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ORIGINAL ARTICLE

Characteristics of Protein S in Koreans by Age and Gender: a Retrospective Analysis based on Results from Korean Referral Laboratories

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SUMMARY

Background: **Protein S, a vitamin K-dependent protein, is crucial in inhibiting blood clotting, and its deficiency increases the risk of thrombotic disease. However, most studies have focused on Western populations. Although Koreans have a lower incidence of thrombotic diseases, the risk is rising due to aging and Westernized lifestyle habits. Therefore, protein S levels should be investigated in Koreans for developing strategies to prevent and manage thrombotic diseases. This study aimed to analyze protein S-related data according to age and gender in Korean adults.**

Methods: **This retrospective study examined protein S activity and free protein S levels from January 2017 through December 2023 in Korean adults, using data from commissioned inspection institutions in Korea. Protein S activity was measured using a coagulation-based assay, while free protein S levels were determined via immunoturbidimetric analysis. Data were categorized by year, gender, age group, and type of protein S deficiency, and trends in test values and frequency were analyzed.**

Results: **A total of 2,470 individuals (907 men and 1,563 women) were included. Protein S activity increased with age until 50 - 59 years, then declined, whereas free protein S levels peaked at 70 - 79 years before slightly decreasing. The number of protein S tests increased steadily over the years, with consistently more tests performed in women than in men throughout. Women showed significantly lower levels of both protein S activity and free protein S than men ($p < 0.001$), and a strong significant positive correlation was observed between the two protein S activity and free protein S tests ($R = 0.543$, $p < 0.001$). Deficiency patterns were classified into three groups based on test results. Among these, the most prevalent group (39.3%) had decreased protein S activity with normal free protein S, particularly among women and individuals aged 20 - 39 years.**

Conclusions: **This study provides critical reference data on protein S levels in Koreans, highlighting significant age- and gender-related differences. These findings contribute to refining thrombotic risk assessment in Korean populations and complement existing Western-based studies. Further research incorporating clinical histories is warranted to enhance the clinical applicability of protein S testing.**

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INTRODUCTION

Protein S (PS) plays an important role in inhibiting blood clotting and is a vitamin K-dependent protein synthesized by the liver [1,2]. PS is present in the blood in two forms: free and bound. Approximately 40% is

present in the free form, and the remainder is bound to C4b-binding protein, rendering it inactive [3,4]. PS acts as a coenzyme for activated protein C, which inhibits thrombus formation and helps maintain blood homeostasis by degrading FVa and FVIIIa during blood clotting [5,6].

PS assays are an important tool for assessing the risk of thrombotic diseases and diagnosing anticoagulant abnormalities such as PS deficiency [7,8]. PS deficiency can result from innate or acquired factors, including genetic mutations, liver disease, certain medications, pregnancy, and autoimmune diseases [9]. PS deficiency is classified into three types: I, II, and III. Type I is characterized by decreased total PS, free PS, and PS activity; type II by decreased total PS and free PS activity; and type III by normal total PS with decreased free PS and PS activity. This distinction is essential for assessing thrombus risk and establishing an appropriate treatment strategy [10].

Nevertheless, most existing studies on PS focus on Western populations and may not accurately reflect the characteristics of Koreans. Koreans have a lower incidence of thrombotic disease than Western populations [11]. However, the risk of thrombotic disease is gradually increasing due to aging and the spread of Westernized lifestyles [12]. Accordingly, studying PS in Korean populations is crucial for advancing its clinical usefulness rather than solely focusing on basic science [13, 14].

Therefore, this study aimed to analyze free PS and PS activity test results obtained from EONE Laboratories, one of South Korea's major reference laboratories, between January 2017 and December 2023 to investigate differences based on gender and age. By identifying the characteristics of PS test results in Koreans, this study seeks to establish fundamental reference data for thrombotic risk assessment. Additionally, although patient medical histories and medication use are not included, this study provides valuable foundational data for understanding PS levels in Koreans. This research is expected to complement existing Western-based studies and contribute to the development of strategies for preventing and managing thrombotic diseases.

MATERIALS AND METHODS

Ethical approval

This study was reviewed by the Clinical Trials Ethics Committee of EONE Laboratory (institutional review board number: 128477-202504-BR330). The study was performed in accordance with the tenets of the Declaration of Helsinki. This study retrospectively analyzed existing test results without including any personal information of the patients. As patient information was not included, obtaining consent was deemed unnecessary.

