Running title: Biochemical relapse in prostate cancer

Factors Predicting Prostate Specific Antigen Failure Following Radical Prostatectomy: Experience with 961 Patients

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ABSTRACT

Objective: To determine disease-related predictors for the occurrence of prostate specific antigen (PSA) failure in Iranian prostate cancer patients who underwent radical prostatectomy.

Methods: In this cohort study, we enrolled eligible patients with prostate cancer who underwent radical prostatectomy at our center between 2001 and 2018. The primary endpoint was the incidence of postoperative biochemical failure, defined as two consecutive PSA levels ≥0.2 ng/dl. Patients with TNM stage ≥ III, Gleason score ≥8, or baseline PSA above our calculated cut-off level were considered as high risk. Kaplan–Meier survival method and Cox proportional hazards regression analysis were used for determining the biochemical relapse-free survival and its predictors.

Results: Data of 959 patients (age=61.2 ± 6.4 years) were analyzed with a median follow up of 36 months (range 6 months to 18 years). A total of 97 patients (10.1%) developed biochemical failure at the time of analysis who had a significantly older age and longer follow-up duration (P=0.024 and P<0.001, respectively). Preoperative PSA level of 8.85 mg/dl could predict the occurrence biochemical failure with a sensitivity of 83.2% and specificity of 39.2% (Area under the curve=0.601, 95% CI: 0.541-0.662; P=0.001). In the multivariate analysis, higher preoperative PSA, Gleason score≥8, and high-risk TNM stage were independent predictors for biochemical relapse (P=0.029, P=0.001, and P=0.008, respectively).

Conclusion: Preoperative PSA, Gleason score, and TNM stage were independent predictors for biochemical failure following radical prostatectomy in prostate cancer patients. We also determined a lower cut-point for PSA that could predict biochemical failure.

KEYWORDS

Prostate Cancer; Biochemical Failure; Cohort study; Survival Rate; Risk Factors

INTRODUCTION

Prostate cancer is one of the most common cancers in males.[1-3]. The age-standardized incidence rate of prostate cancer in Iran has been evaluated by about 9.1%, considering the lack of a large registry system [4]. Early recognition of prostate cancer and baseline prognostication of the patients could help much to reduce the medical costs and burden of the disease.

Recognition of survival factors, particularly predictors of biochemical failure, is essential in the management of prostate cancer. Gleason score and tumor stage have been shown to predict biochemical failure and mortality in some studies [5-8]. The serum prostate-specific antigen (PSA) is a useful biologic parameter that plays a significant role both in the diagnosis and follow-up of prostate cancer [9,10]. On the other hand, it is unknown if the accumulation of these risk factors can exacerbate the risk of biochemical failure or not.

Prostate cancer is among the top five cancers in west Asia with an age-distribution similar to other countries [11]. However, because of no strict national registry for this disease in most countries in this region, the data regarding prostate cancer is limited to local studies. Most of the data on this subject are from the Western and developed countries, such as the United States, Europe, and Eastern Asia; and so far, there were few accurate reports of the rate and predictors of biochemical failure in prostate cancer from West Asia. Therefore, we aimed to assess the role of disease-related factors in predicting the occurrence of biochemical relapse in prostate cancer patients who underwent radical prostatectomy in a referral center in Iran.

METHODS

In this cohort study, we enrolled patients with prostate cancer who underwent radical prostatectomy between 2001 and 2018. The inclusion criteria were a definite diagnosis of prostate cancer underwent radical prostatectomy, having a complete medical record, and at least six months follow-up. Patients who did not have complete clinical records or were not followed-up were excluded. All participants signed informed consent before enrollment to the study. The institutional board of research and committee of medical ethics approved the study protocol. This study was conducted in accordance with the Declaration of Helsinki. A retrospective analysis of a prospectively collected data under a defined protocol was performed.

Adenocarcinoma was confirmed by trans-rectal ultrasound, or Magnetic resonance imaging (MRI) guided biopsy, after diagnosis by elevated serum prostate-specific antigen (PSA) levels or abnormal digital rectal exam (DRE). The demographic and clinical data of the patients were recorded in the first admission time. These data included age, date of diagnosis, baseline PSA level, clinical TNM stage, and biopsy report. After discharge, all patients underwent scheduled follow-up visits, at one, three, and six months, and then every other six months. PSA levels were measured and recorded prospectively in each visit. The patients were followed-up by a phone call in cases we did not have their PSA level for longer than six months. Gleason score and positive margin of surgery were obtained from the biopsy report. A single surgeon performed all surgical procedures.

