

RESEARCH ARTICLE

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Age-Dependent Opposing Associations of ALBI and PALBI with Prostate Cancer Risk: A Prospective Cohort Study

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Abstract

Background: This study evaluated the associations of serum bilirubin, platelet count, and the composite indices ALBI (Albumin–Bilirubin) and PALBI (Platelet–Albumin–Bilirubin) with prostate cancer risk, with a focus on age-related differences. **Methods:** We analyzed data from 83,371 men in the Korean Cancer Prevention Study-II (KCPS-II). During a mean follow-up of 14.1 years, 380 incident prostate cancer cases were identified. Associations were examined for total bilirubin, platelet count, ALBI, and PALBI, stratified by age groups (45–55, 55–65, and >65 years). Quartile analyses, trend tests, and sensitivity analyses were conducted. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models. Age–biomarker interactions and restricted cubic spline (RCS) analyses were performed to assess age-dependent risk patterns. **Results:** ALBI and PALBI showed opposing associations with prostate cancer risk across age groups. Among men aged 45–55 years, ALBI was inversely associated with prostate cancer risk (HR: 0.76, 95% CI: 0.63–0.91), whereas PALBI showed a positive association (HR: 1.43, 95% CI: 1.18–1.72). In contrast, among men aged >65 years, ALBI was positively associated with risk (HR: 1.44, 95% CI: 1.13–1.83), while PALBI demonstrated an inverse association (HR: 0.80, 95% CI: 0.64–1.00). RCS analyses confirmed significant age-dependent variations, and biomarker–age interactions were statistically significant (p for interaction < 0.001). **Conclusions:** ALBI and PALBI exhibited age-dependent and, in some cases, opposing associations with prostate cancer risk. These findings suggest that age may act as an effect modifier in the relationship between endogenous biomarkers and prostate cancer risk.

Keywords: ALBI, PALBI, bilirubin, platelet count, prostate cancer

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Introduction

Prostate cancer is one of the most commonly diagnosed malignancies among men worldwide, with incidence increasing sharply with age. The risk rises substantially after the age of 50, and a large proportion of cases are diagnosed in men aged 65 years or older [1, 2]. This pronounced age dependency suggests that age-related physiological changes, rather than chronological age alone, may play an important role in prostate carcinogenesis.

Aging is accompanied by complex alterations in hormonal, metabolic, immune, and oxidative stress-related pathways. Age-related hormonal changes, including late-onset hypogonadism, have been proposed to influence systemic oxidative and inflammatory states, which are implicated in the development and progression of prostate cancer [3–6]. However, most epidemiologic studies have treated age primarily as a covariate for adjustment, rather

than examining whether associations between biological markers and prostate cancer risk differ across age groups that may reflect underlying physiological transitions. As a result, evidence on age-specific heterogeneity in these associations remains limited.

Bilirubin is a well-established endogenous antioxidant that reflects the capacity to scavenge reactive oxygen species and has been widely studied in relation to oxidative stress-related diseases [7–10]. Platelets, on the other hand, are increasingly recognized as active contributors to tumor-related processes, including modulation of the tumor microenvironment, angiogenesis, and metastasis [11–13]. While these biomarkers represent distinct biological pathways, individual markers may not fully capture the complexity of systemic oxidative and metabolic states.

To address this limitation, composite indices integrating multiple biomarkers have been proposed.

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The Albumin–Bilirubin (ALBI) index combines bilirubin and albumin, and the Platelet–Albumin–Bilirubin (PALBI) index further incorporates platelet count. Although these indices were originally developed for the assessment of liver function, their continuous formulations may reflect broader systemic conditions, including oxidative balance, metabolic status, and tumor-related biological activity. Emerging evidence suggests that such composite indices may capture systemic states relevant to carcinogenesis [14–17]. However, prospective population-based studies evaluating ALBI and PALBI as continuous exposures in relation to prostate cancer incidence, particularly across age strata representing physiological transitions, remain scarce.

Therefore, in this prospective cohort study, we examined the associations of bilirubin, platelet count, and the composite indices ALBI and PALBI with prostate cancer risk. We further conducted age-stratified analyses (45–55 years, 55–65 years, and ≥ 65 years) to assess whether these associations differ across physiological transition periods and to compare patterns observed for individual biomarkers and composite indices.

Materials and Methods

Study Population

This study utilized data from the Korean Cancer Prevention Study-II (KCPS-II), a large-scale prospective cohort comprising 153,971 adults aged 20 to 84 years (mean age: 42 years; standard deviation: 11) who underwent health examinations at 18 medical centers across South Korea between 2004 and 2013. All participants provided written informed consent for the use of their health screening and questionnaire data for research purposes [18]. This study protocol was reviewed and approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (approval number: 4-2011-0277).

Participants with a history of cancer diagnosis at baseline were excluded. In addition, individuals with missing data on key variables were excluded, including smoking status, alcohol consumption, serum bilirubin and albumin levels, platelet count, family history of prostate cancer, and education level. After applying these exclusion criteria, a total of 83,371 male participants were included in the final analysis (Supplementary Figure 1).