Patients and data collection

This study was designed to investigate the blood coagulation characteristics of adults and was conducted as a retrospective analysis based on data provided by EONE Laboratories, one of South Korea's major reference laboratories. Since blood coagulation tests cannot be performed at all hospitals nationwide, samples were sent to EONE Laboratories for testing, and this study was conducted using only the test result data obtained from EONE Laboratories. Between January 2017 and December 2023, a total of 2,849 test results were collected. Out of these, 311 cases without gender or age information, 66 cases from individuals aged < 20 years, and two cases with missing test values were excluded. Consequently, a total of 2,470 valid test results were included in the analysis, comprising 907 men and 1,563 women. This study was conducted in compliance with the ethical guidelines and regulations of the Bioethics Committee. Additionally, as no patient health status or medical history information was provided, all data were analyzed without distinguishing between healthy individuals and patients (Figure 1).

Materials

For specimen collection, venous blood was collected in a BD Vacutainer® tube containing 0.3 mL of 3.2% sodium citrate (Becton Dickinson, USA), and the ratio of blood to anticoagulant was maintained at 9:1. The collected blood was centrifuged at 2,500 g for 15 minutes to separate plasma and was then examined.

PS analyses

PS activity testing was performed using STA®-Staclot® PS (Diagnostica Stago, France) reagent, and PS functional activity was measured using the coagulation method based on factor Va. Free PS levels were determined using STA®-Liatest® Free PS (Diagnostica Stago) reagent to measure the concentration of free PS in plasma based on the immunoturbidimetric method. To ensure the accuracy and reproducibility of testing, internal quality control testing was performed using STA®-System Control N+P, and all tests were conducted strictly according to the manufacturer's instructions.

Statistical analysis

Data were organized and managed using Microsoft Excel® (Microsoft Corporation, USA). The distribution and tendency of the two test results were confirmed by calculating the mean, median, and standard deviation of PS activity and free PS by gender and age. For statistical analysis, an independent sample *t*-test was performed to compare test results between men and women, and one-way analysis of variance (ANOVA) was conducted to evaluate differences among age groups. Additional statistical analyses were performed to assess the significance of the data, and all analyses were conducted using Jamovi 2.3.28 (Jamovi Research, Vienna, Austria). A p-value of less than 0.05 was considered statistically significant.

Table 1. Age-based distribution of protein S activity and free protein S levels.

Age group (years)	PS			FREE		
	mean	SD	CV	mean	SD	CV
20 - 29	57.30	25.68	44.66	70.34	25.71	36.43
30 - 39	60.67	22.08	36.36	76.03	23.72	31.17
40 - 49	60.74	24.98	41.08	77.41	26.17	33.77
50 - 59	61.05	26.69	43.65	78.40	25.22	32.12
60 - 69	58.62	26.38	44.93	80.75	28.14	34.80
70 - 79	61.56	26.77	43.43	83.09	24.50	29.44
≥ 80	54.43	22.84	41.90	77.61	22.39	28.80

PS - protein S, FREE - free protein S, SD - standard deviation, CV - coefficient of variation.

Table 2. *t*-test for mean of protein S measures by gender.

Measure	Group	n	Mean	Median	SD	SE	Statistics	df	p
PS	women	1,563	57.7	56	23	0.6			
	men	907	62.9	62	27.6	0.9	-4.17	1,630	< 0.001
FREE	women	1,563	74.9	73	23.9	0.6			
	men	907	83.5	82	26.5	0.9	-8.08	1,734	< 0.001

This table presents the statistical comparison of protein S activity (PS) and free protein S (FREE) levels between men and women using an independent samples *t*-test. The values are expressed as mean, median, standard deviation (SD), and standard error (SE). The Welch's *t*-test was applied due to the violation of the equal variance assumption, and the degrees of freedom (df) and significance level (p) are reported. $p < 0.05$.
SD - standard deviation, SE - standard error of the mean, df - degrees of freedom, PS - protein S, FREE - free protein S.

Table 3. Grouping of protein S and free protein S test results in the study population.

Group	Category	Count	Proportion (%)
Group 1	normal	1,120	45.3%
Group 2	both decreased	309	12.5%
Group 3	PS decreased, Free normal	970	39.3%
Group 4	other	71	2.9%
Total		2,470	100%

PS - protein S.

RESULTS

Number of tests by year

From January 2017 through December 2023, a total of 2,470 PS activity and free PS tests were conducted, showing a consistent increasing trend over the years. In 2017, a total of 257 tests (92 for men and 165 for women) were performed, and the number gradually increased to 345 tests (138 for men and 207 for women) in 2019, reaching a peak of 421 tests (151 for men and 270 for women) in 2022. In 2023, 403 tests (150 for men and 253 for women) were conducted, maintaining a high testing volume.

