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The Prostate Health Index Selectively Identifies Clinically Significant Prostate Cancer

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Abstract

Purpose—The Prostate Health Index (phi) is a new test combining total, free and [-2]proPSA into a single score. It was recently approved by the FDA and is now commercially available in the U.S., Europe and Australia. We investigate whether phi improves specificity for detecting clinically significant prostate cancer and can help reduce prostate cancer over diagnosis.

Materials and Methods—From a multicenter prospective trial we identified 658 men age 50 years or older with prostate specific antigen 4 to 10 ng/ml and normal digital rectal examination who underwent prostate biopsy. In this population we compared the performance of prostate specific antigen, % free prostate specific antigen, [-2]proPSA and phi to predict biopsy results and, specifically, the presence of clinically significant prostate cancer using multiple criteria.

Results—The Prostate Health Index was significantly higher in men with Gleason 7 or greater and “Epstein significant” cancer. On receiver operating characteristic analysis phi had the highest AUC for overall cancer (AUCs phi 0.708, percent free prostate specific antigen 0.648, [-2]proPSA

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0.550 and prostate specific antigen 0.516), Gleason 7 or greater (AUCs phi 0.707, percent free prostate specific antigen 0.661, [-2]proPSA 0.558, prostate specific antigen 0.551) and significant cancer (AUCs phi 0.698, percent free prostate specific antigen 0.654, [-2]proPSA 0.550, prostate specific antigen 0.549). At the 90% sensitivity cut point for phi (a score less than 28.6) 30.1% of patients could have been spared an unnecessary biopsy for benign disease or insignificant prostate cancer compared to 21.7% using percent free prostate specific antigen.

Conclusions—The new phi test outperforms its individual components of total, free and [-2]proPSA for the identification of clinically significant prostate cancer. Phi may be useful as part of a multivariable approach to reduce prostate biopsies and over diagnosis.

Keywords

biological markers; prostatic neoplasms; early detection of cancer

Screening with serum total PSA measurements has led to a reduction in advanced disease and a decrease in prostate cancer mortality rates. However, due to the limited specificity of the total PSA test, these benefits have come at a cost of unnecessary biopsies and over diagnosis of insignificant disease. In 2012 the USPSTF (U.S. Preventive Services Task Force) recommended against prostate cancer screening[1] and the time has arrived for a major paradigm shift in prostate cancer detection.

Large randomized trials of PSA screening have yielded conflicting results. The ERSPC (European Randomized Study of Prostate Cancer Screening) reported a 21% reduction in prostate cancer mortality with PSA screening.[2] However, the U.S. Prostate, Lung, Colorectal and Ovarian screening trial found no significant difference in prostate cancer mortality between organized PSA and digital rectal examination compared to usual care.[3] Both of these trials were designed in the early 1990s and used total PSA thresholds to determine the need for prostate biopsy.

Since these trials were designed and initiated, various PSA derivatives have been suggested to improve specificity. One is the percentage of PSA circulating in the unbound form (free PSA) that helps distinguish benign conditions from prostate cancer.[4] Free PSA is, in fact, comprised of several different iso forms including [-2]proPSA, which is more specific for prostate cancer than total PSA or free PSA.[5,6]

The Beckman Coulter Prostate Health Index combines total, free and [-2]proPSA into a single score. Large prospective multicenter studies in the U.S. and Europe have demonstrated that phi improves prostate cancer detection,[7] leading to its recent FDA approval as an aid to early prostate cancer detection for men with a PSA of 4 to 10 ng/ml. Several recent international studies have also suggested a role for phi in monitoring patients on active surveillance.[8–10]

In its 2012 recommendation statement the USPSTF emphasized the urgent need to identify new screening methods that can better identify indolent vs aggressive disease.[1] To address research gap and the critical issues of over diagnosis and overtreatment, our objective was to determine whether phi improves the detection of clinically significant prostate cancer.

Material and Methods

From 2004 to 2009, 892 men 50 years old or older with PSA 2 to 10 ng/ml and benign findings on digital rectal examination were enrolled in a prospective multicenter U.S. trial of phi.[7] All men underwent prostate biopsy (97.8% had 10 or more cores, 79.3% initial) and, therefore, had a histologically confirmed diagnosis. The study sought to enroll equal numbers of men diagnosed with prostate cancer and men diagnosed with benign disease to maximize statistical efficiency. The study was approved by the institutional review board and all men provided written informed consent. Of these men 658 had a PSA of 4 to 10 ng/ml (FDA approved range) and constitute the current study population.

