Original Article

Age-specific reference ranges of prostate-specific antigen in the elderly of Amirkola: A population-based study

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Abstract  Objective: To determine the age-specific reference ranges of prostate-specific antigen (PSA) in the older men in the city of Amirkola.
Methods: This cross-sectional study is a part of Amirkola Health and Ageing Project (AHAP) which has been conducted as a cohort study since 2011 in Amirkola, a city in northern Iran. The demographic information of all men aged 60 and older were collected through questionnaires and interviews and the PSA measurements were performed using ELISA and Diametra kit. The acquired data were analyzed afterwards.
Results: A number of 837 elderly men with a mean age of 69.99±7.72 years participated in this study. The serum PSA level (95th percentile) was determined to be 0.9 (0–4.89) ng/mL in the age group of 60–64 years, 1.1 (0–4.88) ng/mL in the age group of 65–69 years, 0.93 (0–9.01) ng/mL in the age group of 70–74 years, 1.3 (0–7.95) ng/mL in the age group of 75–79 years, 1.9 (0–11.98 ng/mL) in the age group of 80–84 years, and 1.45 (0–33.17) ng/mL in the 85 and older group. The serum PSA level was significantly correlated with age (p = 0.000).
Conclusion: This study indicated that there is a direct correlation between the age and serum PSA levels. The use of age-specific reference range could guide clinicians on the incidence of prostate cancer in this population and perhaps reduce the number of unnecessary tests in this population group.
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1. Introduction

Prostate cancer (PCa) is one of the most common types of cancers and the second-leading cause of death in men after lung cancer [1]. Late diagnosis is the main problem in this type of cancer (usually in stages 3 and 4), and its early stages are without any symptoms [2].

One of the tests that has always been used for early detection and screening of prostate cancer is measuring the serum level of prostate-specific antigens (PSAs), which, despite all the limitations of its sensitivity and specificity, is the most commonly used method along with the physical examination [3]. PSA is produced from epithelial cells of the prostate gland in reaction to the activation of its androgenic receptors. Although PSA has relatively high tissue specificity, there are many factors including age, race and ethnicity, lifestyle, geographical area and smoking that can change the serum PSA levels without being related to prostate diseases. The clinical significance of this issue is the disruption in case finding [4,5].

The upper limit of normal PSA (4 ng/mL) is not precise for all ages [6], and the age-specific values of PSA are more useful for screening [7]. Since PSA increases with prostate hyperplasia, its level should be lower in younger individuals. Moreover, a 4 ng/mL cut-off is less successful in estimating the risk of cancer in young individuals and may cause unnecessary biopsy in elderly men with benign prostatic hyperplasia [8–11]. In other words, the aim of using the age-specific reference range of PSA is to improve the diagnostic accuracy of the PSA screening test, which means increasing its sensitivity in younger men and reducing the rate of biopsy in elderly patients [12].

The age-specific reference ranges for PSA were first indicated by Osterling et al. [13]. There is an increasing concern about the general application of these reference ranges. Due to the impact of racial and geographical differences, each community has its own reference range [7,14–17]. Age is one of the key risk factors for prostate disease, in a way that the probability of PCa increases by age [18]. For a healthy man without PCa, the concentration of serum PSA increases by about 3.2% (0.04 ng/mL) per year. Osterling et al. [13] reported that the concentration of serum PSA is directly correlated with age and it is not like we can have one reference range of PSA for men in all age groups.

Many studies are being conducted in this field all around the world [7,14–16], but few of them have been conducted in Iran with fewer samples of elderly men aged 60 and over [5,19,20]. The standard reference range for serum PSA levels in Iranian men without prostate disease is not available and establishing a reference range of serum PSA levels for healthy Iranian men will be desirable. This study is a step for determining an age-specific reference range of PSA for elderly men without prostate cancer. Therefore, the aim of this study is to determine the age-specific reference range of PSA in the age groups of elderly men in Amirkola.

2. Materials and methods

This cross-sectional study is a part of the comprehensive cohort project titled “Amirkola Health and Ageing Project” (AHAP) (registration No. 892917), which has been conducted since 2011 on all individuals aged 60 and over in Amirkola, in northern Iran [21]. AHAP is mainly concerned with geriatric medical problems such as falls, bone fragility and fractures, cognitive impairment and dementia, depression, poor mobility and functional dependence as well as chronic diseases like PCa. People aged 60 years and over were invited to participate in this study through posters distributed all around the city and were assessed by a broad range of biochemical and hormonal tests run at the baseline and the follow-up.

