

Original Article

PROSTATE-SPECIFIC ANTIGEN AND TIME TO PSA NADIR AS PROGNOSTIC SIGNIFICANCE IN CASTRATION-RESISTANT PROSTATE CANCER

Firmantya Hadi Pranata,^{ID} Wahjoe Djatisoesanto,^{ID} Doddy M. Soebadi^{ID}
 Department of Urology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

ABSTRACT

A high mortality rate was often found in castration-resistant prostate cancer (CRPC). This study was to assess the PSA level and time to PSA nadir as a prognostic tool for survival in CRPC patients. Several factors are considered to be useful as prognostic markers in CRPC patients. This study was a descriptive study assessing the survival rate in castration-resistant prostate cancer. Evaluation data included sex, age, initial PSA level, final PSA level, time to PSA nadir (TTN), time to CRPC progression (TTC), and survival status. A total of 24 patients with CRPC were evaluated in this study. Our result revealed that there was a significant difference found in the initial PSA level between survivors (445.7 + 165.6 ng/mL) and non-survivor (200.7 + 144.9 ng/mL). There were no significant differences found in PSA nadir level, TTN, and TTC between survivor and non-survivor groups. However, there was a significant correlation between time to PSA nadir and time to CRPC progression. This study revealed that there was an association between initial PSA level on the survival rate of CRPC patients. Initial PSA level could be used to predict survival prognosis in CRPC patients.

Keywords: Prostate-specific antigen; PSA nadir; prostate cancer; castration-resistant prostate cancer

Correspondence: Doddy Moesbadianto Soebadi, Department of Urology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Email: dmsuebadi@gmail.com

How to cite: Pranata, F. H., Djatisoesanto, W., & Soebadi, D. M. (2022). Prostate-Specific Antigen and Time to PSA Nadir as Prognostic Significance in Castration-Resistant Prostate Cancer. *Folia Medica Indonesiana*, 58(1), 50–55.
<https://doi.org/10.20473/fmi.v58i1.32649>

pISSN:2355-8393 • eISSN: 2599-056x • doi: 10.20473/fmi.v58i1.32649 • Fol Med Indones. 2022;58:50-55
 • Submitted 27 Dec 2021 • Received 27 Jan 2022 • Accepted 12 Feb 2022 • Published 5 Mar 2022
 • Open access under CC-BY-NC-SA license • Available at <https://e-journal.unair.ac.id/FMI/>

H i i j n i j t u r

1. Assessing the survival rate in castration-resistant prostate cancer was descriptived.
2. PSA level between survivor and non survivor was significant but not for PSA nadir level, TTN and TTC.
3. Initial PSA level can predict survival prognosis rate of castration-resistant prostate cancer patients.

INTRODUCTION

Of all-male cancers worldwide, prostate cancer accounted for 15% and became the second most common malignancy in men (Barsouk et al. 2020). The study showed that 1 in 25 men will be most likely to develop prostate cancer in their lifetime (Bray et al. 2018). The gold standard therapy for metastatic prostate cancer was primary androgen deprivation therapy (ADT). Most patients will experience a substantial decline in PSA which leads to undetectable PSA for years. However, even after ADT, PSA level may fail to decrease and disease progression may occur in some cases (Tomioka et al. 2014). This progression is known as castrate-resistant prostate cancer (CRPC). Few are currently understood about the factors

influencing the survival of CRPC patients. The variability in the clinical course of CRPC led to the utilization of several prognostic factors regarding their roles influencing the treatment strategy and its capability to predict the response of therapy. One known factor which could be evaluated as prognostic value is prostate specific antigen (PSA) level, even though using PSA as a single predictor for prognosis in prostate cancer patients may be unreliable (Ørsted et al. 2012). Recent studies have reported the utilization of initial PSA level, time to PSA nadir (TTN), PSA nadir level, and time to CRPC progression (TTC) among other parameters for predicting the prognosis of CRPC patients (Hamano et al. 2019). Several studies have suggested that nadir PSA level was the most significant predictor of CRPC progression. PSA rising after the



nadir value after PADT (primary androgen deprivation therapy) may reveal the sign of CRPC.

The association between time to PSA nadir (TTN) with progression, cancer-specific death, and all-cause mortality was demonstrated in a previous study (Choueiri et al. 2009). A rapid reduction of PSA level after ADT might be due to ablation of androgen receptor function. Since androgen receptor plays a role as a tumor suppressor in prostate cancer, rapid suppression of androgen receptor during ADT may lead to negative effect on a disease progression (Huang et al. 2011). Another study also reported that longer time to CRPC progression may be correlated with improved overall survival (Frees et al. 2018). Therefore, this study aimed to evaluate PSA level and time to PSA nadir (TTN) as a prognostic marker for survival in CRPC patients.

MATERIALS AND METHODS

This is a descriptive study evaluating the characteristics of prostate cancer patients based on the medical record date from Dr. Soetomo General Academic hospital from January 2013 to December 2020. This study has been approved by the ethical committee of Dr. Soetomo General Academic Hospital under a decree number 0392/129/XI/2020. On prostate cancer patients treated with castration-resistant progression were included in this study. Data evaluation consisted of sex, age, initial PSA level, final PSA level, time to PSA nadir (TTN), time to CRPC progression (TTC), and survival status. The progression of CRPC is defined as a rising PSA level and or radiographic progression evidence despite medical or surgical castration (Lowrance et al., 2018). Initial PSA level of the patients is defined as PSA level at the time of admission, whereas final PSA nadir level is defined as the lowest level after castration. Time to PSA nadir is defined as the time from castration until the lowest level of PSA is reached. The time from PSA nadir level to the development of castration resistance is defined as time to CRPC. All variables are presented descriptively in graphs.