Serum samples were collected before biopsy using standard techniques and were processed and frozen within 8 hours. Samples were thawed and tested for total PSA, free PSA and [-2]proPSA concurrently using the Beckman Coulter Access® 2 immunoassay analyzer and the respective Access Hybritech® assays. Phi was then calculated according to the formula, [-2]proPSA/fPSA × √PSA, which was developed to maximize specificity at high sensitivity.[11] (Our results apply to the Hybritech p2PSA, PSA and fPSA assays on the Beckman Coulter Access Immunoassay Systems.)

Statistical Analysis

Descriptive statistics were used to characterize patients based on biopsy outcome. The Wilcoxon rank sum test and chi-square test were used to compare clinical characteristics between men with positive biopsy vs those with negative biopsy, clinically significant vs insignificant histopathology based on the Epstein definition of clinically significant prostate cancer (Gleason 7 or greater,3 or more positive cores, and more than 50% involvement of any core),[12] and Gleason 7 or greater vs Gleason less than 7 disease.

We also compared the specificities of PSA, %fPSA, [-2] proPSA and phi at 80%, 85%, 90% and 95% sensitivities. We compared the estimated specificities using a bootstrap based method to account for sampling variability for estimating the cutoff at each fixed sensitivity value.[13] Stepwise logistic regression was then used for multivariable analysis to evaluate predictors of the presence of prostate cancer, Gleason 7 or greater (vs Gleason less than 7 and benign disease) and Epstein significant cancer (vs insignificant cancer and benign disease) on biopsy. We initially evaluated several variables in a stepwise manner along with phi, including age, race, prior biopsy, prostate volume and PSA. The base model only included the variables that were significantly associated with biopsy outcome (model 1). Due to multicollinearity it was not possible to include phi with %fPSA and [-2]proPSA in the same model, so 2 additional multivariable models were performed with [-2]proPSA (model 2) or %fPSA (model 3) added to the base model. All models included log transformed values of PSA, %fPSA, [-2]proPSA and phi. Receiver operating characteristic analysis was performed and AUC were compared using an empiric method for paired data.[14] All statistical analysis was performed using SAS® version 9.3 and statistical tests were considered significant at $p < 0.05$.

Results

Table 1 shows the clinical characteristics of the study population. Median patient age was 63 years,81% were white and median prostate volume was 46 cc. Overall 324 (49.2%) of 658 men had prostate cancer on biopsy, of which 52.5% was Epstein significant and 33.7% was Gleason 7 or greater. Men with a previous prostate biopsy were significantly less likely to have a positive biopsy or clinically significant disease. Total PSA was not significantly different between men with negative vs positive, insignificant vs significant and Gleason less than 7 vs 7 or greater prostate cancer. In contrast, %fPSA was significantly lower, and [-2]proPSA and phi were significantly higher in men with overall, Epstein significant and Gleason 7 or greater prostate cancer.

Table 2 shows the specificity of each serum marker at set sensitivities of 80%, 85%, 90% and 95%. At any given sensitivity phi had a greater specificity than PSA, [-2]proPSA and %fPSA for overall, Epstein significant and Gleason 7 or greater prostate cancer. For example, using a phi cutoff of 28.6 (the 90% sensitivity cutoff for significant vs insignificant cancer), 10.1% of significant cancers,4.8% of Gleason 3+4 or greater and 1.2% of 4+3 or greater disease would have been missed. Using this phi cutoff we estimate that 30.1% of men with benign disease or insignificant prostate cancer could have been spared a biopsy. For comparison, only 21.7% would have been spared using %fPSA. Thus, an additional 8.4% of biopsies could be avoided using phi compared to %fPSA.

