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Hematological and Immunological parameters in apparently healthy people in Ethiopia: Systematic review and meta-analysis

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Abstract

Background: Hematological and immunological parameters are fundamental components of person's health assessment. Quantitative determination of normal reference range of hematological and immunological parameters of apparently health people used to assist diagnosis of various diseases. The reference values currently used in Asia and Africa have been obtained from researches on populations in developed countries and may not be applicable in most local settings. The local reference values for immunohematological parameters are essential components of evidence based medicine.

Objectives: The aim of the present study was to review exiting literatures and establishing normal reference range of hematological and immunological parameters in Ethiopia.

Result: Meta-analysis by random effect model showed that the estimated pooled mean and 95% CI of red blood cells, white blood cells, and platelets in males was 5.29 x 1012/l (95% CI; 5.15-5.44 x 1012/l) respectively while the mean and 95% CI of red blood cells, white blood cells, and platelets in females was 4.77 x 1012/l (95% CI; 4.61-4.94 x 1012/l) respectively.

Conclusion: the estimated pooled mean and 95% CI of hematological and immunological parameters showed some degree of difference with reference range adopted from developed country.

Background

Hematological and immunological parameters are fundamental components of person's health assessment [1]. Quantitative determination of normal reference range of hematological and immunological parameters of apparently health people used to assist diagnosis of various diseases [2,3]. The reference values currently used in Asia and Africa have been obtained from researches on populations in developed countries and may not be applicable in most local settings [4]. The local reference values for immunohematological parameters are essential components of evidence based medicine [4].

Normal hematological and immunological parameters vary considerably between healthy people by age, gender, ethnicity, genetics, and geographical location [5]. Normal reference intervals (RIs) of hematological and immunological parameters of one population might be the cutoff point of clinical decision for other population [6] This indicates that pre-established hematological reference values from developed countries may lead to misdiagnosis and wrong treatments [7]. That is the reason why Clinical and Laboratory Standards Institute (CLSI) recommended that reference range should be established for each age, gender, ethnicity, and geographical location of the population [8,9].

In clinical practice before clinical decisions are made, patient's laboratory results are compared with the corresponding reference intervals (RIs) [10,11]. Hematological and immunological RIs used in evaluating the state of health of individuals and/or populations [12], and also used in identifying people at risk for disease, in assessing immune status, disease progression and response to treatment [13,14]. Any deviation from normal hematological and immunological reference range is indicative for several human diseases and therefore constitutes important parameters for diagnosis and patient monitoring particularly in this era of evidence-based medicine [15-17].

Hematological and immunological parameters for example used to screen anemia, blood disorders, diseases of the immune system and infection [12]. Of particular importance is the use of reference values as surrogate markers for monitoring disease progression and response to antiretroviral therapy in HIV-infected individuals. For example, decisions to initiate, continue, or change antiretroviral therapy regimens are determined using CD4+ T lymphocyte cell (CD4) counts [18,19]

To our knowledge no meta-analysis conducted on hematological and immunological profiles in Ethiopia. The aim of the present study was to review exiting literatures and establishing normal reference range of hematological and immunological parameters in Ethiopia. This will help policy maker and it also helps health care worker in evidence based clinical medicine.

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Methodology

Objectives: The aim of the present study was to review exiting literatures and establishing normal reference range of hematological and immunological parameters in Ethiopia.

Types of participants

Participants were apparently healthy people; non pregnant women and HIV negative peoples.

Search strategy

We searched literatures published in English until November 2019 on electronic data bases PubMed, EMBASE, African Journal online (AJO) and Google scholar. We have also searched the reference lists of identified papers. Keywords used in the search included those that express hematological and Immunological parameters (e.g. complete blood count, hematological profiles, Immunological profiles, hematological parameters, Immunological parameters, hematological reference intervals, immunological reference intervals) combined with keywords related to population context of the study (e.g. apparently health people, healthy people, HIV negative people, blood donors, and Ethiopia). Full-text articles were retrieved after review of the title and abstract.

