Gabriele Röhrig*, Ingrid Becker, Anna Hagemeyer, Kai Gutensohn^a and Thomas Nebe^a, on behalf of the working group laboratory diagnostics of the German Society of Hematology and Oncology (DGHO) and the working group anemia in the aged of the German Geriatric Society (DGG)

White blood cell counts, CRP, GGT and LDH in the elderly German population

<https://doi.org/10.1515/labmed-2018-0133>

Received September 11, 2018; accepted February 28, 2019; previously published online March 28, 2019

Abstract

Background: Hematological abnormalities are frequently found in geriatric patients. However, little data is available on reference values for total blood cell counts in older patients. This study is focused on the analysis of reference values for white blood cell counts in aged persons ≥ 60 years.

Methods: This was a cross-sectional study of outpatient laboratory data of 2015 from a German country-wide working laboratory company; inclusion criteria: age ≥ 60 years, parameters evaluated by the laboratory company between 1.1.2015 and 31.12.2015; exclusion criteria: glomerular filtration rate (GFR) < 60 mL/min, lack of inclusion criteria; primary objective: mean leukocyte count; secondary objective: mean counts of lymphocytes, eosinophil, neutrophil and basophil leukocytes as well as platelets, C-reactive protein (CRP), γ -glutamyl transferase (GGT) and lactate dehydrogenase (LDH) in hematologically healthy persons aged ≥ 60 years.

Results: Data of 30,611 persons aged ≥ 60 years were evaluated by age groups. Results for leukocytes, basophils, eosinophils, neutrophils and lymphocytes remained within the reference ranges recommended by the German Society of Hematology and Oncology (DGHO) and the

German Association of Specialists in Internal Medicine (BDI); the lower reference limit for normal platelet values in males was below the DGHO reference value with 136,000/ μ L (confidence interval [CI] 129,000;142,000); similarly, our results for normal monocyte values were above the DGHO reference values with 6.0% (5.7;6.2) to 14.3% (13.9;14.8) in males and 5.4% (5.2;5.6) to 12.9% (12.6;13.4) in females; CRP, GGT and LDH values were above the BDI reference values, comparable with the previous data of a senior patient cohort analysis.

Conclusions: Adaptation of reference values for selected laboratory parameters in older German patients should be well considered.

Keywords: geriatrics; leukocytes; platelets; reference values.

Introduction

Laboratory results are important for diagnostic, therapeutic and prognostic decision-making in clinical practice. Correct interpretation of laboratory results, however, is only possible if accurate reference values are provided. Despite the large amount of health care resources spent on the growing number of geriatric patients, there is still a lack of accurate reference values and age adjusted reference limits for laboratory parameters. This is mainly due to the fact that laboratory reference values are established based on samples from evidently healthy individuals, commonly aged < 60 years [1]. Although older patients are meanwhile conceded to be an own entity with a distinct biology, reference intervals derived from younger individuals are still commonly used in geriatric patients [2]. The application of unsuitable reference values, however, is associated with the risk of misinterpretation of clinical conditions, resulting in inadequate, often time-consuming and expensive treatment [3]. Data on reference values for laboratory parameters in geriatric patients are still

*K. Gutensohn and T. Nebe contributed equally to this work.

***Correspondence:** PD Dr. med. habil. Gabriele Röhrig, MPH, Geriatric Diagnostic Center, MVZ Medicum Köln Ost, Johann Classen Str. 68, 51103 Cologne, Germany, Phone: +(49)-221-870 8888, Fax: +(49)-221-870 8878, E-Mail: Gabriele.roehrig-herzog@mvz-koeln-ost.de

Ingrid Becker and Anna Hagemeyer: Institute of Medical Statistics and Computational Biology, University Hospital Cologne, Cologne, Germany

Kai Gutensohn: Aesculabor Hamburg GmbH, Hamburg, Germany

Thomas Nebe: Laboratory of Hematology, Mannheim, Germany

scarce. With the exception of the results obtained within the Canadian Health Measure Survey [4, 5] and the initiation of the Swiss SENIORLAB observational study [3], the majority of studies in this field are either limited to small cohorts [6] or have been published more than 10 years ago [7]. German data on reference ranges for older patients are still scarce and often limited to regional evaluations [8]. Recently, we published the first nationwide analysis on erythrocytic parameters among a large cohort of hematologically healthy German seniors [9]. Based on this large database, we now evaluated the laboratory parameters of white blood cell counts, platelets and anemia-related parameters among obviously hematologically healthy German subjects aged 60 years or older.

