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The Prognostic Value of Proclarix in Prostate Cancer Patients Under Active Surveillance: Predicting Transition to Active Treatment and Disease Progression in a Danish Cohort

Alcibiade Athanasiou [1], Torben F. Hansen [2,7], Jonna S. Madsen [3,7], Mads H. Poulsen [4,7], Mike Allan Mortensen [5], Gitte E. Kissow [6], Louise F. Obro [6,7], Palle J. Osther [6,7], Ralph Schiess [1] and Ahmed H. Zedan [2,*]

[1] Proteomedix AG, Zurich-Schlieren, Switzerland
[2] Department of Oncology, Lillebaelt Hospital, University Hospital of Southern Denmark, Vejle, Denmark
[3] Department of Biochemistry and Immunology, Lillebaelt Hospital, University Hospital of Southern Denmark, Vejle, Denmark
[4] Department of Urology, Esbjerg and Grindsted Hospital, University Hospital of Southern Denmark, Esbjerg, Denmark
[5] Department of Urology, Odense University Hospital of Southern Denmark, Odense, Denmark
[6] Urological Research Center, Department of Urology, Lillebaelt Hospital, University Hospital of Southern Denmark, Vejle, Denmark
[7] Department of Regional Health Research, University of Southern Denmark, Odense, Denmark
* Correspondence: ahmed.zedan@rsyd.dk

Simple Summary

Active surveillance (AS) is the recommended management approach for patients diagnosed with low/intermediate risk prostate cancer. However, 40% of patients under AS will require active active management (AM) within the first 5 years of observation. In this study, Proclarix risk score was investigated as a prognostic tool for both transition from AS o AM and progression of biopsy grade group (GG) using baseline serum samples from a Danish cohort of 132 men under AS. At 5-year follow-up, 82% of men with a baseline Proclarix score >50% had progressed to AM, and 67% showed GG progression at confirmatory biopsy. Proclarix risk score may assisst tailoring monitoring program for prostate cancer patients undergoing AS.

Abstract

Background and Objective: Active surveillance (AS) describes the active monitoring of men with low- to intermediate-risk prostate cancer (PCa), before active management (AM) is needed due to disease progression. A substantial proportion of patients require a switch to AM within a few years of diagnosis. Proclarix is a blood-based diagnostic test that predicts clinically significant PCa (csPCa) and the Proclarix risk score has been shown to correlate with tumor aggressiveness. This study aimed to assess whether Proclarix can predict the likelihood of transition from AS to AM. **Methods:** We retrospectively evaluated the Proclarix risk scores in serum samples from a Danish cohort of 132 men recruited from the PerPros prostate biobank. Most participants had low- to intermediate-risk PCa and were considered eligible for AS at diagnosis. Blood samples were collected before the initial biopsies, and clinical follow-up data were available for every patient for a minimum of 3 and up to 9.5 years. The primary endpoint was the ability of the Proclarix risk score to predict transition from AS to AM. The secondary endpoint was to assess whether Proclarix could identify patients at risk of progression to csPCa. **Results:** Overall, 48 of 132 men (36%) transitioned from AS to AM during follow-up. A baseline Proclarix risk score of >50% was associated with a 79% estimated cumulative probability of switching to AM (HR=4.4, 95% CI: 2.3-8.3, p<0.001). At 5-year follow-up, 82% of men

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with a Proclarix score >50% had progressed to AM, and 67% showed progression to csPCa at confirmatory biopsy. In contrast, amongst men with a Proclarix score ≤50%, only 28% progressed to AM and 32% to csPCa. **Conclusions**: Proclarix risk score may support clinical dicision-making in AS by identifying patients at higher risk of progression and informing follow-up intensity. However, the results should be confirmed in larger prospective study.

Keywords: active surveillance; biomarker; cathepsin D; PerPros biobank; Proclarix; prognosis; prostate cancer; prostate specific antigen; risk score; thrombospondin-1

1. Introduction

Active surveillance (AS) is widely recommended as a preferred management strategy for men diagnosed with low-risk or favorable intermediate-risk prostate cancer (PCa)[1,2]. Since its introduction in the 1990s, AS has aimed to delay or avoid altogether active management (AM), such as radical prostatectomy or radiotherapy, thereby reducing treatment-related morbidity while safely monitoring men with clinically insignificant PCa (ciPCa) [3]. Nevertheless, disease reclassification over time is common, and 20-38% of men transition to AM within five years after diagnostic biopsy [4,5].