Inclusion and exclusion criteria

Inclusion criteria: Without publication year restrictions all studies published in English until November 25/2019 were included in the review. The review considered studies that include the following outcome measures: Mean, standard deviation and reference interval of hematological parameters (Red blood cells (RBCs), White blood cells (WBCs), platelets, WBCs differentials (neutrophil, eosinophil, basophil, monocytes, lymphocytes and immunological parameters (CD4, CD4%, CD8, CD3). Studies considered in this review were those which conducted hematological and immunological parameters using automated hematological analyzers. There was no restriction to study design made.

Exclusion criteria: Any study conducted on symptomatic patient and/or on pregnant women, and/or on HIV positive patients were excluded from the study. Studies which hematological parameters conducted using manual method were excluded. Studies determined hemoglobin concentration using Sahli-hillage and hematocrit using micro-hematocrit centrifuge method were excluded.

Selection of studies

Two authors (EA and KD) independently checked the titles and abstracts resulting from the searches. References of search results were manipulated using Endnote 5 citation manager. Relevant titles and abstracts were then selected by EA, KD and SA. EA and KD assessed all full-text articles for methodological quality.

Assessment of Methodological Quality

Studies selected for inclusion were assessed for methodological quality by two independent reviewers (EA and KD) using standard critical appraisal instruments of the Joanna Briggs Institute (JBI-MAStARI) [20]. For inclusion in the review, both reviewers agreed that a cut-off score of 60% out of 100% be used to determine acceptable quality for inclusion.

Ten methodological assessment criteria for quality assessment of included study were the following: objective of the study clearly described, study design clearly stated, sample size representativeness, method of analysis of hematological parameters, outcome assessed with the objective criteria, were confounders reported, were potential biases reported, was outcome clearly described, appropriate statistical analysis method used, and if whether the context of the study is Ethiopia.

Data extraction

Data were extracted from eligible study by three investigator (EA, KD, SA) using a standardized data extraction form. Then the extracted data were merged together for meta-analysis. Primary outcomes extracted from each study were, the citation details, sample size, year of publication, location of study, mean, standard deviation, and reference intervals of hematological and immunological parameters. Secondary outcome considered were mean, standard deviation, and reference range of hematological and immunological parameters according to age, sex, and population.

Statistical Analysis

The R software was used to pool the mean from the included studies with user contributed commands for meta-analyses: metamean, metainf, metabias, and metareg. The random-effects meta-analysis models were chosen because heterogeneity was demonstrated and it was used to determine the weighted mean difference (WMD) and 95% confidence intervals.

Risk of bias and sensitivity analysis

Statistical heterogeneity was evaluated using Cochrane Q x2 test and I^2 statistic [21]. A significance level of $P<0.10$ and I^2 >50% was interpreted as evidence of heterogeneity [22]. A potential source of heterogeneity was investigated by subgroup analysis and meta-regression analysis [23]. The presence of publication bias was assessed informally by visual inspections of funnel plots [24]. Sensitivity analysis was conducted to explores the effects of the addition/removal of lower quality studies on the results and conclusions of a review was reported [21].

Results

Identified Studies

Following the initial search, 57 studies were reviewed by their title and abstract (Figure 1). Of these, 20 were retrieved for full-text review, 8 did not match the eligibility criteria for the study. Following methodological quality assessment, twelve articles were included in the meta-analysis. In a circumstance two articles reported outcomes from the same study; both articles were treated as a single study [25,26]. So, the final analyses included were 12 independent research studies. In the included studies a total of 8,148 apparently health people assessed for hematological and immunological parameters. All papers were published in English.

Characteristics of included study

The characteristics of the included studies have been shown in (Table 1). Five studies were conducted on different population of the same town Addis Ababa [25-29]. One study was conducted in Gonder [30], one study in Debre Markos [31], one study in Amhara [32], one study in Bahr Dar [33], one study in Mekele [34], one study in Gojam [35], one study in Jimma [36] and one study was conducted in Gilgil Gibe [4].