The primary objective of this evaluation was the determination of age-specific reference limits for leukocyte values of study subjects ≥ 60 years of age. The secondary objective was the determination of age-specific reference limits for white blood cell subgroups (lymphocytes, monocytes; eosinophilic, basophilic and neutrophilic granulocytes), platelets and anemia-related parameters like ferritin, transferrin saturation, soluble transferrin receptor (sTR), C-reactive protein (CRP), lactate dehydrogenase (LDH), γ -glutamyl transferase (GGT), haptoglobin and bilirubin.

This study is registered in the German Clinical Trials Registry (DRKS, Freiburg) with no. DRKS00008792. The Ethics Committee of the University Hospital Cologne approved the study (no. 15–282; 27.10.2015). The study was carried out in accordance with the current version of the Declaration of Helsinki of 2013.

Subjects and methods

The analysis was based on a cross-sectional study design. Methods have been previously described elsewhere [9]. We evaluated anemia-related laboratory data of 30,611 outpatients aged ≥ 60 years from a German nationwide acting laboratory group, not limited to hematologic analysis. The interval of data collection was 12 months, from January 1st, 2015 to December 31st, 2015. All measurements were performed on Sysmex XN 9000 hematology analyzers (Norderstedt, Germany). There was no switch of laboratory device during the time of data collection.

Initially available anemia-related laboratory data included red and white blood cell counts with subtypes, platelets, reticulocytes, CRP, ferritin, glomerular filtration rate (GFR), transaminases and GGT, haptoglobin, LDH, transferrin and transferrin saturation, transferrin receptor, vitamin B12 and folic acid. After the previous analysis

of red blood cells and erythrocytic indices [9], the focus of the present study was on the analysis of white blood cells, platelets and anemia-related biochemical parameters. Study parameters therefore included white blood cell counts with subtypes, platelets, CRP, ferritin, GFR, transaminases and GGT, haptoglobin, LDH, transferrin and transferrin saturation and sTR. For the evaluation of reference values of healthy subjects aged ≥ 60 years, we selected for the analysis of each laboratory value only subjects who showed no deviation from the given reference ranges in all other anemia-related parameters (=inclusion criteria). Reference ranges were based on the recommendations by the German Society of Hematology and Oncology (Deutsche Gesellschaft für Hämatologie und internistische Onkologie, DGHO) [10, 11].

Exclusion criteria were reduced GFR (mL/min) estimated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) formula for subjects ≤ 70 years of age (reference value ≥ 90 mL/min) [12] and for subjects > 70 years of age estimated based on the Berlin Initiative Study (BIS) formula (reference value ≥ 60 mL/min) [8, 13].

Subjects included in the study according to inclusion and exclusion criteria were considered hematologically healthy. For age-specific analysis, age groups were formed by age decades as 60–69 years, 70–79 years, 80–89 years and ≥ 90 years.

Laboratory data were described by mean, standard deviation (STD), median, 2.5th (P2.5) and 97.5th (P97.5) percentiles, minimal and maximal values. Percentiles, together with nonparametric 95% confidence intervals (CIs) by normal approximation [10], were calculated according to the International Federation of Clinical Chemistry guidelines on the statistical treatment of reference values [14]. The distribution of laboratory data was compared between the age groups using Kolmogorov-Smirnov tests.

CRP values less than or equal to 5 mg/L could not be distinguished by the laboratory and were presented as “ < 5 mg/L”. These definitions were set to the value 1 for calculations.

Results of the study were descriptively compared with established reference values issued by medical expert associations like the German Association of Specialists in Internal Medicine [15] (Berufsverband Deutscher Internisten, BDI) for leukocytes, LDH, GGT and CRP, and the DGHO [16] for platelets, neutrophil, eosinophil, basophil leukocytes, monocytes and lymphocytes. For CRP, GGT and LDH, reference limits could be compared with the results of Carlsson et al. [17] by CIs.

All authors have complied with the World Medical Association Declaration of Helsinki regarding ethical

conduct of research involving human subjects and/or animals.

Results

Of 30,611 cases, we excluded 207 cases for lack of blood cell counts. After application of inclusion and exclusion

criteria, analysis of white blood cell counts, platelets and anemia-related parameters was performed among the remaining subjects. Due to the cross-sectional character of the study, not all parameters were sufficiently available for statistical analysis. Therefore, only the following parameters remained for evaluation: leukocytes with subtypes of lymphocyte, monocytes, eosinophils, basophils, neutrophils, platelets, CRP, LDH and GGT.