When comparing test counts by gender, women consistently had a higher number of tests than men throughout the entire period. The number of tests for men increased from 92 in 2017 to 151 in 2022, while for women, it increased from 165 in 2017 to 270 in 2022, showing a rel-

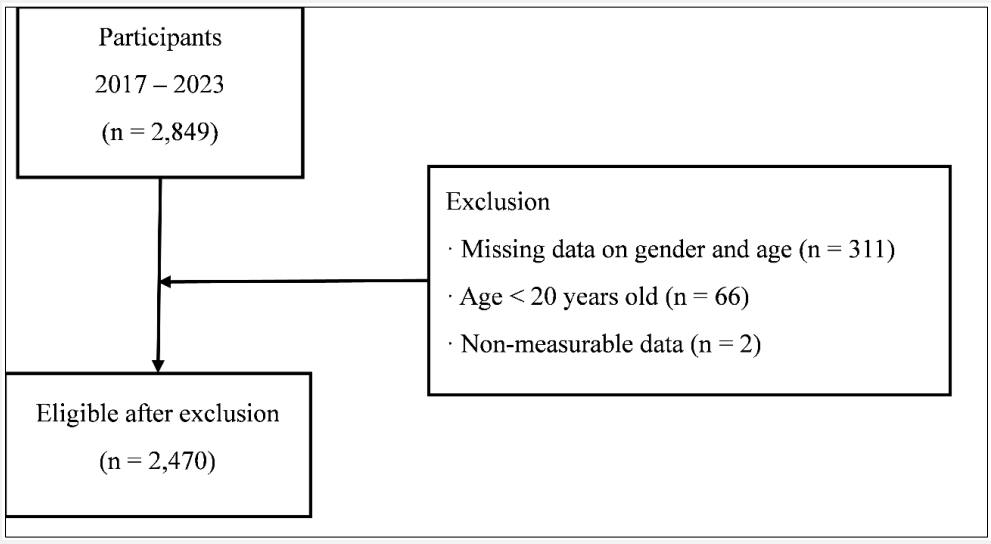

Figure 1. Study sample enrollment process.

n - number of individuals assessed.

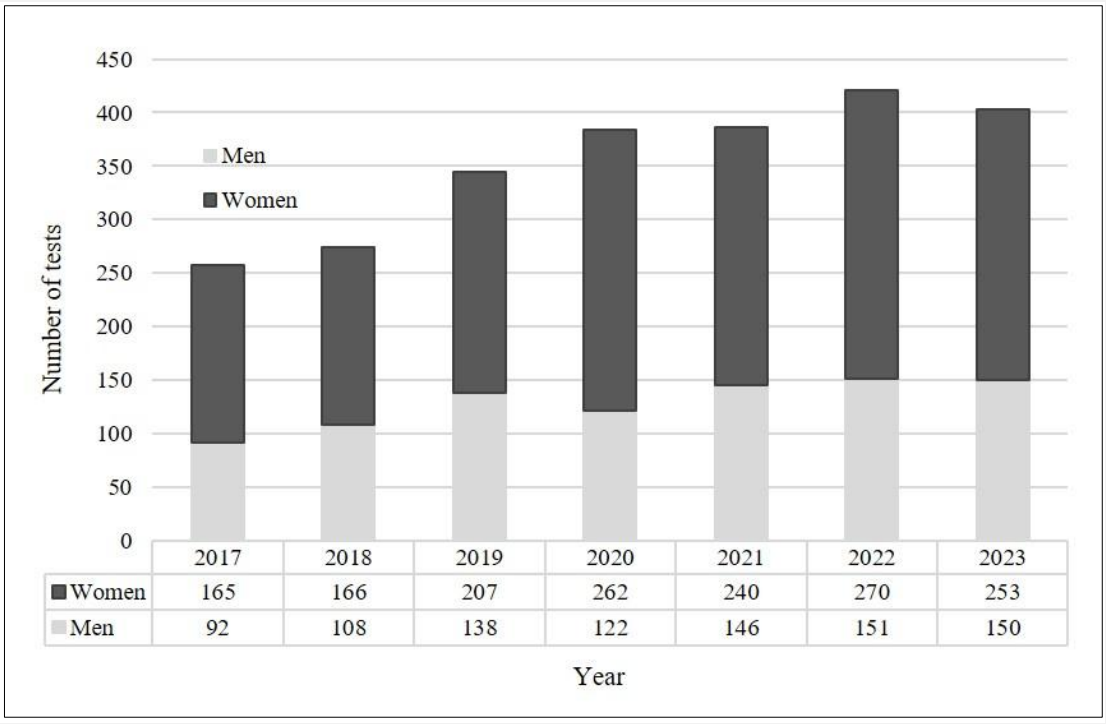

Figure 2. Yearly trends in protein S testing by gender (2017 - 2023).