Their files have been saved at the research center. Therefore, we contacted all of them or their families on the phone in order for a follow-up. In this study, PCa was diagnosed through self-report and medical records. All participants signed a written informed consent. In addition, the AHAP cohort study was approved by the Medical Ethics Committee of Babol University of Medical Sciences (code 1801).

The healthcare practitioners were trained in a workshop to use the questionnaire and assessed the elderly population in public health clinics of Amirkola. All of the elderly people who completed the questionnaire were included in the study. On the other hand, those elderly people who were not able to answer the questions due to cognitive impairment were excluded from the study.

The demographic data of all elderly men (837 individuals) were collected by questionnaires and interviews. The prostate cancer was diagnosed through self-report, in which case the participant was excluded from the study. To evaluate the status of those with prostate cancer, we followed up and contacted all of them or their families at the research center or at home in the second wave of AHAP after 5 years.

All of the participants gave a venous blood sample. The measurement of PSA levels in the serum was performed at the Cellular and Molecular Biology Research Center of the Health Research Institute in Babol University of Medical Sciences using the ELISA method and the Diametra kit made in Foligno (PG) Italy. Like most studies in Iran, the normal cut-off point was considered to be 4 ng/mL [5,20–22] although some researchers applied different values which have more of a research aspect [17].

The quantitative variables were described using the mean and the standard deviation. Moreover, the variable “age” was categorized in several groups and description of the main research variables was based on this categorization. Then, the collected data were analyzed by SPSS18 (SPSS Inc, Chicago, IL, USA) using one-way analysis of variance (ANOVA), t-test and Pearson correlation coefficient and displayed in tables and diagrams. A p-value of less than or equal to 0.05 was considered to be statistically significant.

3. Results

In the present study, 837 elderly men aged 60–92 years were studied. The mean age of the individuals was 69.99±7.72 years. Overall, 443 elderly men (53%) were in the age group of 60–69 years and 394 individuals (47%) were in the age group of 70 years and over. The majority of
the participants (60.7%) were illiterate and 34.5% were smokers (Table 1).

The descriptive statistics of PSA levels in men of each age group in Table 2 indicated that there was a significant difference between PSA levels in different age groups ($p<0.000$). The lowest mean PSA level ($1.47\pm1.78$ ng/mL) belonged to the young stage group (60–64 years) and the highest mean PSA level ($3.91\pm8.45$ ng/mL) belonged to the oldest one ($85+$ years).

Overall, seven elderly people had PSA levels higher than or equal to 19.9 ng/mL or over. Since the files for the information of these elderly people were kept at the research center, all of them or their families were contacted after 5 years in order for a follow-up. The results showed that only two of them had died—one of them from PCa and another one from myocardial infarction. Two of the remaining men had benign prostatic hyperplasia (BPH) and were still alive and three others had urinary problems but not cancer or BPH.

According to Table 3, the normal range of PSA (95th percentile) increased by age (from $4.89$ ng/mL in the age group of 60–64 years to $33.17$ ng/mL in the $85+$ age group).

Based on these values, the reference range of PSA level was determined to be $0.9$ ng/mL (range: $0$–$4.89$ ng/mL) for the age group of 60–64 years, $1.1$ ng/mL (range: $0$–$4.88$ ng/mL) for the age group of 65–69 years, $0.93$ ng/mL (range: $0$–$9.01$ ng/mL) for the age group of 70–74 years, $1.3$ ng/mL (range: $0$–$7.95$ ng/mL) for the age group of 75–79 years, $1.9$ ng/mL (range: $0$–$11.98$ ng/mL) for the age group of 80–84 years, and $1.45$ ng/mL (range: $0$–$33.17$ ng/mL) for the $85+$ age group.

Generally, the mean serum PSA level of the elderly had increased in different age groups with the increase of age (Fig. 1).

Moreover, the Pearson correlation test indicated that there was a significant relation between PSA levels and age ($r=0.18$, $p<0.001$). In other words, with the increase of age, the serum PSA levels increased too. The relation between the serum PSA levels and smoking was not significant (Figs. 2 and 3).

### 4. Discussion

PCa is a major public health problem and one of the leading causes of death among the men around the world [28]. The main problem with the PCas is that it is usually diagnosed very late and its early stages are without any symptoms [1]. PSA-based screening is useful for early diagnosis of PCa [29]. Based on the results of the present study, the serum PSA level increases with age in all age groups of the elderly people.
In other similar studies too, the PSA levels increased with age \([7,16,30,31]\). Since the PSA levels are influenced by various factors such as age and race, the determination of the age-specific reference range for PSA in each community can increase the value of the PSA test \([7,20]\).