Table 1: C-reactive protein (CRP in mg/L) by gender and age decade.

	n	Mean	STD	Median	Min	Max	P2.5	P97.5
All females	846	3.89	9.749	1.00	1	157	1.00	24.00
All males	544	4.73	11.105	1.00	1	96	1.00	34.13
Females 60–69 years	387	3.76	8.822	1.00	1	126	1.00	19.30
Males 60–69 years	270	5.03	11.942	1.00	1	96	1.00	36.05
Females 70–79 years	379	3.92	10.973	1.00	1	157	1.00	26.50
Males 70–79 years	244	4.62	10.756	1.00	1	92	1.00	36.00
Females 80–89 years	76	4.26	7.836	1.00	1	51	1.00	27.88
Males 80–89 years	29	2.48	2.995	1.00	1	13	1.00	–
Females ≥90 years	4	5.75	6.185	4.00	1	14	1.00	–
Males ≥90 years	1	13.00	–	13.00	13	13	13.00	13.00

STD, standard deviation; min, minimum; max, maximum; P2.5, 2.5th percentile; P97.5, 97.5th percentile, indicating reference intervals for CRP.

Table 2: γ -Glutamyl transferase (GGT in U/L) by gender and age decade.

	n	Mean	STD	Median	Min	Max	P2.5	P97.5
All females	1.943	30.05	38.798	21.00	6	741	11.00	99.00
All males	1.813	42.27	56.024	30.00	11	1689	14.00	140.00
Females 60–69 years	840	32.20	51.526	22.00	8	741	11.00	109.93
Males 60–69 years	847	46.73	69.554	33.00	11	1689	14.00	155.80
Females 70–79 years	925	28.84	25.633	21.00	6	364	11.00	95.85
Males 70–79 years	863	38.21	39.740	28.00	11	549	14.00	117.40
Females 80–89 years	168	26.63	21.853	21.00	9	189	10.23	93.43
Males 80–89 years	101	39.96	44.811	28.00	11	390	12.00	155.45
Females ≥90 years	10	18.00	5.354	18.00	10	27	10.00	–
Males ≥90 years	2	22.00	7.071	22.00	17	27	17.00	–

STD, standard deviation; min, minimum; max, maximum; P2.5, 2.5th percentile; P97.5, 97.5th percentile, indicating reference intervals for GGT.

Table 3: Lactate dehydrogenase (LDH in U/L) by gender and age decade.

	n	Mean	STD	Median	Min	Max	P2.5	P97.5
All females	726	215.71	41.978	212.00	109	452	147.00	317.65
All males	652	206.46	42.115	201.00	109	447	141.33	307.35
Females 60–69 years	304	208.87	40.829	206.00	109	452	137.50	308.88
Males 60–69 years	261	202.68	39.978	198.00	109	447	140.55	296.00
Females 70–79 years	357	218.17	39.714	216.00	118	361	151.95	305.65
Males 70–79 years	350	207.81	42.519	203.00	109	363	142.55	326.92
Females 80–89 years	60	232.00	51.509	224.00	125	377	138.13	359.68
Males 80–89 years	39	217.54	49.538	214.00	127	368	127.00	–
Females ≥90 years	5	260.20	55.351	261.00	198	343	198.00	–
Males ≥90 years	2	248.50	47.376	248.50	215	282	215.00	–

STD, standard deviation; min, minimum; max, maximum; P2.5, 2.5th percentile; P97.5, 97.5th percentile indicating reference intervals for LDH.

Table 4: Leukocytes by gender and age decade.

	n	Mean	Median	STD	Min	Max	P2.5	P97.5
All females	2.607	6.52	6.30	1.675	3	21	3.80	10.40
All males	2.283	6.88	6.60	1.728	3	20	4.30	10.89
Females 60–69 years	1.158	6.51	6.30	1.694	3	15	3.90	10.70
Males 60–69 years	1.078	7.01	6.70	1.785	3	15	4.40	11.20
Females 70–79 years	1.209	6.54	6.30	1.678	3	21	3.80	10.38
Males 70–79 years	1.062	6.77	6.60	1.702	3	20	4.16	10.40
Females 80–89 years	227	6.43	6.30	1.576	3	17	3.67	9.53
Males 80–89 years	139	6.66	6.40	1.406	4	11	4.10	9.75
Females ≥90 years	13	6.24	6.00	1.614	4	10	4.10	–
Males ≥90 years	4	7.08	7.40	0.789	6	8	5.90	–

STD, standard deviation; min, minimum; max, maximum; P2.5, 2.5th percentile; P97.5, 97.5th percentile indicating reference intervals for leukocytes.