The primary endpoint of the study was the incidence of postoperative biochemical failure, defined as two consecutive PSA levels ≥0.2 ng/dl. Patients with TNM stage ≥III, Gleason score ≥8, or baseline PSA above our calculated cut-off level were considered as high risk. Accordingly, the number of risk factors was calculated based on the presence of any of these factors.

Statistical analysis

Quantitative data are shown as mean (standard deviation) for data with normal distribution or median [interquartile range] for non-normally distributed data. The normality of the data was tested using the Kolmogorov-Smirnov test. Categorical data were shown as frequency (percentage) and were compared between groups using a Chi-square test. Quantitative data were compared between the positive and negative biochemical failure groups by Student's t-test or Fisher's exact probability test, where applicable. For defining a cutoff point for preoperative PSA, we used the area under the receiver operating characteristic (ROC) curve with a 95% confidence interval (CI). The cut-off level was defined by plotting the optimum point for the false-positive rate (1-specificity) against the true-positive rate (sensitivity). Biochemical relapse-free survival rates were calculated using the Kaplan–Meier survival method, including a log-rank test to biochemical relapse-free survival rates among subgroups. We used univariate and multivariate Cox proportional hazards regression analysis to recognize the predictors for biochemical failure and reported them through hazard ratio with a 95% CI. According to our cut-off level, the prognostic performance of preoperative PSA was also calculated. We utilized SPSS version 21.0 software (IBM Corporation, Armonk, NY, USA) for statistical analysis. Two-tailed P-values <0.05 were considered for the statistical level of significance.

RESULTS

From a total of 1057 prostate cancer patients, 959 patients (age=61.2±6.4 years) met our study criteria, and their data were analyzed. The median follow-up of the patients was 36 months (range 6months to 18 years). A total of 97 patients (10.1%) developed biochemical failure at the time of analysis. Patients with biochemical failure had a significantly older age and longer follow-up duration (P=0.024 and P<0.001, respectively). Moreover, the frequency of patients with a positive margin of surgery, higher Gleason score, and higher TNM stage was significantly higher in the biochemical failure group (P=0.035, P=0.001, and P=0.012, respectively). The patients in the biochemical failure group also had significantly more risk factors (P<0.001). The details of these comparisons are shown in Table-1.

Results of the ROC curve analysis showed that a preoperative PSA level of 8.85 mg/dl could predict the occurrence of biochemical failure with a sensitivity of 83.2% and specificity of 39.2% (Area under the curve=0.601, 95% CI: 0.541-0.662; P=0.001).

In the univariate analysis, higher preoperative PSA (P<0.001), the positive margin of surgery (P=0.019), Gleason score≥8 (P<0.001), high-risk TNM stage (P<0.001), and having multiple risk factors (P<0.001) could significantly predict the occurrence of biochemical failure. In the multivariate analysis, higher preoperative PSA, Gleason score≥8, and high-risk TNM stage were independent predictors for biochemical relapse (P=0.029, P=0.001, and P=0.008, respectively). The results of the univariate and multivariate survival analyses are shown in Table-2. Kaplan-Meier estimate of biochemical failure-free survival based on the preoperative PSA, Gleason score, TNM stage, and the number of risk factors subgroups are shown in Figure-1. Prognostic performance of the preoperative PSA level based on our cut-off level is described in Table-3.

Finally, biochemical relapse occurred in seven percent of patients with no pre-operative risk factors, 10.8% with one, and 16.4% with multiple pre-op risk factors. ($p<0.001$)

DISCUSSION

The current study showed that preoperative PSA, Gleason score and TNM stage were shown to be independent predictors for biochemical failure in cancer patients. Moreover, we found that preoperative PSA can predict biochemical failure at a cut-off level of 8.85 mg/dl with high sensitivity.

Biochemical failure following radical prostatectomy is an important issue in patients with prostate cancer because there is no definite treatment for patients who experience biochemical failure, and over one-third of such patients are prone to metastatic disease and thereby, death[12-14].

Prognostication of patients with prostate cancer, particularly those with intermediate-risk is not easy, because several factors may intervene. Various studies have discussed predictors of biochemical relapse following radical prostatectomy in prostate cancer with controversial results. These predictors include general or disease-related factors. Examples of general factors include older age [15], excessive body mass index [16-18], smoking [19], use of statins [20,21], taking Aspirin [22], and delay in performing radical prostatectomy [23].

