# What are optimum target levels of hemoglobin in older adults?

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**Keywords:** anemia, hemoglobin, geriatric assessment, elderly

**Conflict of interest:** None.

**Funding:** This research did not receive any funding from agencies in the public, commercial, or not-for-profit sectors.

**Word count for abstract:** 250

**Word count for main text:** 4896

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**ABSTRACT (250/250)**

**Aim:** The aim of this study is to identify optimum target levels of hemoglobin (Hgb) in older males and females according to cognitive performance, mood state, nutrition intake, balance-walking functions, muscle strength and performance in daily life activities.

**Method:** A total of 1942 geriatric patients who had undergone comprehensive geriatric assessment were evaluated. The patient's demographic characteristics, comorbid diseases, number of drugs, cognitive performance, mood and nutritional states, basic and instrumental daily living activity indexes were obtained from hospital files. Hgb levels were analyzed on the same day. Receiver Operating Characteristic analysis was used to detect the optimum level of Hgb according to best performance of geriatric assessment parameters.

**Results:** 1095 participants took part of who 71.9% were female and the mean age was 76.92±7.38 years (65-103 years). There was a significant negative correlation between age, number of drugs used, Geriatric Depression Scale-15, Timed Up and Go test and Hgb in both sexes while a significant positive correlation was found between Barthel and Lawton activities of daily living, Tinetti test, Mini Nutritional Assessment, Mini Mental State Examination and Hgb ($p<0.05$). The optimum Hgb levels were ≥13.0 for females and ≥ 13.9 in males.

**Conclusion:** Findings from the present study in relation to Hgb and key geriatric evaluation parameters suggests that the optimum level of Hgb for older females and males is higher than the level of Hgb in current definitions. Data from this study suggest that the optimum value of the Hgb level is 13.0 for females and 13.9 for males.

## INTRODUCTION

The World Health Organization (WHO) defines a level of hemoglobin (Hgb) below 12 g/dL in females, 13 g/dl in males and 11 g/dL in those who are pregnant as anemia [1]. It is important to note though that these "thresholds" of Hgb were determined 53 years ago. When describing anemia in laboratory terms, the most important factor is the level of Hgb, but also the Hgb sub-type distribution and altitude are important in oxygen release to tissues, gendercity and age are also noteworthy [2]. As a result of chronic disruption of tissue oxygenation, many metabolic problems can occur, as well as a reduction in quality- and enjoyment of life.

Anemia is one of the most common health problems affecting people of all age groups worldwide, with estimates suggesting more than one and half billion people suffer globally [3]. Literature shows that the proportion of older adults is increasing on a global scale. Moreover, life expectancy is increasing and is now close to exceeding the 80 year threshold for both sexes [4]. It is indeed plausible that the WHO definition of anemia developed over half a century ago is no longer suitable for present populations and may need to be redefined especially for the aging (geriatric) population.

The prevalence of anemia has been estimated to be between 17-24% in the aging population and can vary depending on the development of the residential area in which older adults live [5]. Worryingly, the prevalence of anemia has been found to be as high as 55% among the geriatric population living in nursing homes [6]. Literature has shown that those with anemia report a lower quality of life, exclusion from social activities owing to reasons such as chronic diseases, decreased functional capacity, cognitive impairments, gait and balance problems, malnutrition, muscle weakness and the other geriatric syndromes [7]. Moreover, it is well known that anemia increases the severity of all these conditions in older adults or facilitates their occurrence. Therefore, the Hgb value at the threshold of 12 and 13 g/dl may be inappropriate for the current aging population and the cut-off values derived decades ago may be different from today's cut-off values. Thus, we believe that there is a need for new cut-off values to determine the Hgb threshold for older adults, which should logically be higher than the Hgb threshold in young and middle aged adults.

The aim of this study is to determine the optimum target level of Hgb in older males and females according to cognitive performance, mood state, nutrition status, balance-walking functions, muscle strength and the best performance in daily life activities, which are important parameters of geriatric evaluation. Findings from this study may then be utilized as a platform for an updated definition of anemia in older adults.

## METHODS

**Participants:** 1942 elderly patients who attended a single geriatric outpatient clinic in Turkey/Istanbul and underwent comprehensive geriatric evaluation (CGA) were evaluated retrospectively.

