Retrospective Analysis of Changes in Pseudocholinesterase (Butyrylcholinesterase) Values Based on Gender and Year

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Abstract

Aim: Increased serum pseudocholinesterase (PChE) levels over time in different populations lead to faster metabolism of anesthetic agents. This, in turn, shortens the duration of paralysis and reduces the need for additional doses. This makes the assessment of serum PChE levels an important issue for anesthesia safety.

Methods: In this retrospective cross-sectional study, preoperative serum PChE levels of 8,951 patients were examined over a seven-year period. Differences by year, the years between which the differences occurred, gender-related changes, and year-gender interactions were analyzed.

Results: The mean serum PChE level in all patients was 10.621 ± 0.24 U/L. Linear regression analysis revealed a mean annual increase of 233.66 U/L across years. Male PChE levels were significantly higher than female PChE levels. The Year × Gender interaction was also found to be significant. In conclusion, it was found that the rate of increase was faster in men than in women. Furthermore, serum PChE levels were higher in women among individuals over 65 years of age. The highest serum PChE levels were observed in individuals under 15 years of age.

Conclusions: Differences between men and women may be due to biological differences related to sex, while the overall increase over time may be due to metabolic changes or environmental factors within the population. Therefore, our results suggest that individual sex and hormonal variations, as well as trends in serum PChE levels across populations, may be critical for anesthesia safety.

Keywords: *Pseudocholinesterase; butyrylcholinesterase; gender difference; annual trend; anesthesia safety; regression analysis*

1. Introduction

Butyrylcholinesterase (BChE), more classically known as pseudocholinesterase (PChE), is a glycoprotein esterase synthesized primarily in the liver and circulating in plasma. Studies on its substrate specificity, molecular structure, and enzyme kinetics have shown that this enzyme is important both in hydrolyzing ester-based muscle relaxants such as succinylcholine, mivacurium, and procaine, as well as some local anesthetics, and in regulating cholinergic signaling.[1-3] However, in cases where this enzyme is deficient or high, it is possible that the expected effect may not be seen.

PChE deficiency, the best-known and most clinically dangerous condition, can lead to life-threatening complications such as prolonged neuromuscular block, prolonged apnea, and the need for ventilatory support after succinylcholine administration.[4] Elevated serum PChE activity, while less recognized, has become increasingly important in clinical practice in recent years. It has been shown that PChE activity, when very high, rapidly inactivates succinylcholine and similar agents, significantly shortening their effects.[5] Therefore, high mean PChE levels in the population are important to evaluate because they may lead to a shorter-than-expected duration of succinylcholine effect and the need for additional doses.[6-10] The time-dependent increase in mean PChE levels in the population also has important implications for epidemiological, metabolic, and clinical anesthesia safety. Therefore, the evaluation of regional PChE data is a critical predictor for both public health and clinical practice.[11]

Based on this information, this study aimed to evaluate the changes in serum PChE levels measured in the Antalya sample between 2019 and 2025, by year and gender, and to investigate potential biological and epidemiological explanations for the observed increase. The findings from our study may inform risk management in anesthesia practices, preoperative screening policies, and regional public health approaches, as well as serve as a basis for other studies.

2. Materials and Methods

Demographic characteristics, clinical data, and PChE levels

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recorded between January 1, 2019, and February 12, 2025, from patients scheduled for surgical procedures at Antalya Atatürk State Hospital were used in our study. This cross-sectional study was approved by the Akdeniz University Medical Scientific Research Ethics Committee on May 28, 2025, under number 775. A total of 8,951 patients, including 4,140 females and 4,811 males, were included in the study. Patients were stratified by gender and age, with age categories based on the literature's age distribution: <15 years (Children), 16-40 years (Juniors), 41-64 years (Middle-aged), and >65 years (Elderly).[12,13]