Table 1. Characteristics of included study

Author	Study site	Year	sample size	study design	study subject
Aster Tsegaye	Aqaqi qaliti	1999	142	Cross-sectional	Factory workers
K Nebecka	Addis Ababa	2012	1,868	Cross-sectional	Bank worker
Bamlaku Enawgaw	Amhara	2018	967	Cross-sectional	Blood donors
Bayeh Abera	Bahr Dar	2012	405	Cross-sectional	VCT seeking adult
Tigist Tadele	Debre Markos	2016	250	Cross-sectional	Blood donors
Eskedar Awelachew	Addis Ababa	2016	360	Cross-sectional	Blood donors
T. Messele	Addis Ababa	1999	52	Cross-sectional	Healthy adults
Afework Kassu	Aqaqi qaliti	2001	218	Cross-sectional	Factory workers
Tewelde Tesfaye	Mekele	2015	2282	Cross-sectional	Factory workers
Wondemagegn Mulu	Gojjam	2017	481	Cross-sectional	Community
Aregawi Yalew	Gonder	2016	240	Cross-sectional	Blood donors
Lealem Gedefaw	Jimma	2018	883	community-based Cross-sectional	Community

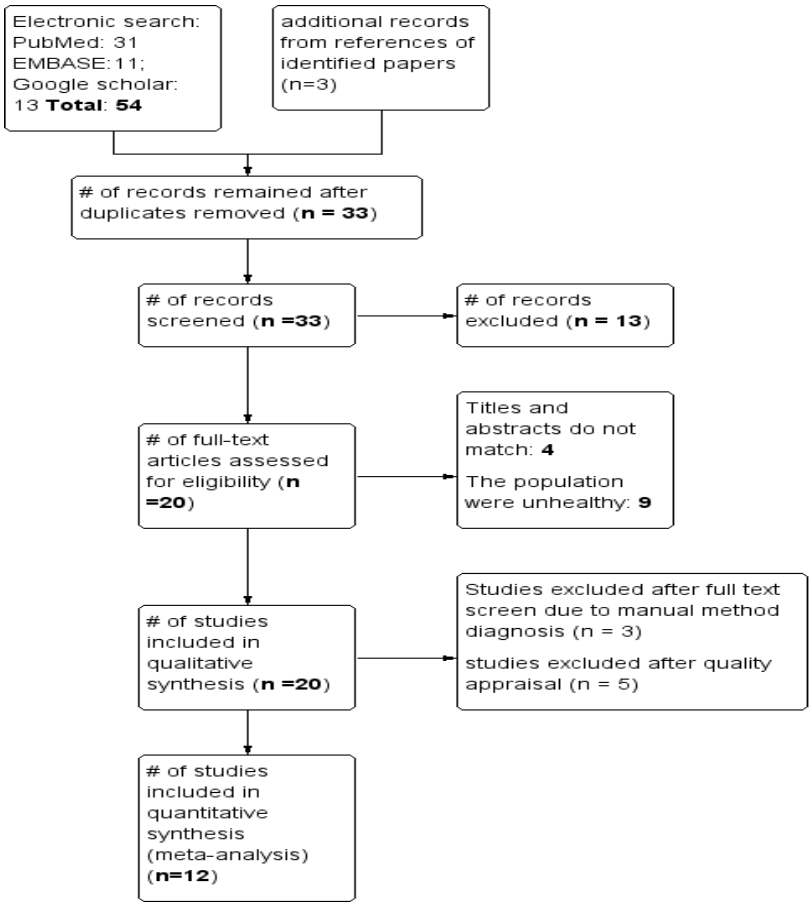

Figure 1. Flow chart of the search and study inclusion

Qualitative summary

From the total of 12 study included in the Meta analysis, all of them were cross-sectional study. Most of the studies conducted hematological and immunological parameters investigation by automated machine.

Meta-analysis outcome

According to data from eight included studies meta-analysis by random effect model showed that the estimated pooled mean of red blood cells is 5.29 x 10^{12}/l (95% CI; 5.15-5.44 x 10^{12}/l) in male and 4.77 x 10^{12}/l (95% CI; 4.61-4.94 x 10^{12}/l) in female (Table 2) (Figure 2). Test of heterogeneity showed that it is heterogeneous (Quantifying heterogeneity: $t^2 = 0.0437$; $I^2 = 99\%$, $P < 0.01$) (Figures 3 and 4) (Table 3).