To evaluate potential age-related differences in the associations between biological markers and prostate cancer risk, the study population was stratified into three age groups: 45–55 years, 55–65 years, and ≥ 65 years, with 20,285, 5,919, and 1,631 participants in each group, respectively. Participants younger than 45 years were excluded from age-stratified analyses due to the extremely low incidence of prostate cancer in this group.

Cancer Case Ascertainment

Incident prostate cancer cases were identified through annual linkage of each participant's resident registration number to the National Cancer Center (NCC) Registry, which captures virtually all cancer diagnoses in South Korea. Under the Cancer Control Act, all hospitals are

required to report newly diagnosed cancer cases to the NCC. Prostate cancer was defined using the International Classification of Diseases, 10th Revision (ICD-10) code C61. During follow-up, a total of 380 incident prostate cancer cases were identified.

Person-time was calculated from the date of baseline examination to the date of prostate cancer diagnosis, death, or the end of follow-up, whichever occurred first. To minimize potential reverse causality, cases diagnosed within the first three years of follow-up were excluded from the analysis.

The mean follow-up duration for the overall cohort was 14.1 years. Among prostate cancer cases, the median follow-up time was 14.1 years (interquartile range [IQR]: 13.4–14.6 years). Stratified by age group, 144 cases occurred among men aged 45–55 years (median follow-up: 10.2 years, IQR: 6.6–12.8), 140 cases among men aged 55–65 years (median: 9.4 years, IQR: 5.2–12.1), and 81 cases among men aged ≥ 65 years (median: 5.1 years, IQR: 1.3–8.9).

Statistical Analysis

Descriptive statistics were used to summarize baseline characteristics across age groups.

The ALBI and PALBI indices were categorized into quartiles based on their distribution in the overall male population. Additional analyses using age-specific quartiles were conducted as sensitivity analyses. Associations between quartiles and prostate cancer incidence were evaluated using Cox proportional hazards regression models. Linear trends across quartiles were assessed by assigning the median value of each quartile and modeling it as a continuous variable.

The ALBI score was calculated as:

$$\text{ALBI} = (\log_{10} \text{bilirubin } [\mu\text{mol/L}] \times 0.66) + (\text{albumin } [\text{g/L}] \times -0.085) [19].$$

Serum bilirubin values were converted from mg/dL to $\mu\text{mol/L}$ ($1 \text{ mg/dL} = 17.1 \mu\text{mol/L}$) to ensure consistency with the original formulation.

The PALBI score was calculated as:

$$\text{PALBI} = \log_{10}(\text{platelet count} \times 10^9/\text{L}) - 2.02 \times \text{albumin (g/dL)} - 0.37 \times \log_{10}(\text{bilirubin [mg/dL]}) [20].$$

Units were standardized according to the requirements of each formula.

In addition to the composite indices, individual biomarkers, including total bilirubin and platelet count, were analyzed separately. Each biomarker was standardized to its standard deviation, and hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated for a one standard deviation increase using Cox proportional hazards models.

Restricted cubic spline models with five knots (5th, 27.5th, 50th, 72.5th, and 95th percentiles) were used to flexibly assess potential nonlinear dose–response relationships between biomarkers and prostate cancer risk. Nonlinearity was evaluated using likelihood ratio tests comparing models with only linear terms to

those including spline terms. To assess potential effect modification by age, additional spline-based Cox models including biomarker-by-age interaction terms were fitted. The statistical significance of interactions was evaluated using likelihood ratio tests comparing models with and without interaction terms.

The proportional hazards assumption was assessed using Schoenfeld residuals, and no significant violations were observed. Multivariable models were adjusted for age, smoking status, alcohol consumption, body mass index, family history of prostate cancer, and education level. These covariates were selected based on prior literature and their known associations with prostate cancer risk. Smoking and alcohol information were obtained from self-administered baseline questionnaires.

All biomarkers were measured at baseline prior to cancer diagnosis. Serum bilirubin, albumin, and platelet counts were measured in clinical laboratories at participating hospitals. All laboratories adhered to internal and external quality control procedures in accordance with the standards of the Korean Association of Laboratory Quality Control, with inter-laboratory correlation coefficients ranging from 0.96 to 0.99 [18]. Due to additional missing values in platelet count during index calculation, the number of cases slightly differed in analyses involving PALBI. To assess the robustness of the findings, sensitivity analyses were performed with additional adjustment for serum uric acid and creatinine, which are also related to endogenous antioxidant and metabolic status. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Characteristics of the study population

As presented in Table 1, the study population included 83,371 men. Among them, 20,285 were aged 45–55 years, 5,919 were aged 55–65 years, and 1,631 were aged >65 years. During follow-up, 144, 140, and 81 prostate cancer cases occurred among men aged 45–55, 55–65, and >65 years, respectively. The analyzed variables included age, body mass index, serum bilirubin, serum albumin, platelet count, alcohol consumption, and smoking status.