Those with acute anemia (e.g. gastrointestinal tract bleeding) and those who cannot undergo CGA due to their current clinical condition (e.g. delirium or sepsis, stroke, malignancy, paraneoplastic syndrome, acute coronary syndrome, and similar serious comorbidities), patients with end-stage kidney disease, patients with Class III and IV hearth failure according to the New York Heart Association, patients with Gold stage III and IV chronic obstructive pulmonary disease, patients with neurodegenerative diseases such as dementia and Parkinson's disease and immobile patients, those who have severe vision and hearing impairment that prevent communication and understanding commands during the examination, those who refused to participate, and those who have terminal disease were not included in the study. After applying this exclusion criteria to the sample, a total of 1095 patients were available for study analysis.

**Comprehensive Geriatric Assessment:** Recorded data reported, demographic information (patient age, gender), comorbidities, the number of drugs used, Barthel basic daily living activities scale (BADL), Lawton instrumental daily living activities scale (IADL), Tinetti balance and gait scale, Mini nutritional assessment (MNA) test, Geriatric depression scale-15 (GDS-15), Mini mental state examination (MMSE), Time up and go (TUG) test were performed. Hand grip strength (HGS) measurements were made from the dominant hand and the highest of the three attempts was considered. [8,9]. According to these parameters, BADL scores ≥ 91) [10], IADL scores ≥ 17) [11], Tinetti Total Scores >19) and TUG < 13,5 sec) [12], MNA Scores > 23.5, [13]; GDS scores <5 [14] MMSE scores ≥ 23 [15]; HGS (female: > 16 kg, male: > 27 kg) were considered healthy [16].

**Definition of Anemia:** Blood was obtained from the participants after a 12-hour fast and after the patient had been in the sitting or supine position for at least 15 minutes. Hgb levels were analyzed using the hematology auto-analyzer. Anemia was defined using the WHO criteria: Hgb concentration below 12 g/dL in female and below 13 g/dL in male [1].

**Statistical Analyses:** IBM SPSS statistics 22.0 program was used for statistical analysis. Descriptive statistics were carried out to assess central tendency and distribution of study variables (e.g. mean, standard deviation, median, frequency). Skewness and kurtosis values were used together with the Shapiro-Wilk test to test for normal distribution of the data. While the one-way ANOVA test was used to compare more than two normally distributed variables, the Kruskal Wallis test was used to evaluate more than two non-normally distributed variables. Again, the chi-square test was used to evaluate the relationship between variables. In order to evaluate the correlation between data, Pearson correlation analysis was used for normally distributed data, and spearman correlation analysis was used for data that did not show normal distribution. ROC (Receiver Operating Characteristic) analysis was used to evaluate hemoglobin cut-off levels. Sensitivity and specificity were calculated for the optimum Hgb cutoff levels to detect the desirable cutoff values of BADL, IADL, MNA, Tinetti, TUG, MMSE, GDS and HGS. Results were evaluated at 95% confidence interval and significance level of $p < 0.05$.

## RESULTS

A total of 1095 participants, 787 female (71.9%), were included in the study. The mean age of the participants was 76.92 ± 7.38 years (65-103 years), while it was 76.98 ± 7.93 years for male and 76.89 ± 7.16 years for female (p=0.847). The average number of drugs used was 4.61±2.99 (0-15); while it was 4.31 ± 3.29 for female and 4.73±2.86 for male (p=0.055). The frequency of hypertension and coronary heart disease were more common in males than females ($p<0.05$) and there was no differences in terms of diabetes mellitus, congestive heart failure, chronic kidney disease, chronic obstructive pulmonary disease, cerebrovascular disease, hypothyroidism in both sexes.

While the Hgb levels of 1095 participants were 13.58 ±1.77 (7.8-18.6) g/dl, it was 14.46 ± 1.94 (8.7-18.6) g/dl for males and 13.24±1.56 (7.8-18.3) g/dl for females ($p<0.001$). We divided the patients into groups in homogeneous numbers of participants with 1.5 g/dl Hgb intervals in order to carry out analyses. The relationships of CGA parameters with Hgb sub-groups are shown separately for females and males in **Table 1** and **Figure 1.**

When we evaluated the correlation between age and geriatric evaluation parameters and Hgb levels, a significant negative correlation was found between age, the number of drugs used, GDS, TUG test and Hgb in both genders while a significant positive correlation was found between BADL, IADL, Tinetti total, MNA, MMSE and Hgb ($p<0.05$) (**Supplementary Table 1.**). Since there was a significant negative correlation between the Hgb levels and age, in order to examine the possible effect of this situation on the results, it was seen that the available graphs and results remained similar regardless of age, when the Hgb groups were compared separately in patients over 75 years of age and in both genders.

