Title

Individual Patient Data Meta-analysis of Discrimination of the Four Kallikrein Panel Associated With the Inclusion of Prostate Volume.

Authors

Vertosick, Emily A
Zappala, Stephen
Punnen, Sanoj
et al.

Publication Date

2021-11-01

DOI

10.1016/j.urology.2021.08.014

Peer reviewed

HHS Public Access

Author manuscript

Urology. Author manuscript; available in PMC 2022 November 01.

Published in final edited form as:

Urology. 2021 November ; 157: 102–106. doi:10.1016/j.urology.2021.08.014.

Individual patient data meta-analysis of discrimination of the four kallikrein panel associated with the inclusion of prostate volume

Emily A. Vertosick[1], **Stephen Zappala**[2], **Sanoj Punnen**[3], **Jonas Hugosson**[4], **Stephen A. Boorjian**[5], **Alexander Haese**[6], **Peter Carroll**[7], **Matthew Cooperberg**[7,8], **Anders Bjartell**[9], **Hans Lilja**[10], **Andrew Vickers**[1]

[1]Department of Epidemiology & Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York, USA

[2]Andover Urology, Andover, MA, Tufts University School of Medicine, Boston, MA, USA

[3]Department of Urology, University of Miami and Sylvester Comprehensive Cancer Center, Miami, FL, USA

[4]Department of Urology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Göteborg, Göteborg, Sweden

[5]Department of Urology, Mayo Clinic, Rochester, MN, USA

[6]Martini-Clinic Prostate Cancer Center, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[7]Department of Urology, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA

[8]Department of Epidemiology and Statistics, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA

[9]Department of Urology, Skåne University Hospital Malmö, Lund University, Sweden

[10]Departments of Laboratory Medicine, Surgery, and Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA, Department of Translational Medicine, Lund University, Malmö, Sweden

Abstract

Corresponding author: Andrew J. Vickers, Memorial Sloan Kettering Cancer Center, 485 Lexington Avenue, New York, NY 10017 USA, vickersa@mskcc.org, (P): 646-888-8233.

Disclosures:

Stephen A. Boorjian: Consultant for Ferring, Sanofi, ArTara, FerGene

Hans Lilja holds a patent on assays to measure intact PSA and is together with Andrew Vickers named on a patent for a statistical method to detect prostate cancer that has been commercialized as 4Kscore test by OPKO Health. Andrew Vickers and Hans Lilja receive royalties from sales of the test. Hans Lilja has stock and Andrew Vickers and Stephen Zappala have stock options in OPKO Health.

Objective—To assess whether adding prostate volume to the kallikrein panel improves discrimination for ISUP Grade Group 2 or higher (GG2+) disease, as some men may have volume measurements available at the time of blood draw. While prostate volume predicts biopsy outcome, it requires an imaging procedure for measurement. The four kallikrein panel - commercially available as the 4Kscore - predicts risk of GG2+ disease and requires only a blood draw.

Materials and Methods—9,131 patients with available prostate volume and total PSA ≤25 ng/ml from 5 historical (sextant biopsy, pre-ISUP 2005 grading) and 4 contemporary cohorts (10+ cores, ISUP 2005 grading). Previously published kallikrein panel models were used to predict risk of GG2+. Volume was added to the model in each cohort and change in discrimination was meta-analyzed.

Results—Increased prostate volume was associated with decreased risk of GG2+ disease after control ling for the kallikrein panel in 7/9 cohorts. However, kallikrein panel discrimination (0.817, 95% CI 0.802, 0.831) was not improved after including volume (AUC difference 0.002, 95% CI −0.003, 0.006). Heterogeneity ($p<0.0001$) was driven by an AUC increase in one cohort of academic cancer centers (0.044, 95% CI 0.025, 0.064), with no evidence of heterogeneity after excluding this cohort ($p=0.15$).

Conclusion—The kallikrein panel provides a non-invasive approach to assess the risk of high-grade prostate cancer. Our results do not justify the inclusion of prostate volume in the four kallikrein panel. There is some evidence that the predictive value of prostate volume is provider dependent: further research is needed to address this question.