Associations of ALBI and PALBI with prostate cancer risk

Table 2 presents the associations of 1-SD increases in ALBI and PALBI with prostate cancer risk by age group. In the overall male population, ALBI was not significantly associated with prostate cancer risk, whereas PALBI showed a borderline positive association (HR = 1.11, 95% CI: 1.00–1.24, $p = 0.0560$). Among men aged 45–55 years, ALBI was inversely associated with prostate cancer risk (HR = 0.76, 95% CI: 0.63–0.91, $p = 0.0022$), whereas PALBI was positively associated with risk (HR = 1.43, 95% CI: 1.18–1.72, $p = 0.0002$). In men aged 55–65 years, neither ALBI nor PALBI was significantly associated with prostate cancer risk. Among men aged >65 years, ALBI was positively associated with risk (HR = 1.44, 95% CI: 1.13–1.83, $p = 0.0035$), whereas PALBI was inversely associated with risk (HR = 0.80, 95% CI: 0.64–1.00, $p = 0.0493$) (Table 2, Figure 1).

Associations of individual biomarkers with prostate cancer risk

Table 3 presents the associations of 1-SD increases in

Table 1. Baseline Characteristics of Korean Cancer Prevention Study-II Participants*

Characteristics	Men (n=83,371, All men)	Men (n=20,285, 45-55 years)	Men (n=5,919, 55-65 years)	Men (n=1,631, > 65 years)
Age, y	46.6 (9.53)	49.2 (3.04)	59.5 (2.79)	69.7 (3.54)
Body mass index†	24.4 (2.89)	24.4 (2.60)	24.3 (2.51)	24.0 (2.68)
Serum bilirubin, mg/dl				
Total	0.95 (0.38)	0.94 (0.37)	0.91 (0.38)	0.87 (0.32)
Indirect	0.59 (0.26)	0.59 (0.27)	0.58 (0.28)	0.56 (0.25)
Direct	0.36 (0.14)	0.35 (0.14)	0.33 (0.14)	0.33 (0.14)
Albumin, g/dL	4.58 (0.25)	4.56 (0.25)	4.53 (0.27)	4.47 (0.30)
platelet, 10 ³ /μL	246.27 (52.72)	242.33 (53.76)	237.39 (56.83)	229.74 (59.70)
Alcohol drinking, g/d	22.67(29.45)	26.29 (33.14)	28.36 (38.36)	27.38 (40.35)
Smoking status, %				
Never	22.7	19.9	23.3	32.3
Previous	32.7	41.5	47.1	46
Current	44.6	38.6	29.6	21.7
Any alcohol use, %				
Never	5.8	6.8	16	23.3
Previous	7.9	8.4	8.7	8.6
Current	86.3	84.8	75.4	68.1

*Data are expressed as mean (SD) unless otherwise indicated. Participants with missing data on smoking, alcohol, bilirubin, albumin, platelet count, family history, and education level were excluded. †Body mass index was calculated as weight in kilograms divided by the square of height in meters.

