

The reference values of ischemia modified albumin levels in healthy people admitted to a university hospital

[Bir üniversite hastanesine başvuran sağlıklı insanlarda iskemi modifiye albuminin referans değerleri]

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ABSTRACT

Objectives: The Ischemia Modified Albumin (IMA) test is a myocardial ischemia marker which may have potential use for the diagnosis of Acute Coronary Syndrome. The aim of this study was determine reference values of IMA test on the healthy people over the age of 15 who's admitted to Çanakkale Onsekiz Mart University.

Methods: This study was performed on 582 people over 15 years old and healthy in appearance who had presented at the Çanakkale Onsekiz Mart University Faculty of Medicine Research and Application Hospital. The year 2011 population of Turkey was taken as the reference in the distribution of the study group according to age group and gender. A survey which queried the demographic features and health problems was administered to the participants of the study and 9 cc venous blood was drawn. IMA levels were measured by using the spectrophotometric method defined by Bar-Or. The mean, standard deviation, median, minimum, maximum, and 2.5 % - 97.5 % interval were used in order to detect the IMA reference values.

Results: A total of 274 males (47.1 %) and 308 women (52.9 %) were studied. The mean IMA value of the examined group was 0.339 ± 0.093 , and the median was 0.343 (Min-Max: 0.053-0.631), while the 2.5 % - 97.5 % percentil values were 0.145 - 0.530.

Conclusion: Studies that indicate the reference levels of the IMA for the diagnosis of ischemic conditions are insufficient. Our study is expected to contribute to closing this gap.

Key Words: Ischemia, Ischemia-modified albumin, Reference range

Conflict of Interest: The authors do not have a conflict of interest regarding the subjects related to this manuscript.

ÖZET

Amaç: İskemi modifiye albumin (IMA) akut koroner sendromun tanısında potansiyel kullanımını olabilecek bir miyokardiyal iskemi belirteçidir. Bu çalışmada amacımız Çanakkale Onsekiz Mart Üniversitesi'ne başvuran 15 yaşın üzerindeki sağlıklı insanlarda IMA testinin referans değerlerini belirlemektir.

Gereç ve Yöntemler: Bu çalışma Çanakkale Onsekiz Mart Üniversitesi Tıp Fakültesi Araştırma ve Uygulama Hastanesine başvuran 15 yaş ve üzeri ve görünürde sağlıklı 582 kişi üzerinde gerçekleştirilmiştir. Çalışma grubunun yaş ve cinsiyet dağılımı belirlenirken 2011 yılı Türkiye nüfusu referans olarak alınmıştır. Katılımcılara demografik özelliklerinin ve sağlık problemlerinin sorgulandığı bir anket formu uygulandı ve 9 ml venöz kan alınmıştır. IMA düzeyleri Bar-Or tarafından tanımlanan spektrofotometrik metot kullanılarak ölçülmüştür. IMA referans değerlerini saptamak için ortalama, standart sapma, ortanca, minimum, maksimum ve % 2,5 - % 97,5 persentil değeri kullanılmıştır.

Bulgular: Toplamda 274 erkek (% 47,1) ve 308 kadın (% 52,9) değerlendirildi. Çalışılan grupta ortalama IMA değeri $0,339 \pm 0,093$, ortanca değeri 0,343 (Min-Maks: 0,053 - 0,631), % 2,5 - % 97,5 persentil değeri 0,145-0,530'dir.

Sonuçlar: İskemik durumların tanısında IMA'nın referans değerlerini vurgulayan çalışmalar yetersizdir. Bizim çalışmamızın bu açığı kapatmaya katkıda bulunacağını beklemekteyiz.

Anahtar Kelimeler: İskemi, İskemi Modifiye Albumin, Referans aralık

Çıkar Çatışması: Yazarların makale konusu dâhilinde herhangi bir çıkar çatışmaları bulunmamaktadır.