Table 5: Platelets by gender and age decade.

	n	Mean	Median	STD	Min	Max	P2.5	P97.5
All females	2.674	260.35	255.00	60.00	43.00	658.00	153.00	389.000
All males	2.242	229.09	227.00	53.17	16.00	506.00	136.00	343.92
Females 60–69 years	1.185	264.300	259.00	57.91	59.00	521.00	153.65	387.00
Males 60–69 years	1.033	236.12	234.00	54.06	49.00	506.00	144.40	350.45
Females 70–79 years	1.232	258.66	252.00	60.13	43.00	658.00	157.82	389.52
Males 70–79 years	1.063	223.82	221.00	52.16	46.00	469.00	133.60	341.40
Females 80–89 years	243	249.50	246.00	66.77	45.00	461.00	135.00	394.00
Males 80–89 years	142	217.29	218.00	47.95	16.00	333.00	127.77	306.40
Females ≥90 years	14	262.21	254.00	74.40	76.00	363.00	76.00	–
Males ≥90 years	4	234.000	221.00	39.38	205.00	289.00	205.00	–

STD, standard deviation; min, minimum; max, maximum; P2.5, 2.5th percentile; P97.5, 97.5th percentile indicating reference intervals for platelets.

Table 6: Basophils by gender and age decade.

	n	Mean	Median	STD	Min	Max	P2.5	P97.5
All females	3.495	0.80	–80	0.328	0	2	0.30	1.50
All males	2.842	0.77	0.70	0.330	0	4	0.30	1.50
Females 60–69 years	1.487	78	0.70	0.327	0	2	0.30	1.50
Males 60–69 years	1.308	0.76	0.70	0.323	0	2	0.30	1.50
Females 70–79 years	1.652	81	0.80	0.326	0	2	0.30	1.50
Males 70–79 years	1.354	0.77	0.70	0.339	0	4	0.30	1.50
Females 80–89 years	338	0.83	0.80	0.339	0	2	0.30	1.60
Males 80–89 years	173	0.71	0.70	0.305	0	2	0.20	1.37
Females ≥90 years	18	0.91	0.80	0.319	0	2	0.40	–
Males ≥90 years	7	0.81	0.50	0.441	0	2	0.40	–

STD, standard deviation; min, minimum; max, maximum; P2.5, 2.5th percentile; P97.5, 97.5th percentile indicating reference intervals for basophils.

With regard to the nonagenarians, however, statistical power is limited due to the very small number of subjects in this age decade. Nevertheless, for the sake of completeness, results are presented. Tables 1–10 show the descriptive results of all laboratory data by gender and age decade.

Comparison of 2.5th to 97.5th percentile value of study parameters with the recommended DGHO reference ranges [16] for the study parameters revealed accordance with basophil, eosinophil and neutrophil leukocytes as well as lymphocytes (Table 11). In platelets, however, the lower reference limit for normal platelet values in males

Table 7: Eosinophils by gender and age decade.

	n	Mean	Median	STD	Min	Max	P2.5	P97.5
All females	2542	2.59	2.30	1.632	0	16	0.30	6.60
All males	2.234	3.03	2.60	1.898	0	17	0.70	7.90
Females 60–69 years	1.124	2.57	2.20	1.643	0	16	0.30	6.70
Males 60–69 years	1.023	2.94	2.60	1.822	0	17	0.60	7.60
Females 70–79 years	1.179	2.61	2.30	1.604	0	15	0.50	6.60
Males 70–79 years	1.065	3.13	2.70	1.955	0	15	0.80	8.24
Females 80–89 years	227	2.62	2.20	1.735	0	11	0.00	6.60
Males 80–89 years	142	2.88	2.60	1.985	0	16	0.60	8.81
Females ≥90 years	12	2.27	2.05	1.231	0	5	0.30	–
Males ≥90 years	4	3.10	3.80	1.625	1	4	0.70	–

STD, standard deviation; min, minimum; max, maximum; P2.5, 2.5th percentile; P97.5, 97.5th percentile indicating reference intervals for eosinophils.