Introduction

Total prostate-specific antigen (PSA) elevation can be attributed to benign or malignant causes. The most common benign cause, benign prostatic hyperplasia (BPH), results from enlargement of the prostate, while there is no important corresponding increase in volume accompanying PSA increases with localized prostate cancer. Elevated PSA in older men is commonly due to the high prevalence of benign disease, with approximately half of men aged 50 or older affected[1], making it difficult to differentiate between elevated PSA due to malignant vs benign causes.

Prostate volume is widely known to be a predictor of clinically significant prostate cancer: for any given PSA having a higher prostate volume is associated with a lower risk of high-grade prostate cancer. Some efforts have been made to incorporate prostate volume into biopsy decision-making, for example, with the use of PSA density or addition of prostate volume to risk calculators.[2] However, prostate volume is not commonly utilized in screening as, until recently, it had to be measured through a transrectal ultrasound (TRUS), an invasive test.

A statistical model based on a panel of four kallikrein markers, commercialized as the 4Kscore (OPKO Health: Miami, FL), has been shown to predict risk of ISUP 2005 Grade Group 2 or higher (GG2+) prostate cancer on biopsy. The kallikrein markers can be measured from the venous blood sampled that was used for the PSA test and have a much higher predictive discrimination than PSA alone in men with elevated PSA.[3,4] The 4Kscore

is also highly correlated with prostate volume and has similar discrimination for identifying high grade prostate cancer. It has therefore been suggested that the 4K score could replace the use of TRUS-estimated prostate volume for identifying patients at risk for aggressive disease.[5] However, the 4Kscore would not be a good substitute for prostate volume in this context if prostate volume added to the 4Kscore, as this would imply that substituting the 4Kscore alone would not adequately represent the patient's risk.

In recent years, prostate multi-parametric magnetic resonance imaging (MRI) has been recommended for use in conjunction with PSA screening to increase specificity and for purposes of targeting suspicious lesions in patients planning to undergo prostate biopsy.[6–8] Prostate volume may also be available for patients who have had prior negative biopsies or who have been diagnosed with indolent prostate cancer and elected upon active surveillance. Since the 4Kscore is used in clinical practice, it is important to investigate ways that it could potentially be improved. For patients with available prostate volume measurements, it is possible that prostate volume could provide additional information to the four kallikrein panel. Our aim was to assess the value of adding prostate volume to the four kallikrein panel for the prediction of grade group 2 or higher prostate cancer.

Methods

A total of 9,702 patients from 9 cohorts were eligible for inclusion in this individual patient data meta-analysis to assess whether prostate volume added significantly to the kallikrein panel. Five historical cohorts were included: two screening-naive cohorts (Göteborg ERSPC round 1[9] and Rotterdam ERSPC round 1[10]), two previously-screened cohorts (Göteborg ERSPC round 2[11] and Rotterdam ERSPC rounds 2 and 3[12]) and one cohort of previously-biopsied men (Rotterdam Repeat Biopsy[13]). There were also 4 contemporary cohorts included: one from a study of the kallikrein panel in clinical practice ("academic cancer centers cohort")[14], UPCA[15], the OPKO Health study[16] and the Veterans Affairs (VA) study[17]. Historical cohorts used sextant biopsy in most cases while contemporary cohorts typically performed biopsies with 12 cores or more. All patients who were missing prostate volume (N=357), had total PSA measurements > 25 ng/ml (N=213) or were missing high grade status (N=1) were excluded, leaving a total of 9,131 patients in the analysis.

To assess whether any of the biomarkers included in or related to the four kallikrein panel were correlated with prostate volume, we created scatterplots for each biomarker - total PSA, free PSA, intact PSA, human kallikrein-related peptidase 2 (hK2), nicked PSA (intact PSA subtracted from free PSA), free-to-total PSA ratio and nicked-to-total PSA ratio - plotted against prostate volume among all cohorts combined. We also calculated the Spearman correlation between each biomarker and prostate volume.