ROC analysis for the optimum level of Hgb in older females and males who were healthier according to the cutoff values of BADL, IADL, MNA, Tinetti, TUG, MMSE, GDS and HGS are shown in **Table 2.** ROC analysis of the Hgb cut-off levels to detect the desirable values of these geriatric assessment parameters were shown in Figure 2.

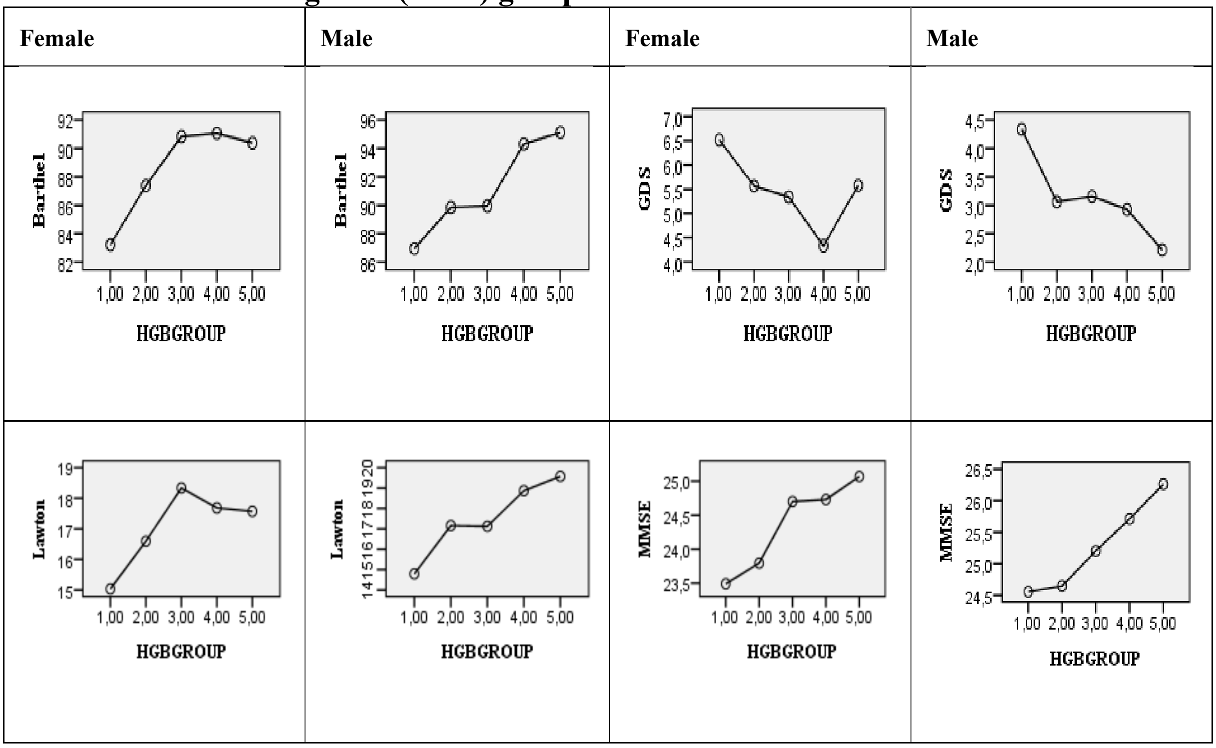
**Table 1: Evaluation of the relationship between geriatric assessment parameters and Hemoglobin groups in older females and older males**

