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ORIGINAL RESEARCH

Prognostic significance of a novel indicator (PSA$_{postd3}$/PSA$_{pre}$) for PSA recurrence in patients after radical prostatectomy

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Purpose: Radical prostatectomy (RP) is a common treatment for prostate cancer, but a fraction of patients may experience PSA recurrence after surgery, manifesting as an elevation in prostate specific antigen (PSA). Vast literature has reported different prognostic factors for PSA recurrence without reaching a consensus. This retrospective study investigated the efficacy of a new indicator in predicting PSA recurrence in patients after RP.

Patients and methods: From October 2000 to December 2015, 102 PCa patients who underwent laparoscopic prostatectomy in the Urology Department of Peking Union Medical College Hospital were analyzed. We calculated PSA$_{postd3}$/PSA$_{pre}$, defined as the ratio of the PSA on day 3 postop as the numerator and the pre-operative PSA as the denominator, in these patients to represent PSA decrement after surgery, and investigated its relationship with PSA recurrence during follow-up.

Results: The receiver operating characteristic (ROC) curve of PSA$_{postd3}$/PSA$_{pre}$ derived a cut-off at 0.453 (sensitivity=0.704, specificity=0.853, $P<0.0001$), suggesting an increased risk of PSA recurrence in patients whose PSA on day 3 postop did not decrease to approximately half of their preoperative levels. Among several factors, PSA$_{postd3}$/PSA$_{pre}$ ($P<0.0001$), pathological T stage ($P=0.042$) and Gleason Grade ($P=0.021$) were determined to be significantly associated with PSA recurrence by Fisher's exact test, while only PSA$_{postd3}$/PSA$_{pre}$ ($P<0.001$) was significantly related to PSA recurrence-free survival (PRFS) by multivariate logistic regression analysis.

Conclusion: These results imply that PSA$_{postd3}$/PSA$_{pre}$ could provide substantial information for PSA recurrence prediction in patients after RP.

Keywords: prognosis, prostate cancer, prostate-specific antigen

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Introduction

Radical prostatectomy (RP) is one of the most common and effective methods to treat prostate cancer (PCa). However, 15–33% of patients develop PSA recurrence, ie, a prostate-specific antigen (PSA) increase to 0.2 ng/mL or greater in 8–8.8 years after surgery.[1,2] According to the previous literature, elevation of PSA after RP mainly originates from remnant active tumour cells, and the retained benign prostate tissue contributes little to PSA increases.[3,4] Hence, a postoperative PSA elevation indicates recurrence of PCa theoretically, and PSA recurrence is a common outcome surrogate in current studies. In addition, much of the literature has reported that postoperative PSA is associated with PSA recurrence, although most studies have focused on the absolute value of PSA, measured from 1 month to 3 years after RP.[5–7] Other studies have implied that the kinetics of PSA can predict prognosis more accurately.[8]

A high level of postoperative PSA might suggest the existence of remnant tumour cells,[3] which could lead to PSA recurrence and even clinical recurrence (CLR). As the half-life period of PSA is 2–3 days,[9,10] we hypothesize that patients with a >50% drop in PSA on day 3 postop compared with preoperative PSA are less likely to develop PSA recurrence. We defined PSA_{postd3}/PSA_{pre} as the ratio of the PSA on day 3 postop as the numerator and the pre-operative PSA as the denominator. This study aimed to investigate the efficacy of PSA_{postd3}/PSA_{pre} in PSA recurrence prediction.

Materials and methods
Study population and data collection
The present study was a retrospective study approved by the Institutional Review Board (IRB) of Peking Union Medical College Hospital (PUMCH). According to the National Comprehensive Cancer Network (NCCN) Guidelines on prostate cancer, a total of 102 patients diagnosed with PCa received laparoscopic prostatectomy in the Urology Department of PUMCH from Oct. 2000 to Dec. 2015. The inclusion criteria are listed as follows: 1) patients who were diagnosed with localized PCa and received laparoscopic RP in PUMCH; 2) patients with complete preoperative clinical data and records; 3) patients with available PSA data in a week before surgery and on day 3 postop; 4) patients who had been followed up for at least two years with a complete follow-up record; and 5) patients who did not receive endocrine therapy or radiotherapy before or after surgery. Written informed consent was obtained from all of the participants.