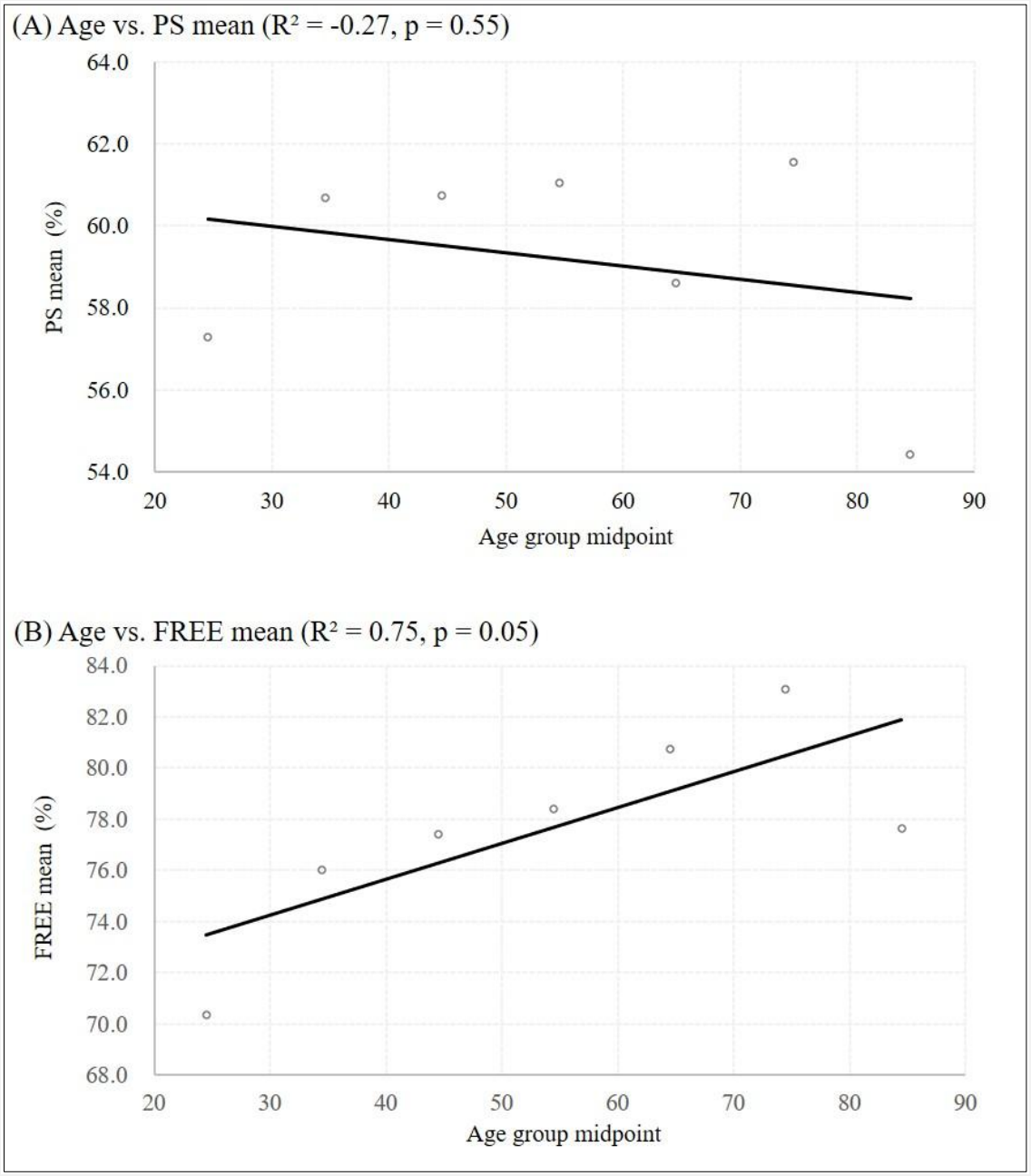

Figure 3. Age-related changes in free protein S activity and protein S activity.

A - protein S activity graph, B - free protein S graph. R^2 - coefficient of determination, p - statistical significance threshold ($p < 0.05$). FREE - free protein S.

atively larger increase (Figure 2).