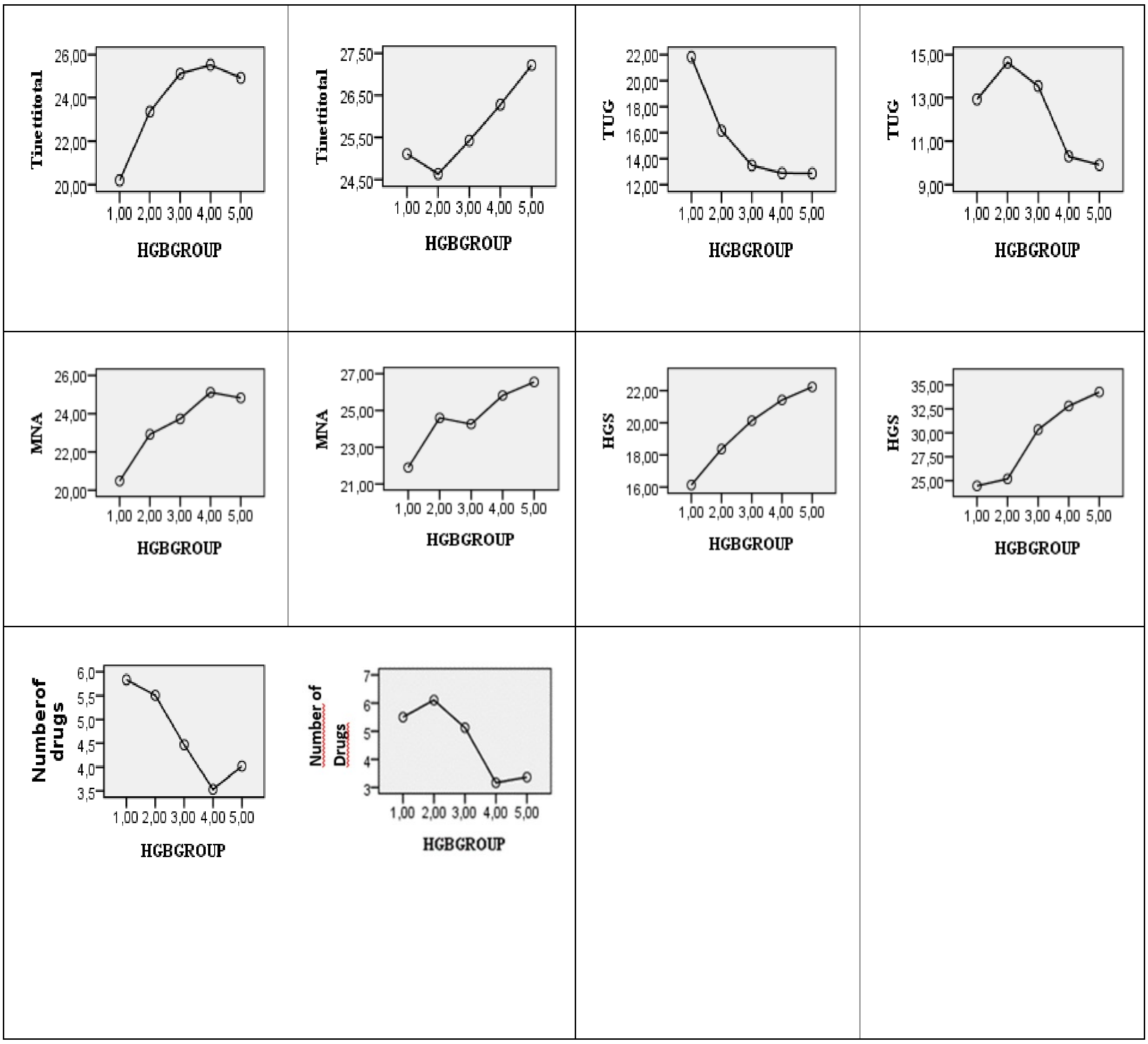
| Female | Group 1<br>Hgb <11 g/dl<br>n:61 | Group 2<br>Hgb:11-12.4 g/dl<br>n:252 | Group 3<br>Hgb:12.5-13.9 g/dl<br>n:301 | Group 4<br>Hgb:14-15.4 g/dl<br>n:123 | Group 5<br>Hgb ≥15.5 g/dl<br>n:49 | *p value* |
|---|---|---|---|---|---|---|
| Barthel | *83.21±12.04* | *87.38±13.53* | *90.83±8.31* | *91.06±8.11* | *90.37±5.58* | ***0.001*** |
| Lawton | *15.03±5.79* | *16.60±5.22* | *18.34±3.12* | *17.28±5.48* | *17.57±5.20* | ***0.001*** |
| Tinetti Total | *20.19±7.71* | *23.36±1.93* | *25.11±1.57* | *25.52±2.43* | *24.31±1.89* | ***0.001*** |
| MNA | *20.48±4.66* | *22.91±4.20* | *23.73±3.65* | *25.11±3.34* | *24.82±3.37* | ***0.001*** |
| GDS | *6.51±4.58* | *5.56±4.40* | *5.34±4.07* | *4.33±4.14* | *5.57±4.42* | ***0.018*** |
| MMSE | *23.49±5.33* | *23.79±4.66* | *24.70±3.69* | *24.73±4.44* | *25.07±2.97* | ***0.119*** |
| TUG (sec) | *21.80±14.87* | *16.13±8.82* | *13.47±6.92* | *12.86±6.01* | *12.84±7.99* | ***0.001*** |
| HGS (Kg) | *16.13±8.07* | *18.36±6.41* | *20.13±5.84* | *21.41±5.29* | *22.23±7.15* | ***0.001*** |
| Medication number | *5.84±3.20* | *5.51±2.89* | *4.47±2.74* | *3.53±2.60* | *4.02±1.96* | ***0.001*** |
| Test and Scale Name<br>**Male** | Group 1<br>Hgb <11 g/dl<br>n:20 | Group 2<br>Hgb:11-12.4 g/dl<br>n:38 | Group 3<br>Hgb:12.5-13.9 g/dl<br>n:90 | Group 4<br>Hgb:14-15.4 g/dl<br>n:54 | Group 5<br>Hgb ≥ 15.5 g/dl<br>n:107 | *p value* |