For the individual patient data meta-analysis, we first generated predictions for the risk of high-grade disease (ISUP 2005 Grade Group ≥ 2, Gleason score ≥ 7) based on the kallikrein panel using three previously published models. The first model, the Goteborg model, was replaced by the Rotterdam model when IgG-based capture was switched to F(ab')2-capture in order to reduce the nonspecific interference in the analysis of intact PSA and hK2.[18] Both the Göteborg and Rotterdam models were created on historical cohorts using sextant

biopsy. To reflect changes in both biopsy practice (use of extended biopsy schemes) and grading (some Gleason grade 3 cancers being redefined as Gleason grade 4), the ProtecT model[19]was subsequently developed for contemporary cohorts. Models were applied to each cohort as per the original publication: the Göteborg model[9] was applied to the Göteborg ERSPC cohorts, the Rotterdam model[10] was applied to the Rotterdam ERSPC cohorts, and the ProtecT model[19] was applied to the contemporary cohorts. This last model has the same algorithm as the 4Kscore used in contemporary clinical practice. The area under the ROC curve (AUC) for the kallikrein panel was calculated separately for each cohort. In addition to the kallikrein markers, the models included age and DRE status (normal or abnormal).

We created a univariable logistic regression model to test the association between prostate volume and high-grade disease in each cohort. To assess whether prostate volume added to the kallikrein panel, we then created a logistic regression model for each cohort with high-grade disease as the outcome and kallikrein panel risk and prostate volume as predictors. If prostate volume was found to be associated with high grade disease when controlling for kallikrein panel risk, we then calculated the AUC for this model in each cohort. If any increase in discrimination was seen when adding prostate volume to the kallikrein model, we then calculated the difference in AUC between the kallikrein panel and the kallikrein panel and prostate volume model. The standard error for the difference in AUCs was calculated using bootstrap resampling. The differences in AUC and corresponding standard errors were then meta-analyzed across all cohorts. As a sensitivity analysis, we repeated this analysis only among patients who had had a prior biopsy, as these are the patients who would have prostate volume available in a clinical practice setting. Analyses were performed using Stata 15 (StataCorp, College Station, TX) and R 3.6.1.

Results

Patient and disease characteristics are presented for the entire population in Table 1 and separately by historical cohorts (Supplementary Table 1) and contemporary cohorts (Supplementary Table 2). Five biomarkers (total PSA, free PSA, intact PSA, hK2, and nicked PSA) and two biomarker ratios (free-to-total PSA and nicked-to-total PSA) were studied. Supplementary figure 1 shows scatterplots of prostate volume against each biomarker. While all biomarkers were significantly correlated with prostate volume ($p<0.0001$), free PSA and nicked PSA had the highest correlation (0.50 and 0.48 respectively). Correlation between prostate volume and total PSA was 0.20, intact PSA was 0.41, hK2 was 0.32, free-to-total was 0.40 and nicked-to-total was 0.42.

Increased prostate volume was significantly associated with a decreased risk of high-grade cancer in all cohorts ($p \leq 0.011$). When adding prostate volume to the kallikrein panel risk, increased prostate volume was found to be significantly associated with a lower risk of high-grade cancer in 7 of 9 cohorts (Table 2). We then calculated the AUC for both the kallikrein panel and the kallikrein panel plus volume models. Discrimination of the kallikrein panel alone for high grade cancer in the six included cohorts ranged from 0.762 to 0.902, while discrimination when including prostate volume in the model ranged from 0.757 to 0.894 (Table 2). Including prostate volume in the model along with the kallikrein panel decreased the AUC for 5 of 9 cohorts, with decreases ranging from 0.005 to 0.067. Four

cohorts saw an increase in AUC, three of which were small, ranging from 0.002 to 0.006 and not statistically significant, and one with an increase of 0.044. The overall fixed-effects estimate was 0.002 (95% CI −0.003, 0.006, Figure 2), indicating a non-significant increase in discrimination when adding prostate volume to the kallikrein panel (p=0.4). There was also significant heterogeneity for the change in AUC across all cohorts (p<0.0001).

To investigate the source of this heterogeneity, we initially repeated the meta-analysis excluding the academic cancer centers cohort which had a significant increase in AUC associated with adding prostate volume to the kallikrein panel. After excluding this cohort, there was no significant change in AUC associated with including prostate volume, with an overall fixed-effects estimate of 0.000 (95% CI-0.005, 0.004, p=0.9). The p-value for heterogeneity was 0.15, suggesting that the academic center centers cohort was the source of the heterogeneity. This cohort was comprised of patients biopsied at three institutions (Mayo Clinic, Rochester, MN, University of California San Francisco, San Francisco, CA and Martini Clinic, Hamburg, Germany) that participated in a prospective study on the discrimination of the four kallikrein panel and the ability of these cancer centers to measure the four kallikrein panel.