Introduction

Numerous studies have been done on the use of Ischemia Modified Albumin (IMA) in the diagnosis of acute coronary syndrome [1-3]. Some of these studies also define the decision values regarding the presence or absence of acute coronary syndrome in patients who come to the emergency service with acute chest pain [4, 5]. On the other hand, there are also studies stating that IMA levels increase in pathologies other than acute coronary syndromes and they may be a diagnostic marker in these pathologies as well [6-9]. In fact, some of these studies also suggested IMA as a marker for oxidative stress [10, 11]. However, the number of studies defining the normal population is inadequate. There is especially no study that identifies the Turkish population. In order to define the critical value of IMA that will be able to identify pathologic situations, the normal values in different age groups and genders should first be defined. Determining the normal IMA values of the population in different age groups and genders will help to identify the critical values in pathological conditions.

The aim of this study was to determine the reference values of the IMA test in people over the age of 15 who had no respiratory system and cardiac problems, chronic diseases such as hypertension, or any other health issue. The results obtained are expected to help in determining the critical value in pathological conditions such as the coronary syndrome in the long term.

Material and Methods

Study population and sample

This study was conducted at Çanakkale 18 Mart University Faculty of Medicine, Research and Application Hospital between May and July 2012. A total of 61070 people presented at the hospital outpatients in the same period. The gender distribution was 58.8% female and 41.2% male (35919 and 25151 respectively). We planned to reach a total of 600 subjects over the age of 15 who had presented at the hospital outpatients, were healthy in appearance, and had no respiratory system and cardiac problems or chronic diseases such as hypertension. The 2011 population of Turkey was taken as the reference for the distribution of the study groups according to the age group and gender. According to the Turkey Statistical Institute Address-Based Population Registration System, the population aged 15 and over in 2011 is 55,837,694. The gender distribution is 50.1 % female and 49.9 % male. In order to determine the distribution according to the age groups, we divided the population by age group (15-19, 20-24, 25-29, ... 90+) and stratified the subjects. Table 1 provides the distribution of reference, targeted and reached population according to the age groups. In the end, we identified 582 volunteers meeting the inclusion criteria of the study [12].

Procedure and measures of data collection

The study was conducted at the Çanakkale Onsekiz Mart University Application and Research Hospital by the Biochemistry Department. Research assistants of the Department of Biochemistry interviewed the patients who had presented at the hospital's outpatients for examination. After the patients were informed verbally and in writing, volunteers who had presented to the hospital outpatients over the age of 15, who were healthy in appearance, had no respiratory system and cardiac problems or chronic diseases such as hypertension participated in the study. The volunteers participating in the study were asked to fill a questionnaire containing demographic information and personal health history.

A total of 9 cc of venous blood was taken from IMA participants for determination of the reference value.

Laboratory analysis

The blood samples were transferred to plain tubes containing no preservatives. Clot formation was allowed for 30 minutes and the blood samples were centrifuged before separating the serum. Then, the obtained serum samples were subjected to measurement immediately. ACB was analyzed according to the method described by Bar-Or et al. In this method, 200 µL of serum is added to the water solution of 50 µL 0.1 % (w/v) cobalt chloride (CoCl₂•6H₂O; Sigma-Aldrich Inc., St Louis, MO, USA). It is mixed gently and left to sit for 10 minutes to allow for sufficient cobalt-albumin binding to occur. Then, 50 µL of dithiothreitol (1.5mg•mL⁻¹H₂O; Sigma-Aldrich Inc.) is added as a colorizing agent. After waiting for 2 minutes, 1.0 mL of 0.9% NaCl is added to stop the cobalt-albumin binding process. Next, absorbance is measured using a spectrophotometer at 470 nm. A blank sample without dithiothreitol is used as the blind. The results are reported in absorbance units (ABSU) [13].

Statistical evaluation

The data of the study were transferred to the SPSS 19.0 package program and the analysis was performed in this program. In order to detect the IMA reference values, mean, standard deviation, mean, minimum, maximum, and 2.5 % - 97.5 % interval were used. These values were calculated in five age groups over the age of 15 for both genders. The conformance of the IMA value with the normal distribution of the male, female and combined groups was evaluated with the Kolmogorov-Smirnov test and each of the three distributions was found to conform to the normal distribution (Figure 1).