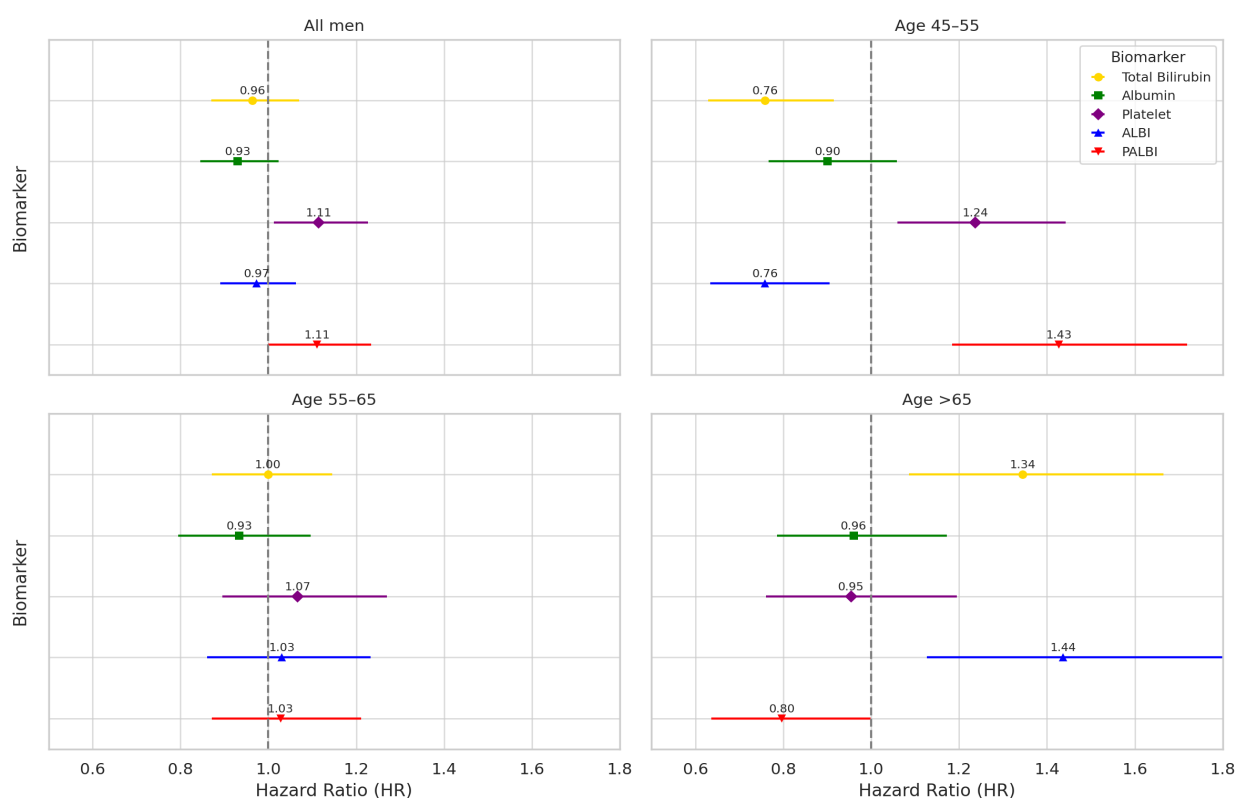


Figure 1. Age-Specific Associations Between 1-SD Increases in Biomarkers and Prostate Cancer Risk. Hazard ratios for prostate cancer risk associated with a one-standard-deviation increase in total bilirubin, albumin, platelet count, ALBI, and PALBI, stratified by age group. This figure provides a graphical summary of the results presented in Tables 2 and 3.

total bilirubin, albumin, and platelet count with prostate cancer risk by age group. In the overall male population, total bilirubin and albumin were not significantly associated with prostate cancer risk, whereas platelet count showed a positive association (HR = 1.12, 95% CI: 1.01–1.23, $p = 0.0266$). Among men aged 45–55 years, total bilirubin was inversely associated with risk (HR = 0.76, 95% CI: 0.63–0.92, $p = 0.0038$), while platelet count was positively associated with risk (HR = 1.24, 95% CI: 1.06–1.44, $p = 0.0068$). Albumin was not significantly associated with prostate cancer risk. In men aged 55–65 years, none of the three biomarkers was significantly associated with prostate cancer risk. Among men aged

>65 years, total bilirubin was positively associated with risk (HR = 1.35, 95% CI: 1.09–1.67, $p = 0.0065$), whereas albumin and platelet count were not significantly associated with risk (Table 3, Figure 1).

Quartile analyses

In the quartile analysis, ALBI showed a decreasing trend in prostate cancer risk among men aged 45–55 years (p for trend = 0.0073). Compared with Q1, the HRs were 0.60 (95% CI: 0.38–0.97) for Q3 and 0.51 (95% CI: 0.32–0.83) for Q4. In the same age group, PALBI showed an increasing trend (p for trend = 0.0001), with HRs of 1.65 (95% CI: 1.04–2.62) for Q3 and 2.54 (95% CI: 1.57–4.12) for Q4. Among men aged >65 years, ALBI

Table 2. Association Between a 1-SD Increase in ALBI (Albumin-Bilirubin) and PALBI (Platelet-Albumin-Bilirubin) and the Risk of Prostate Cancer by Age Group

Age	Indicators	Case (Median Follow-Up Time, IQR)	HR (95% CI) §	P-value
All men	ALBI	380 (14.1, 13.4–14.6)	0.97 (0.87–1.09)	0.6217
	PALBI	357 (14.1, 13.4–14.6)	1.11 (1.00–1.24)	0.056
45-55 years	ALBI	144 (10.2, 6.6–12.8)	0.76 (0.63–0.91)	0.0022
	PALBI	139 (10.2, 6.6–12.8)	1.43 (1.18–1.72)	0.0002
55-65 years	ALBI	140 (9.4, 5.2–12.1)	1.03 (0.86–1.23)	0.7412
	PALBI	130 (9.4, 5.2–12.1)	1.03 (0.87–1.21)	0.744
> 65 years	ALBI	81 (5.1, 1.3–8.9)	1.44 (1.13–1.83)	0.0035
	PALBI	75 (5.1, 1.3–8.9)	0.80 (0.64–1.00)	0.0493

Abbreviations: CI, confidence interval; HR, hazard ratio. §The Cox proportional hazards model was adjusted for age, smoking status, alcohol use, body mass index, family history of prostate cancer, and education level. No additional biomarkers (e.g., serum uric acid, creatinine) were adjusted in this main analysis.

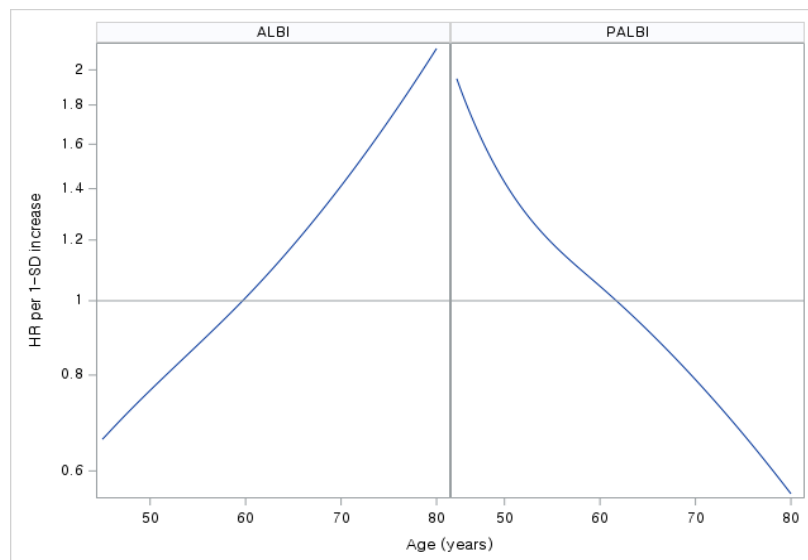


Figure 2. Age-Varying Associations Between 1-SD Increases in ALBI and PALBI and Prostate Cancer Risk. The interaction between each biomarker and age was evaluated using likelihood ratio tests. Significant age interaction was observed for both ALBI and PALBI (p for interaction < 0.001).

showed a positive trend with prostate cancer risk (p for trend = 0.0055), with an HR of 2.05 (95% CI: 1.05–4.01) for Q4. PALBI showed an inverse association in Q4 (HR = 0.34, 95% CI: 0.12–0.99), although the overall trend was of borderline significance (p for trend = 0.0562) (Table 4).