According to the findings of this study, the normal range of PSA (95th percentile) has increased by age and the values for each age group of the study were determined to be as follows: The normal range of PSA is 4.89 ng/mL for the age group of 60–64 years, 4.88 ng/mL for the age group of 65–69 years, 7.95 ng/mL for the age group of 70–74 years, 11.98 ng/mL for the age group of 80–84 years, and 33.17 ng/mL for the 85+ age group, respectively. In a similar study conducted in Beijing, China, the normal range of PSA was 4.11 ng/mL in the age group of 60–69 years, 5.56 ng/mL in the age group of 70–79 years, and 7.28 ng/mL in the age group of 80 and over \([12]\), which had a significantly lower PSA level in each age group compared to our study. In another similar study in Syria, conducted on men with no prior history of PCa, the normal range of PSA was 4.8 ng/mL in the age group of 60–69 years and 5.8 ng/mL in the age group of 70–80 years \([29]\). In addition, in another study in Qazvin, Iran, the amount of PSA (95th percentile) was 5.7 ng/mL in the age group of 60–69 years, and 6.8 ng/mL in the age group of 70–79 years \([27]\), which were close to the values of the present study. Accordingly, it can be said that in addition to age, race has a great impact on the amount of PSA in individuals.

The findings of this study indicated that the lowest mean and standard deviation of PSA level (1.47 ± 1.78 ng/mL) were associated with the young stage group (60–64 years) and the highest mean and standard deviation of PSA level (3.91±8.45 ng/mL) belonged to the old stage group (85+ years). In another study, the lowest mean serum PSA level in men belonged to the young stage group (40–49 years) with 0.55 ng/mL and the highest mean belonged to the old stage group (over 80 years) with 2.24 ng/mL \([12]\). Moreover, in another similar study in Iran, the mean PSA level increased by age, but the mean PSA level in each age group was lower compared to the present study \([5]\). In another study in Beijing, China, the mean PSA levels (95th percentile) were reported to be 1.16 (4.11) ng/mL, 1.34 (5.56) ng/mL and 2.97
In this study, the mean PSA level and the confidence interval of 95% were 1.47 (1.26–1.68) ng/mL in the age group of 60–64 years, 1.63 (1.28–1.99) ng/mL in the age group of 65–69 years, 2.01 (1.47–2.54) ng/mL in the age group of 70–74 years, 2.12 (1.64–2.61) ng/mL in the age group of 75–79 years, 3.05 (1.94–4.16) ng/mL in the age group of 80–84 years and 3.91 (1.28–6.54) ng/mL in the age group of 85 years and over. Although the mean PSA level increased with age but it was not noticeable for the trend of median of PSA level through the age groups specially aged 85 years and over. It seems that elderly people with severe or advanced disease may have died before this age. These people are probably healthier people. In another study conducted on men without prostate cancer in Nigeria, this amount was 1.68 (1.58–1.78) ng/mL in the age group of 40–49 years, 1.93 (1.84–2.00) ng/mL in the age group of 50–59 years and 2.73 (2.27–3.18) ng/mL in the age group of 60–69 years, which were all higher than the values acquired in our study [32].

Regarding the results of the present study, the normal PSA level increased by age from 2.5th percentile to 95th percentile. As a result, the normal PSA level increased from 0.00 ng/mL to 4.89 ng/mL in the age group of 60–64 years and 0.0 ng/mL to 33.17 ng/mL in the age group of 85 years and over. According to these values, the reference range of PSA level was more than 4 ng/mL (normal PSA cutoff point) in all age groups. In a similar study in Australia, the PSA values increased from 5th percentile to 95th percentile in a way that the normal PSA level increased from 0.4 ng/mL to 7.5 ng/mL in the age group of 70–74 years and 0.1 ng/mL to 18.0 ng/mL in the age group of 90 years and over [16]. In another study in China, the PSA values increased from 5th percentile to 95th percentile and the increase was from 0.4 ng/mL to 4.42 ng/mL in the age group of 60–69 years and 0.34 ng/mL to 6.52 ng/mL in the age group of 70–79 years [33]. Moreover, in a study in Taiwan, China, the PSA values increased from 5th percentile to 95th percentile and the increase was from 0.33 ng/mL to 5.11 ng/mL in the age group of 60–69 years and 0.30 ng/mL to 6.24 ng/mL in the age group of 70–79 years [7]. This difference might have been due to the genetic, environmental, nutritional, geographical or other unknown factors.