Table 8: Lymphocytes by gender and age decade.

	n	Mean	Median	STD	Min	Max	P2.5	P97.5
All females	2.568	31.58	31.50	7.36	7.80	51.40	17.82	45.70
All males	2.278	29.22	29.00	7.29	9.90	49.20	15.70	43.50
Females 60–69 years	1.122	32.71	32.55	6.99	7.80	51.40	19.01	45.89
Males 60–69 years	1.036	29.85	29.50	7.10	11.00	49.20	16.70	43.80
Females 70–79 years	1.201	31.00	30.90	7.43	12.20	48.50	17.20	45.09
Males 70–79 years	1.080	28.90	28.40	7.28	9.90	48.00	15.80	43.40
Females 80–89 years	233	29.30	29.10	7.85	12.80	48.10	16.38	46.00
Males 80–89 years	158	27.34	26.35	8.21	11.60	46.40	14.08	43.41
Females ≥90 years	12	27.95	26.45	7.26	19.10	44.80	19.10	–
Males ≥90 years	4	27.37	29.50	6.26	18.40	32.10	18.40	–

STD, standard deviation; min, minimum; max, maximum; P2.5, 2.5th percentile; P97.5, 97.5th percentile indicating reference intervals for lymphocytes.

Table 9: Monocytes by gender and age decade.

	n	Mean	Median	STD	Min	Max	P2.5	P97.5
All females	2.513	8.60	8.40	1.93	3.70	28.00	5.40	12.91
All males	2.208	9.46	9.30	2.12	3.30	22.20	6.02	14.37
Females 60–69 years	1.107	8.37	8.20	1.88	3.70	14.70	5.17	12.50
Males 60–69 years	1.011	9.30	9.10	2.08	3.30	22.20	5.93	13.90
Females 70–79 years	1.165	8.69	8.50	1.91	4.00	28.00	5.60	13.00
Males 70–79 years	1.052	9.61	9.50	2.14	4.20	17.80	6.10	14.60
Females 80–89 years	226	9.12	8.95	1.98	4.70	15.80	5.70	13.79
Males 80–89 years	141	9.48	9.10	2.21	5.50	20.70	5.72	15.24
Females ≥90 years	15	11.12	10.50	3.01	7.20	16.10	7.20	–
Males ≥90 years	4	10.82	10.05	2.14	9.30	13.90	9.30	–

STD, standard deviation; min, minimum; max, maximum; P2.5, 2.5th percentile; P97.5, 97.5th percentile indicating reference intervals for monocytes.

was below the DGHO reference values with 136,000 (CI 129,000;142,000). In monocytes, our results were above the DGHO reference values with 6.0 (5.7;6.2) to 14.3 (13.9;14.8) in males and 5.4 (5.2;5.6) to 12.9 (12.6;13.4) in females (Table 11). CRP, GGT and LDH values were above the BDI reference values, comparable with the previous data of a senior patient cohort analysis [17] (Table 11).

We additionally compared the complete distribution between males and females and among age groups based on the Kolmogorov-Smirnov test. There was no significant difference revealed except for platelets: they were significantly lower in males than in females ($p < 0.001$) and significantly declined over age decades ($p < 0.001$).

Table 10: Neutrophils by gender and age decade.

	n	Mean	Median	STD	Min	Max	P2.5	P97.5
All females	2.521	56.06	56.20	7.70	33.30	75.60	41.50	70.10
All males	2.158	56.99	57.30	7.25	33.6	74.70	42.19	69.70
Females 60–69 years	1.114	55.39	55.50	7.47	34.10	75.00	41.50	69.91
Males 60–69 years	9.6	56.80	57.00	7.14	38.10	74.20	42.19	69.40
Females 70–79 years	1.173	56.32	56.40	7.82	33.30	75.60	41.17	70.06
Males 70–79 years	1.019	57.05	57.40	7.29	33.60	74.70	42.10	69.75
Females 80–89 years	222	57.80	57.80	7.93	40.00	73.30	41.53	71.02
Males 80–89 years	139	57.86	58.20	7.78	37.10	72.00	41.30	70.20
Females ≥90 years	12	58.82	59.35	6.55	45.30	68.50	45.30	–
Males ≥90 years	4	58.12	57.70	3.85	54.00	63.10	54.00	–

STD, standard deviation; min, minimum; max, maximum; P2.5, 2.5th percentile; P97.5, 97.5th percentile indicating reference intervals for neutrophils.

Table 11: Comparison of study results with reference values.