The following information was evaluated for all patients: medical history, physical examination, digital rectal examination and serum PSA. Clinical staging was based on digital rectal examination and, when clinically indicated, chest radiography, bone scintigraphy, CT-scan and/or magnetic resonance imaging (MRI) of the pelvis.

All RP surgeries were performed by experienced surgeons in the Department of Urology of PUMCH. Surgery was performed by a pure laparoscopic prostatectomy, with the extent of pelvic lymph node dissection based upon the risk category of the patient. Serum total PSA measurements were analysed by the Clinical Laboratory of PUMCH, adopting the chemiluminescent microparticle immunoassay method with the ARCHITECT PSA-T kit (Abbott, Lake Bluff, Illinois, United States). The prostatic specimens were evaluated by the pathologists at PUMCH, who also reported Gleason score and surgical margin status. Serum PSA was continuously monitored by follow-up clinics at PUMCH, ie, every 3 months in the first 2 years after RP and every 6 months afterward. The primary outcome of the present study was PSA recurrence, which is defined as PSA >0.2 ng/mL. All patients with PSA recurrence were confirmed by more than two PSA tests.

Statistical analysis
Independent samples t-test was used to compare the differences of PSA_{postd3}/PSA_{pre} between PSA recurrence-free group and PSA recurrence group. A receiver operating characteristic (ROC) curve of PSA_{postd3}/PSA_{pre} was plotted, and the area under the curve (AUC) was calculated. The cut-off value of PSA_{postd3}/PSA_{pre} was derived when the Youden index was maximal (0.557). The correlation of preoperative PSA with PSA on day 3 postop was examined by Spearman's rank correlation test. The Fisher's exact test was applied to analyse the PSA recurrence rate in patients with different PSA_{postd3}/PSA_{pre} value, pT stage, postoperative Gleason Grade, age grouping and surgical margin status. Kaplan-Meier curves of each investigated factor were plotted, and the Log Rank test was adopted to examine significance in PRFS. Multivariate analysis of PSA recurrence predictors was performed using a logistic regression analyses. The alpha level for all tests is 0.05. A P-value <0.05 was considered to be significant. Statistical analyses were performed using SPSS software 21 (IBM Inc., Armonk, New York, United States) and GraphPad Prism 8 (GraphPad Software, La Jolla, California, United States).

Results
Baseline data
Clinical and pathological characteristics are shown in Table 1. A total of 102 patients diagnosed with PCa were analysed after RP. The median (interquartile range, IQR) age of the patients was 66.5 years old (61–70). The median (IQR) prostate volume was 35 mL (30–45). The median (IQR) preoperative PSA was 10.0 ng/mL (6.4–16.5). After a median (IQR) follow-up time of 56.4 months (40.7–74.8), 27 (26.5%) patients developed PSA recurrence, and the median (IQR) time from surgery to PSA recurrence was 22 months (12–33). One patient died of lung cancer during follow up. None was discovered to develop metastasis from PCa by the end of this study.

Table 1 Clinical and pathological characteristic of the population

Variable	Value
Number of patients	102
Median (IQR) age at surgery, years	66.5(61,70)
Median (IQR) prostate volume, ml	35(30,45)
Median (IQR) preoperative PSA level, ng/mL	10(6.4,16.5)
Median (IQR) follow-up time, months	56.4(40.7,74.8)
N (%):	
Pathological stage:	
pT2	76(74.5)
pT3a	10(9.8)
pT3b	16(15.7)
Postoperative Gleason Grade:	
1	31(30.4)
2–3	50(49.0)
4–5	21(20.6)
Surgical margins:	
Negative	57(55.9)
Positive	45(44.1)
PSA recurrence	
Yes	27(26.5)
No	75(73.5)

Abbreviations: IQR, interquartile range; PSA, prostate specific antigen.