As an exploratory analysis, we calculated the AUC of the kallikrein panel alone and the AUC for PSA density in each cohort and compared the kallikrein panel to PSA density. The meta-analytic estimate for PSA density was 0.759 (95% CI 0.743, 0.776), which is lower than the estimate for the kallikrein panel (0.817, 95% CI 0.802, 0.831, p<0.0001).

As a sensitivity analysis, we included only those patients who had had a prior prostate biopsy, as these represent patients in clinical practice who would have prostate volume routinely available. There were 1,418 patients included from four cohorts (Rotterdam Repeat Biopsy, academic cancer centers cohort, OPKO and Veterans Affairs). There was no evidence of an increase in discrimination with the addition of volume for patients who had a prior prostate biopsy (change in AUC −0.022, 95% CI −0.056, 0.011, p=0.2). There was no significantly heterogeneity between these cohorts (p=0.12).

Discussion

We found that, while prostate volume was significantly associated with high grade prostate cancer when added to the kallikrein panel, the addition of prostate volume to the kallikrein panel did not improve discrimination of the kallikrein panel for high grade prostate cancer on biopsy. In one contemporary cohort, consisting of patients biopsied at academic centers, an increase in discrimination was seen with the addition of prostate volume, possibly due to increased expertise in measuring prostate volume at these specialist centers.

Carlsson et al. found a significant correlation between the kallikrein panel and TRUS-estimated prostate volume (Spearman's correlation 0.57 for the Göteborg cohort and 0.60 for the Rotterdam cohort).[5] Their results were consistent with the results of our analysis: the addition of TRUS-estimated prostate volume to the kallikrein panel and DRE for the outcome of high-grade cancer did not significantly improve discrimination for either cohort,

with an increase of only 0.004 for the Rotterdam cohort and no increase in discrimination in the Göteborg cohort.

It does seem natural to suppose that the value of prostate volume depends on the radiographic accuracy of volume measurements. Centers with experienced urologic radiologists may be able to more accurately estimate prostate volume than radiologists with less experience or radiologists who do not specialize in prostate imaging. Several studies have shown significant differences in measurement of prostate volume between experienced and non-experienced TRUS practitioners. Choi et al. reported on two experienced radiologists, who had performed more than 2500 TRUS procedures each, and one fourth-year radiology resident who had performed approximately 150 TRUS procedures. Each estimated TRUS prostate volume for the same set of patients. Intra-observer variability was seen between both the two experienced radiologists and one experienced radiologist and the radiology measurement. However, there was less variability between the two experienced readers, and the difference between the reader's measurement and the mean prostate volume measurement was significantly larger for the radiology resident than for the experienced radiologist. [20]

Sech et al. performed a similar study in which urology residents and an experienced urologist measured TRUS prostate volume on the same patients. The authors found that the difference between estimated prostate volume and the mean prostate volume between readers was highest for the second-year urology resident, lower for the fourth-year urology resident, and lower for the attending urologist, concluding that "more experienced examiners had better reproducibility."[21] The more precise measurement of volume by experienced practitioners in these studies supports the hypothesis that volume measurements performed by specialized urologists or urologic radiologists at specialist centers are more accurate than measurements performed by non-specialized urologists or radiologists in community practice.

One limitation of this study is that a number of cohorts are historical cohorts in which six-core biopsies and pre-2005 grading were used. However, results were similar between historical and contemporary cohorts, with all historical cohorts and all contemporary cohorts except one finding no significant improvement on the four kallikrein panel with the addition of prostate volume. Volume measurements in these cohorts were also measured using TRUS rather than MRI, although there is some evidence that radiologist or urologist experience would affect MRI volume measurements similarly to TRUS measurements, indicating that a similar effect may be seen if using MRI-estimated volume instead. The use of TRUS rather than MRI for prostate biopsy and measurement of prostate volume is also still common in clinical practice: a recent German survey of urologists reported that fewer than half of urologists regularly used MRI for prostate biopsy, and fewer than 40% would use MRI for a biopsy naïve patient.[22]