PChE level data were obtained by screening PChE results measured by the colorimetric method (Architect System, Cholinesterase G43948R04) in blood samples collected from individuals included in the study before the surgical procedure. Patients using acetylcholinesterase inhibitors, anticholinesterases, cytotoxic agents, metoclopramide, steroids, ester-type local anesthetics, hexafluronium, pancuronium, oral contraceptives, or antidepressants; those with liver or kidney disease; those with malnutrition; those with malignancy or extensive burn injuries; pregnant patients; and patients undergoing cardiopulmonary bypass were excluded from the study. The results of 8951 individuals who presented to surgical outpatient clinics and did not meet the exclusion criteria were evaluated between 2019 and 2025. All 8951 patient data points represent a single measurement and do not include repeated measurements. The expanded sample size we obtained in the study enabled more precise detection of low-frequency conditions and increased predictive power in multivariate regression analyses.[14,15]

The Architect System performs kinetic colorimetric determination of cholinesterase in serum or plasma. Butyrylthiocholine is used as the specific substrate for cholinesterase, which catalyzes the hydrolysis of butyrylthiocholine substrate by forming butyrate and thiocholine. Thiocholine reduces hexacyanoferrate (III) to hexacyanoferrate (II). The decrease in absorbance is directly proportional to the cholinesterase activity in the sample. Calibration is stable for 30 days. If control results fall outside the accepted ranges, recalibration may be necessary. The reference range is defined as (4,389-10,928 U/L) for men and (2,879-12,669 U/L) for women.

2.1. Statistical Analyses

Data were analyzed using the SPSS 23 software package (SPSS Inc, Chicago, IL, USA) and reported as mean ± standard deviation. Unless otherwise stated, data were reported as mean (standard error) or number of patients (n), as appropriate. Normality of data was assessed using the Shapiro-Wilk and Levene tests for homogeneity. Differences between years were assessed using one-way ANOVA, and Tukey post hoc analysis was used to examine which years showed significant differences. The trend of PChE values by year was assessed by linear regression analysis. The independent samples t-test was used to evaluate the effect of gender (female-male difference). Two-way ANOVA (year x gender interaction) was used to evaluate the dependence of changes by year on gender.

3. Results

The Preoperatively, 8,951 patients (4,140 women and 4,811 men) were included in the study, and their demographic characteristics are presented in Table 1. Only 60 males had serum PChE levels below the reference value (<5100), while only 28 females had serum PChE levels below the reference value (<4000). The mean age of all patients was 30.54 years, and the mean PChE level was 10.621 ± 0.24 U/L.

Table 1

Distribution of patients according to gender and age distribution.

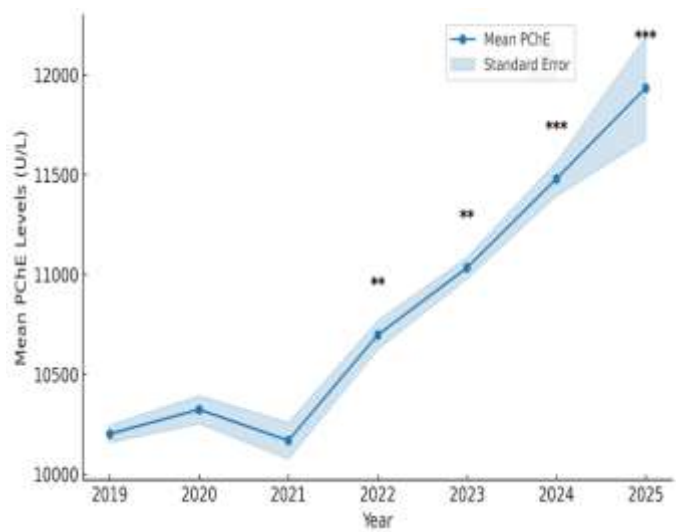
	Gender Female (n=4140)	Male (n=4811)	Total (n=8951)
Age	n	n	n
≤15	867	1895	2762
16-40	1886	1658	3544
41-64	1088	976	2064
≥65	299	282	581

3.1. Change Between Years

A significant difference was found between 2019 and 2025, and mean PChE levels were found to increase regularly every year [F(6,8943)=0.55.143, p<0.001, and Cohen's d=0.72]. The difference between 2019, 2020, and 2021 was found to be insignificant (p>0.05). However, mean PChE levels in 2022, 2023, 2024, and 2025 were found to be significantly higher than in previous years (p<0.001). This indicates that the increase in PChE levels is statistically significant and clinically meaningful, and that there is a trend of increasing PChE activity over time. Therefore, it indicates that the overall PChE enzyme levels of the population living in Antalya have increased over the years (Figure 1).

