflammation, liver disease, and estrogen therapy can result in elevated Cp levels [3]. The antioxidant effects of Cp could have important implications for various neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease in which iron deposition is known to occur [15]. In addition, several studies have investigated the correlation between serum Cp concentration and the occurrence of atherosclerosis and other cardiovascular diseases [16]. In these diseases, the incidence of which increases with age, it is very important to establish accurate RIs for Cp testing in the older age group to ensure accurate clinical interpretation.

According to EP28-A3c, it is an accepted approach to calculate reference ranges from laboratory data in challenging sampling situations, such as pediatric and geriatric age groups [5, 17].

In this study, we calculated the RIs for the Cp test using laboratory data from patients aged 1–80 years, including both pediatric and geriatric age groups. The Bhattacharya method was used to analyze the distribution of the data set and to determine RIs in our study.

Table 3. Age and gender partitioned reference intervals for ceruloplasmin

Ceruloplasmin (mg/dl)						
Age group	**Gender**	**No. of patients**	**Mean**	**Standard deviation**	**Lower limit**	**Upper limit**
1–5 years	Both	2844	31.86	5.32	23.00	48.20
5–10 years	Both	2564	25.85	1.46	23.00	38.20
10–15 years	Both	3700	26.67	3.96	20.50	36.30
15–20 years	Female	2669	24.75	3.66	19.00	33.50
15–20 years	Male	4318	22.92	3.59	17.00	31.30
20–40 years	Female	4070	27.20	4.19	19.60	36.80
20–40 years	Male	4472	24.06	3.67	17.80	34.50
40–60 years	Female	5357	29.23	4.69	20.40	42.00
40–60 years	Male	3332	25.58	4.35	18.60	38.00
60–80 years	Female	2262	30.72	4.80	23.50	45.00
60–80 years	Male	2110	30.02	4.25	22.70	40.50

In 1967, Bhattacharya developed a statistical method to distinguish between distributions representing healthy and non-healthy individuals. He proposed that the distribution is a combination of components corresponding to different populations. The method involves determining the relative frequency and frequency distribution, often assumed to be normal, and using a statistical approach to resolve overlapping Gaussian distributions [8]. Baadenhuijsen and Smit emphasized that the Bhattacharya technique requires a large amount of data to effectively apply the method and minimize statistical fluctuations. They recommended collecting more than 1500 values for each analyte. The algorithm assumes that a significant portion of the total population can be considered "normal" and that there is only partial overlap between the healthy and abnormal parts of the distribution [9].

According to the observed box plot, our study has confirmed that age has a significant impact on Cp concentrations. Cp levels decrease with age from 1 year to 15 years and increase after age 20–80 years. We employed the Lahti algorithm to categorize the Cp test data into subgroups based on age and gender. We utilized the Tukey method to remove outliers within each group, and each group consisted of more than 1500 data points, as shown in Table 2. Based on the Lahti criteria, no significant effect of gender on Cp concentrations during childhood was observed in our study. However, it was found to have an impact in adulthood. The assay manufacturer established a reference range of 20–60 mg/dl for the Cp test based on samples from healthy adult donors. However, the user manual does not provide specific information regarding the age and gender range of the RI study. The lower reference limit (LRL) and upper reference limit (URL) of Cp estimated in different populations and using various analyzers exhibit some differences [2,18–23]. The Canadian Laboratory Initiative for Pediatric RIs (CALIPER) conducts RI studies for the pediatric age group using samples obtained from healthy community children and adolescents. Cp serum concentration measurements were performed on Abbott ARCHITECT ci4100 assays to establish age- and sex-specific RIs [18]. In our study, we found that the age and gender division and LRL for the pediatric age group in the Cp assay were similar to CALIPER, while the URL was lower. In contrast to our study and CALIPER, Clifford et al. [19] observed that the lower reference limits for females were lower than those for males.

In the study of Iicol and Aslan, the RIs for Cp in females were reported to be 17–40 mg/dl, and for males, it was 18–33 mg/dl [20]. In this study, both direct and indirect methods were utilized to establish RIs for Cp in adults, and the results from both methods were found to be consistent with each other [20]. Our findings revealed that URL values for both males and females were similar. However, for females, LRL values were found to be higher.

As far as we know, there is a lack of studies on Cp RIs representing the advanced age group of 60 years and older. For this reason, we determined RIs for both females and males in the age range of 60–80 years. Our findings indicated that the RIs for this specific age group were higher when compared to those of young adults.

The present study has some limitations. First, a reference population was not used to establish a RI and thereby our study lacks the comparison of RIs established by direct and indirect methods. In addition, due to the unavailability of complete patient data, we were unable to apply all of the intended exclusion criteria. Specifically, patients without a recorded diagnosis were not excluded from the study.

Conclusion

This study revealed significant independent effects of age and gender on Cp concentrations. Our observations indicate that the reference ranges of Cp were highest during early childhood, decreased during adolescence, and then increased again in adulthood and the elderly population. In addition, after the age of 15, gender-specific partitioning was necessary. While our method allowed us to obtain only approximate RIs for Cp, our findings highlight the importance of age and gender adjustment in establishing RIs.

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