Conclusion

The kallikrein biomarkers in the 4Kscore provide a non-invasive approach to assessing risk of high-grade prostate cancer, and our results do not justify the inclusion of prostate volume

in the 4Kscore. There is some evidence that TRUS-estimated prostate volume could be informative if measured by experienced and specialized practitioners, for example those at specialist centers. However, additional research is necessary to determine the potential utility of prostate volume in this setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

This work was supported in part by the National Institutes of Health/National Cancer Institute (NIH/NCI) with a Cancer Center Support Grant to Memorial Sloan Kettering Cancer Center [P30 CA008748], a SPORE grant in Prostate Cancer to Dr. H. Scher [P50-CA92629]. This work was also supported in part by the Swedish Cancer Society (Cancerfonden project 20 1354 PjF), the Swedish Research Council (VR-MH project no. 2016-02974), and General Hospital in Malmö Foundation for Combating Cancer.

Jonas Hugosson: Swedish Cancer Society Contract 17-0596, The Swedish Research Council

References

1. Chughtai B, Forde JC, Thomas DD, et al. Benign prostatic hyperplasia. Nature reviews Disease primers. 2016;2:16031.
2. van Vugt HA, Roobol MJ, Kranse R, et al. Prediction of prostate cancer in unscreened men: external validation of a risk calculator. European journal of cancer (Oxford, England : 1990). 2011;47(6):903–909.
3. Vertosick EA, Haggstrom C, Sjoberg DD, et al. Prespecified Four Kallikrein Marker Model (4Kscore) at Age 50 or 60 for Early Detection of Lethal Prostate Cancer in a Large Population-Based Cohort of Asymptomatic Men Followed for 20 Years. The Journal of urology. 2020:101097ju0000000000001007.
4. Sjoberg DD, Vickers AJ, Assel M, et al. Twenty-year Risk of Prostate Cancer Death by Midlife Prostate-specific Antigen and a Panel of Four Kallikrein Markers in a Large Population-based Cohort of Healthy Men. European urology. 2018;73(6):941–948. [PubMed: 29519548]
5. Carlsson SV, Peltola MT, Sjoberg D, et al. Can one blood draw replace transrectal ultrasonography-estimated prostate volume to predict prostate cancer risk? BJU international. 2013;112(5):602–609. [PubMed: 23448270]
6. Ward RD, Purysko AS. Magnetic Resonance Imaging of Prostate Adenocarcinoma: Detection and Staging. Topics in magnetic resonance imaging: TMRI. 2020;29(1):17–30. [PubMed: 32015292]
7. Haffner J, Lemaitre L, Puech P, et al. Role of magnetic resonance imaging before initial biopsy: comparison of magnetic resonance imaging-targeted and systematic biopsy for significant prostate cancer detection. BJU international. 2011;108(8 Pt 2):E171–178. [PubMed: 21426475]
8. Grenabo Bergdahl A, Wilderang U, Aus G, et al. Role of Magnetic Resonance Imaging in Prostate Cancer Screening: A Pilot Study Within the Goteborg Randomised Screening Trial. European urology. 2016;70(4):566–573. [PubMed: 26724840]
9. Vickers AJ, Cronin AM, Aus G, et al. A panel of kallikrein markers can reduce unnecessary biopsy for prostate cancer: data from the European Randomized Study of Prostate Cancer Screening in Goteborg, Sweden. BMC medicine. 2008;6:19. [PubMed: 18611265]
10. Vickers A, Cronin A, Roobol M, et al. Reducing unnecessary biopsy during prostate cancer screening using a four-kallikrein panel: an independent replication. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2010;28(15):2493–2498. [PubMed: 20421547]
11. Vickers AJ, Cronin AM, Aus G, et al. Impact of recent screening on predicting the outcome of prostate cancer biopsy in men with elevated prostate-specific antigen: data from the

European Randomized Study of Prostate Cancer Screening in Gothenburg, Sweden. Cancer. 2010;116(11):2612–2620. [PubMed: 20336781]