The mean and reference interval of hematological and immunological parameters of apparently healthy people of Ethiopia is summarized in the Table 4 according to the sex of the person.

Risk of bias and sensitivity analysis

Subgroup analysis was conducted to see the possible cause of heterogeneity. The possible cause of heterogeneity probably be the altitude of the participants gender as shown on the figure above. Unfortunately, the specific cause of heterogeneity cannot be identified due to limited population characteristic are available.

The funnel plot helped us distinguish between publication bias and other causes of the asymmetry. We demonstrated no publication bias (t

Table 2. The estimated pooled mean and 95% CI of Hematological and Immunological parameters among apparently healthy people in Ethiopia, 2019

Parameters	Male		Female	
	Mean	(95% CI)	Mean	(95% CI)
RBCs (10^{12}/l)	5.29	5.25 – 5.44	4.77	4.61 - 4.96
WBCs (10^9/l)	6.26	3.9 - 6.62	6.38	5.99 – 6.77
Hemoglobin (g/dl)	15.49	14.53 -16.45	13.79	13.13 -14.45
Hematocrit (%)	46.72	45.57 – 47.87	43.69	40.41 – 46.96
MCV (fl)	90.65	85.74 – 95.55	90.96	85.01 – 96.91
MCH (pg)	29.97	28.80 - 31.14	29.80	28.94 – 30.66
MCHC (g/dl)	33.15	31.93 – 34.35	32.63	31.42 – 33.83
RDW	13.17	12.13 – 14.21	13.21	12.40 – 14.03
Platelets (10^6/mm^3)	194.80	69.72 – 319.89	264.17	222.33 – 306.01
Neutrophil (10^9/l)	3.52	3.27 - 3.77	3.64	3.24 – 4.04
Monocyte (10^9/l)	0.42	0.30 – 0.54	0.40	0.23 - 0.56
Lymphocyte (10^9/l)	1.96	1.78 – 2.14	2.0	1.77 – 2.23
CD4	734.94	674.41 – 795.46	839.42	750.46 – 928.37
CD8	679.09	603.21 – 754.97	620.02	574.38 – 665.66
CD3	1449	1234.27 – 1665.13	1463.96	1335.82 – 1592.10

Table 3. Influential analysis (Fixed effect model)

I^2	Mean	95%-CI	p-value	tau^2
K Nebecka (2012)	44.4442	[44.3374; 44.5511]	13.6053	99.7%
Bamlaku Enawgaw (2018)	43.4609	[43.3291; 43.5928]	17.3135	99.6%
Bayeh Abera (2012)	44.2502	[44.1424; 44.3580]	12.7778	99.6%
Tigist Tadele (2016)	44.3560	[44.2483; 44.4637]	13.7316	99.7%
Eskedar Awelachew (2016)	44.2374	[44.1292; 44.3457]	12.9909	99.6%
Aregawi Yalew (2016)	44.3954	[44.2887; 44.5022]	13.4608	99.7%
Lealem Gedefaw (2018)	44.3057	[44.1914; 44.4199]	16.3622	99.7%
K Nebecka (2012)	44.5076	[44.4009; 44.6143]	13.0406	99.6%
Bamlaku Enawgaw (2018)	46.0353	[45.9119; 46.1586]	5.7873	98.9%
Bayeh Abera (2012)	44.4221	[44.3145; 44.5297]	13.9281	99.7%
Tigist Tadele (2016)	44.4426	[44.3363; 44.5488]	13.3383	99.7%
Eskedar Awelachew (2016)	44.4408	[44.3345; 44.5472]	13.3980	99.7%
Aregawi Yalew (2016)	44.2915	[44.1848; 44.3983]	11.7934	99.6%
Lealem Gedefaw (2018)	44.4814	[44.3734; 44.5894]	13.9776	99.7%
Pooled estimate	44.4306	[44.3246; 44.5366]	13.2753	99.6%