Some metabolism-related genetic risk factors for biochemical relapse has also been introduced, such as paired-like homeodomain transcription factor 2 (PITX2) gene [24], Sulfite oxidase expression [25], CRTC2 [26], and long noncoding RNAs [27]. However, these novel factors still need to be carefully studied and demand further research.

One histopathologic predictor for biochemical relapse is the presence of peri-neural invasion [28,29]. Irrespective of perineural invasion status, pure sympathetic nerve density without tumor invasion can also independently predict biochemical relapse[30]. Other prognostic pathologic features include lymphovascular invasion and lymph node involvement [31,32]. However, some of these features were not analyzed in our study, and thereby, the data was not proper for statistical analysis.

In our study, Gleason score ≥8 showed to be a potent predictor factor for biochemical relapse. In terms of Gleason pattern, pattern five has been recognized as a significant predictor for biochemical relapse [33,34].

In one study in Turkey, capsule invasion was the sole independent predictor for biochemical relapse in 504 patients who underwent radical prostatectomy due to prostate cancer [35].

Most of the studies that investigated the risk factors for biochemical relapse have used a cut-point level of 20 ng/dl for preoperative PSA levels [34,36]. However, some recent studies have introduced lower cut point levels for preoperative PSA that are more similar to our cut-point level. In a large cohort of 3576 prostate cancer patients, preoperative PSA levels above 10 ng/dl could independently predict the occurrence of biochemical failure [37]. In another study in Poland, the preoperative PSA level above 8 ng/ml could predict biochemical relapse with a sensitivity of 73.2%and a specificity of 56.2% [38], which is in line with our findings. Therefore, it seems that the cut-point level of preoperative PSA for predicting the risk of biochemical relapse should be revised based on these new findings and various populations.

A positive surgical margin is another risk factor that has been confirmed as a potential predictor of biochemical relapse in many studies, as well as ours. One study showed that the number of positive margins, Length of positive margin, and location of margin could all contribute to the risk

of biochemical relapse [39]. It has also been proposed that the tumor grade at the site of the positive margin has a prognostic value, and biochemical failure occurs earlier in patients with positive surgical margin and a high-grade tumor [40,41]. Therefore, the positive surgical margin can be effectively used as an excellent prognostic tool while making decisions in prostate cancer patients.

We showed that the number of risk factors could also predict the occurrence of biochemical relapse, which is in line with previous studies. We considered preoperative PSA, Gleason score and TNM stage as the main risk factors in this evaluation. However, other studies have used a different combination of risk factors. For example, in a cohort of 481 Japanese patients, patients were classified based on tumor stage, Gleason score, and preoperative PSA into three categories with cut-off levels different from ours. Their results showed that only the number of intermediate risk factors was significantly associated with biochemical failure-free survival following radical prostatectomy [42]. Beauval et al. also showed that the number of risk factors worsens the biochemical relapse-free survival; however, their risk factors were lymph node invasion, preoperative PSA>20, and positive surgical margin [43]. In another study on 191 high-risk prostate cancer patients, those with more risk factors had shorter biochemical relapse-free survival [44]. The studied risk factors so far comprised of the initial PSA level, pathological Gleason score, seminal vesicle invasion, extraprostatic extension, and intraductal carcinoma of the prostate. So, despite the differences in defining the risk factors, the number of risk factors is overall a good predictor for biochemical relapse-free survival, and further studies are required to decide on the type of risk factors.

In general, none of the above-mentioned risk factors can solely predict biochemical relapse-free survival, and thereby, a combination of them should be validated in a scoring system to assist the urologists in decision making for patients with prostate cancer.

To our knowledge, there is a lack of study on this issue in west Asia, and most of the data about this subject are from western and developed countries. The strength of this study is that it is one of the few studies in West Asia that has investigated the new cut-point for pre-operative PSA and other predictors for biochemical failure in a large number of prostate cancer patients who were operated by a single surgeon. Also, our patients had regular follow-up visits, and very few patients were missed to follow. However, it would be better if other predictors, like neuro-vascular invasion, body mass index and longer follow-up duration, were available for analysis. One other limitation of our study is that, those who had a biochemical failure were more committed to present for the follow-up visits and therefore their follow up durations were significantly longer than the relapse-free individuals.