12. Vickers AJ, Cronin AM, Roobol MJ, et al. A four-kallikrein panel predicts prostate cancer in men with recent screening: data from the European Randomized Study of Screening for Prostate Cancer, Rotterdam. Clinical cancer research : an official journal of the American Association for Cancer Research. 2010;16(12):3232–3239. [PubMed: 20400522]
13. Gupta A, Roobol MJ, Savage CJ, et al. A four-kallikrein panel for the prediction of repeat prostate biopsy: data from the European Randomized Study of Prostate Cancer screening in Rotterdam, Netherlands. British journal of cancer. 2010;103(5):708–714. [PubMed: 20664589]
14. Lonergan PE, Vertosick E, Assel M, et al. Prospective validation of microseminoprotein-β added to a four kallikrein panel in predicting high grade prostate cancer in an international multi-center academic cohort. BJU Int. 2020;In Press.
15. Braun K, Sjoberg DD, Vickers AJ, Lilja H, Bjartell AS. A Four-kallikrein Panel Predicts High-grade Cancer on Biopsy: Independent Validation in a Community Cohort. European urology. 2016;69(3):505–511. [PubMed: 25979570]
16. Parekh DJ, Punnen S, Sjoberg DD, et al. A multi-institutional prospective trial in the USA confirms that the 4Kscore accurately identifies men with high-grade prostate cancer. European urology. 2015;68(3):464–470. [PubMed: 25454615]
17. Punnen S, Freedland S, Polascik TJJU. A multi-institutional prospective trial in the Veterans Affairs Health System confirms the 4Kscore maintains its predictive value among African American men. 2018;199:1459–1463.
18. Väisänen V, Peltola MT, Lilja H, Nurmi M, Pettersson K. Intact free prostate-specific antigen and free and total human glandular kallikrein 2. Elimination of assay interference by enzymatic digestion of antibodies to F(ab')2 fragments. Analytical chemistry. 2006;78(22):7809–7815. [PubMed: 17105175]
19. Bryant RJ, Sjoberg DD, Vickers AJ, et al. Predicting high-grade cancer at ten-core prostate biopsy using four kallikrein markers measured in blood in the ProtecT study. Journal of the National Cancer Institute. 2015;107(7).
20. Choi YJ, Kim JK, Kim HJ, Cho KS. Interobserver variability of transrectal ultrasound for prostate volume measurement according to volume and observer experience. AJR American journal of roentgenology. 2009;192(2):444–449. [PubMed: 19155408]
21. Sech S, Montoya J, Girman CJ, Rhodes T, Roehrborn CG. Interexaminer reliability of transrectal ultrasound for estimating prostate volume. The Journal of urology. 2001;166(1):125–129. [PubMed: 11435838]
22. Saar M, Linxweiler J, Borkowetz A, et al. Current Role of Multiparametric MRI and MRI Targeted Biopsies for Prostate Cancer Diagnosis in Germany: A Nationwide Survey. Urologia internationalis. 2020;104(9-10):731–740. [PubMed: 32640460]