Current AS monitoring is largely based on a combination of clinical assessment, serial serum prostate-specific antigen (PSA) measurements, and multiparametric magnetic resonance imaging (mpMRI), often complemented by repeat biopsies. However, limited consensus on the optimal intensity and frequency of follow-up has contributed to heterogenous implementation and suboptimal uptake of AS worldwide. Despite broad guideline support, a considerable proportion of men (around 40%) with ciPCa still undergo potentially unnecessary definitive treatment [6].

To refine patient selection and tailored follow-up intensity, multiple approaches have been proposed, including clinical risk factors [7,8] risk-stratifications nomograms [9], and both tissue- and blood-based biomarkers [10–12]. Yet these tools have only modestly improved the ability to balance the competing risks of overtreatment and delayed intervention. There is a clear need for better strategies that identify men who can be safely monitored with less intensive follow-up and those at higher risk of progression who may benefit from earlier treatment.

Proclarix is a CE-IVD certified blood test developed to support early detection of csPCa. It provides an individualised risk score derived from the tumour-associated biomarkers Cathepsin D (CTSD) and Thrombospondin 1 (THBS1), combined with total PSA, percent free PSA, and age. Multiple studies have shown that Proclarix predicts clinically significant PCa (csPCa) in biopsy- naïve men with suspected disease, with a reported negative predictive value of approximately 95%, enabling the avoidance of unnecessary biopsies [13–17]. In addition, the Proclarix risk score has been shown to correlate with tumor aggressiveness [18].

On this basis, we hypothesised that Proclarix could also be useful in the AS setting to estimate the likelihood of transition to AM and to identify men at increased risk of progression from ciPCa to csPCa, independent of clinical staging.

2. Materials and Methods

2.1. Study Design and Population

Proclarix risk scores were measured retrospectively in baseline serum samples from 132 men diagnosed with PCa who were managed with AS according to the Danish guidelines [19] . Patients had been prospectively enrolled in the PerPros (Personalized Management of Prostate Cancer) biobank at the Department of Urology, Lillebaelt Hospital, University Hospital of Southern Denmark, Vejle, Denmark (jr.nr: 18/11174).

Participants were referred to the Department of Urology at Vejle or Esbjerg Hospital for further evaluation of suspected PCa, most commonly due to elevated PSA levels. Decisions regarding

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initiation of AS and subsequent transition to AM during follow-up were made predominantly at the Department of Urology, Odense University Hospital of Southern Denmark, Odense, Denmark. All participants provided written informed consent. The study workflow is summarized in Figure 1.

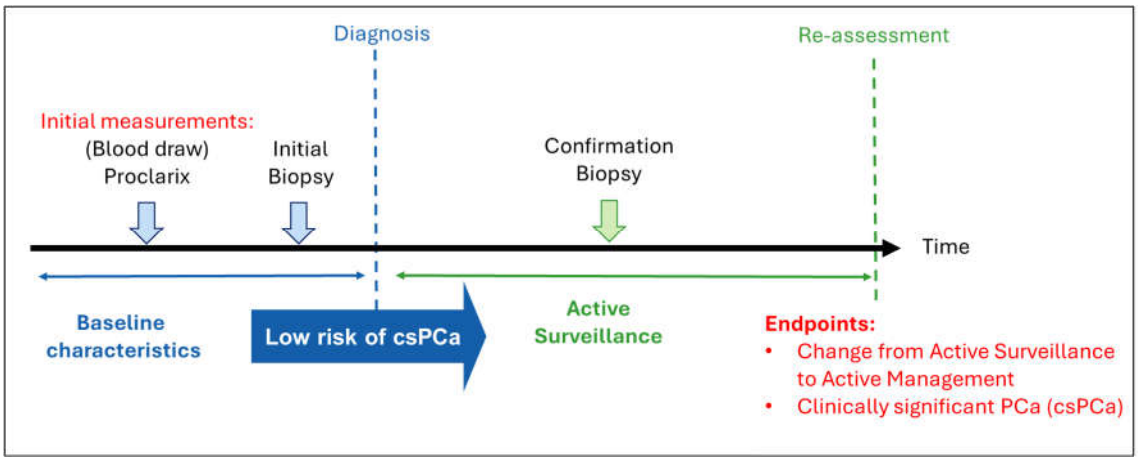

Figure 1. Schematic overview of the study design. Proclarix was measured retrospectively in baseline blood samples collected prospectively before biopsy. Endpoints were transition from AS to AM and progression to csPCa during follow-up.