Ethical approval

Consent was obtained from the Çanakkale Onsekiz University Clinical Studies Ethical Committee for this study (Decision Number: 2012-2, Date: 11.01.2012).

Results

A total of 582 subjects consisting of 274 males (47.1 %)

Table 1. Reference, Sample and Distribution of Reached Population According to the Age Groups and Gender, 2012, Canakkale, Turkey

Age Groups	REFERENCE POPULATION *						SAMPLE						ACHIEVED					
	Total		Male		Female		Total		Male		Female		Total		Male		Female	
	N	%	n	%	N	%	n	%	n	%	n	%	n	%	n	%	n	%
15 – 19	6317583	11.3	3240196	11.6	3077387	11.0	68	11.3	35	11.6	33	11.0	40	6.9	14	5.1	26	8.4
20 – 24	6224591	11.1	3173618	11.4	3050973	10.9	67	11.1	34	11.4	33	10.9	47	8.1	23	8.4	24	7.8
25 – 29	6306233	11.3	3210343	11.5	3095890	11.1	68	11.3	34	11.5	33	11.1	54	9.3	20	7.3	34	11.0
30 – 34	6495634	11.6	3285387	11.8	3210247	11.5	70	11.6	35	11.8	35	11.5	60	10.3	22	8.0	38	12.3
35 – 39	5632742	10.1	2837182	10.2	2795560	10.0	61	10.1	30	10.2	30	10.0	63	10.8	26	9.5	37	12.0
40 – 44	4770774	8.5	2430841	8.7	2339933	8.4	51	8.5	26	8.7	25	8.4	55	9.5	33	12.0	22	7.1
45 – 49	4786084	8.6	2405435	8.6	2380649	8.5	51	8.6	26	8.6	26	8.5	59	10.1	24	8.8	35	11.4
50 – 54	3792436	6.8	1909912	6.9	1882524	6.7	41	6.8	21	6.9	20	6.7	49	8.4	26	9.5	23	7.5
55 – 59	3454415	6.2	1716102	6.2	1738313	6.2	37	6.2	18	6.2	19	6.2	47	8.1	22	8.0	25	8.1
60 – 64	2566487	4.6	1231274	4.4	1335213	4.8	28	4.6	13	4.4	14	4.8	48	8.2	27	9.9	21	6.8
65 – 69	1868175	3.3	876489	3.1	991686	3.5	20	3.3	9	3.1	11	3.5	22	3.8	11	4.0	11	3.6
70 – 74	1451368	2.6	649739	2.3	801629	2.9	16	2.6	7	2.3	9	2.9	15	2.6	8	2.9	7	2.3
75 – 79	118310	2.0	497023	1.8	621287	2.2	12	2.2	5	1.8	7	2.2	15	2.6	12	4.4	3	1.0
80 – 84	688840	1.2	260355	0.9	428485	1.5	7	1.2	3	0.9	5	1.5	6	1.0	6	2.2	0	0.0
85 – 89	284594	0.5	94160	0.3	190434	0.7	3	0.5	1	0.3	2	0.7	1	0.2	0	0.0	1	0.3
90 - +	79428	0.1	20159	0.1	59269	0.2	1	0.1	0	0.1	1	0.2	1	0.2	0	0.0	1	0.3
Toplam	55837694	100.0	27838215	50.1	27999479	49.9	600	100.0	299	49.9	301	50.1	582	100.0	274	47.1	308	52.9

* Turkey Statistical Institute 2011 Address-Based Population Registration System Data