On multivariable analysis prior prostate biopsy and larger prostate volume were associated with a significantly lower risk of overall and Epstein significant prostate cancer (table 3). In the base model with prior biopsy and prostate volume, phi was a significant predictor of overall prostate cancer (OR 4.87, 95% CI 3.01–7.89, $p < 0.001$), Epstein significant disease (OR 4.83, 95% CI 2.85–8.20, $p < 0.001$) and Gleason 7 or greater disease (OR 5.36, 95% CI 3.00–9.56, $p < 0.001$). Two additional models were also performed including %fPSA or [-2]proPSA, and in both cases phi remained the strongest predictor of overall, significant and high grade prostate cancer ($p < 0.001$ for all models). In contrast, %fPSA and [-2]proPSA were no longer statistically significant predictors of the outcomes after adjusting for phi in the multivariable models.

As shown in figure 1, A, phi offered the greatest discrimination of total prostate cancer detection on biopsy (AUCs phi 0.708, %fPSA 0.648, [-2]proPSA 0.550 and PSA 0.516). Figure 1, B and C show that phi also had the greatest predictive accuracy for Epstein significant cancer (AUCs phi 0.698, %fPSA 0.654, [-2]proPSA 0.550, PSA 0.549) and Gleason 7 or greater disease on biopsy (AUCs phi 0.707, %fPSA 0.661, [-2]proPSA 0.558, PSA 0.551).

Discussion

The Prostate Health Index was recently approved by the FDA for prostate cancer detection in men with a PSA of 4 to 10 ng/ml. Large studies from the U.S., Europe and Asia have uniformly demonstrated that phi improves specificity and provides a greater net benefit for prostate cancer detection compared to total and free PSA.[5,7,15–17] A recent systematic

review by Filella and Gimenez including 8 studies on phi concluded that it increases the specificity for prostate cancer detection[18] and it is mentioned in the 2014 National Comprehensive Cancer Network Guidelines.[19]

The current study builds on these findings to demonstrate that phi also outperformed its individual components of total, free and [-2]proPSA for the identification of clinically significant prostate cancer. Using a phi threshold of 28.6 could potentially avoid 30% of biopsies with indolent or no prostate cancer.

These new data from the U.S. are in line with the findings of Roobol el al in a large multicenter European population.[20] Specifically, adding phi to the multivariable ERSPC risk calculator increased the predictive accuracy for overall and serious prostate cancer in men undergoing initial and repeat biopsy. On decision curve analysis phi resulted in a net benefit at threshold probabilities greater than 30% and the authors concluded that phi is useful as part of a multivariable approach to reduce unnecessary biopsies. This multivariable risk calculator that includes phi is now available as a mobile application on smartphones and tablets for more convenient use in the clinical setting.[21]

In addition to the decision about whether to perform a prostate biopsy, another major challenge is determining which men need radical treatment and which can be safely monitored. Although in the current study we did not evaluate an active surveillance population, in a multicenter study Hirama et al recently found that phi was useful to predict reclassification during active surveillance.[10] Similar results were previously reported by Tosoian et al in men from the Johns Hopkins active surveillance program.[9] In this study the baseline phi measurement was significantly associated with subsequent progression, suggesting it may be useful for initial patient selection. In addition, longitudinal values of phi during surveillance were also significant predictors of biopsy progression, with a high concordance index (C-index) of 0.820. It is noteworthy that the same group reported that PCA3 did not predict short-term biopsy progression during active surveillance.[22]

A study by Ferro et al of men with PSA 2 to 10 ng/ml undergoing prostate biopsy compared the performance of phi and PCA3.[23] Although both tests significantly outperformed %fPSA to predict biopsy results, on decision curve analysis phi had a greater net benefit than PCA3 at threshold probabilities greater than 25%. The authors concluded that “owing to its easier and cheaper technology, its lower discomfort for the patients and its better ability to reduce unnecessary biopsies (as shown by decision curve analysis), phi should probably be recommended as the best assay in addition to PSA as first line diagnostic test for prostate cancer detection.” Because no single test is perfect, we recommend phi as part of a multivariable approach to screening and treatment decisions.

A limitation of our study is the use of biopsy criteria to define clinical significance. Although biopsy criteria are frequently used, these end points are not perfect and other factors such as life expectancy also have a key role in defining over diagnosis.[24] In addition, data on other new tests like PCA3 and magnetic resonance imaging were not available in the current study, and the confidence intervals in some of our subanalyses were wide. Strengths of our study include the prospectively enrolled source population including a large number

of men from multiple centers across the U.S. All men had a histological diagnosis for end point assessment and in a direct comparison phi was shown to outperform its individual components.