2.2. Proclarix Assessment

Baseline blood samples were obtained prior to the initial prostate biopsy. To obtain serum, blood samples were allowed to clot for a timeframe of 30-60 minutes before being centrifuged at 2,000g for 10 min at room temperature. Serum was aliquoted and stored at -80°C until analysis.

Proclarix is a blood-based biomarker test that combines age, tPSA, %fPSA, and the two tumour markers CTSD, and THBS1 in an algorithm generating a 0-100% risk score, originally designed to predict csPCa [14] . Proclarix measurements were performed blinded to all clinical information and biopsy results.

For all samples, serum tPSA and %fPSA were remeasured using the Roche Cobas immunoassay system (Roche Diagnostics, Rotkreuz, Switzerland), THBS1 and CTSD were quantified using the CE-marked Proclarix kit (Proteomedix, Zurich-Schlieren, Switzerland) [20].

2.3. Study Outcomes

The primary endpoint was the ability of the baseline Proclarix risk score to predict a change in management from AS to AM (surgery, radiotherapy or androgen deprivation therapy alone) within 3 years and 5 years after the initial biopsy.

The secondary endpoint was the association between the baseline Proclarix risk score and the risk of progression from the initial biopsy Grade Group (GG) to csPCa on subsequent biopsies within 3- and 5-year follow-up periods. In this study csPCa was defined as GG ≥2, according to the International Society of Urological Pathology criteria [21]. Follow-up was censored on 2nd of May 2025.

2.4. Statistical Analysis

Group comparisons (progression vs no progression) were performed using a t-test. Time-to-event analyses were conducted using Kaplan-Meier methods to compare cumulative event probabilities between low and high-risk groups, and Cox proportional hazards models were fitted to estimate hazard ratios (HRs) with 95% confidence intervals and Wald p-values.

For analyses of both transition from AS to AM and progression to csPCa, patients were stratified into low-risk and high-risk groups using a Proclarix risk score cut-off of 50%. This threshold was

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selected to yield a high-risk group with a cumulative probability >75% at 5 years following the initial biopsy.

Analyses were performed in R (version 4.0.2, The R Foundation for Statistical Computing, Vienna, Austria), using the *survival* and *survminer* packages, in addition to basic R functions. A two-sided p-value of <0.05 was considered statistically significant.

3. Results

3.1. Baseline Characteristics

Between October 2015 and May 2022, 132 men diagnosed with localized PCa and managed with AS were eligible for inclusion. Initial prostate biopsies were performed as transrectal ultrasound (TRUS)-guided systematic biopsies in 105/132 (80%) patients and as mpMRI-guided biopsies in 27/132 (20%) patients. During follow-up, 98/132 (74%) patients underwent at least one confirmatory biopsy. Among these, 72/98 (73%) had at least one confirmatory biopsy performed with mpMRI guidance. Most of the patients had a baseline tPSA <10 ng/mL (105/132, 80%), while 7/132 (5%) had a tPSA >20 ng/mL. At the initial biopsy, most patients were classified as Grade Group (GG) 1 (107/132, 81%), 23/132 (17%) were GG2, and 2/132 (2%) were >GG2 (one GG3, one GG5). Over the available follow-up period, 48/132 (36%) patients transitioned from AS to AM within the available patient's follow up period of time. Median follow-up after diagnosis was 6.3 years (range: 3.0-9.4 years). Baseline demographics and clinical characteristics are summarized in Table 1.

Table 1. Patient demographics.