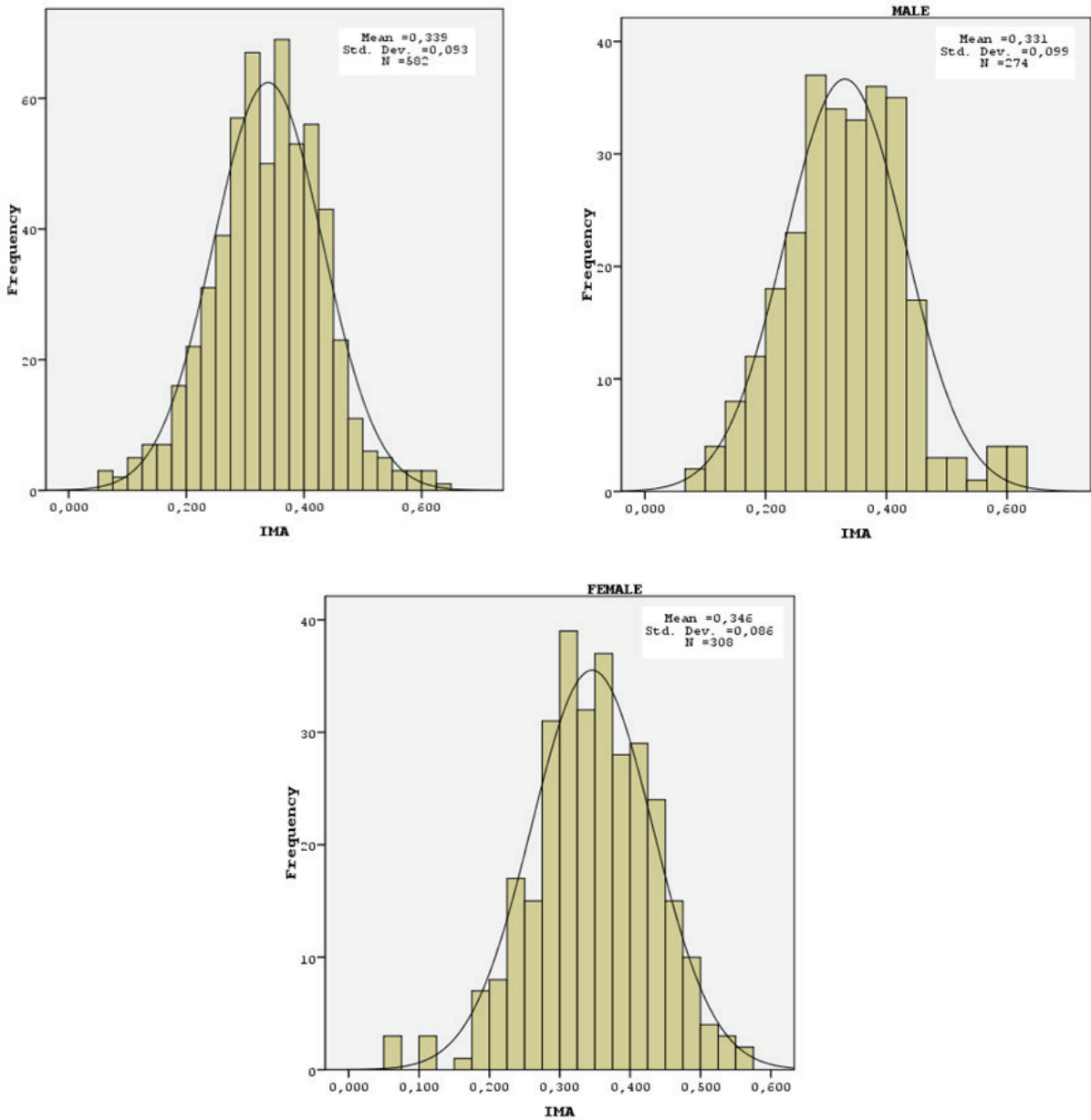


Figure 1. Distribution of IMA Values According to Gender, 2012, Canakkale, Turkey

and 308 women (52.9 %) were examined in this study. The mean age of the subjects was 43.1 ± 16.5 (male 45.5 ± 17.1 , female 40.9 ± 15.7) years. The 2011 population based on the Turkey Statistical Institute Address-Based Population Registration System was taken as the reference population. The distribution of the reference population, targeted and reached population according to the age groups is seen in Table 1.

The mean IMA value of the examined group was 0.339 ± 0.093 , the median 0.343 (Min-Max: 0.053 - 0.631), while the 2.5 % - 97.5 % interval values were 0.145-0.530 (Table 2). IMA value reference intervals of the age groups according to gender have been provided in Table 3, and the distributions of 50 %, 2.5 % and 97.5 % values of the

IMA values can be observed in Figure 2. There was no statistically significant difference the values according to age group. IMA values were observed to comply with the normal distribution in males and females and the total study group.