| | | | | | | |
|---|---|---|---|---|---|---|
| Barthel | *86.95±12.32* | *89.84±13.41* | *89.94±14.61* | *94.30±12.28* | *95.11±6.95* | ***0.002*** |
| Lawton | *14.79±5.45* | *17.16±5.74* | *17.12±5.79* | *18.87±5.00* | *19.57±3.80* | ***0.001*** |
| Tinetti Total | *25.10±4.38* | *24.63±2.19* | *25.42±2.83* | *26.27±3.76* | *27.21±2.38* | ***0.003*** |
| MNA | *21.89±5.10* | *24.59±3.37* | *24.25±3.41* | *25.81±2.84* | *26.54±2.09* | ***0.001*** |
| GDS | *4.33±4.67* | *3.05±3.53* | *3.15±3.82* | *2.92±3.42* | *2.21±3.24* | ***0.132*** |
| MMSE | *24.56±2.81* | *24.65±4.44* | *25.20±3.55* | *25.71±3.51* | *26.76±3.33* | ***0.043*** |
| TUG (Sec) | *12.93±4.33* | *14.63±7.21* | *13.54±8.26* | *10.29±4.70* | *9.90±2.80* | ***0.001*** |
| HGS (Kg) | *24.45±8.62* | *25.18±7.11* | *30.33±8.86* | *32.80±8.01* | *34.26±7.79* | ***0.001*** |
| Medication number | *5.50±4.28* | *6.11±3.69* | *5.13±3.16* | *3.17±3.10* | *4.31±3.29* | ***0.001*** |

**Barthel:** Barthel basic daily living activities scale, **Lawton:** Lawton instrumental daily living activities scale, **MNA:** Mini nutritional assessment test, **GDS:** Geriatric depression scale, **MMSE:** Mini mental state examination, **TUG:** Time up and go test, **HGS:** Hand grip strength

**Figure 1: Evaluation of the relationship between the geriatric evaluation parameters of individuals and Hemoglobin (HGB) groups in older females and older males**






**Barthel:** Barthel basic daily living activities scale, **Lawton:** Lawton instrumental daily living activities scale, **MNA:** Mini nutritional assessment test, **GDS:** Geriatric depression scale, **MMSE:** Mini mental state examination, **TUG:** Time up and go test, **HGS:** Hand grip strength

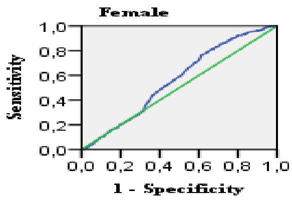
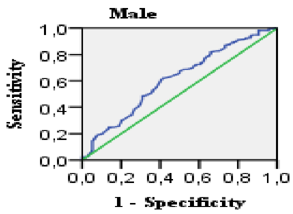
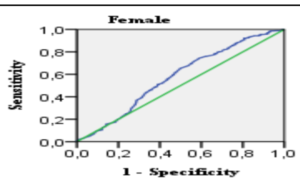
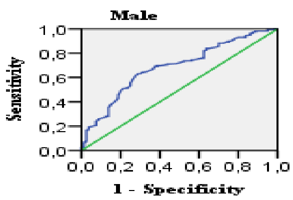
## Table 2: Evaluation of cut-off values of hemoglobin with ROC analysis