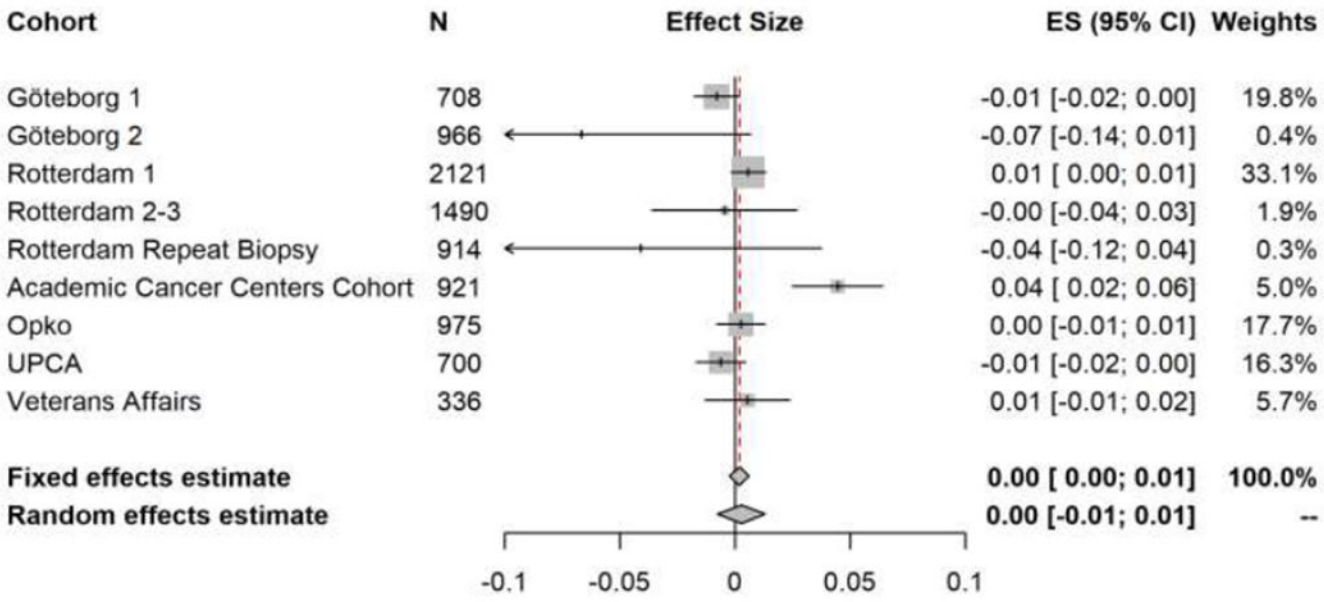

Figure 1.

Forest plot for the difference in discrimination between the kallikrein panel and the kallikrein panel including volume.

Table 1.

Patient and disease characteristics, N=9,131. Data are presented as median (quartiles) or frequency (%).

Age at biopsy	**65 (60, 69)**
Abnormal DRE (N=9110)	1983 (22%)
Prior negative biopsy (N=9108)	1418 (16%)
TRUS prostate volume (cc)	43 (33, 56)
Biopsy outcome	
Negative	6352 (70%)
Low grade cancer (GG1)	1739 (19%)
High grade cancer	1040 (11%)
GG2/GG3	786 (8.6%)
GG4/GG5	248 (2.7%)
Unknown	3 (<0.1%)
Clinical T stage at diagnosis (N = 2779)	
T1	1400 (50%)
T2	764 (27%)
T3/T4	142 (5.1%)
Unknown	473 (17%)

Table 2.

Association between prostate volume and risk of high grade cancer after adjusting for kallikrein risk, discrimination of four kallikrein panel and four kallikrein panel plus prostate volume models, and difference in discrimination between models with 95% confidence intervals. The odds ratio for the association between prostate volume and risk of high grade cancer is reported per 10 ml increase in volume.

Cohort	OR	95% CI	p value	Kallikrein Model	Kallikrein + Volume Model	Difference in AUCs
Göteborg 1	0.91	0.72, 1.14	0.4	0.902 (0.838, 0.965)	0.894 (0.825, 0.963)	−0.008 (−0.018, 0.002)
Göteborg 2	0.62	0.43, 0.88	0.008	0.845 (0.764, 0.926)	0.778 (0.687, 0.869)	−0.067 (−0.140, 0.007)
Rotterdam 1	0.84	0.76, 0.94	0.001	0.857 (0.827, 0.888)	0.863 (0.834, 0.893)	0.006 (−0.002, 0.013)
Rotterdam 2-3	0.63	0.51, 0.77	<0.0001	0.798 (0.748, 0.847)	0.793 (0.743, 0.843)	−0.005 (−0.036, 0.027)
Rotterdam Repeat Biopsy	0.63	0.42, 0.94	0.024	0.883 (0.802, 0.963)	0.842 (0.730, 0.953)	−0.041 (−0.119, 0.037)
Academic cancer centers cohort	0.70	0.64, 0.77	<0.0001	0.786 (0.751, 0.820)	0.830 (0.800, 0.860)	0.044 (0.025, 0.064)
OPKO	0.85	0.79, 0.92	<0.0001	0.813 (0.781, 0.846)	0.816 (0.783, 0.849)	0.003 (−0.008, 0.013)
UPCA	0.89	0.78, 1.01	0.070	0.763 (0.716, 0.811)	0.757 (0.709, 0.805)	−0.006 (−0.017, 0.005)
Veterans Affairs	0.88	0.77, 0.99	0.040	0.762 (0.707, 0.816)	0.767 (0.712, 0.821)	0.005 (−0.013, 0.024)
Overall fixed effects estimate				0.817 (0.802, 0.831)	0.823 (0.808, 0.837)	0.002 (−0.003, 0.006)
Overall random effects estimate				0.819 (0.789, 0.849)	0.816 (0.787, 0.844)	0.003 (−0.008, 0.013)