Coefficients of skewness and kurtosis of the examined group was found to be 0.101, 0.202 respectively. Skewness and kurtosis, respectively, 0.139, 0.277 were determined as in woman. In man, skewness and kurtosis was found to be 0.147 and 0.293 respectively.

Discussion

IMA is an early indicator of cardiac ischemia that develops before necrosis. However, a change in IMA levels

Table 2. Distribution of IMA Values According to the Age Groups, 2012, Canakkale, Turkey

Age Groups	Total		
	Mean±SD	Median(Min-Max)	2.5-97.5% Interval
15 – 19	0.330±0.098	0.355(0.062-0.475)	0.064-0.474
20 – 24	0.319±0.085	0.329(0.079-0.517)	0.092-0.500
25 – 29	0.349±0.087	0.342(0.167-0.613)	0.183-0.581
30 – 34	0.340±0.093	0.349(0.053-0.585)	0.088-0.565
35 – 39	0.353±0.102	0.357(0.100-0.631)	0.107-0.623
40 – 44	0.322±0.099	0.312(0.099-0.576)	0.105-0.550
45 – 49	0.352±0.101	0.364(0.112-0.609)	0.128-0.600
50 – 54	0.326±0.100	0.330(0.072-0.561)	0.092-0.544
55 – 59	0.350±0.080	0.359(0.204-0.532)	0.207-0.523
60 – 64	0.338±0.081	0.331(0.147-0.565)	0.155-0.540
65 – 69	0.333±0.070	0.322(0.202-0.467)	0.202-0.467
70 – 74	0.310±0.086	0.322(0.140-0.415)	0.140-0.415
75 – 79	0.361±0.107	0.370(0.126-0.572)	0.126-0.572
80 – 84	0.348±0.070	0.350(0.259-0.447)	0.259-0.447
85 – 89	0.285*	---	---
90 - +	0.456*	---	---
Total	0.339±0.093	0.343 (0.053-0.631)	0.145-0.530