Figure 1 Comparison of PSA_{postd3}/PSA_{pre} between PSA recurrence groups and PSA recurrence-free groups.
Abbreviation: PSA_{postd3}/PSA_{pre}, The ratio of the prostate-specific antigen (PSA) on day 3 postop as the numerator and the pre-operative PSA as the denominator.

Figure 2 Receiver operating characteristic (ROC) curve of PSA_{postd3}/PSA_{pre} to predict PSA recurrence (n=102, area under curve=0.760, cut-off=0.453, Youden=0.557, sensitivity=0.704, 1-specificity=0.147, $P<0.0001$).
Abbreviation: PSA_{postd3}/PSA_{pre}, The ratio of the prostate-specific antigen (PSA) on day 3 postop as the numerator and the pre-operative PSA as the denominator.

Based on the NCCN Guidelines on prostate cancer,[11] the pathological T stage of these patients ranged from T2a to T3b. 76 (74.5%) of them were in stage T2 and 26 (25.5%) were in stage T3. The occurrence rates of PSA recurrence were 21.1% and 42.3% in T2 and T3 patients, respectively. Pathological analysis showed that 71 (69.6%) patients had a Gleason Grade ≥2, and 45 (44.1%) had a positive surgical margin (PSM).

The predictive ability of PSA_{postd3}/PSA_{pre} for PSA recurrence

As the half-life of PSA is 2–3 days, we analysed the relationship between PSA_{postd3}/PSA_{pre} and PSA recurrence. PSA_{postd3}/PSA_{pre} was not associated with the absolute value of preoperative PSA ($P>0.05$).

The PSA_{postd3}/PSA_{pre} was significantly higher in PSA recurrence patients compared with PSA recurrence-free patients ($P<0.0001$) (Figure 1). The ROC curve of PSA_{postd3}/PSA_{pre} is shown in Figure 2 with an area under the curve (AUC) of 0.760. The cut-off of PSA_{postd3}/PSA_{pre} was derived at 0.453 (sensitivity=0.704, specificity=0.853, positive predictive value=0.633, negative predictive value=0.889,
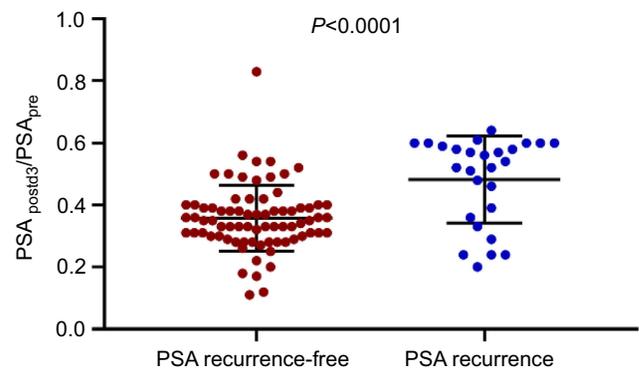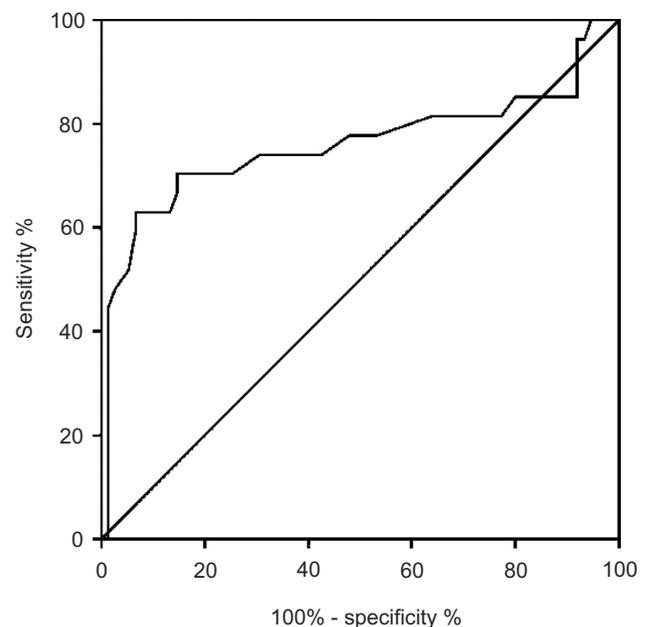
$P<0.0001$). This outcome indicated that the risk of PSA recurrence increased in patients with a $PSA_{postd3}/PSA_{pre}>0.453$.