Figure 1

Annual trend of mean serum PChE activity in Antalya (2019–2025).



*Data are shown as means with 95% confidence intervals (shaded area). (**p < 0.01, ***p < 0.001, ns: non-significant).*

3.2. Gender Effect

When changes were examined by gender, men were found to have significantly higher PChE levels than women *(t(8949)=−24.20, p<0.001, Cohen's d=0.51) (Figure 2). Cohen's d is a measure of effect size and answers the question of how large and significant the difference is. A comparison of the effect sizes of the results across age groups is also presented in Table 2.

Changes in PChE Values in Males and Females by Age Groups

The changes in mean PChE values of men and women according to age groups are given in detail in Figure 3.

Table 2

Comparison of effect sizes based on patient gender and age distribution.

Age group	Female (F) Mean ± SD	Male (M) Mean ± SD	p	Cohen's d	Effect Size	Direction
<15	11559 ± 2093	11704 ± 2276	0.100	0.07	Very small	M > F
16–40	9236 ± 1968	10905 ± 2368	<0.001	0.77	Big	M> F
41–64	9928 ± 2275	11192 ± 2457	<0.001	0.53	Middle	M> F
≥65	10123 ± 2218	9302 ± 2580	<0.001	0.34	Small– Middle	F > M

Under 15 Group:

In the age group under 15 years, the mean plasma PChE levels were found to be 11.559 ± 2.093 U/L in women (n = 867) and 11.704 ± 2.276 U/L in men (n = 1.895). Since Levene's test showed inequality of variances (F = 3.984, p = 0.046), Welch t-test was applied. No significant difference was observed between genders (t(1813.49) = −1.645, p = 0.100). The mean difference (female − male) was −145.2 U/L (95% CI: −318.3, 27.9), Cohen's d ≈ 0.07 (very small effect). This finding shows that there is no significant PChE difference between genders under the age of 15.

16-40 Age Group:

In the 16-40 age group, mean serum PChE level was found to be 9.236 ± 1.968 U/L in females (n=1886) and 10.905 ± 2.368 U/L in males (n=1658). Levene's test revealed heterogeneity of variances (F=37.747, p<0.001). The difference between genders was statistically significant (t(3232.18) = -22.65, p <0.001), and males had higher mean PChE levels than females (mean difference: 1669.5 U/L; 95% CI: 1525.0-1814.1). The mean difference was 1,669.5 U/L (95% CI: 1,525.0–1,814.1) with Cohen's d = 0.77, indicating a large effect size of gender on PChE activity.

41-64 Age Group:

In the 41–64 age group, the mean PChE level was 9.928 ± 2.275 U/L in women (n=1088) and 11.192 ± 2.457 U/L in men (n=976). Levene's test showed equal variances (F=3.807, p=0.051). According to the independent samples t-test results, PChE levels in men were significantly higher than in women (t(2062)=−12.13, p<0.001; difference=−1,263.5 U/L; 95% CI: −1,467.8, −1,059.3; Cohen's d=0.53). This difference represents a medium effect size.

Over 65:

In individuals aged 65 years and over, the mean PChE level in women was 10.123 ± 2.218 U/L (n=299) and in men was 9.302 ± 2.580 U/L (n=282). Since homogeneity of variance was not ensured, Welch t-test was applied. PChE levels in women were significantly higher than in men [t(555.02)=4.105, p<0.001; difference=821.5 U/L; 95% CI: 428.4, 1214.6; Cohen's d=0.34]. This difference has a low to moderate effect size.