According to the findings of the present study, the concentration of the serum PSA in participants was positively correlated with their age ($r=0.18$, $p<0.001$). There was also a positive correlation in other similar studies in China ($r=0.31$, $p<0.001$) [7], and Shiraz (Iran) ($r=0.28$, $p<0.001$) [20].

Among all elderly people who participated in the present study ($n=837$), only seven people had a PSA level higher than or equal to 20 ng/mL, of whom only one died from prostate cancer after a 5-year follow-up. Although we did not do a biopsy to detect PCa, it seems reasonable that if the high PSA level was due to PCa, it should have appeared in their clinical manifestations during this 5 years period.

Table 4 summarizes the present study’s results in comparison with the previous reports. It shows that PSA levels are higher than some other studies. However, these findings are similar to the results of another study in Iran [27] and a study in the United States [25]. This difference might have been due to genetic, racial differences, dietary habits or environmental factors [7,12,23–27].

One of the strengths of the present study was the conduction of a population-based cohort study and the high participation rate of the elderly men in Amirkola. On the other hand, as self-reported diagnosis was a major limitation, the true incidence of PCa maybe higher than reported. However, in a population based study with a large sample size that most of them did not have any PCa, it was not possible and logical to get prostate tissue samples or digital rectal examination from elderly people without any indication. Also culturally, it was not acceptable to do a digital rectal examination for elderly people without any problem. Another limitation was that some older people might have had PCa in the early stages but had died from other diseases before the diagnosis of PCa.

5. Conclusion

This study indicated that the PSA level was affected by age and the age-specific reference range of PSA in Iranian men was different with other races. Using the reference range could guide clinicians on the incidence of PCa in this population and perhaps reduce the number of unnecessary tests in this population group where there is a low mortality rate from PCa.

Author contributions

Study design: Hosseini Seyed Reza.
Data acquisition: Habibian Tara.
Data analysis: Bijani Ali.
Drafting of manuscript: Zabihi Ali.
Critical revision of the manuscript: Hosseini Seyed Reza, Zabihi Ali.
Conflicts of interest
The authors declare no conflict of interest.