*: Value of a single person

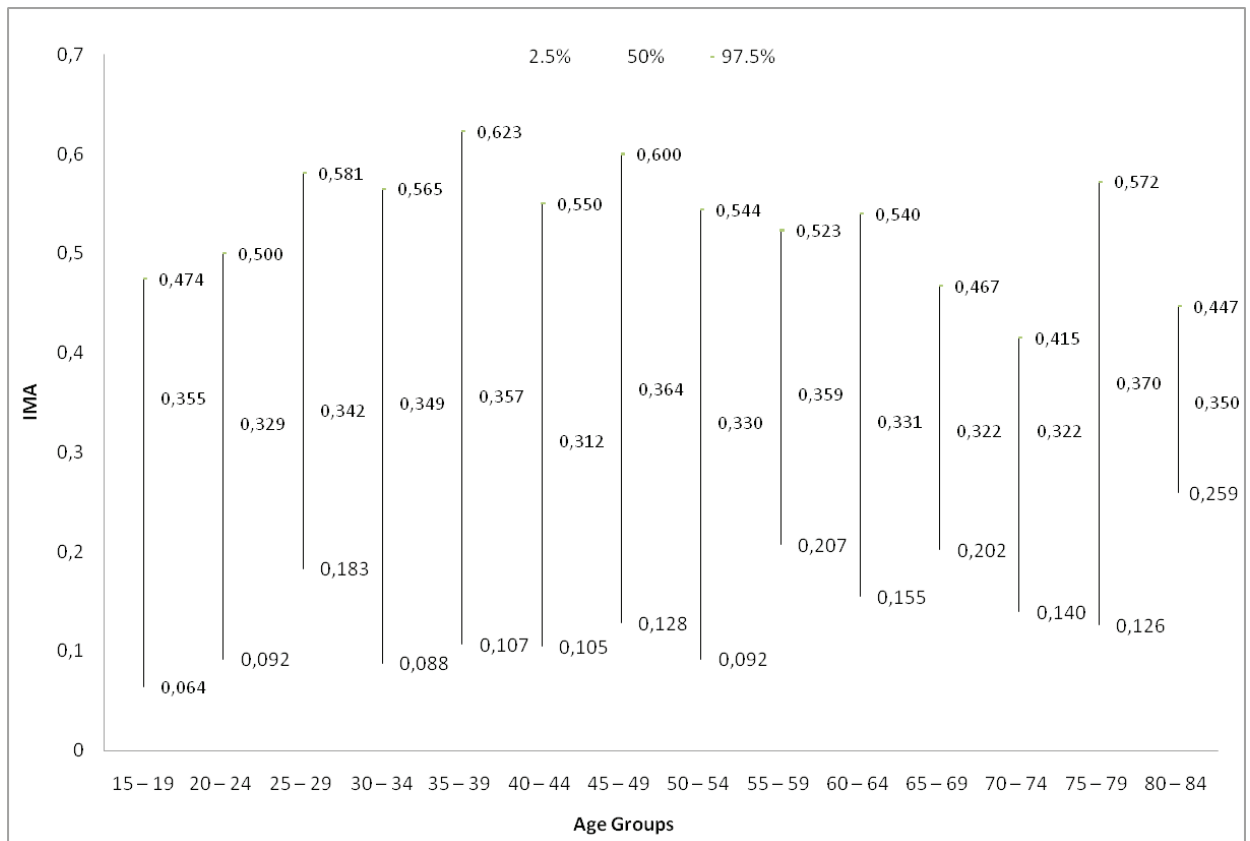


Figure 2. Distribution of IMA 2.5%, 50%, 97.5% Values According to the Age Groups, 2012, Canakkale, Turkey

Table 3. Distribution of IMA Values According to the Age Groups and Gender, 2012, Canakkale, Turkey

AgeGroups	Male			Female			p*
	Mean±SD	Median(Min-Max)	2.5-97.5% Interval	Mean±SD	Median(Min-Max)	2.5-97.5% Interval	
15 – 19	0.325±0.090	0.352(0.168-0.467)	0.168-0.467	0.332±0.103	0.355(0.062-0.475)	0.062-0.475	0.769
20 – 24	0.274±0.088	0.277(0.079-0.417)	0.079-0.417	0.361±0.057	0.366(0.222-0.517)	0.222-0.517	0.001
25 – 29	0.333±0.099	0.335(0.167-0.613)	0.167-0.613	0.359±0.079	0.356(0.217-0.529)	0.217-0.529	0.220
30 – 34	0.332±0.082	0.318(0.209-0.585)	0.209-0.585	0.344±0.100	0.354(0.053-0.548)	0.053-0.548	0.345
35 – 39	0.362±0.118	0.364(0.100-0.631)	0.100-0.631	0.347±0.090	0.350(0.113-0.520)	0.113-0.520	0.655
40 – 44	0.305±0.111	0.387(0.099-0.576)	0.099-0.576	0.347±0.074	0.334(0.206-0.476)	0.206-0.476	0.081
45 – 49	0.359±0.125	0.375(0.144-0.369)	0.144-0.609	0.348±0.082	0.350(0.112-0.496)	0.112-0.496	0.787
50 – 54	0.321±0.078	0.323(0.164-0.440)	0.164-0.440	0.332±0.121	0.337(0.072-0.561)	0.072-0.561	0.645
55 – 59	0.360±0.082	0.369(0.204-0.532)	0.204-0.532	0.341±0.079	0.354(0.221-0.489)	0.221-0.489	0.371
60 – 64	0.315±0.084	0.320(0.147-0.454)	0.147-0.454	0.366±0.070	0.335(0.236-0.565)	0.236-0.565	0.059
65 – 69	0.357±0.080	0.362(0.202-0.467)	0.202-0.467	0.309±0.052	0.300(0.232-0.419)	0.232-0.419	0.076
70 – 74	0.321±0.106	0.377(0.140-0.415)	0.140-0.415	0.299±0.062	0.290(0.194-0.403)	0.194-0.403	0.397
75 – 79	0.363±0.111	0.369(0.126-0.572)	0.126-0.572	0.354±0.109	0.370(0.238-0.455)	0.238-0.455	0.945
80 – 84	0.348±0.070	0.350(0.259-0.447)	0.259-0.447	---	---	---	---
85 – 89	---	---	---	0.285***	---	---	---
90 - +	---	---	---	0.456***	---	---	---
Toplam	0.331±0.099	0.331(0.079-0.631)	0.138-0.577	0.346±0.086	0.350 (0.053-0.565)	0.170-0.517	0.058**