It is noteworthy that the value of PSA_{postd3}/PSA_{pre} has a great overlap between PSA recurrent patients and patients without PSA recurrence (Figure 1). Among 27 patients with PSA recurrence, there were 8 patients with PSA_{postd3}/PSA_{pre} ≤0.453, while among 75 patients without PSA recurrence there were 11 patients with $PSA_{postd3}/PSA_{pre} >0.453$ (Table 2). We divided these patients into four subgroups according to whether they had PSA recurrence and whether PSA_{postd3}

Table 2 Fisher's exact test results of different factors (n=102)

	PSA recurrence	PSA recurrence-free	P-value
Age at operation (years old)			
≤70	21	56	
>70	6	18	>0.999
Preoperative PSA (ng/mL)			
≤10 ng/mL	11	41	
>10 ng/mL	16	34	0.264
Surgical margin status			
Negative	14	43	
Positive	13	32	0.657
Pathological T stage			
T2	16	60	
T3	11	15	0.042*
Postoperative Gleason Grade			
1	4	27	
2–3	13	37	
4–5	10	11	0.021*
PSApostd3/PSApre			
≤0.453	8	64	
>0.453	19	11	<0.0001*

Notes: *$P<0.05$ is considered to be statistically significant.
Abbreviations: PSA, prostate specific antigen; PSA_{postd3}/PSA_{pre}= The ratio of the PSA on day 3 postop as the numerator and the pre-operative PSA as the denominator.

/PSA_{pre} was greater than 0.453. The Fisher's exact test was conducted to reveal the difference of the clinical and pathological characteristic of these patients, including their age at operation, pathological T stage, surgical margins, preoperative PSA and postoperative Gleason Grade. The result was only significant for pT staging ($P=0.035$), with an interesting finding that all 11 patients with PSA recurrence-free and PSA_{postd3}/PSA_{pre} >0.453 belonged to pT2. This supported the important influence of pT on PSA recurrence outcome, which the multivariate analysis did not reveal (see below), probably due to a small sample size.

The association between PSA recurrence and multiple factors

Previous studies have suggested that PSA recurrence is associated with many preoperative and postoperative factors (see discussion). In this study, based on the accessible data, the relationships of PSA recurrence and the following indicators were investigated: age at operation (>70 or ≤70 years old),

preoperative PSA (>10 or ≤10 ng/mL), surgical margin status (positive or negative), pathological T stage (pT stage, ie T2 or T3), postoperative Gleason Grade (1, 2–3 or 4–5) and PSA_{postd3}/PSA_{pre} (>0.453 or ≤0.453). Fisher's exact test was applied to all of the indicators, and the P-values were presented in Table 2. Patients with different PSA_{postd3}/PSA_{pre} ($P<0.0001$), pT stage ($P=0.042$) and Gleason Grade ($P=0.021$) had significantly different PSA recurrence rates.

A multivariable logistic regression model was established to identify factors associated with PSA recurrence rates, and the results were shown in Table 3. On multivariate analysis of the entire cohort, only PSA_{postd3}/PSA_{pre} ($P<0.001$) was significantly related to PRFS. Figure 3 shows the probability of PRFS over time in patients with different values of PSA_{postd3}/PSA_{pre}. The probability of PRFS in patients with PSA_{postd3}/$PSA_{pre}≤0.453$ was significantly higher than in patients with $PSA_{postd3}/PSA_{pre}>0.453$.