3.3. Linear Regression Analysis of Annual PChE Trend (2019-2025)

A simple linear regression model was applied to examine the temporal trend in serum PChE levels and was found to be statistically significant (F(1,8949) = 293.82, p < 0.001), indicating that year is a significant predictor of serum PChE activity. The unstandardized regression coefficient (β = 233.66, 95% CI [206.94-260.38]) showed that serum PChE levels increased by approximately 234 U/L per year on average during the study period. The positive slope and high t-value (t = 17.14, p < 0.001) confirm a consistent increasing trend over the seven-year period, and the correlation between PChE levels and year was moderate (Pearson r = 0.178, p < 0.001) (Figure 4).

These results therefore suggest a significant and consistent increase in mean serum PChE levels over the seven-year period, suggesting potential population-level or methodological changes affecting enzyme activity.

Figure 2

Gender difference in serum PChE levels in Antalya (2019–2025). Bars represent mean ± 95% confidence interval.

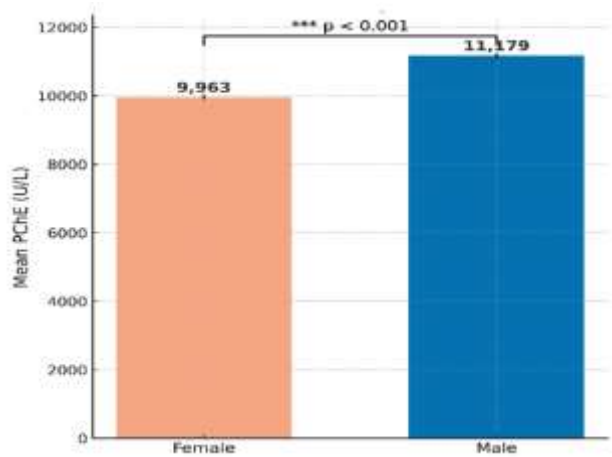


Figure 3

Graph showing the change in mean PChE levels in the age distribution of men and women <15 (F: 867, M: 1895), 16-40 (F: 1886, M: 1658), 41-64 (F: 1088, M: 976), 65> (F: 299, M: 282).

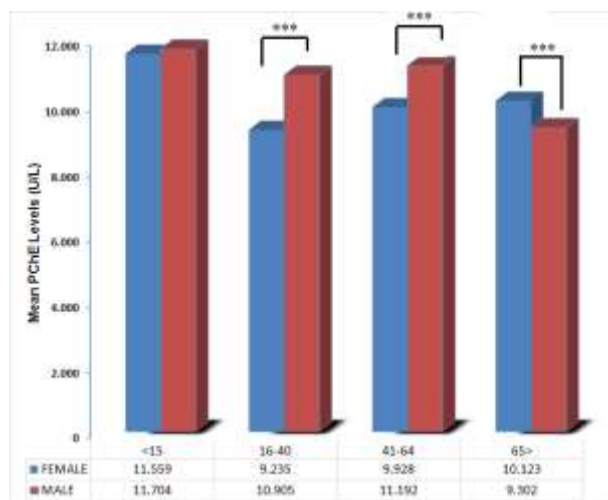
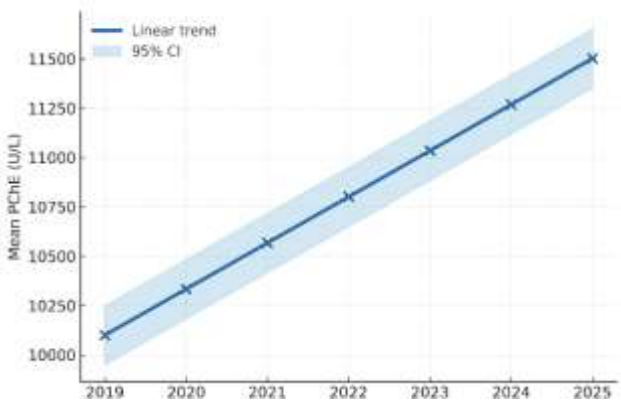


Figure 4

Linear regression analysis showing a significant positive temporal trend in serum PChE levels between 2019 and 2025. The solid line indicates the fitted regression line, and the shaded area indicates the 95% confidence interval.