Age-varying associations and sensitivity analyses

Age-varying associations between 1-SD increases in ALBI and PALBI and prostate cancer risk were evaluated using restricted cubic spline interaction models. Likelihood ratio tests indicated statistically significant interactions between age and both ALBI and PALBI (p for interaction < 0.001). The estimated hazard ratio for ALBI increased with advancing age, whereas that for PALBI decreased across age (Figure 2). Sensitivity analyses with additional adjustment for uric acid and creatinine yielded results that were largely consistent

with the primary findings, with minimal changes in effect estimates (Supplementary Tables 1 and 2).

Discussion

This large-scale prospective study, based on approximately 14 years of follow-up from the Korean Cancer Prevention Study-II (KCPS-II), evaluated the associations of serum total bilirubin, platelet count, and the composite indices ALBI and PALBI with prostate cancer risk. Although no clear associations were observed in the overall male population, age-stratified analyses revealed distinct patterns among men aged 45–55 years and those aged >65 years. In particular, ALBI and PALBI showed opposing associations with prostate cancer risk in some age groups, and analyses treating age as a continuous variable demonstrated significant biomarker-by-age

Table 3. Association Between a 1-SD Increase in Total Bilirubin, Albumin, and Platelet Levels and the Risk of Prostate Cancer by Age Group

Age	Indicators	Case (Median Follow-Up Time, IQR)	HR (95% CI) §	P-value
All men	Total Bilirubin	380 (14.1, 13.4–14.6)	0.96 (0.87–1.07)	0.4719
	Albumin	380 (14.1, 13.4–14.6)	0.93 (0.85–1.02)	0.1397
	Platelet	357 (14.1, 13.4–14.6)	1.12 (1.01–1.23)	0.0266
45–55 years	Total Bilirubin	144 (10.2, 6.6–12.8)	0.76 (0.63–0.92)	0.0038
	Albumin	144 (10.2, 6.6–12.8)	0.90 (0.77–1.06)	0.2037
	Platelet	139 (10.2, 6.6–12.8)	1.24 (1.06–1.44)	0.0068
55–65 years	Total Bilirubin	140 (9.4, 5.2–12.1)	1.00 (0.87–1.15)	0.9899
	Albumin	140 (9.4, 5.2–12.1)	0.93 (0.80–1.10)	0.4039
	Platelet	130 (9.4, 5.2–12.1)	1.07 (0.90–1.27)	0.4656
> 65 years	Total Bilirubin	81 (5.1, 1.3–8.9)	1.35 (1.09–1.67)	0.0065
	Albumin	81 (5.1, 1.3–8.9)	0.96 (0.79–1.17)	0.6859
	Platelet	75 (5.1, 1.3–8.9)	0.95 (0.76–1.20)	0.1009

Abbreviations: CI, confidence interval; HR, hazard ratio. §The Cox proportional hazards model was adjusted for age, smoking status, alcohol use, body mass index, family history of prostate cancer, and education level. No additional biomarkers (e.g., serum uric acid, creatinine) were adjusted in this main analysis.

Table 4. Association Between Total Bilirubin, ALBI, and PALBI and Prostate Cancer Risk by Age Group: Quartile and Trend Analysis

Age	Indicators	Case (Median Follow-Up Time, IQR)	Q1 HR (95% CI) §	Q2 HR (95% CI) §	Q3 HR (95% CI) §	Q4 HR (95% CI) §	p value for Trend
All	ALBI	380 (14.1, 13.4–14.6)	1	0.85 (0.62-1.16)	0.9 (0.67-1.23)	0.93 (0.69-1.26)	0.9055
men	PALBI	357 (14.1, 13.4–14.6)	1	1.02 (0.79-1.33)	1.25 (0.95-1.65)	1.24 (0.89-1.74)	0.08
45-55	ALBI	144 (10.2, 6.6–12.8)	1	0.71 (0.44-1.14)	0.6 (0.38-0.97)	0.51 (0.32-0.83)	0.0073
years	PALBI	139 (10.2, 6.6–12.8)	1	1.23 (0.78-1.96)	1.65 (1.04-2.62)	2.54 (1.57-4.12)	0.0001
55-65	ALBI	140 (9.4, 5.2–12.1)	1	0.95 (0.55-1.65)	1.07 (0.64-1.81)	1.11 (0.65-1.87)	0.5605
years	PALBI	130 (9.4, 5.2–12.1)	1	0.87 (0.56-1.34)	1.17 (0.76-1.80)	0.69 (0.36-1.33)	0.7229
> 65	ALBI	81 (5.1, 1.3–8.9)	1	0.83 (0.38-1.81)	1.28 (0.63-2.62)	2.05 (1.05-4.01)	0.0055
years	PALBI	75 (5.1, 1.3–8.9)	1	0.96 (0.57-1.63)	0.77 (0.41-1.45)	0.34 (0.12-0.99)	0.0562