Table 3 Multivariable logistic regression analyses for developing PSA recurrence

Variable	Multivariate analysis	
	HR (95%CI)	P-value
Age(years)		
≤70	1	
>70	1.277(0.314–5.194)	0.733
Preoperative PSA(ng/ml)		
≤10	1	
>10	2.616(0.717–9.538)	0.145
Surgical margin status		
Negative	1	
Positive	0.750(0.234–2.409)	0.629
Pathological T stage		
T2	1	
T3	3.911(0.968–15.805)	0.056
Postoperative Gleason Grade		
1	1	
2–3	2.899(0.582–14.431)	0.194
4–5	5.263(0.924–29.981)	0.061
PSA_{postd3}/PSA_{pre}		
≤0.453	1	
>0.453	27.415(6.795–110.605)	<0.001*

Notes: *$P<0.05$ is considered to be statistically significant.
Abbreviations: HR, hazard ratio; CI, confidence interval; PSA, prostate specific antigen; PSA_{postd3}/PSA_{pre}, The ratio of the PSA on day 3 postop as the numerator and the pre-operative PSA as the denominator.
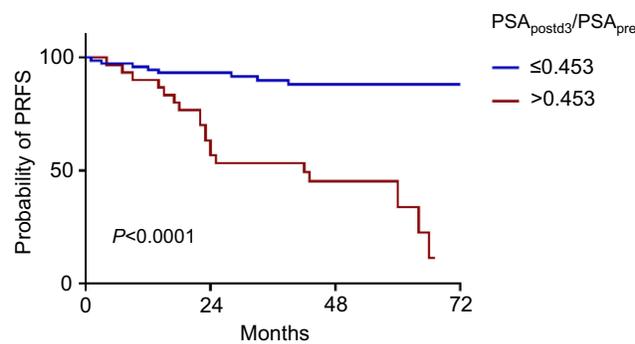
Figure 3 Kaplan-Meier estimates of the probability of PRFS according to PSA_{postd3}/PSA_{pre}.
Abbreviations: PRFS, PSA recurrence-free survival; PSA_{postd3}/PSA_{pre}, The ratio of the prostate-specific antigen (PSA) on day 3 postop as the numerator and the preoperative PSA as the denominator.

Discussion

Many studies have explored the prognostic value of different preoperative and postoperative factors for PSA recurrence, but no consensus has been reached. Commonly investigated indicators include the following. 1) Preoperative PSA: Most studies have concluded that a high level of preoperative PSA was associated with PSA recurrence,[6,7,12–15] although Takeuchi[16] and Aguilera[17] reported insignificant results. Preoperative PSA doubling time (PSADT) has been a rising indicator in recent years, especially early PSADT and ultrasensitive PSADT, but their relationships with PSA recurrence are controversial.[8] 2) Pathological Gleason score: Much evidence has supported that a higher Gleason score increases the risk of PSA recurrence,[7,13–18] while a few studies have also reported insignificant results.[12,19] 3) Pathological T stage: Generally, a higher T stage suggests a greater probability of developing PSA recurrence.[7,12,14–16] 4) Age: According to Wang et al, patients older than 70 years old were less likely to undergo PSA recurrence than those who were younger,[12] although most other studies have reported an insignificant relationship between age and PSA recurrence.[7,14,16,20,21] 5) Positive surgical margin: The prognostic value of PSM has been controversial.[7,14,15,17,19,20] Yossepowitch et al concluded in a review in 2014 that positive margins were associated with a twofold increased hazard of biochemical relapse.[22] Other previously investigated pathological indicators include capsule invasion,[20] extracapsular extension,[13,20] lymph node invasion,[15,19] and seminal vesicle invasion.[18,20] In our study, several possible prognostic factors besides postoperative PSA were also investigated. According to our results, patients with different PSA_{postd3}/PSA_{pre} ($p<0.0001$), pT stage ($P=0.042$) and Gleason Grade ($P=0.021$) had significantly different PSA recurrence rates by Fisher's exact test, while on

multivariate analysis of the entire cohort, only PSA_{postd3}/PSA_{pre} ($P<0.001$) was significantly related to PRFS.