* : Mann-Whitney U Test

** : Independent Sample T Test

*** : Value of a single person

does not only indicate cardiac pathology as IMA levels are also elevated in individuals with skeletal muscle ischemia [14, 15].

The study by Troxler et al. [16] revealed that skeletal muscle ischemia increased IMA levels in major arterial surgical procedures. Similar results were also reported by Montagnana et al. [17] during orthopedic surgical procedures.

There are no reference studies in the literature on IMA where normal reference ranges can be found. The majority of existing studies are in the form of comparison of ischemic situations with the controls without the relevant ischemic condition. In addition, the separation values for controls and patients in different diseases are very different. Türedi et al., in their study on patients with cardiac arrest, determined the mean IMA value of the ABSU type as 0.16 for the control group and 0.25 in the cardiac arrest group with an unfavorable prognosis [18]. Gündüz et al. found mean IMA values as 0.280 in patients with brain infarction and 0.172 for the control group [19]. However, in a study that evaluated IMA as a marker of oxidative stress in patients with beta thalassemia, IMA values were 0.725 in the thalassemia group and 0.554 in the control group [10]. An attempt has been made to estimate the IMA cut-off value in ischemic events from these studies. Chen et al defined the ABSU type mean IMA value in healthy people as a high value, 0.855, and the cut-off value for myocardial infarction as 0.906 [4]. The reference ranges of healthy individuals are required to find the pathological diagnosis values for IMA. It is not possible to say that the comparisons made with healthy groups in the studies are sufficient to provide these reference values. Shen et al found a value of 0.55 in subjects with Acute Coronary Syndrome and recommended a value of 0.34 for the control group [5].

The mean IMA value of 582 subjects over 15 years of age who presented at the Çanakkale Onsekiz Mart University Outpatients in our study was 0.339 ± 0.093 , the median 0.343 (Min-Max: 0.053 - 0.631), while the 2.5 % - 97.5 % interval values were 0.145-0.530.

Evaluation of the data we obtained in our study without considering age groups and gender provided results in support of Shen et al. [5]. However, the normal definition of a variable requires the taken sample to represent the universe in size and nature. A sample similar to the gender and age groups of the reference population that can be considered as the universe should therefore be selected. Although our study was conducted in the Çanakkale Province, we tried to use the Turkish population as the reference population in distribution when determining the distribution of sample size according to age and gender. Deviations in some age groups and in males are due to conduct of the study on patients who presented at the university hospital. A total of 61070 patients presented at the hospital outpatients during May-July 2012, when the study data was collected, of which 58.8

% (35919) were female and 41.2 % (25151) were male. This difference was naturally reflected in our study group. It was therefore quite hard to find a male patient who met the study inclusion criteria in some groups. Such studies that provide the normal IMA values are rare in the literature. Information about normal IMA values is usually obtained from the control groups consisting of small samples in studies that try to determine ischemic conditions. This is not a suitable method to find the reference ranges. Despite the problems with the age groups in our study, a sample that may close the gap in the literature has been studied. However, we need more studies that can represent the current population. The reference intervals, IMA level assessment of myocardial ischemia, distinguishing be used for diagnosis and follow-up. However, positive and negative predictive value that's the data to be obtained from the patient, the possibility to remain outside the reference range is not known. New studies are needed using the reference range values on patients diagnosed with myocardial infarction.

These studies will provide guidance in determining the pathological thresholds of IMA in ischemic conditions. The differences between the cut-off values currently obtained from the different studies in the literature can thus be decreased.

Conflict of Interest

There is no conflict of interest.

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