Conclusions

In our cohort of U.S. men with a PSA of 4 to 10 ng/ml, phi had greater predictive accuracy for clinically significant prostate cancer than its individual components of PSA, free PSA and [-2]proPSA. Use of a phi cutoff of 28.6 could potentially avoid approximately 30% of biopsies in men with benign or insignificant disease while missing or delaying the diagnosis of 10% or fewer prostate cancers with some aggressive features. Phi is a simple blood test that we recommend for use as part of a multivariable approach to reduce unnecessary biopsies and over diagnosis.

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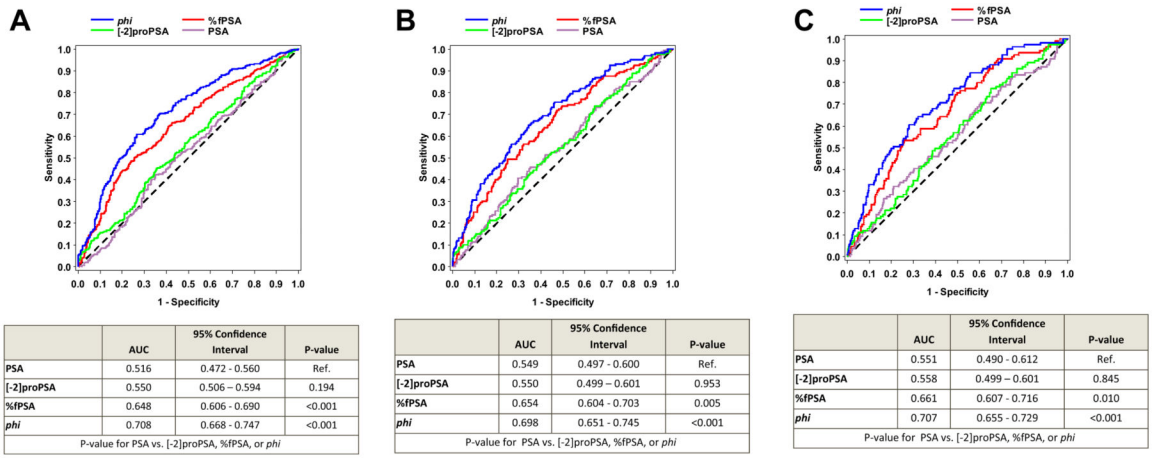
Abbreviations and Acronyms

FDA	U.S. Food and Drug Administration
fPSA	free prostate specific antigen
%fPSA	percent free prostate specific antigen
PCA3	prostate cancer antigen 3
phi	Prostate Health Index
PSA	prostate specific antigen



	AUC	95% Confidence Interval	P-value
PSA	0.516	0.472 - 0.560	Ref.
[-2]proPSA	0.550	0.506 – 0.594	0.194
%fPSA	0.648	0.606 - 0.690	<0.001
phi	0.708	0.668 - 0.747	<0.001
P-value for PSA vs. [-2]proPSA, %fPSA, or *phi*			

	AUC	95% Confidence Interval	P-value
PSA	0.549	0.497 - 0.600	Ref.
[-2]proPSA	0.550	0.499 – 0.601	0.953
%fPSA	0.654	0.604 - 0.703	0.005
phi	0.698	0.651 - 0.745	<0.001
P-value for PSA vs. [-2]proPSA, %fPSA, or *phi*			

	AUC	95% Confidence Interval	P-value
PSA	0.551	0.490 - 0.612	Ref.
[-2]proPSA	0.558	0.499 – 0.601	0.845
%fPSA	0.661	0.607 - 0.716	0.010
phi	0.707	0.655 - 0.729	<0.001
P-value for PSA vs. [-2]proPSA, %fPSA, or *phi*			

Figure 1.

Receiver operating characteristic analysis for prostate cancer detection on biopsy comparing PSA, %fPSA, [-2]proPSA and phi for overall prostate cancer (*A*), Epstein significant cancer (*B*) and Gleason score 7 or greater cancer (*C*) on biopsy.