Parameter	Description	Value
Total patients, n (%)	-	132 (100%)
Age, median (min-max)	-	66 (50-81)
tPSA, n (%)	< 10 ng/mL	105 (80%)
	10-20 ng/mL	20 (15%)
	> 20 ng/mL	7 (5%)
clinical stage, n (%)	cT1	7 (5%)
	cT1b	77 (58%)
	cT2	10 (8%)
	cT2a	10 (8%)
	cT2b	7 (5%)
	cT2c	1 (1%)
	cT3	1 (1%)
	NA	19 (14%)
GG at first biopsy, n (%)	GG1	107 (81%)
	GG2	23 (17%)
	>GG2	2 (2%)
GG after max. years of follow up, n (%)	GG1	63 (48%)
	GG2	54 (41%)
	>GG2	15 (11%)
EAU risk groups, n (%)	Low	81 (61%)
	Intermediate favorable	39 (30%)
	Intermediate unfavorable	6 (4.5%)
	High	6 (4.5%)
Management change after max years of follow up, n (%)	AS to AM	48 (36%)
Number of patients with follow-up	3 years	132 (100%)
	5 years	95 (72%)
	7 years	83 (63%)
	9 years	57 (53%)

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AM: active management, AS: active surveillance, GG: Grade Group, PSA: prostate-specific antigen.

3.2. Change to Active Management

At three years of follow up, 31/132 (23%) patients had transitioned from AS to AM and at five years of follow up, 38/104 (37%) patients (Figure 2). The baseline Proclarix risk score was significantly associated with the transition from AS to AM in both the 3-year and 5-year follow-up cohorts (p<0.001, Figure 2).

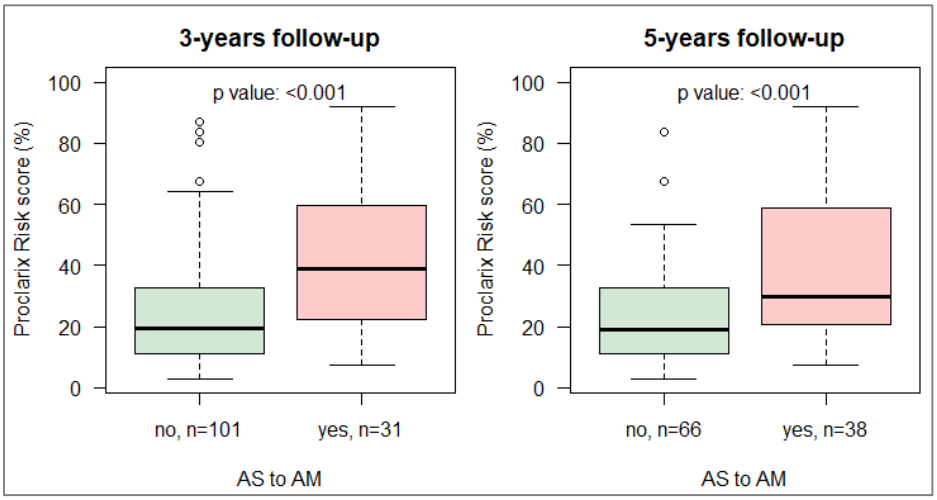
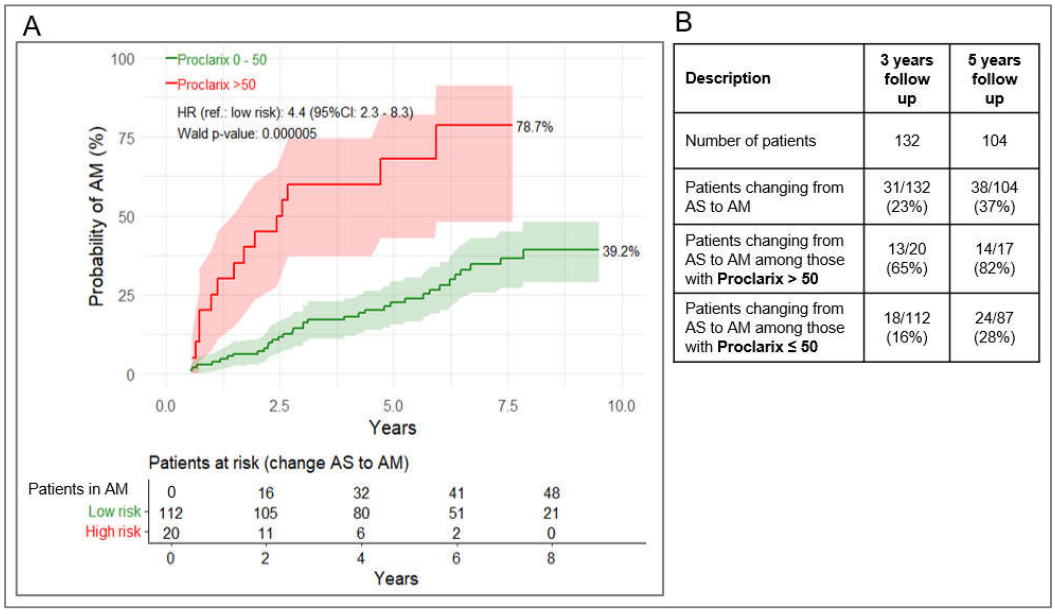


Figure 2. Boxplot of baseline Proclarix risk score by transition from AS to AM. Left: At least 3-years follow-up. Right: At least 5-years follow-up.