Abbreviations: CI, confidence interval; HR, hazard ratio. §The Cox proportional hazards model was adjusted for age, smoking status, alcohol use, body mass index, family history of prostate cancer, and education level. No additional biomarkers (e.g., serum uric acid, creatinine) were adjusted in this main analysis.

interactions. These findings suggest that age may act not only as an adjustment variable but also as a potential effect modifier in the associations between endogenous biomarkers and prostate cancer risk.

Previous epidemiologic studies of antioxidant-related biomarkers, including bilirubin, have reported inconsistent or inconclusive findings [21–24], and most have treated age primarily as an adjustment variable. In contrast, the present study found that associations not apparent in the overall population emerged in specific age groups, with some biomarkers showing different directions of association across age strata. To our knowledge, no previous prospective cohort study has specifically evaluated whether ALBI and PALBI show age-dependent and potentially opposing associations with prostate cancer risk. This finding highlights the novelty of assessing composite biomarker indices in an age-stratified framework.

The observed age-specific patterns may be partly related to age-associated changes in hormonal, metabolic, and oxidative stress-related profiles. Aging is accompanied by changes in endocrine function and oxidative-inflammatory balance [3–9], and the age range of 45–55 years may represent a transitional period during which such physiological changes begin to emerge. Therefore, the associations of bilirubin, platelet count, ALBI, and PALBI with prostate cancer risk may reflect differences in systemic physiological status across age groups, although the underlying mechanisms require further investigation.

Bilirubin and platelet count provide distinct biological information that may be relevant to prostate cancer risk. Bilirubin reflects endogenous antioxidant capacity [10–12], whereas platelets have been implicated in tumor-related processes, including the tumor microenvironment,

angiogenesis, and metastasis [15–17]. Because ALBI and PALBI integrate bilirubin with albumin and platelet count, these indices may capture broader systemic profiles than individual biomarkers alone. Although originally developed to assess liver function and prognosis in liver disease, ALBI and PALBI have recently been evaluated as markers of prognosis or systemic status in several cancers [25–28]. In the present study, their age-dependent and directionally different associations with prostate cancer risk suggest that these composite indices may reflect integrated biological information derived from antioxidant, hepatic, and platelet-related pathways.

Sensitivity analyses with additional adjustment for serum uric acid and creatinine yielded results that were largely consistent with the primary findings, indicating that the results were not materially altered after accounting for additional metabolic and antioxidant-related factors [29–35]. Future studies are needed to replicate these age-dependent patterns in independent cohorts and diverse populations, clarify the biological mechanisms involved, and evaluate whether these findings have implications for prostate cancer risk stratification.

In conclusions, this study demonstrates that serum bilirubin, platelet count, and the composite indices ALBI and PALBI exhibit age-dependent and, in some cases, opposing associations with prostate cancer risk. Notably, contrasting patterns were observed between men aged 45–55 years and those aged ≥65 years, and these patterns were consistent across both individual biomarkers and composite indices. These findings suggest that age should be considered not only as a confounder but also as a potential effect modifier when evaluating associations between endogenous biomarkers and prostate cancer risk. The observed age-specific patterns may reflect underlying

physiological changes across the lifespan and may have potential implications for risk stratification.

Limitations

Several limitations should be considered. First, because this was an observational study, the associations between ALBI, PALBI, individual biomarkers, and prostate cancer risk cannot be interpreted as causal. Second, biomarkers were measured only once at baseline; therefore, changes in biomarker levels during follow-up or long-term exposure patterns could not be captured. Third, participants with missing data were excluded, and the possibility of selection bias cannot be completely ruled out. Fourth, although we adjusted for age, smoking status, alcohol consumption, body mass index, family history of prostate cancer, and education level, information on PSA screening, dietary factors, medication use, including statins and aspirin, and circulating testosterone levels was not available. Therefore, detection bias related to differences in PSA screening and residual confounding due to unmeasured factors may remain. In particular, because testosterone levels were not directly measured, mechanistic interpretations related to hormonal changes should be considered hypothesis-generating and interpreted with caution. Fifth, the number of prostate cancer cases was relatively small in the oldest age group, which may have limited the precision of the estimates. In addition, survival bias or healthy participant bias may exist because older men who participated in health examinations may represent a relatively healthier survivor population. Because subgroup analyses were conducted across multiple biomarkers and age groups, the possibility of chance findings due to multiple testing should also be considered. Finally, the study population consisted exclusively of Korean men, which may limit the generalizability of the findings to other racial, ethnic, or geographic populations. Future studies with repeated biomarker measurements, information on PSA screening, medication use, dietary factors, hormonal profiles, and independent validation in diverse populations are warranted.