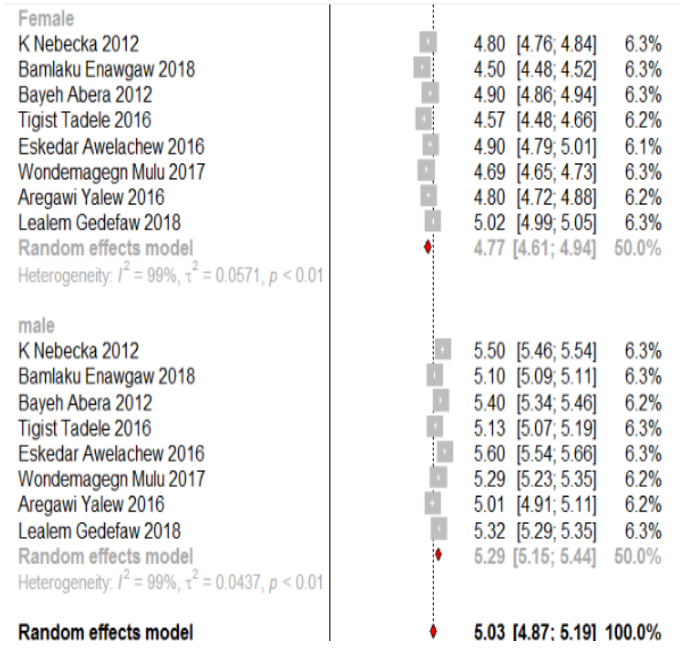

Figure 2. Mean of red blood cells in apparently health male and female in Ethiopia

= -1.3505, df = 11, p-value = 0.1927). we have also conducted influence analysis of individual studies (Table 3).

Discussion

The aim of the review was to estimate the mean and 95% confidence interval of hematological and immunological parameters in apparently healthy Ethiopian. In this review some hematological and immunological parameters showed significant difference from the guideline currently used in the country.

Table 4. Comparison between current review and Reference range currently used in Ethiopia

Parameters		Mean of present review	Mean reference [37]
RBCs (10^{12}/l)	Male	5.29	5.4
	Female	4.77	4.8
WBCs (10^9/l)	Male	6.26	7.2
	Female	6.38	
Hemoglobin (g/dl)	Male	15.49	14.3
	Female	13.79	14.0
Hematocrit (%)	Male	46.72	46.0
	Female	43.39	42.0
MCV (fl)	Male	90.65	91
	Female	90.96	
MCH (pg)	Male	29.97	31
	Female	29.80	
MCHC (g/dl)	Male	33.15	34
	Female	32.63	
RDW	Male	13.17	12.8
	Female	13.21	
Platelets (10^6/mm^3)	Male	185.80	280
	Female	264.17	
Neutrophil (10^9/l)	Male	3.52	3.0
	Female	3.64	
Monocyte (10^9/l)	Male	0.42	0.4
	Female	0.40	
Lymphocyte (10^9/l)	Male	1.96	0.9
	Female	2.0	
CD4	Male	734.94	753
	Female	839.42	816
CD8	Male	679.09	777
	Female	620.02	692