Using a 50% Proclarix risk score cut-off, patients with a >50% baseline score showed an estimated 78.7% cumulative risk of transitioning from AS to AM during follow-up (Figure 3A). A baseline Proclarix risk score of >50% was associated with a markedly four times increased risk of transition to AM compared with ≤50% (HR=4.4, 95% CI: 2.3-8.3, p<0.001). In the 3- and 5-year follow-up cohorts, 65% and 82% of patients with Proclarix risk score >50% transitioned to AM, compared with 16% and 28% amongst those with a Proclarix risk score ≤50%, respectively (Figure 3B).



B

Description	3 years follow up	5 years follow up
Number of patients	132	104
Patients changing from AS to AM	31/132 (23%)	38/104 (37%)
Patients changing from AS to AM among those with **Proclarix > 50**	13/20 (65%)	14/17 (82%)
Patients changing from AS to AM among those with **Proclarix ≤ 50**	18/112 (16%)	24/87 (28%)

Figure 3. (A) Kaplan-Meier curves for cumulative probability of transition from AS to AM stratified by Proclarix risk score >50% vs ≤50%. (B) Proportion transitioning after at least 3 and 5 years.

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3.3. Progression to Clinically Significant Prostate Cancer

At the initial biopsy, 25/132 (19%) patients were diagnosed with csPCa (GG≥2). These patients were excluded from the analyses assessing progression from GG1 to csPCa during follow-up. Consequently, 107 patients were included in the 3-year progression analysis and 83 patients in the 5-year analysis.

During the follow-up, 25/107 (23%) and 31/83 (37%) patients progressed to csPCa after at least 3- and 5-year analysis of follow-up, respectively (Figure 4). Baseline Proclarix risk scores were significantly associated with progression to csPCa in both analyses (p=0.018 at 3 years and p=0.042 at 5 years, Figure 4.

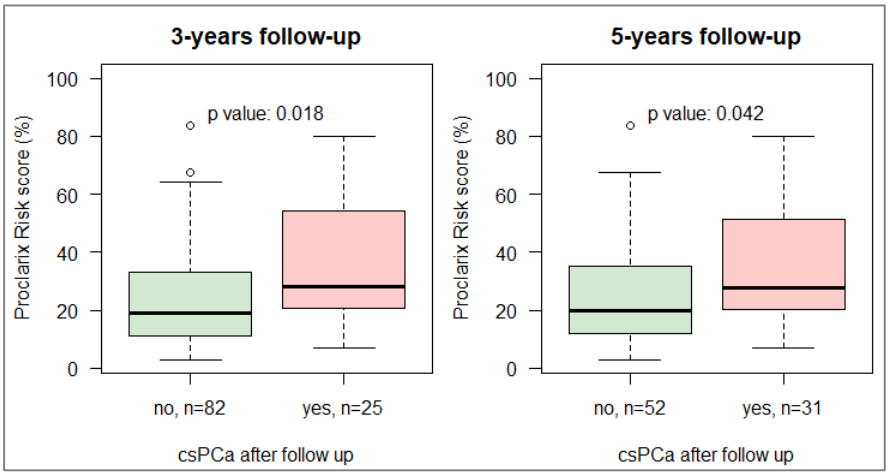
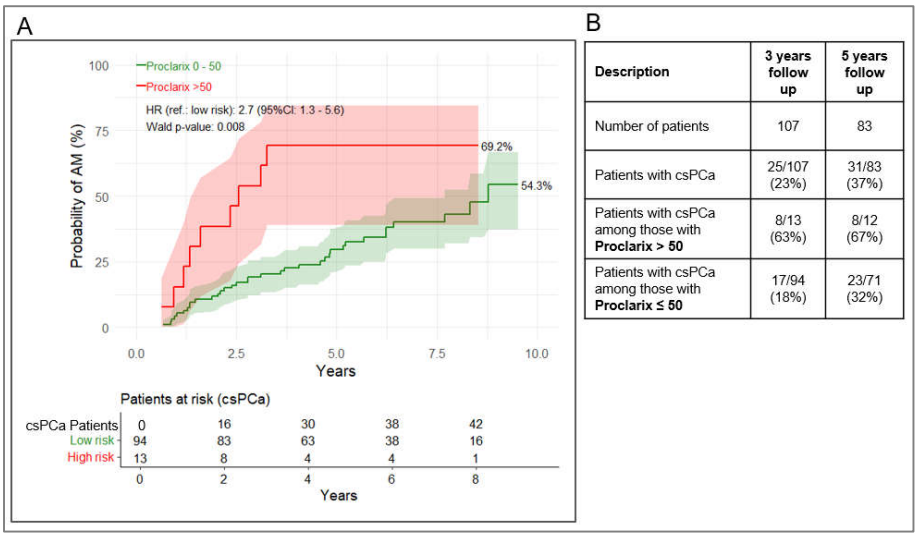