PS values by age group

The analysis of the mean, standard deviation, and coefficient of variation for PS activity and free PS revealed significant trends across different age groups (Table 1). First, examining the mean values of PS activity, a gradual increase was noted from age 20 - 29 years (57.30%) to age 50 - 59 years (61.05%). However, a slight decline was observed at age 60 - 69 years (58.62%), with the

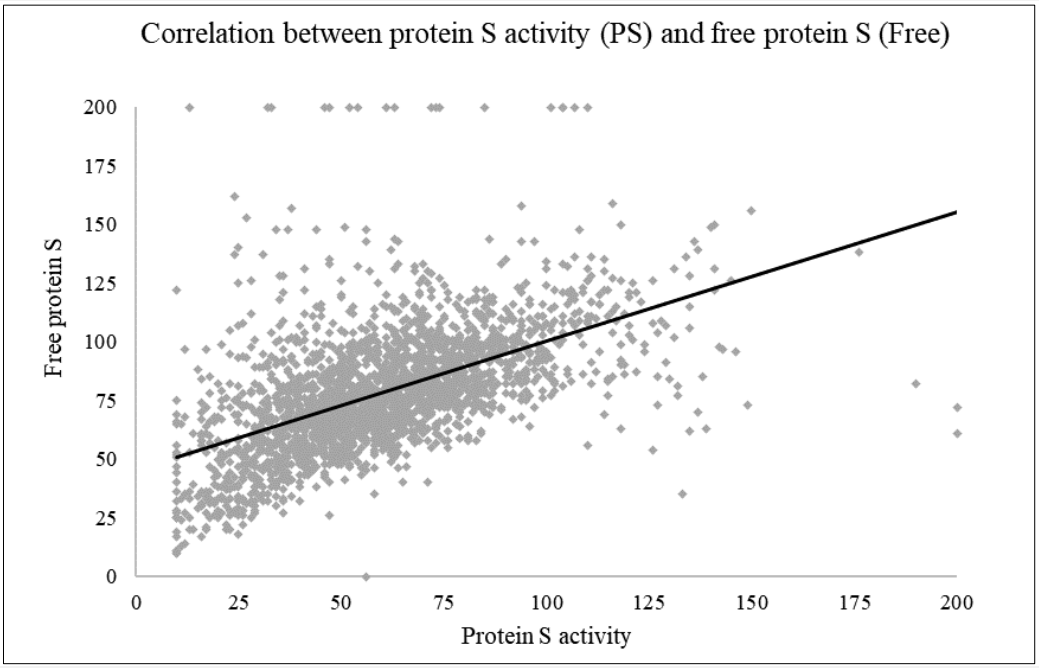

Figure 4. Correlation between protein S activity and free protein S.

lowest value recorded at age ≥ 80 years (54.43%). The standard deviation ranged between 22 and 27 across all age groups, while the coefficient of variation remained within 36 - 45%. In contrast, the mean values of free PS showed an increasing trend from age 20 - 29 years (70.34%) to age 30 - 39 years (76.03%) and age 40 - 49 years (77.41%), reaching its peak at age 50 - 59 years (78.40%) and age 60 - 69 years (80.75%). The highest value was observed at age 70 - 79 years (83.09%), followed by a slight decrease at age ≥ 80 years (77.61%). The standard deviation ranged between 22 and 28 across all age groups, while the coefficient of variation decreased progressively from age 20 - 29 years (36.43%) to its lowest at age ≥ 80 years (28.80%).

Overall, PS activity increased up to age 50 – 59 years before declining, whereas free PS peaked at age 70 – 79 years and slightly decreased at age ≥ 80 years. Additionally, comparing the coefficient of variation, PS activity exhibited greater variability than free PS, indicating a greater degree of irregular changes across different age groups. Correlation analysis, which was performed to determine whether PS activity and free PS levels showed a significant association with increasing age, revealed no significant correlation between age and PS activity ($R = -0.272$, $R^2 = 0.074$, $p = 0.555$). For free PS, the correlation with age approached statistical significance ($R = 0.754$, $R^2 = 0.568$, $p = 0.050$), suggesting a potential positive trend in which free PS levels may increase with age. However, given the borderline p-value, this finding should be interpreted with caution (Figure 3).

PS values by gender

Independent sample *t*-tests, which were employed to analyze gender-based differences in PS activity and free PS, revealed that both variables were significantly higher in men than in women. The mean PS value was 62.9% in men and 57.7% in women, with Welch's *t*-test showing a statistically significant difference ($p < 0.001$). Similarly, the mean free PS value was 83.5% in men and 74.9% in women ($p < 0.001$), also indicating a significant difference (Table 2).