Author Contribution Statement

JWS: Developed the study hypothesis, designed the study, and performed statistical analysis. JWS: Carried out the conceptualization and methodology development. SHJ, JWS, and NTM: Conducted the investigation, performed data analysis, and validated the results. JWS: Drafted the manuscript and made subsequent revisions.

Acknowledgements

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Severance Hospital, Yonsei University Health System (approval number: 4-2011-0277). Written informed consent was obtained from all participants at the time of cohort enrollment. The present study was conducted as a secondary analysis of anonymized data, and all procedures involving human participants were

performed in accordance with the Declaration of Helsinki and relevant institutional guidelines.

Availability of data and materials

The datasets, including summary statistics and R code generated during the current study, are available from the corresponding author upon reasonable request. Due to privacy and ethical restrictions, raw data are not publicly available.

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Competing interests

The authors declare that they have no competing interests.

References

1. National Cancer Institute. SEER Cancer Stat Facts: Prostate Cancer [Internet]. Bethesda (MD): National Cancer Institute; [cited 2026 Oct 19]. Available from: <https://seer.cancer.gov/statfacts/html/prost.html>.
2. Cancer Research UK. Prostate cancer incidence statistics [Internet]. London: Cancer Research UK; [cited 2026 Oct 19]. Available from: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer/incidence>.
3. Brawer MK. Testosterone replacement in men with andropause: an overview. *Reviews in urology*. 2004;6(Suppl 6):S9.
4. Singh P. Andropause: Current concepts. *Indian J Endocrinol Metab*. 2013;17(9):621. <https://doi.org/10.4103/2230-8210.123552>
5. Rebello RJ, Oing C, Knudsen KE, Loeb S, Johnson DC, Reiter RE, et al. Prostate cancer. *Nat Rev Dis Primers*. 2021;7(1):9. <https://doi.org/10.1038/s41572-020-00243-0>
6. Tserotas K, Merino G. Andropause and the Aging Male. *Arch Androl*. 1998;40(2):87-93. <https://doi.org/10.3109/01485019808987931>
7. Cruz-Topete D, Dominic P, Stokes KY. Uncovering sex-specific mechanisms of action of testosterone and redox balance. *Redox Biol*. 2020;31:101490. <https://doi.org/10.1016/j.redox.2020.101490>
8. Prudova A, Albin M, Bauman Z, Lin A, Vitvitsky V, Banerjee R. Testosterone Regulation of Homocysteine Metabolism Modulates Redox Status in Human Prostate Cancer Cells. *Antioxid Redox Signal*. 2007;9(11):1875-1882. <https://doi.org/10.1089/ars.2007.1712>
9. Kościuszko M, Buczyńska A, Krętowski AJ, Popławska-Kita A. Could Oxidative Stress Play a Role in the Development and Clinical Management of Differentiated Thyroid Cancer?. *Cancers*. 2023;15(12):3182. <https://doi.org/10.3390/cancers15123182>
10. Stocker R, Yamamoto Y, McDonagh AF, Glazer AN, Ames BN. Bilirubin Is an Antioxidant of Possible Physiological Importance. *Science*. 1987;235(4792):1043-1046. <https://doi.org/10.1126/science.2805822>