Figure 4. Boxplot of baseline Proclarix risk score by progression to csPCa at follow-up biopsy. Left: At least 3-years follow-up. Right: At least 5-years follow-up.

Using the 50% cut-off, patients with baseline Proclarix risk score >50% had an estimated 69.2% probability of progression to csPCa during follow-up (Figure 5A). Proclarix risk score >50% was associated with a 2.7 times higher risk of progression compared with ≤50% (HR=2.7, 95% CI: 1.3-5.6, p=0.008). In the 3- and 5-year of follow-up cohorts, 63% and 67% of patients with Proclarix risk score >50% progressed to csPCa, whereas 18% and 32% of patients with Proclarix risk score ≤50% progressed, respectively (Figure 5B).



Description	3 years follow up	5 years follow up
Number of patients	107	83
Patients with csPCa	25/107 (23%)	31/83 (37%)
Patients with csPCa among those with **Proclarix > 50**	8/13 (63%)	8/12 (67%)
Patients with csPCa among those with **Proclarix ≤ 50**	17/94 (18%)	23/71 (32%)

Figure 5. (A) Kaplan-Meier curves for cumulative probability of progression to csPCa stratified by Proclarix risk score >50% vs ≤50%. (B) Proportion transitioning after at least 3- and 5-years follow-up.

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4. Discussion

This study provides initial evidence that the Proclarix risk score may have clinical value as a prognostic tool in men managed with AS. Specifically, a high Proclarix risk score at baseline was associated with both (i) a high probability of transition from AS to AM and (ii) a higher risk of progression to csPCa during follow-up.

Proclarix was developed to identify csPCa prior to prostate biopsy, but evidence suggests that the risk score provides relevant information about tumour aggressiveness. Previous work has reported an association between the Proclarix risk score and baseline diagnostic GG, clinical tumor stage (cT), adverse pathology, and biochemical recurrence after primary treatment [18]. These observations formed the rationale for evaluating whether Proclarix may also inform outcomes that are central to AS programs, namely, the need for treatment escalation and the prediction of histologic progression.

In our cohort, the Proclarix risk score at baseline showed a statistically significant association with both endpoints. Patients with a Proclarix risk score >50% had a markedly higher cumulative probability of transitioning to AM and a higher risk of progression to csPCa compared with those with a risk score ≤50%. At 5 years follow-up, 82% of patients with a Proclarix risk score >50% transitioned to AM and 67% progressed to csPCa, whereas the corresponding proportions in the group with a risk score ≤50% were 28% and 32%, respectively. Together, these findings suggest that Proclarix could enable a more individualized surveillance strategy, helping to identify men who may benefit from closer monitoring and earlier confirmatory assessment, while allowing less intensive follow-up in men at lower risk.

The study population was selected according to EAU risk stratification [1], reflecting a real-world AS setting. Most men were classified as low risk or favourable intermediate risk, and nearly all had localised disease (cT ≤ cT2c). A small number of patients had features that would be considered higher risk (e.g., PSA >20 ng/mL, ≥GG3 at baseline, or cT3), yet were managed with AS based on shared decision-making and patient preference. We intentionally retained these patients to reflect routine clinical practice, acknowledging that this choice may introduce heterogeneity but improves the clinical relevance of the cohort.