Correlation between PS activity and free PS

A positive correlation between PS activity and free PS levels ($R = 0.543$, $p < 0.001$) was confirmed, with the following regression equation derived through linear regression analysis:

free PS = 0.551 × PS activity + 45.25

This indicates that as PS activity increases, free PS levels tend to increase moderately, supporting a close correlation between the results of the two tests. This correlation further suggests that using both tests may provide an important basis for clinical decision-making (Figure 4).

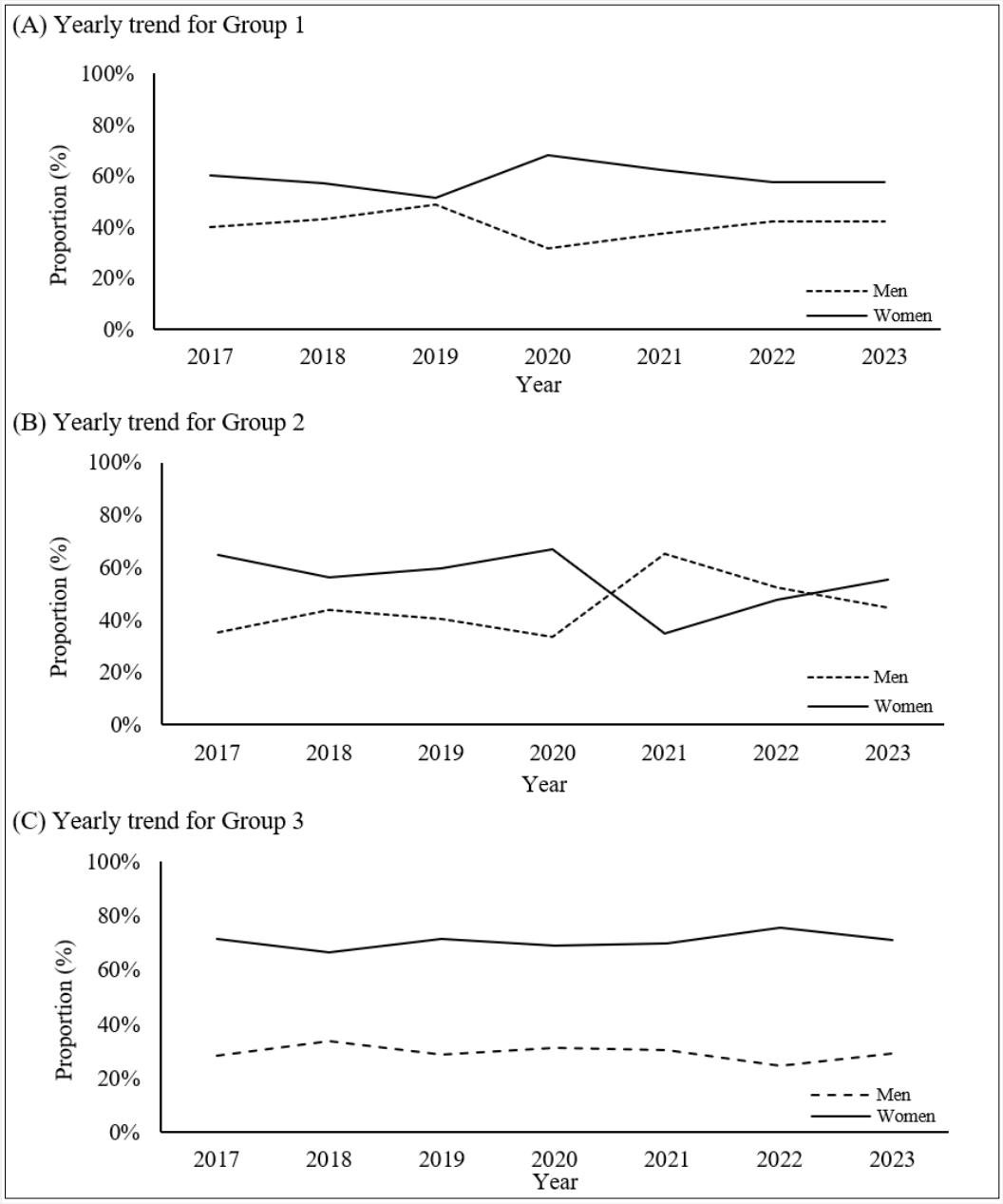

Figure 5. Temporal changes in gender distribution by group (2017 – 2023).