CONCLUSION

In this study, we found that prostate cancer patients with higher preoperative PSA, higher Gleason score and higher TNM stage were significantly more prone to biochemical failure following radical prostatectomy. We also determined a lower cut-point for PSA that could predict biochemical failure, and this necessitates performing a meta-analysis to reconsider and modify the current guidelines. As biochemical failure predisposes the patients to metastatic disease and death, more careful consideration should be given to patients who are at a higher risk for biochemical failure. Treatment plans with curative intent could help much in this regard, and future studies should focus on more intensive treatments for prostate cancer. Finally, the development of a national registry for prostate cancer is highly recommended.

Conflict of interest: None of the authors has any personal or financial conflict of interest.

Ethical issues:

This study is exempted from ethical approval by the institutional ethics committee and does not contain any studies with animals performed by any of the authors.

Informed consent was obtained from all individual participants included in the study.

Author's contribution:

NS: protocol project, project development, data management, manuscript writing, critical revision, and final approval

MD: project development, data collection and analysis, manuscript writing, critical revision, and final approval

PM: data collection, critical revision, and final approval

AS: Drafting, data analysis, critical revision, and final approval

MB: data collection, critical revision, and final approval

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FIGURE LEGENDS

Figure-1: Kaplan–Meier: biochemical relapse-free survival following radical prostatectomy by A) Preoperative PSA level categories; B) Gleason score; C) TNM stage; and D) the number of risk factors.