Appropriate monitoring is crucial, because a substantial proportion of men on AS will undergo treatment escalation within five years after diagnosis [5]. In our study, 37% of men transitioned from AS to AM within 5 years, which aligns with discontinuation rates reported in large AS cohorts such as PRIAS (where approximately one-third discontinue due to protocol-based reclassification at 5 years) [2,5,22]. This concordance supports the external plausibility of our cohort and our endpoint definitions. We chose 5-year follow-up as a clinically meaningful time horizon: it is sufficiently long to capture early reclassification events consistent with pre-existing aggressive biology, while beyond this timeframe it becomes increasingly difficult to disentangle baseline aggressiveness from *de novo* progression and to determine whether curative treatment remains appropriate as age and comorbidity accumulate.

Current guideline-based follow-up strategies rely primarily on PSA, digital rectal examination, and MRI, with confirmatory biopsies performed depending on baseline risk and subsequent findings [1]. Importantly, PSA kinetics or MRI changes (while still organ-confined) generally should not trigger definitive treatment without histologic confirmation, underscoring the need for tools that can help determine who requires earlier and more intensive confirmatory evaluation. [23,24].

Several tissue-based genomic tests (e.g., Oncotype Dx, Prolaris, Decipher, and ProMark) have been proposed to refine risk stratification in AS [25], but their broader uptake is limited by the need for biopsy tissue, cost, and limited comparative evidence. Consequently, there remains an unmet medical need for non-invasive, reproducible biomarkers that can help to personalise AS intensity.

In this context, serum-based biomarkers have gained attention. PSA density is promising [26], yet published cut-offs vary widely (approximately 0.08 to 0.2) [27–30], limiting consistency across cohorts and creating uncertainty regarding generalisability. The 4Kscore has also been associated with csPCa outcomes in AS populations [31,32]. Notably, Hougen et al. [32] reported that a 4KScore

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cut-off of 20%, stratified cumulative per-protocol progression rates over 36 months. While cross-study comparisons must be interpreted cautiously due to differences in cohorts, endpoints, and follow-up schedules, our results suggest that Proclarix may provide more meaningful risk separation for both treatment escalation and histologic progression.

Strengths of this study include recruitment through the PerPros biobank framework, blinded Proclarix assessment, and the long-term follow-up. Key limitations are the sample size (only 48 transitions to AM), the retrospective design, and changes in biopsy technique over time (limited MRI-targeted biopsies at baseline but more frequent during confirmatory biopsies), which may contribute to grade migration [33].

Larger, prospective studies are needed to validate these results and the proposed cut-off, and to assess the added value of Proclarix beyond established clinical variables and MRI. Ideally, future work should include longitudinal Proclarix measurements to evaluate whether changes over time further improve risk prediction and guide surveillance intensity.

5. Conclusions

In this exploratory study, a baseline Proclarix risk score measured prior to the initial prostate biopsy was associated with adverse pathological findings at confirmatory biopsy and with a higher likelihood of transition from AS to AM. These results support the potential role of Proclarix as a non-invasive prognostic tool to aid risk stratification and guide individualized monitoring intensity in men undergoing AS. Prospective studies in larger cohorts are warranted to confirm these findings and to define clinically meaningful cut-offs and integration with established clinical and imaging parameters.

Author Contributions: AA, RS, and AZ analyzed and interpreted the results. AA, and AZ were major contributors in writing the manuscript. All authors read and approved the final manuscript.

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Institutional Review Board Statement: The study was approved by The Regional Committees on Health Research Ethics for Southern Denmark (S-20220048) and by The Danish Data Protection Agency according to Danish law (24/38777).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of Interest: Some of the authors received or held stock options and salaries (AA, RS) and founder shares (RS) of Proteomedix. AA and RS are inventors of the following patent application (WO2018011212) as well as RS on patent application (WO2009138392).

Abbreviations

AS	Active surveillance
AM	Active Management
CE	Conformité Européenne
CTSD	Cathepsin D
csPCa	Clinically significant prostate cancer
ciPCa	Clinically insignificant prostate cancer or indolent prostate cancer (iPCa)
DRE	Digital rectal examination
GG	Grade Group
IVD	In Vitro Diagnostic
MRI	Magnetic resonance imaging

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NPV	Negative predictive value
PerPros	Personalized Management of Prostate Cancer
PSA	Prostate specific antigen
THBS1	Thrombospondin 1
TRUS	Transrectal ultrasound

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