The figure shows the yearly proportion trends of men and women in each group. The dashed line indicates the proportion of men, while the solid line represents the proportion of women. These lines illustrate how gender distribution has changed over the years within each group.

Distribution of PS deficiency types

Although this study cannot directly determine the type of PS deficiency, it provides a framework for comparison with previous studies by establishing and analyzing groups with similar deficiency patterns (Table 3) as follows.

1) Based on test results for PS activity and free PS levels, the participants were classified into three groups: a normal group, in which both test results were within the normal range; a low activity/low level group, in which both PS activity and free PS levels were below the normal range; and a low activity/normal level group, in

which PS activity was reduced but free PS was within the normal range. The normal group accounted for the highest proportion at 45.3% (1,120 cases), followed by the low activity/normal level group at 39.3% (970 cases) and the low activity/low level group at 12.5% (309 cases). The remaining 2.9% (71 cases) did not meet the three criteria described above. The distribution of deficiency types differed depending on age group and gender, with the normal group showing the highest proportion across all age groups and both genders. However, the low activity/normal level group had a relatively high proportion among participants aged 20 - 39 years. 2) When data were analyzed by year, fluctuations were noted in the normal group in terms of gender ratios, with the ratio of women consistently higher than that of men. In 2020, the proportion of women was the highest at 68.3%, while that of men was the lowest at 31.7%. In 2023, the distribution was more stable at 42.3% for men and 57.7% for women. In the low activity/low level group, large changes were noted in the gender ratio by year. In 2021, the proportion of men increased sharply to 65.1%, exceeding that of women, but in 2023, the normal ratios were restored at 44.8% for men and 55.2% for women. This change suggests potential data bias in a specific year or increased use of testing. In contrast, the gender distribution in the low activity/normal level group consistently showed a higher proportion of women than men each year. The proportion of women started at 71.6% in 2017 and peaked at 75.4% in 2022. The proportion of men was the highest at 33.6% in 2018 but has since oscillated somewhat, reaching 29.0% in 2023 (Figure 5).

DISCUSSION

From 2017 through 2023, 2,470 PS activity and free PS tests were performed, and the annual number of tests showed a continuous increase. In particular, the number of tests reached its peak in 2022 (n = 421), which may indicate an increased need for diagnosis and risk factor assessment owing to the recent increase in the occurrence of thrombotic diseases [13]. The PS test plays a central role in coagulation control and is an important test for evaluating thrombotic diseases. In particular, because PS testing can simultaneously evaluate functional deficiency and antigen deficiency, it could potentially be used as an efficient diagnostic method [5,15]. In addition, a tendency for women to be tested more frequently than men was observed, which may reflect pregnancy, oral contraceptive use, and postmenopausal hormonal changes that are more likely to be associated with an increased thrombosis risk, as reported previously [12,16,17]. This trend is consistent with the present results, perhaps because women in Korea are more likely to receive thrombotic risk factor management and preventive monitoring than men.

Previous studies have reported that PS values increase with age [18,19]. The present analysis by age group showed that average PS activity did not show a significant difference by age group, whereas free PS level displayed a tendency to increase with age. In contrast to the present results, wherein PS activity was not significantly related to age, a study from China reported that PS activity increases with age [20]. To understand this difference more clearly in the future, comparative analysis with studies conducted in other countries is necessary, and additional research should consider various factors that may affect PS activity.

Consistent with the findings of previous reports, men in the present study had significantly higher levels of both PS activity and free PS than women ($p < 0.01$), possibly due to the influence of female hormones [12,21]. In addition, free PS levels tend to increase again in postmenopausal women due to a natural decrease in hormones, which is consistent with the present results demonstrating an increase in free PS levels in older women [18]. Meanwhile, some studies have reported that postmenopausal hormone replacement therapy may decrease PS levels and increase the risk of thrombosis [22]. These results suggest that pregnancy, oral contraceptive use, and postmenopausal changes may affect blood coagulation control and that clinical interpretation should consider these factors when diagnosing thrombotic diseases.

Moreover, results confirmed a significant positive correlation between PS activity and free PS levels ($p < 0.001$), with the regression model indicating that free PS increases by approximately 0.55% for every 1% increase in PS activity. This moderate association suggests that the two tests often produce concordant results, supporting their combined use in clinical evaluation. However, whether this relationship holds across different deficiency types remains unclear and warrants further investigation. Previous studies have emphasized that a single test may not reliably identify all forms of PS deficiency, especially types II and III. Therefore, parallel testing of both PS activity and free PS may enhance diagnostic accuracy in assessing thrombotic risk [16,23,24].