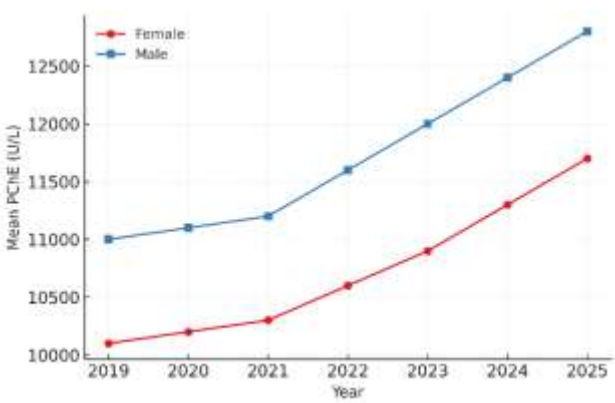


3.4. Time and Gender Change Together

The Year × Gender interaction was found to be significant ($F(6, 8937)=5.02$, $p<0.001$). The increase in serum PChE levels over time was observed to be faster in men than in women. Therefore, this result indicates that the rate of increase varies by gender. In the graph of the increase over time for both genders, the slope is seen to be steeper in men (Figure 5).

Figure 5

Interaction graph of serum PChE levels by year and gender (***, $p<0.001$).



4. Discussion

Although both increases and decreases in serum PChE levels can have important clinical consequences, determining preoperative serum PChE levels remains an overlooked practice in many clinical settings. PChE enzyme levels are known to be influenced by numerous physiological, metabolic, and environmental factors.[16] In our country, there is not enough data on PChE levels in the general population and their changes over time and by gender.

Therefore, in our study, PChE levels measured in preoperative serum samples of 8,951 individuals in Antalya province between 2019 and 2025 were examined and the relationship between PChE levels in these individuals age and gender differences was evaluated. Although normal levels of serum PChE are reported as 4650 U/L - 10,440 U/L[12,17], these value ranges may vary in different populations. For example, in a study conducted among Iranian and Irish populations, serum PChE activity was found to be significantly higher in the Irish than in the Iranians (7.82 ± 0.14 vs 5.22 ± 0.09 u/ml).[18] In a study conducted in the Turkish population, the frequency of carriers of the K variant (K-variant of Kallikrein), which causes an approximately 40% decrease in PChE activity, was found to be higher than in other ethnic groups.[19] Considering this information together, it can be concluded that serum PChE levels in the Turkish population may be influenced by both genetic factors and population-specific and metabolic differences. The fact that the mean serum PChE level observed in the Antalya province population is close to the upper limit of the normal range suggests that both regional and demographic characteristics may influence PChE activity. This highlights the importance of assessing preoperative PChE levels and the need to establish population-specific reference ranges. To our knowledge, our study is the first to examine serum PChE levels in such a large population in Turkey and to investigate the trend of change.

Our study found that the increase in PChE levels varied by gender and was higher in men than in women. A study conducted in Brazil showed that men had significantly higher PChE activity than women.[20] Studies in French and Croatian adult populations have also reported that men have higher mean PChE levels than women, and that age and gender may be determinants of PChE activity.[21]

In our study, serum PChE levels differed from earlier ages in women in the postmenopausal period, when estrogen levels were low, and in men over the age of 65, reflecting low testosterone levels.[22,23] Accordingly, in our study, decreased serum PChE levels were observed in men aged 65 and older compared to those aged 16–40 and 41–64, and increased serum PChE levels were observed in women aged 65 and older compared to those aged 16–40 and 41–64. These findings may indicate that the enhancing effects of androgens on hepatic enzyme synthesis decrease in men after age 65, and that this is due to the disappearance of the suppressive effect of estrogen on PChE synthesis in women.

It has been reported that there are no significant age-related or gender-specific differences in serum PChE activity in children under 15 years of age. Our study data indicate similar PChE activity between boys and girls during childhood. The lack of a difference in PChE activity between genders may be due to the fact that the sex hormones estrogen and testosterone have not yet reached adult levels.[24] Serum PChE levels are higher under age 15 compared to other age groups due to age-related sex hormone levels. Male estrogen levels increase slightly during puberty and remain stable until adulthood.[25] PChE levels in men begin to decline slightly from age 16. PChE levels are higher than in women until age 65, but they are higher in women at age 65. This may indicate hormonal balance. In females, the highest serum PChE levels observed under age 15 may be related to the fact that estrogen levels in this age group have not yet reached the level required to increase hepatic synthesis. This is because the highest estrogen levels in females, particularly estradiol, generally occur in the middle of the reproductive years, between the ages of 20 and 30.[26] These results also indicate that these changes may determine the duration and intensity of the effects of the anesthetic agents used.