Parameter	Reference values by DGHO (Onkopedia guideline 1&2)	Reference values by BDI	Our study results (P2.5 [CI]–P97.5 [CI])	Carlsson et al. [17]
Platelets, 10 ³ /μL	>150,000/μL (M, F)	/	136,000–343,000 (M) 15,300–38,900 (F)	/
Leukocytes, 10 ³ /μL	/	3800–10,500 (M, F)	4300–10,800 (F) 3800–10,400 (M)	/
Basophil leukocytes, %	0–1 (M, F)	/	0.3–1.5 (M, F)	/
Eosinophil leukocytes, %	2–4 (M, F)	/	0.7–7.9 (M) 0.3–6.6 (F)	/
Neutrophil leukocytes, %	40–70 (segmented) 3–5 (core) (M, F)	/	41.5–70.1 (F) 42.2–69.7 (M) (no core/segmented differentiation)	/
Monocytes, %	3–7 (M, F)	/	6.0–14.3 (M) 5.4–12.9 (F)	/
Lymphocytes, %	20–40 (M, F)	/	15.7–43.5 (M) 17.8–45.7 (F)	/
C-reactive protein, mg/L	/	<5 (M, F)	<5 [;<5]^a–34 [22;75] (M) <5 [;<5]^a–24 [17;34] (F)	0.33 [0.3;0.4]–12.6 [9.1;16.1] (M) 0.34 [0.3;0.4]–12.42 [8.5;16.3] (F)
γ-Glutamyl-transferase, U/L	/	6–28 (M) 4–18 (F)	14 [13;15]–140 [121;175] (M) 11 [10;12]–99 [88;114] (F)	10.7–114.5 (M) 8.3–71.9 (F)
Lactate-dehydrogenase, U/L	/	135–225 (M) 135–214 (F)	141 [136;147]–307 [294;345] (M) 147 [134;153]–317 [301;343] (F)	95–227,9 (M) 89–233 (F)

M, males; F, females; BDI, Berufsverband Deutscher Internisten (German Association of Specialists in Internal Medicine); DGHO, Deutsche Gesellschaft für Hämatologie und internistische Onkologie (German Society of Hematology and Oncology). ^aValues <5 were not distinguished by the laboratory, therefore a lower confidence level is not given; 76% of the CRP values were <5. Bold values: study results deviating from reference values.

The correlation analysis of mean cell volume (MCV) and platelets did not reveal any association ($r = -0.06$).

Discussion

The aim of the study was the analysis of laboratory blood parameters of hematologically healthy patients aged

60 years or older to assess normal value ranges and check for deviation from established reference values issued by medical expert associations.

The results of our analysis revealed that the leukocyte levels remained within the reference interval recommended by the BDI. For the leukocyte subtypes eosinophils, basophils, neutrophils (without differentiation between the segmented and the core type in our study) and lymphocytes, the reference intervals found in

this study group were also in accordance with the reference values of younger patients as recommended by the DGHO and the BDI. For monocytes, however, our study revealed higher upper limits than those recommended by the DGHO. Given the fact that monocytes play a central role in both the initiation and resolution of inflammation [18] and are subject to immunosenescence [19], this finding might point to the age-associated process of inflammation, called “inflamm-aging” [20]. This idea is supported by our finding of elevated CRP values in this study group: the results showed no clinically relevant difference between gender age groups, while comparison with younger patients (BDI) revealed that the upper limits in this aged patient group were elevated. This finding is in accordance with the results by Carlsson et al. [17], who analyzed laboratory parameters like CRP among Swedish persons aged ≥ 70 years [17]. Given the fact that values of monocytes in this hematologically healthy patient group are also higher than the reference values among younger patients [15, 16], these findings might possibly point to this age-associated underlying chronic low-grade inflammation with increased levels of proinflammatory cytokines [21], which is meanwhile widely acknowledged to occur with rising age [22]. Interestingly, Leng et al. reported similar findings in their study group of frail older women, revealing elevated white blood cell counts, albeit under the upper limit of the normal range referred to, but associated with elevated counts of monocytes [23, 24]. The upregulation of monocytes has been supposed to be a response to the activation of an inflammatory pathway, a molecular mechanism leading to chronic inflammation, which is a risk factor for frailty [25]. Additionally, previous studies have also shown an association between elevated inflammatory molecules like CRP and frailty syndrome in older patients [26]. As the inclusion criteria of this study were intended to select hematologically healthy seniors, no reliable estimation about the frailty status can be made. If elevated levels of inflammatory molecules and cells might be precursors of a developing frailty syndrome remains speculative and should be subject to further studies.

Based on these findings, one can conclude that laboratory test results for CRP and monocytes should be interpreted carefully and depending on patients' age. Thus, the establishment of age-dependent reference values is required.