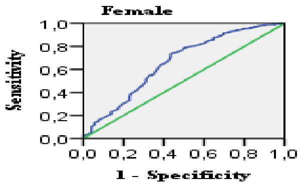
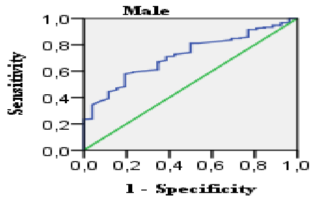
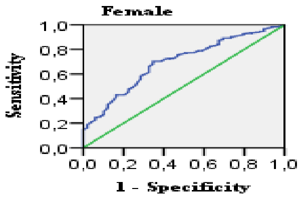
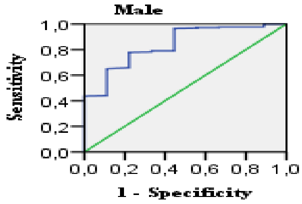
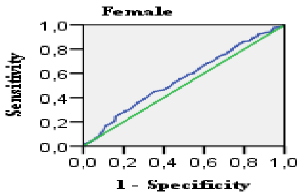
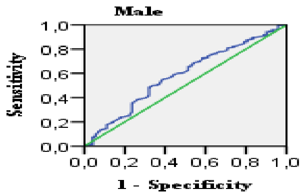
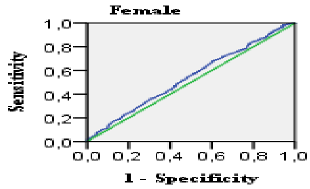
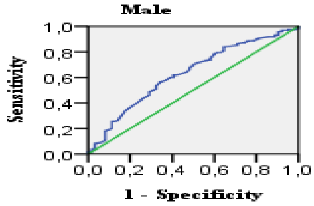
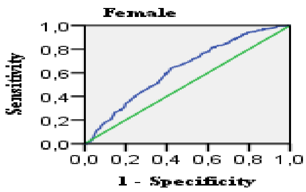
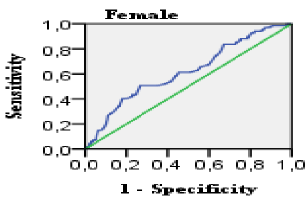
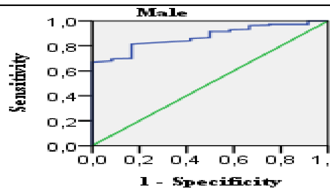
| **Female**<br>**Factor** | AUC (%95) | Hemoglobin Cut off | p | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|
| Barthel (Scores ≥ 91) | *0,563 (0,523-0,603)* | *13,28* | *0,002* | *0,552* | *0,533* |
| Lawton (Scores ≥ 17) | *0,575 (0,531-0,618)* | *13,21* | *0,001* | *0,559* | *0,562* |
| Tinetti Total (Scores >19) | *0,659 (0,602-0,716)* | *13,01* | *0,001* | *0,608* | *0,631* |
| MNA ( Scores > 23,5) | *0,694 (0,623-0,766)* | *13,03* | *0,001* | *0,582* | *0,714* |
| GDS ( Scores < 5 ) | *0,555 (0,514-0,596)* | *13,31* | *0,009* | *0,525* | *0,546* |
| MMSE ( Scores ≥ 23 ) | *0,541 (0,496-0,585)* | *13,28* | *0,72* | *0,530* | *0,518* |

| | | | | | |
|---|---|---|---|---|---|
| TUG ( < 13,5 sn) | *0,671 (0,601-0,741)* | *13,21* | *0,001* | *0,596* | *0,599* |
| HGS (Female> 16 kg) | *0,666 (0,624-0,709)* | *13,11* | *0,001* | *0,620* | *0,624* |
| **Male** **Factor** | AUC (%95) | Hemoglobin Cut off | p | Sensitivity (%) | Specificity (%) |
| Barthel (Scores ≥ 91) | *0,612 (0,543-0,680)* | *14,38* | *0,002* | *0,603* | *0,596* |
| Lawton (Scores ≥ 17) | *0,686 (0,620-0,752)* | *14,15* | *0,002* | *0,667* | *0,638* |
| Tinetti Total (Scores >19) | *0,717 (0,631-0,803)* | *14,01* | *0,001* | *0,645* | *0,654* |
| MNA ( Scores > 23,5) | *0,839 (0,717-0,960)* | *13,93* | *0,002* | *0,646* | *0,889* |
| GDS ( Scores < 5 ) | *0,582 (0,506-0,658)* | *14,45* | *0,037* | *0,570* | *0,569* |
| MMSE ( Scores ≥ 23 ) | *0,631 (0,553-0,709)* | *14,33* | *0,002* | *0,600* | *0,597* |
| TUG ( < 13,5 sn) | *0,632 (0,592-0,672)* | *14,15* | *0,001* | *0,652* | *0,627* |
| HGS (Male > 27 Kg) | *0,725 (0,664-0,787)* | *14,28* | *0,001* | *0,660* | *0,667* |