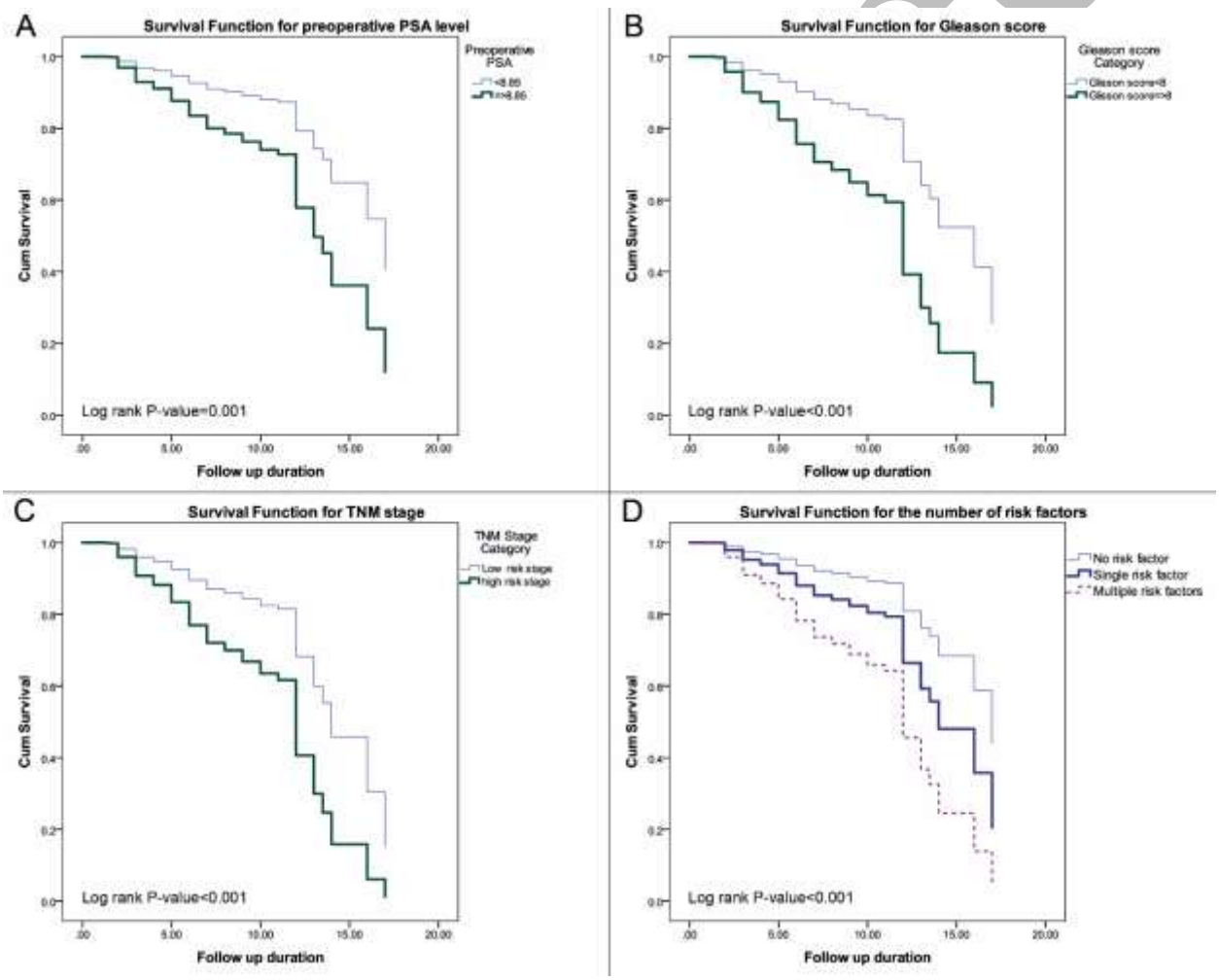

Table-1: Baseline characteristics of the study population and the comparison between the groups with and without biochemical failure.

Characteristics*	**Total (n=959)**	**Relapse free (n=862)**	**Biochemical failure (n=97)**	**P-value****
Age, yr	61.2 (6.4)	61.0 (3.4)	62.6 (6.7)	0.024
Follow up duration, yr	3.0 [2.0, 6.0]	3.0 [2.0, 5.0]	5.0 [3.0, 8.0]	<0.001
Preoperative PSA, mg/dl	11.0 [7.0, 19.0]	10.6 [7.0, 18.0]	14.0 [9.0, 25.0]	0.124
Positive margin of surgery, n (%)	312 (32.5)	270 (34.5)	42 (45.7)	0.035
Glisson score, n (%)				0.001
6	337 (35.1)	315 (36.5)	22 (22.7)	
7	363 (37.9)	332 (38.5)	31 (32.0)	
8	120 (12.5)	97 (11.3)	23 (23.7)	
9	12 (12.5)	104 (12.1)	16 (16.5)	
10	13 (1.4)	11 (1.3)	2 (2.1)	
Glisson score≥8, n (%)	253 (26.5)	212 (24.7)	41 (43.6)	<0.001
TNM stage, n (%)				0.012
T2	637 (68.6)	581 (69.9)	56 (58.4)	
T3	275 (29.6)	240 (28.8)	35 (36.5)	
T4	16 (1.7)	11 (1.3)	5 (5.2)	
High risk stage, n (%)	291 (30.5)	251 (30.2)	40 (41.7)	0.021
Number of risk factors				<0.001
No risk factor	511 (53.3)	475 (55.1)	36 (37.1)	
Single risk factor	221 (23.2)	197 (22.9)	24 (24.7)	
Multiple risk factors	225 (23.5)	188 (21.8)	37 (38.1)	
Preoperative PSA≥8.8	586 (63.1)	507 (60.8)	79 (83.2)	<0.001

* The continuous variables are shown as mean (standard designation) or median [interquartile range] were applicable. Categorical variables are shown as frequency (percentage)

** P<0.05 was considered as statistically significant.

PSA: prostate specific antigen; TNM: Tumor, node, metastasis;

Table-2: Univariate and multivariate survival analyses of prostate cancer patients.

Characteristic	Hazard ratio	95% Confidence interval	P-value*
Univariate			
Age	1.03	0.99-1.06	0.12
Preoperative PSA	1	1.00-1.01	<0.001
Positive margin of surgery	1.64	1.08-2.48	0.019
Gleason score≥8	2.71	1.79-4.1	<0.001
High risk TNM stage	2.36	2.56-3.57	<0.001
Number of risk factors			
No risk factor	ref	ref	Ref
Single risk factor	1.93	0.99-3.74	0.052
Multiple risk factors	3.7	1.96-6.97	<0.001
Multivariable			
Preoperative PSA	1.003	1.000-1.006	0.029
Gleason score≥8	2.15	1.38-3.45	0.001
High risk stage	1.84	1.17-2.89	0.008

* P<0.05 was considered as statistically significant.

PSA: prostate specific antigen; TNM: Tumor, node, metastasis;

Table-3: Prognostic performance of preoperative PSA level based on a cut-off level=8.8

Statistic	**Value**	**95% confidence interval**
Sensitivity	83.16	74.10, 90.06
Specificity	39.21	35.88, 42.62
Positive likelihood ratio	1.37	1.23, 1.52
Negative likelihood ratio	0.43	0.27, 0.68
Positive predictive value	13.48	12.30, 14.76
Negative predictive value	95.34	92.84, 96.99
Accuracy	43.7	40.48, 46.96