In our patient group, platelet values were higher in women than in men and significantly decreased ($p < 0.001$) among men with rising age. This finding is in accordance with a previous Italian study on age- and gender-related changes in platelet counts [27]. The study group concluded that laboratory reference values should be adapted

to age classes with estimated levels of 122–350,000/ μL for older men and 140–379,000/ μL for older women [27]. The reason for this age-associated decline of platelets is still unclear. In a recent review, Jones addressed these gaps to our knowledge about decline, function and biochemical changes in platelets of patients aged >75 years [28]. While there are sufficient data about platelet count, function and platelet biochemistry derived from younger patients, a reliable database for geriatric patients aged >75 years is lacking. Our results are in accordance with these previous findings and underline the recommendation of adapting laboratory platelet reference values to older age [27, 28]. An association between platelets and MCV, typical for myelodysplastic syndromes, was not seen in this patient cohort [29]. The finding of an age-associated decline of platelets in men will be of particular clinical importance in connection with poly medication and drug-induced thrombocytopenia in geriatric patients [30]. However, further research is needed before general recommendations can be given.

In our study, women had lower, but not significantly lower, GGT values than men. The upper limit of GGT values is higher in this aged study group than that recommended by the BDI [15]. Our results, however, are in accordance with the results of a Swedish study research group, revealing higher limits of GGT among their study patients aged ≥ 70 years [17]. A possible explanation for this finding might be found when considering the role of GGT as a cardiovascular risk factor and its association with increased risk of fatal outcome in chronic heart failure patients [31]. Comorbidity of our study patients remains unclear and inclusion in the study only required lack of hematological disease. Given the increasing prevalence of cardiovascular comorbidity with rising age, the elevated GGT levels in this study group may suggest an association. It would be of interest to study GGT levels in aged patients without cardiovascular disease.

Interestingly, in our study group, the upper limits of LDH were higher than in the younger patients (BDI) and also higher than in the Swedish peer group [17]. The reason for this finding remains unclear, but comorbidity (e.g. skeletal muscle or cancer disease) might play a role, as our patients had only been selected to be hematologically healthy.

Our study has some limitations: Due to the cross-sectional character, data for statistical evaluation were not available for all study parameters. Additionally, we did not get any information about patients' smoking habits, medication or comorbidities which might have a negative impact on study parameters.

The virtues of our study are the large number of patients and the unique character, because there have not

been any comparably large evaluations on aged persons in Germany before.

Our findings underline that some laboratory parameters seem to be age-dependent and change with growing older. Others, however, like leukocytes and leukocyte subtypes (except monocytes) seem to remain stable independent of age. The adaptation of reference values for selected laboratory parameters like platelets (in men), monocytes, CRP, GGT and LDH in older German patients should be well considered and patients' age and comorbidity should be taken into account for the interpretation of laboratory test results.

Acknowledgments: We thank Detlev Zimmermann (LADR) for the kind provision of data.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