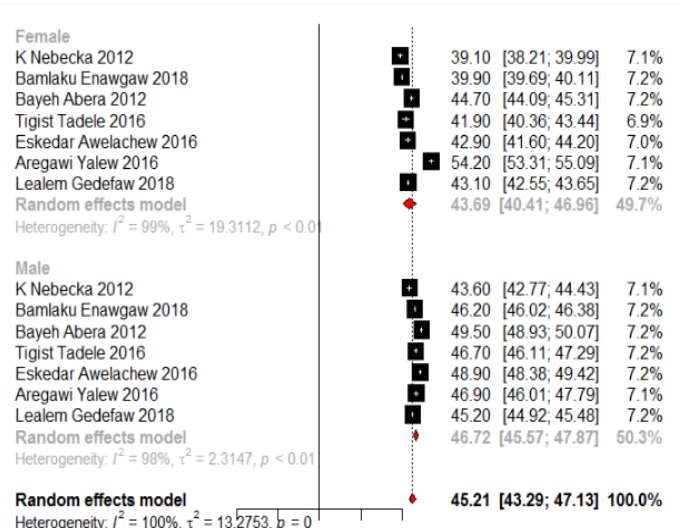

Figure 3. Mean of hematocrit in apparently health people in Ethiopia

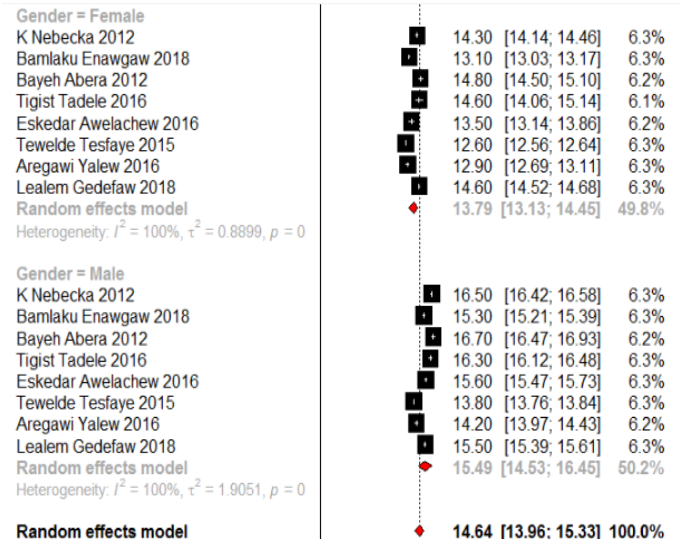

Figure 4. Mean of hemoglobin in apparently health people in Ethiopia

In Ethiopia the difference between highest mean hematocrit value and lowest mean hematocrit value was 5.7% [27,33]. In Ethiopia study conducted on commercial bank worker in Addis Ababa showed lowest mean of platelets among male participant [27].

The mean and 95% CI of hematological and immunological parameters varies depending age, gender, and altitude. In this review we demonstrated heterogeneity. Subgroup analysis was conducted to see the possible cause of heterogeneity by variable gender. Unfortunately the specific cause of heterogeneity cannot be identified. The unresolved heterogeneity could be due to merged report of hematological and immunological parameters for both participants of lowland and highland in some of included studies [35]. The possible cause of heterogeneity probably is the altitude of the participants, age of participant and other but we couldn't able to get data on hematological and immunological parameters according to age category, and altitude of participants residence.

To explain the specific causes of heterogeneity, we did meta-regression and subgroup analyses on various variables including altitude, gender from which heterogeneity might come from. Other potential causes of heterogeneity may include age, sample size, and detection methods. Unfortunately, we did not analyze them, as there were not enough available data. By metabias computation we detected no publication bias (z = -0.98689, p-value = 0.3237).

When compared to national guideline (14.3g/dl) the present review showed higher mean of hemoglobin in male but have comparable mean hematocrit value both in male and female (Figure 4). On the other hand in this review mean hemoglobin concentration (MCH) and platelets counts both in male and female were lower than national guide line (31pg, 280 respectively). The comparable results of the present study and national reference range have been summarized in Table 4 [37].

However this review came up with pooled estimate of mean and 95% confidence interval of hematological and immunological parameters in apparently healthy people, we acknowledge few limitations of the present meta-analysis, which may affect the results. First of all however we conducted pooled mean for both with and without missing value, we reported the result of pooled mean and 95% CI of pooled mean without missing value.

Conclusion

The results of our meta-analysis showed high and/or low mean and 95% CI of hematological and immunological parameters in apparently healthy people when compared to RIs currently used in the Ethiopia.

Declarations

Conflicts of interest

There are no conflicts of interests to declare.

Availability of data and materials

All the datasets generated and analyzed during the review are included in this article.

Author's contribution

EA, KD and SA designed the study, extracted, critically reviewed and analyzed data and wrote the first draft of the manuscript, and approved the manuscript.

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Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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