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References
[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7–30.
[2] Zaytsev S, Nikitaev V, Pronichev A, Nagornov O, Polyakov E, Romanov N, et al. A method of data structuring in the decision-making support system in oncological diagnostics of prostate diseases. J Phys Conf Ser 2017;798:12132.
[3] Ankerst DP, Pollock BH, Liang Y, Dizdarevic N, Kyrilenko S, Boec K, et al. Trends and co-trends of prostate-specific antigen and body mass index in a screened population. Urology 2011;78:10–6.
[4] Liu M, Wang J, Zhu L, Wan G. Body mass index and serum lipid profile influence serum prostate-specific antigen in Chinese men younger than 50 years of age. Asien J Androl 2011;13:640.
[5] Rahimifar S, Montazeri A. Age-related prostate specific antigen reference ranges in healthy northern Iranian men. Iran J Immunol 2018;15:68–73.
[6] Loeb S, Roehl KA, Catalona WJ, Nadler RB. Prostate specific antigen velocity threshold for predicting prostate cancer in young men. J Urol 2007;177:899–902.
[7] Lin KJ, Pang ST, Chang YH, Wu CT, Chuang KL, Chuang HC, et al. Age-related reference levels of serum prostate-specific antigen among Taiwanese men without clinical evidence of prostate cancer. Chang Gung Med J 2010;33:182–7.
[8] Liu Z, Sun Y, Xu C, Gao X, Zhang L, Ren S. Age-specific PSA reference ranges in Chinese men without prostate cancer. Asian J Androl 2009;11:100.
[9] Nadler RB. The case for prostate-specific antigen screening starting at age 40. Cancer 2008;113:1278–81.
[10] Mouw JW, Sun L, Hotaling JM, Fitzsimons NJ, Polascik TJ, Robertson CN, et al. Age adjusted prostate specific antigen and prostate specific antigen velocity cut points in prostate cancer screening. J Urol 2007;177:499–504.
[11] Thompson IM, Pauler DK, Goodman PJ, Tangen CM, Lucia MS, Parnes HL, et al. Prevalence of prostate cancer among men with a prostate-specific antigen level <4.0 ng per milliliter. N Engl J Med 2004;350:2239–46.
[12] Liu X, Wang J, Zhang SX, Lin Q. Reference ranges of age-related prostate-specific antigen in men without cancer from Beijing area. Iran J Public Health 2013;42:1216–22.
[13] Oesterling JE, Jacobsen SJ, Chute CG, Guess HA, Girman CJ, Panser LA, et al. Serum prostate-specific antigen in a community-based population of healthy men: establishment of age-specific reference ranges. JAMA 1993;270:860–4.
[14] Woo HY, Park H, Kwon MJ, Chang Y, Ryu S. Association of prostate specific antigen concentration with lifestyle characteristics in Korean men. Asian Pac J Cancer Prev 2012;13:5695–9.
[15] Casey R, Hegarty P, Conroy R, Rea D, Butler M, Grainger R, et al. The distribution of PSA age-specific profiles in healthy Irish men between 20 and 70. ISRN Oncol 2012;2012:1–4.
[16] Litchfield MJ, Cumming RG, Smith DP, Naganathan V, Le Couteur DG, Walte LM, et al. Prostate-specific antigen levels in men aged 70 years and over: findings from the CHAMP study. MJA 2012;196:395–8.
[17] Safarinejad MR. Population-based screening for prostate cancer by measuring free and total serum prostate-specific antigen in Iran. Ann Oncol 2006;17:1166–71.
[18] Shah S, Jha B, Khanal MP. Effects of aging and ethnicity on serum free prostate specific antigen. Asian Pacific J Cancer Prev 2011;12:2509–12.
[19] Mehrabi S, Shirazi HG, Rasti M, Bayat B. Analysis of serum prostate-specific antigen levels in men aged 40 years and older in Yasuj, Iran. Urol J 2009;2:189–92.
[20] Khezri AA, Shirazi M, Ayatollahi SMT, Lotfi M, Askarian M, Ariafar A, et al. Age-specific reference levels of serum prostate-specific antigen, prostate volume and prostate specific antigen density in healthy Iranian men. Iran J Immunol 2009;6:40–8.
[21] Hosseini SR, Cumming RG, Kheirkhah F, Noorreddini H, Baiani M, Mikaniki E, et al. Cohort profile: the Amirkola health and ageing project (AHAP). Int J Epidemiol 2014;43:1393–400.
[22] Hosseini SY, Moharrammadeh M, Ghadian AR, Hooshyar H, Lashay AR, Safarinejad MR. Population-based screening for prostate cancer by measuring total serum prostate-specific antigen in Iran. Int J Urol 2007;14:406–11.
[23] Kamal BA, Ali GA, Taha SA. Prostate specific antigen reference ranges in Saudi men. Saudi Med J 2003;24:665–8.
[24] Saw S, Aw TC. Age-related reference intervals for free and total prostate-specific antigen in a Singaporean population. Pathology 2000;32:245–9.
[25] Morgan TO, Jacobsen SJ, McCarthy WF, Jacobson DJ, McLeod DG, Mouw JW. Age-specific reference ranges for serum prostate-specific antigen in black men. N Engl J Med 1996;335:304–10.
[26] Choi YD, Kang DR, Nam CM, Kim YS, Cho SY, Kim SJ, et al. Age-specific prostate-specific antigen reference ranges in Korean men. Urology 2007;70:1113–6.
[27] Pourmand G, Ayati M, Razi A, Karami A, Ramazani R, Ahmad A, et al. Age-specific reference ranges of serum prostate-specific antigen in Iranian men. Tehran Univ Med J (TUMJ) 2015;73:360–7.
[28] Zhou CK, Check DP, Lortet-Tieulent J, Laversanne M, Jemal A, Ferlay J, et al. Prostate cancer incidence in 43 populations worldwide: an analysis of time trends overall and by age group. Int J Cancer 2016;138:1388–400.
[29] Bakir MA, Abo-Daher D. Age-specific reference ranges for prostate-specific antigen among healthy Syrian men. Int J Biol Markers 2012;27:152–9.
[30] Liu X, Wang J, Zhang S, Lin Q. [Age-related reference ranges of serum prostate-specific antigen in men free of prostate cancer in Beijing]. Nan Fang Yi Ke Da Xue Xue Bao 2013;33:1704–8 [Article in Chinese].
[31] Gilbert R, Tilling K, Martin RM, Lane JA, Davis M, Hamdy FC, et al. Developing new age-specific prostate-specific antigen thresholds for testing for prostate cancer. Cancer Causes Control 2018;29:383–8.
[32] Ikuerowo SO, Ajalor AA, Obalarinwa AA, Omasioje OA. Age-specific serum prostate specific antigen ranges among apparently healthy Nigerian men without clinical evidence of prostate cancer. Niger J Surg 2016;22:5–8.
[33] Yuan X, Dong Z, Zhang H, Lin H, Song X, Niu Z, et al. Distribution of serum prostate-specific antigen in Chinese healthy men: a population-based study. Chin Med J 2011;124:1189–92.