Sex differences in BChE activity are closely related not only to biological sex hormones but also to individuals' metabolic status, dietary habits, and environmental and occupational exposures. Experimental studies have shown that, since BChE is an enzyme largely synthesized in the liver, estrogen and other sex steroids may have regulatory effects on enzyme expression and circadian rhythm. Female animals have been reported to have higher BChE activity than males.[27] Furthermore, the direction and magnitude of gender differences in PChE are strongly correlated with individuals' body mass index (BMI) and metabolic syndrome prevalence. Clinical studies have shown that BChE activity has a positive correlation with obesity, dyslipidemia, insulin resistance, and metabolic syndrome components, and that this relationship may exhibit different distributions in women and men.[11,28,29]. Socioeconomic differences and related occupational exposures are also important environmental factors determining PChE levels. Organophosphates and carbamates suppress cholinesterase activity, particularly in agricultural workers and groups exposed to pesticides.[30,31]

Our results demonstrated a significant and sustained increase in mean serum PChE levels over time. This increase is thought to be related to lifestyle factors and metabolic status A positive correlation between PChE activity and obesity, abdominal fat, insulin resistance, and dyslipidemia has been reported in the literature.[22,23] Given the increasing prevalence of obesity in Turkey, obesity and insulin resistance are thought to be one of the underlying factors for the PChE increase observed over time in our study. Furthermore, our study observed that serum PChE levels in women increased more slowly over time than in men. There are case reports suggesting that high PChE activity can inactivate agents such as succinylcholine or mivacurium more rapidly, shortening their effects.[5-7] Therefore, the higher mean PChE levels observed in our population may shorten the duration of action of these drugs and lead to their more rapid metabolism. These findings highlight the clinical importance of preoperative PChE assessment and the establishment of population- and gender-specific reference ranges.

In conclusion, our study demonstrated a significant and sustained increase in mean serum PChE levels, with a gender-specific difference. The findings highlight the need for both a review of clinical practices regarding anesthesia safety and a detailed examination of population-level biomedical and environmental factors affecting PChE levels. Serum PChE determination should be included in routine laboratory panels during hospitalization or outpatient evaluations; it can also be added to emergency examination panels upon request. The cost of PChE testing is comparable to the cost of routinely performed biochemical parameters.[16] PChE levels can be considered as one of the prognostic parameters supporting the clinical decision process.

4.1. Limitations

Because our study is a retrospective, cross-sectional study, data were collected from hospital laboratory records. Therefore, confounding variables such as medication use, comorbidities, nutritional status, or inflammatory processes could not be controlled. Because liver function tests and inflammatory markers were not analyzed in parallel, the impact of hepatic or systemic changes on PChE changes in the results could not be fully distinguished. Furthermore, the lack of data on the relationship between metabolic markers and metabolic syndrome and the impact of PChE levels in female participants limited our ability to assess their relationship. The lack of data on menopausal status and hormone levels in female participants also limits the interpretation of gender differences. Furthermore, because our study is a single-center study, its generalizability to the Turkish population is limited.

Statement of ethics

This cross-sectional study was approved by the Akdeniz University Medical Scientific Research Ethics Committee on May 28, 2025, under number 775.

genAI

No artificial intelligence-based tools or generative AI technologies were used in this study. The entire content of the manuscript was originally prepared, reviewed, and approved by both authors.

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Conflict of interest statement

The authors declare that they have no conflict of interest.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author contributions

Concept/Design: ADA. Data Collection and Curation: KBK. Data Processing: EA. Data Analysis and Interpretation: ADA, AA. Literature Search: DK. Drafting the Article: EA. Critical Revision of the Article: ADA. Advisor: KBK.

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