Postoperative PSA after RP is a frequent factor included in various clinical outcome (including PSA recurrence) prediction tools in PCa patients.[23] Previous research usually focused on the relationship between the absolute value of postoperative PSA and PSA recurrence.[5–7,23–26] For example, Vesely held that PSA on day 30 postop was significantly associated with PSA recurrence, but such an association was not observed with PSA on day 14 postop.[23] Furthermore, Skove et al concluded that men with a detectable PSA nadir after RP had an increased risk of PSA recurrence, and a shorter time to nadir suggested a higher risk of PSA recurrence.[26] Little research has been implemented to reveal the relationship between PSA recurrence and postoperative PSA at as early as the first week after surgery. Only one study investigated the ratio of PSA on the 5th day after salvage radiotherapy (PSA5) and pre-treatment PSA (PSART) and found that PSA5/PSART <1 was a significant predictor of PSA recurrence.[27] This study provided some information about the relationship of early postoperative PSA decline with biochemical failure in patients receiving RP and salvage radiotherapy.

Based on the half-life of PSA, the present study discovered that PSA_{postd3}/PSA_{pre} was an efficacious predictor for PSA recurrence. This indicator has the following advantages: 1) the specificity and negative predictive value of PSA_{postd3}/PSA_{pre} were high, which could prevent overtreatment as a screening method; 2) it allowed for early recognition for possible PSA recurrence during the first week after RP; and 3) it was an easily measurable indicator. Because preoperative PSA is often high, ultrasensitive PSA equipment is not necessary to detect an approximately 50% decline. However, PSA_{postd3}/PSA_{pre} has some shortcomings: 1) its sensitivity is not very high, thus long term follow up with PSA tests is indispensable, even in patients with a low PSA_{postd3}/PSA_{pre}; and 2) because PSA is metabolized by the liver and kidneys mainly,[28] insufficiency of these organs might influence PSA kinetics and thus impair the predictive value of PSA_{postd3}/PSA_{pre}.

The present study has several limitations.

1. The sample size of PSA on day 3 postop was relatively small, future study should expand the sample size to reduce error. In addition, further studies may complete PSA measurements on day 1–7 postop to compare the AUC of the PSA ratio on

different days and to identify the optimal time to measure postoperative PSA during the first week.

2. Though commonly considered an outcome surrogate for PCa patients, PSA recurrence remains controversial for its clinical significance and interpretation. Some research has shown that PSA recurrence had limited significance in disease progression and mortality in PCa patients after RP. 66.7–74% of PSA recurrence patients did not develop CLR or metastasis,[1,2,29] and the overall survival rates in PSA recurrence and PSA recurrence-free patients were not significantly different (88% vs 93%, P=0.94).[29] Similar conclusions were drawn regarding cancer-specific mortality (P=0.23).[15] Therefore, interpretation of this study should be cautious.

3. The follow-up was relatively short in this study, with a median follow-up of 56.4 months. However, a previous study reported that the mean time to PSA recurrence was 38.4 months,[30] and 77% of cases of PSA recurrence occurred within 2 years after RP,[31] so the majority of PSA recurrence events should have been observed. The patients in the present study would be continuously followed up to observe other outcomes, such as CLR, metastasis and death.

Conclusion

In conclusion, the present study identified a new indicator, PSA_{postd3}/PSA_{pre}, for predicting PSA recurrence in patients after RP. Patients with a PSA_{postd3}/PSA_{pre} >0.453 were more likely to develop PSA recurrence than those with a lower PSA_{postd3}/PSA_{pre}, with an increased risk of 9–20 times. By a convenient test of preoperative PSA and PSA on day 3 postop and simple calculation, PSA_{postd3}/PSA_{pre} might serve as an early indicator for PSA recurrence in the future, which may facilitate recognition of potential relapse and could translate into more intense follow-up and even efficacious salvage therapy in selected patients.

Abbreviation list

AUC, area under the curve; CLR, clinical recurrence; IQR, interquartile range; IRB, institutional review board; NCCN, national comprehensive cancer network; PCa, prostate cancer; PRFS PSA, recurrence-free survival; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; PSA_{postd3}/PSA_{pre}, the ratio of the PSA on day 3 postop as the numerator and the pre-operative PSA as the denominator; PSM, positive surgical margin; PUMCH, Peking Union Medical College Hospital; ROC, receiver operating characteristic; RP, radical prostatectomy.

Ethics approval and informed consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board (IRB) of Peking Union Medical College Hospital (PUMCH) and with the 1975 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study.

Data availability

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

Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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