- Plebani M, Lackner K. Reference values: still a critical issue in laboratory medicine. *Clin Chem Lab Med* 2010;48:577–8.
- Edvardsson M, Levander MS, Ernerudh J, Theodorsson E, Grodzinsky E. Clinical use of conventional reference intervals in the frail elderly. *J Eval Clin Pract* 2015;21:229–35.
- Risch M, Nydegger U, Risch L. SENIORLAB: a prospective observational study investigating laboratory parameters and their reference intervals in the elderly. *Medicine* 2017;96:1–8.
- Adeli K, Higgins V, Nieuwesteeg M, Raizman JE, Chen Y, Wong SL, et al. Biochemical marker reference values across pediatric, adult, and geriatric ages: establishment of robust pediatric and adult reference intervals on the basis of the Canadian Health Measures Survey. *Clin Chem* 2015;61:1049–62.
- Adeli K, Raizman JE, Chen Y, Higgins V, Nieuwesteeg M, Abdelhal-eem M, et al. Complex biological profile of hematologic markers across pediatric, adult, and geriatric ages: establishment of robust pediatric and adult reference intervals on the basis of the Canadian Health Measures Survey. *Clin Chem* 2015;61:1075–86.
- Milan Calenti JC, Sanchez A, Lotenzo Lopez L, Maseda A. Laboratory values in a Spanish population of older adults: a comparison with reference values from younger adults. *Maturitas* 2012;71:396–401.
- Tsang CW, Lazarus R, Smith W, Mitchell P, Koutts J, Burnett L. Hematological indices in an older population sample: derivation of healthy reference values. *Clin Chem* 1998;44:96–101.
- Ittermann T, Roser M, Wood G, Preez H, Lüdemann J, Völzke H, et al. Reference intervals for eight measurands of the blood count in a large population based study. *Clin Lab* 2010;56:9–19.
- Röhrig G, Güttgemann I, Gutensohn K, Nebe T. Red blood cell counts and indices in the elderly German population. *J Lab Med* 2018;42:131–9.
- Harris EK, Boyd JC. Statistical bases of reference values in laboratory medicine (Statistics: a series of textbooks and monographs) – First Edition (ISBN 0-8247-9339-0). New York: Marcel Dekker, Inc., 1995.
- Hastka J, Metzgeroth G. Rational diagnostic work-up of anemia. *J Lab Med* 2015;39:273–289.
- Canal C, Pellicer R, Facundo C, Gràcia-García S, Montañés-Bermúdez R, Ruiz-García C, et al. Tables for estimating the glomerular filtration rate using the new CKD-EPI equation from serum creatinine concentration. *Nefrologia* 2014;34:223–9.
- Schaeffner ES, Ebert N, Delanaye P, Frei U, Gaedeke J, Jakob O, et al. Two novel equations to estimate kidney function in persons aged 70 years or older. *Ann Intern Med* 2012;157:471–81.
- Horowitz G, Altaie S, Boyd JS, Ceriotti F, Garg U, Horn P, et al. Defining, establishing, and verifying reference intervals in the clinical laboratory; Approved Guideline – Third Edition CLSI document C28-A3 (ISBN 1-56238-663-8). Wayne, PA: Clinical and Laboratory Standards Institute, vol. 28(30), 2008.
- German Association of Specialists in Internal Medicine (Beruf-sverband Deutscher Internisten). <https://www.internisten-im-netz.de/mediathek/blutbild-erklaerung/leukozyten.html>. Accessed 20 Aug 2018.
- Onkopedia guideline: hematologic diagnostic steps. Available at: <https://www.onkopedia.com/de/onkopedia/guidelines/>. Accessed 20 Aug 2018.
- Carlsson L, Lind L, Larsson A. Reference values for 27 clinical chemistry tests in 70-year-old males and females. *Gerontology*. 2010;56(3):259–65.
- Albright JM, Dunn RC, Shults JA, Boe DM, Afshar M, Kovacs EJ. Advanced age alters monocyte and macrophage responses. *Antioxid Redox Signal* 2016;25:805–15.
- Linton PJ, Thoman ML. Immunosenescence in monocytes, macrophages, and dendritic cells: lessons learned from the lung and heart. *Immunol Lett* 2014;162:290–7.
- Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. *Ann NY Acad Sci* 2000;908:244–54.
- Michaud M, Balardy L, Moulis G, Gaudin C, Peyrot C, Vellas B, et al. Proinflammatory cytokines, aging, and age-related diseases. *J Am Med Dir Assoc* 2013;14:877–82.
- Cevenini E, Monti D, Franceschi C. Inflamm-aging. *Curr Opin Clin Nutr Metab Care* 2013;16:14–20.
- Leng SX, Xue QL, Tian J, Walston JD, Fried LP. Inflammation and frailty in older women. *J Am Geriatr Soc*. 2007;55:864–71.
- Leng SX, Xue QL, Tian J, Huang Y, Yeh SH, Fried LP. Associations of neutrophil and monocyte counts with frailty in community-dwelling disabled older women: results from the Women's Health and Aging Studies I. *Exp Gerontol* 2009;44:511–6.
- Qu TT, Yang H, Walston JD, Fedarko JS, Leng SX. Upregulated monocytic expression of CXCL10 (CXCL-10) and its relationship with serum interleukin-6 levels in the X, syndrome of frailty. *Cytokine* 2009;46:319–24.
- Chen X, Mao G, Leng SX. Frailty syndrome: an overview. *Clin Interv Aging* 2014;9:433–41.

27. Biino G, Santimone I, Minelli C, Sorice R, Frongia B, Traglia M, et al. Age- and sex-related variations in platelet count in Italy: a proposal of reference ranges based on 40987 subjects' data. *PLoS One* 2013;8:e54289.
28. Jones CI. Platelet function and ageing. *Mamm Genome* 2016;27:358–66.
29. Vašeková P, Szépe P, Marcinek J, Balhárek T, Plank L. Clinically relevant possibilities and limits of differential diagnosis of megaloblastic anemia and myelodysplastic syndrome - refractory anemia type in bone marrow biopsies. *Vnitr Lek* 2016;62:692–7.
30. Röhrig G, Becker I, Pappas K, Polidori MC, Schulz RJ. Analysis of cytopenia in geriatric inpatients. *Z Gerontol Geriatr* 2018;51:231–6.
31. Poelzl G, Eberl C, AchRAINER H, Doerler J, Pachinger O, Frick M, et al. Prevalence and prognostic significance of elevated gamma-glutamyltransferase in chronic heart failure. *Circ Heart Fail* 2009;2:294–302.