**Barthel:** Barthel basic daily living activities scale, **Lawton:** Lawton instrumental daily living activities scale, **MNA:** Mini nutritional assessment test, **GDS:** Geriatric depression scale, **MMSE:** Mini mental state examination, **TUG:** Time up and go test, **HGS:** Hand grip strength, **AUC:** Area under the curve

**Figure 2. ROC analysis of the Hemoglobin cut-off levels to detect the desirable values of geriatric assessment parameters**

| Factor | Female | Male |
|---|---|---|
| Barthel (Scores ≥ 91) |   |   |
| Lawton (Scores ≥ 17) |   |   |

| | | |
|---|---|---|
| Tinetti Total<br><br>(Scores >19) |  |  |
| MNA<br><br>( Scores > 23,5) |  |  |
| GDS<br><br>( Scores < 5 ) |  |  |
| MMSE<br><br>( Scores ≥ 23 ) |  |  |
| TUG<br><br>( < 13,5 sn) |  |  |
| HGS<br><br>(Female> 16 kg)<br><br>(Male > 27 Kg) |  |  |

**Barthel:** Barthel basic daily living activities scale, **Lawton:** Lawton instrumental daily living activities scale, **MNA:** Mini nutritional assessment test, **GDS:** Geriatric depression scale, **MMSE:** Mini mental state examination, **TUG:** Time up and go test, **HGS:** Hand grip strength

## DISCUSSION

In this study, it was found that anemia in older adults is directly or inversely correlated with many geriatric assessment parameters that show real life quality. Increase in Hgb levels in both females and males correlates with the age of the patient, the number of drugs used, a decrease in depressive symptoms and the risk of falling, an increase in independence and cognitive performance in activities of daily living, improvement in nutritional status and muscle strength. With the exception of cognitive functions in females, all values were more favorable in the Hgb range of 14.0-15.5 g/dl, while they were best in males ≥ 15.5 g/dl. According to the geriatric evaluation parameters, the lowest value of the optimum Hgb level in females was 13.0 g/dl, while it was 13.9 g/dl in males.

The average and the lowest Hgb values for older females and males found in our study were consistent with findings from previous literature [17,18]. The aim of this study was to identify an Hgb threshold where patients can successfully perform geriatric assessment tests that represent quality of life and functionality with criteria closest to real life data. In other words, our primary aim in the present study was to determine the Hgb level at which older adults reach optimal quality of life and functionality. For this, BADL and IADL were used to evaluate functionality [19]. In studies conducted with BADL, it has been shown that anemic elderly patients are more dependent on others than non-anemic patients and that they are not able to fully care for themselves [20]. In the study conducted by Röhrig et al. [20] BADL score was found to be decreased in anemic patients (47.9 points vs 54.3 points respectively) and the most adversely affected components of the BADL included climbing the stairs and showering. In our study, It was observed that the lower the Hgb level, the lower the BADL score (BI score for group 1: 84.09 points and group 2: 87.7 points) as similar to the aforementioned study. The results of 91 points and above, the value for which the BI score is considered successful, was observed in group 4 and group 5 patients (BI score for group 4: 92.05 and group 5: 93.6). For a successful BADL, the median Hgb level was 13.3 g/dL in older females and 14.4 g/dL in older males. IADL, one of the daily living activity assessment scale, is more related to cognitive functional capacity than physical strength, when compared with BADL. In a study conducted by Bosco et al [21] , it was found that elderly patients without anemia are better able to achieve skills on the IADL and have more ability to live alone. It is an expected result that the aforementioned findings are consistent with this study. In our study, the median Hgb value of older females who scored 17 and above on the Lawton scale was 13.2 g/dL for older females and 14.2 g/dL for older males.

TUG test is a low cost and time efficient method used to evaluate functional capacity and general health status [22]. In a recent study by Ki Young Son et al. [23], a negative correlation was shown between anemia and TUG test in both genders. Our TUG test results were significantly longer in patients of both genders in group 1 and 2. In our study, for an desirable TUG test result (similar to BADL), the Hgb value for older males was 14.2 g/dL, while it was 13.2 g/dL for older females.