Table 1

Patient characteristics by diagnosis, Gleason score and Epstein criteria

			Ca									
			Epstein Criteria			Gleason Score*						
		Benign		Total Ca	Not Significant		Significant		Less than 7		7 or Greater	All Pts
No. pts	334		324		145		160		214	109		658	
Median age (range)	63.0	(50–84)	63.0	(50–84)	63.0	(50–84)	62.0	(50–83)	63.0	(50–84)	64.0	(51–83)	63.0	(50–84)
No. race (%):														
Black	17	(5.1)	18	(5.6)†	9	(6.2)	7	(4.4)†	15	(7.0)†	3	(2.8)	35	(5.3)
White	259	(77.5)	275	(84.9)†	120	(82.8)	140	(87.5)†	178	(83.2)†	97	(89.0)	534	(81.2)
Other	58	(17.4)	31	(9.5)†	16	(11.0)	13	(8.1)†	21	(9.8)†	9	(8.2)	83	(13.5)
No. prior biopsy (%)	92	(27.5)	44	(13.6)†	21	(14.5)†	17	(10.6)†	33	(15.4)†	10	(9.2)†	136	(20.7)
Median cc prostate vol (range)‡	53.0	(16–202)	40.5	(14–120)†	38.0	(15–202)†	44.0	(14–108)†	43.0	(14–113)†	38.0	(15–120)†	46.0	(14–202)
Median ng/ml PSA (range)	5.7	(4.0–10.0)	5.9	(4.00–9.8)	5.9	(4.0–9.4)	6.0	(4.1–9.8)	5.9	(4.0–9.8)	6.0	(4.1–9.8)	5.8	(4.0–10.0)
Median pg/ml [-2]proPSA (range)	14.0	(3.6–43.5)	15.2	(5.3–93.5)†	15.0	(5.5–51.1)	15.6	(5.3–93.5)†	15.1	(5.5–93.5)	15.9	(5.3–90.8)†	14.7	(3.6–93.5)
Median%fPSA (range)	18.1	(3.1–50.1)	14.6	(3.7–42.5)†	15.1	(3.7–37.2)†	13.8	(3.7–42.5)†	15.1	(3.7–42.5)†	12.8	(3.7–33.6)†	16.5	(3.1–50.1)
Median phi (range)	32.4	(14.0–98.2)	44.4	(14.0–325.8)†	43.6	(14.0–153.3)†	47.8	(15.8–325.8)†	42.9	(14.0–227.9)†	50.1	(15.8–325.8)†	37.9	(14.0–325.8)

*Gleason score missing for 1 patient with cancer.

†p <0.05 for Pearson's chi-square test or Wilcoxon rank sum test vs benign disease.

‡Biopsy volume missing for 113 patients.

Table 2

Comparison of specificity at various sensitivity levels for men with PSA 4 to 10 ng/ml

	Prostate Ca (324 with + 334 without)			Significant Prostate Ca (160 with + 479 without or with nonsignificant prostate Ca)*			Biopsy Gleason Score (109 with 7 or greater + 548 with less than 7 or without prostate Ca)		
% Sensitivity	Cutoff	% Specificity	95% CI	Cutoff	% Specificity	95% CI	Cutoff	% Specificity	95% CI
80:									
PSA	4.7	21.0	15.4–27.9	4.9	26.7	19.3–35.8	4.9	25.9	17.6–36.4
[-2]proPSA	10.4	25.4	19.2–32.9	10.5	25.3	18.1–34.1	10.9	27.9	19.3–38.6
%fPSA	20.5	37.1†	29.7–45.2	19.5	37.6†	28.7–47.4	18.9	39.1†	28.7–50.5
phi	31.3	46.1†	38.1–54.3	33.8	45.5†	36.0–55.4	34.4	46.4†	35.3–57.8
85:									
PSA	4.5	15.6	10.8–22.0	4.6	18.0	11.9–26.2	4.5	15.3	9.3–24.3
[-2]proPSA	9.6	20.7	14.9–27.8	9.8	20.9	14.2–29.6	10.2	23.0	14.9–33.7
%fPSA	22.0	28.4†	21.6–36.4	20.2	33.8†	24.9–44.0	19.6	36.1†	25.6–48.2
Phi	28.9	37.7†	29.9–46.2	31.0	37.2†	27.9–47.5	31.9	38.9†	27.9–51.0
90:									
PSA	4.4	10.8	6.8–16.6	4.3	9.6	5.5–16.2	4.3	7.8	4.0–14.9
[-2]proPSA	8.2	12.9	8.4–19.2	8.8	15.2	9.5–23.6	8.6	13.1	7.3–22.4
%fPSA	24.1	19.8†	13.9–27.3	22.7	21.7†	14.3–31.5	20.6	31.6†	20.9–44.6
Phi	27.0	31.1†	23.5–39.9	28.6	30.1†	21.0–41.0	28.9	29.7†	19.4–42.6
95:									
PSA	4.2	7.5	4.2–13.1	4.2	6.3	3.0–12.7	4.1	4.7	1.9–11.4
[-2]proPSA	7.4	9.0	5.2–15.1	8.0	10.6	5.6–19.3	7.9	9.9	4.6–20.0
%fPSA	27.9	9.9	5.8–16.3	27.4	9.6	5.0–17.8	26.3	10.8	5.1–21.4
phi	22.1	14.1†	8.8–21.7	24.1	16.3†	9.3–26.9	28.1	27.4†	15.9–42.9