- doi.org/10.1126/science.3029864
11. Kapitulnik J. Bilirubin: an endogenous product of heme degradation with both cytotoxic and cytoprotective properties. *Mol Pharmacol*. 2004;66(4):773-779. <https://doi.org/10.1124/mol.104.002832>
12. Vitek L. The Role of Bilirubin in Diabetes, Metabolic Syndrome, and Cardiovascular Diseases. *Front Pharmacol*. 2012;3. <https://doi.org/10.3389/fphar.2012.00055>
13. Belinskaia DA, Voronina PA, Shmurak VI, Jenkins RO, Goncharov NV. Serum Albumin in Health and Disease: Esterase, Antioxidant, Transporting and Signaling Properties. *Int J Mol Sci*. 2021;22(19):10318. <https://doi.org/10.3390/ijms221910318>
14. Roche M, Rondeau P, Singh NR, Tarnus E, Bourdon E. The antioxidant properties of serum albumin. *FEBS Letters*. 2008;582(13):1783-1787. <https://doi.org/10.1016/j.febslet.2008.04.057>
15. Chen L, Zhu C, Pan F, Chen Y, Xiong L, Li Y, et al. Platelets in the tumor microenvironment and their biological effects on cancer hallmarks. *Front Oncol*. 2023;13:1121401. <https://doi.org/10.3389/fonc.2023.1121401>
16. Bian X, Yin S, Yang S, Jiang X, Wang J, Zhang M, Zhang L. Roles of platelets in tumor invasion and metastasis: A review. *Heliyon*. 2022;8(12):e12072. <https://doi.org/10.1016/j.heliyon.2022.e12072>
17. Labelle M, Begum S, Hynes RO. Platelets guide the formation of early metastatic niches. *Proc Natl Acad Sci U S A*. 2014;111(30):E3053-61. <https://doi.org/10.1073/pnas.1411082111>
18. Jee YH, Emberson J, Jung KJ, Lee SJ, Lee S, Back JH, et al. Cohort profile: The Korean cancer prevention study-ii (kcps-ii) biobank. *Int J Epidemiol*. 2018;47(2):385-6f. <https://doi.org/10.1093/ije/dyx226>
19. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of Liver Function in Patients With Hepatocellular Carcinoma: A New Evidence-Based Approach—The ALBI Grade. *Journal of Clinical Oncology*. 2015;33(6):550-558. <https://doi.org/10.1200/JCO.2014.57.9151>
20. Wikström Shemer EA, Stephansson O, Thuresson M, Thorsell M, Ludvigsson JF, Marschall H. Intrahepatic cholestasis of pregnancy and cancer, immune-mediated and cardiovascular diseases: A population-based cohort study. *Journal of Hepatology*. 2015;63(2):456-461. <https://doi.org/10.1016/j.jhep.2015.03.010>
21. Seyed Khoei NS, Carreras-Torres R, Murphy N, Gunter MJ, Brennan P, Smith-Byrne K, et al. Genetically Raised Circulating Bilirubin Levels and Risk of Ten Cancers: A Mendelian Randomization Study. *Cells*. 2021;10(2):394. <https://doi.org/10.3390/cells10020394>
22. Kim YR, Choi CK, Lee Y, Choi S, Kim H, Shin M, Kweon S. Association between Albumin, Total Bilirubin, and Uric Acid Serum Levels and the Risk of Cancer: A Prospective Study in a Korean Population. *Yonsei Med J*. 2021;62(9):792. <https://doi.org/10.3349/ymj.2021.62.9.792>
23. Kühn T, Sookthai D, Graf ME, Schübel R, Freisling H, Johnson T, et al. Albumin, bilirubin, uric acid and cancer risk: results from a prospective population-based study. *Br J Cancer*. 2017;117(10):1572-1579. <https://doi.org/10.1038/bjc.2017.313>
24. Inoguchi T, Nohara Y, Nojiri C, Nakashima N. Association of serum bilirubin levels with risk of cancer development and total death. *Sci Rep*. 2021;11(1):13224. <https://doi.org/10.1038/s41598-021-92442-2>
25. Chen L, Tan C, Li Q, Ma Z, Wu M, Tan X, et al. Assessment of the albumin-bilirubin score in breast cancer patients with liver metastasis after surgery. *Heliyon*. 2023;9(11):e21772. <https://doi.org/10.1016/j.heliyon.2023.e21772>
26. Kut E, Menekse S. Prognostic significance of pretreatment albumin-bilirubin (albi) grade and platelet-albumin-bilirubin (palbi) grade in patients with small cell lung cancer. *Sci Rep*. 2024;14(1):1371. <https://doi.org/10.1038/s41598-024-51375-2>
27. Kim D, Lee J, Cho E, Shin S, Lee HS, Koh H, et al. Clinical Significance of Combining Preoperative and Postoperative Albumin-Bilirubin Score in Colorectal Cancer. *Cancer Res Treat*. 2023;55(4):1261-1269. <https://doi.org/10.4143/crt.2022.1444>
28. Shi X, Zhang S, Bao B, Cong H, Lu X, Shi A. Albumin-bilirubin score: a promising predictor of postoperative distant metastasis in patients with colorectal cancer. *Biomark Med*. 2025;19(3):73-79. <https://doi.org/10.1080/17520363.2025.2455928>
29. Shin JW, Sull JW, Minh NT, Jee SH. Sex-specific associations of creatinine and antioxidant biomarkers with lung cancer risk by drinking and smoking behavior: A prospective cohort study. *Cancer Epidemiol*. 2026;101:102993. <https://doi.org/10.1016/j.canep.2026.102993>
30. Shin JW, Jee Y, Yang YS. Endogenous antioxidant biomarkers and cancer risk among men with concurrent smoking and alcohol use: A prospective cohort study. *Cancer Epidemiol*. 2026;103:103083. <https://doi.org/10.1016/j.canep.2026.103083>
31. Comparison Of Serum Uric Acid Levels Between Prostate Cancer Patients And A Control Group. *Cent European J Urol*. 2018;. <https://doi.org/10.5173/ceju.2018.1619>
32. Lee YHA, Chan JSK, Leung CH, Hui JMH, Dee EC, Ng K, et al. Association between serum uric acid and prostate cancer mortality in androgen deprivation therapy: A population-based cohort study. *Cancer Med*. 2023;12(16):17056-17060. <https://doi.org/10.1002/cam4.6344>
33. Yan Y, Lin H, He Z, Wang L. Serum uric acid and prostate cancer: findings from the NHANES (2007–2020). *Front Oncol*. 2024;14:1354235. <https://doi.org/10.3389/fonc.2024.1354235>
34. Yan W, Xiang P, Liu D, Zheng Y, Ping H. Association between the serum uric acid levels and prostate cancer: evidence from National Health and Nutrition Examination Survey (NHANES) 1999–2010. *Transl Cancer Res*. 2024;13(5):2308-2314. <https://doi.org/10.21037/tcr-24-46>
35. Weinstein SJ, Mackrain K, Stolzenberg-Solomon RZ, Selhub J, Virtamo J, Albanes D. Serum Creatinine and Prostate Cancer Risk in a Prospective Study. *Cancer Epidemiol Biomarkers Prev*. 2009;18(10):2643-2649. <https://doi.org/10.1158/1055-9965.EPI-09-0322>



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