In this study, the participants were divided into three groups based on the results of PS activity and free PS tests, and the distribution by age and gender was analyzed. Although this does not directly confirm the type of PS deficiency, it aims to provide a framework for comparison with previous studies by establishing groups with similar deficiency patterns. The low PS activity/normal free PS level group accounted for the highest proportion at 39.3%, displaying a similar trend to that of type II deficiency, which was the most common in a study from Japan. In addition, the low PS activity/low free PS level group comprised 12.5%, thus showing a tendency that is somewhat consistent with type I deficiency exhibiting the lowest frequency in the study from Japan [25,26]. These results suggest that type II deficiency may be more common than other types, and further studies including total PS tests are needed to allow for a clearer comparison of types.

Furthermore, the proportion of women was higher than that of men in both the normal group and the low PS activity/normal free PS level group. This may simply be due to the difference in examination frequency, but it may also suggest that changes in PS levels could be more prominent in women due to physiological factors. Previous studies have reported that hormonal changes in women can affect blood coagulation; in particular, PS activity tends to decrease during pregnancy [27,28]. In addition, as mentioned above, oral contraceptives and postmenopausal hormonal changes can affect coagulation factors, and these changes may also affect the risk of thrombosis with age [12]. In the present study, women were particularly prone to cases where free PS levels were normal but PS activity was reduced, suggesting that hormonal changes or physiological characteristics may influence PS activity. Even when free PS levels are normal, PS activity can still be reduced in some instances, impairing the anticoagulant function and increasing the risk of thrombosis. Therefore, since a single test may not accurately diagnose the type of PS deficiency, it is important to consider both PS activity and free PS when assessing thrombosis risk, as a decrease in PS activity may indicate an increased risk of thrombosis.

In the low PS activity/low free PS level group, the gender ratio clearly changed by year. Women accounted for a higher proportion, but after 2020, the number of men increased rapidly, exceeding the number of women in 2021. This may be due to the increased demand for testing for thrombotic diseases during the COVID-19 pandemic: the risk of thrombosis increased after COVID-19 vaccination; decreased PS levels have been observed in patients with COVID-19 [29,30]. Therefore, future studies need to further analyze whether a significant decrease in PS is observed in patients with COVID-19.

This study analyzed PS activity and free PS test data in Koreans and found that women underwent PS testing more frequently than men and had significantly lower levels of both PS activity and free PS compared to men. Additionally, a positive correlation between PS activity and free PS was observed, and the proportion of women with decreased PS activity but normal free PS was higher than that of men. These findings provide important foundational data for interpreting PS test results and assessing thrombosis risk in Koreans.

This study provides valuable data for thrombosis risk assessment by analyzing the age- and gender-related characteristics of PS activity and free PS levels in the Korean population. Given the relative scarcity of research on PS in Koreans, this study offers novel insights into PS activity and free PS levels, making a significant contribution to thrombosis risk evaluation. These findings have important educational and practical implications: they highlight the need for increased awareness of age- and gender-related differences in Protein S levels among healthcare professionals and support the development of population-specific guidelines for thrombosis risk assessment and prevention strategies in Korea.

However, this study has some limitations. It relied solely on data from a referral laboratory and lacked access to clinical factors such as patients' medical history, pregnancy status, lifestyle, liver function, inflammatory status, and hormonal influences. This limitation restricted the ability to account for various factors that may affect PS levels. Therefore, further research is needed for a more precise evaluation of thrombosis risk.

Future studies should include total PS and genetic analysis to provide a more specific classification of PS deficiency types and consider patients' medical history and medication use. This approach will generate important data for more accurately assessing thrombosis risk and improving clinical applicability. Furthermore, multicenter prospective studies will help refine thrombosis diagnosis and prevention strategies, contributing to the development of diagnostic criteria and prevention methods optimized for the Korean population.

CONCLUSION

This study analyzed the age- and gender-related characteristics of PS activity and free PS levels, providing important foundational data for thrombosis risk assessment in Koreans. By confirming testing patterns in women and older patients and demonstrating a positive correlation between PS activity and free PS, these findings emphasize the need for the combined use of both tests. The study findings can help in the development of thrombosis diagnosis and prevention strategies in Koreans and highlights the need for research on PS deficiency types, including total PS and genetic analysis. Furthermore, multi-center prospective studies will help refine thrombosis risk assessment and diagnostic criteria.

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Declaration of Interest:
The authors have no financial conflicts of interest to declare.

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