*Significant cancer per Epstein histopathological criteria, ie Gleason score greater than 6,3 or more positive cores or more than 50% core involvement with cancer. There were 19 cases lacking sufficient detail on biopsy report to be categorized as Epstein significant vs insignificant.

†$p < 0.05$ for comparison with PSA.

Table 3

Multivariable models to predict total, Epstein significant and high grade prostate cancer using phi and other variables

	Model 1 OR (95% CI)/p Value			Model 2 OR (95% CI)/p Value			Model 3 OR (95% CI)/p Value		
Outcome	**Prostate Ca**	**Significant Epstein Criteria**	**Gleason Score 7 or Greater**	**Prostate Ca**	**Significant Epstein Criteria**	**Gleason Score 7 or Greater**	**Prostate Ca**	**Significant Epstein Criteria**	**Gleason Score 7 or Greater**
Variable									
Prior biopsy:									
No	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Yes	0.46 (0.28–0.76)/ 0.002	0.45 (0.24–0.87)/ 0.018	0.37 (0.16–0.83)/ 0.015	0.46 (0.28–0.76)/ 0.002	0.45 (0.24–0.87)/ 0.018	0.37 (0.16–0.83)/ 0.016	0.46 (0.28–0.76)/ 0.002	0.45 (0.23–0.87)/ 0.017	0.36 (0.16–0.82)/ 0.015
Unknown	1.57 (0.25–10.07)/ 0.632	4.68 (0.72–30.44)/ 0.107	3.85 (0.67–22.17)/ 0.132	1.59 (0.25–10.20)/ 0.627	4.67 (0.72–30.41)/ 0.107	3.83 (0.67–21.95)/ 0.132	1.54 (0.24–9.77)/ 0.650	4.49 (0.70–28.76)/ 0.114	3.74 (0.67–21.06)/ 0.135
Prostate vol (per +10 cc)	0.84 (0.76–0.92)/ <0.001	0.80 (0.71–0.91)/ <0.001	0.87 (0.77–1.00)/ 0.044	0.84 (0.76–0.92)/ <0.001	0.81 (0.71–0.92)/ 0.001	0.88 (0.76–1.01)/ 0.070	0.85 (0.77–0.93)/ <0.001	0.82 (0.72–0.93)/ 0.002	0.89 (0.77–1.02)/ 0.090
Log_e (%fPSA)							0.90 (0.55–1.49)/ 0.693	0.83 (0.48–1.43)/ 0.508	0.80 (0.44–1.46)/ 0.469
Log_e ([-2]proPSA)				1.05 (0.64–1.71)/ 0.848	0.99 (0.58–1.68)/ 0.963	0.94 (0.52–1.70)/ 0.839			
Log_e (phi)	4.87 (3.01–7.89)/ <0.001	4.83 (2.85–8.20)/ <0.001	5.36 (3.00–9.56)/ <0.001	4.72 (2.64–8.43)/ <0.001	4.87 (2.56–9.21)/ <0.001	5.58 (2.76–11.27)/ <0.001	4.69 (2.80–7.86)/ <0.001	4.50 (2.56–7.94)/ <0.001	4.92 (2.65–9.15)/ <0.001