Depression is common (10-20%) in older people [24]. In the InCHIANTI social observation study, depressive symptoms were found at a rate of 15% in anemic patients, while this rate was 8% in non-anemic patients [25]. Previous studies report that low Hgb aggravates depression in the elderly [26]. While the GDS score was found to be > 5 in the patients in Group 1 and 2, the GDS score decreased linearly with the increase in Hgb levels (Group 3: 4.85, Group 4: 3.90, Group 5: 3.22), differences in GDS scores in group distributions between both sexes may be explained by older females experiencing postmenopausal hormonal changes, a high frequency of anemia, socio-economic differences, and differences in education and income levels. The desired level of GDS results (<5 points) were observed at Hgb of 13.3 g/dL in older females, and Hgb of 14.5 g/dL in older males. When looking at Hgb level with optimum MMSE, just like GDS, it was identified to be13.3 g/dL in females and 14.3 g/dL in males. There are many studies in the literature that show the relationship between anemia and cognitive impairment and dementia risk with conflicting results [27,28]. When we analyze the relationship between hemoglobin subgroups and MMSE score, no negative difference was shown between groups or genders (MMSE score group 1: 23.77 points, group 5: 25.91 points). There are studies supporting our results [29], as well as those showing the relationship of anemia with cognitive impairment and dementia risk [30,31]. The reasons for this distinct difference between studies may be due to the patients' hospitalization status, SSRI / tranquilizer-type drug use that affects cognitive functions, socio-economic and educational status.

Falls and falls-related injuries are a common problem in older adults. Although contradictory results were encountered in the studies conducted, falls should logically be related to the degree of anemia. In the Kora-Age study, no statistically significant results were shown between anemia and falls in multivariable adjusted or non-adjusted models [32]. In the study conducted by Dharmarajan et al., it was shown that falls were observed more frequently in elderly anemic patients and every 1 g/dL increase in Hgb value reduced the risk of falling by 22% [33]. In our study, we used the Tinetti test to evaluate the risk of falling and a positive improvement was observed in the Tinetti total score with the increase in Hgb. Median Hgb value was found to be

13.0 g / dL in older females and 14.0 g / dL in older males with an optimal Tinetti total score. One potential reason for the observed difference between previous studies and this study is that anemia is not the only cause of falls in the elderly, muscle mass, concomitant diseases, orthostatic hypotension and polypharmacy are also important risk factors for falling.

Muscle weakness in the elderly causes limitations in physical activity and mobility [34]. It has often been shown in the literature that as the severity of anemia increases, HGS decreases. Alley et al [35] showed that HGS decreased in elderly anemic Australian patients. The correlation between low HGS and anemia was also found in older females [36] in the study conducted by Santos et al. In the present study, in line with the results in the literature, low HGS was found in group 1 in females and in groups 1 and 2 in males. An optimal HGS score was obtained with a median Hgb level of 13.1 g/dL in older females and 14.3 g/dL in older males.

A clear strength of the present work is that multiple geriatric assessments and Hgb could be evaluated at the same time and this is the first study to investigate the optimal levels of Hgb for each geriatric assessment parameters in the literature. However, findings from this study must be interpreted in light of the studies limitations: the study is cross-sectional in design limiting our understanding of the direction of the observed evaluations. Data were not collected on some other parameters which might increase ones risk of anemia, such as iron, vitamin B12, and ferritin. Finally, another limitation may be that disease-specific target Hgb levels (eg., diabetes mellitus, congestive heart failure) could not be analyzed separately.

In conclusion, the concept of anemia, which thresholds were identified over 50 years ago, should be recalculated considering age. In the new definition of anemia, the amount of Hgb to be determined for older females and males is much higher than the level of Hgb in the current definition of anemia. The optimum target value of the Hgb level identified in this study is 13.0 g/dL for older females and 13.9 g/dL for older males. Large-scale, prospective, and international studies are now needed for the development of precise definitions.

**Compliance with ethical standards**

**Conflict of Interest:** None

**Description of authors' roles:** P Soysal designed the study, collected the paper. Osman Kara wrote the paper. L Smith supervised and edited the paper. M Kiskac was responsible for the statistical design of the study and for carrying out the statistical analysis.

**Ethical approval** The study design and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Ethics Committee of Bezmialem Vakif University—14/300) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Human and animal rights disclosure This article does not contain any studies with animals performed by any of the authors. Informed consent Informed consent was obtained from all individual participants included in the study.

**Availability of data and material:** All data generated or analyzed during this study is available for proposals and can be obtained from the corresponding author.

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