The normality of distribution was performed with a Shapiro-Wilk test. If the data was normally distributed, an Independent T-test was performed to evaluate the differences for numerical variables between the surviving and non-surviving groups of patients, otherwise a Mann-Whitney U test would be used. To evaluate the correlation between numeric variables, we used Pearson correlation test. P value of less than 0.05 was considered to be significant.

RESULTS

Baseline characteristics

In this study, 24 patients with CRPC were included. The average age of the samples was 65.54 ± 7.5 years old. The patients' initial PSA was 388.57 ± 596.7 ng/mL. Four patients were performed medical castration, while 20 patients were performed surgical castration. It took approximately 308.4 ± 293.7 days for PSA level to reach PSA nadir. The lowest PSA level was 46.4 ± 112.5 ng/mL on average. The average time for the patients to develop CRPC was 554.1 ± 437.1 days. Baseline characteristic of the patient was shown in Table 1.

Table 1. Baseline characteristics of the patients

Variables (mean)	Value
Age	65.54
Initial PSA level (ng/ml)	388.57 ± 596.7
Castration (n)	
Medical castration	4
Surgical castration	20
PSA nadir (ng/ml)	46.4 ± 112.5
Time to PSA nadir/TTN (days)	308.4 ± 293.7
Time to CRPC/TTC (days)	554.1 ± 437.1

Initial PSA and patient survival

There were seven patients who died and 17 patients who survived until the last period of observation. The average initial PSA level of surviving patients was 445.7 ± 165.6 ng/mL, whereas the PSA level for patients who did not survive was 200.7 ± 144.9 ng/mL. Because the Shapiro-Wilks test result suggested that the data had a normal distribution ($p > 0.05$), an independent T-test was used for a comparative analysis. As indicated in Figure 1, there was a significant difference in initial PSA level between the groups ($p < 0.05$) as shown in Table 2.

Table 2. The association between initial PSA level, PSA nadir, time to PSA nadir level and time to CRPC progression to patient survival

Variables	Survivor	Non-survivor	p-value
Initial PSA level	445.7 ± 165.6	200.7 ± 144.9	< 0.05
PSA nadir	42.8 ± 131.9	42.7 ± 48.7	> 0.05
Time to PSA nadir	318.5 ± 176.9	284.1 ± 510.5	> 0.05
Time to CRPC progression	598.9 ± 431.1	445.2 ± 499.2	> 0.05

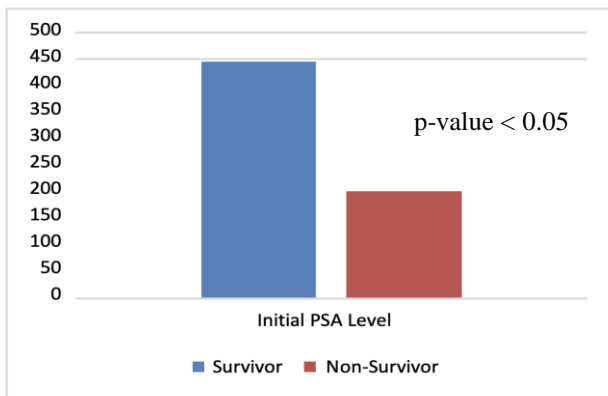


Figure 1. Initial PSA level differences between surviving and non-surviving patients

PSA Nadir and patient survival

The average PSA nadir level among patients who survived was 42.8+131.9 ng/dL, while the average PSA nadir level among patients who died was 42.7+48.7 ng/dL. To compare both groups, we used Mann-Whitney test, due to abnormal data distribution ($p < 0.05$). The difference between both groups in Figure 2 was insignificant ($p > 0.05$) as shown in Table 2.

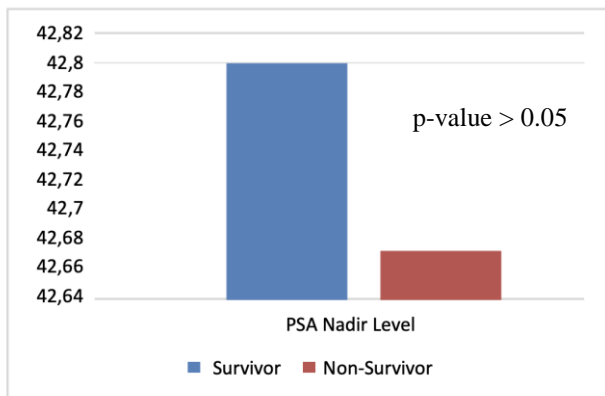


Figure 2. PSA Nadir level differences between surviving and non-surviving patients

TTN and patient survival

The average TTN of the surviving patients was 318.5+176.9 day, whereas the TTN of patients who died was 284.1+510.5 days. Due to abnormal distribution of the data, Mann-Whitney test was used for comparison ($p < 0.05$). As indicated in Figure 3, the study revealed no statistically significant difference between two groups ($p > 0.05$) as shown in Table 2.

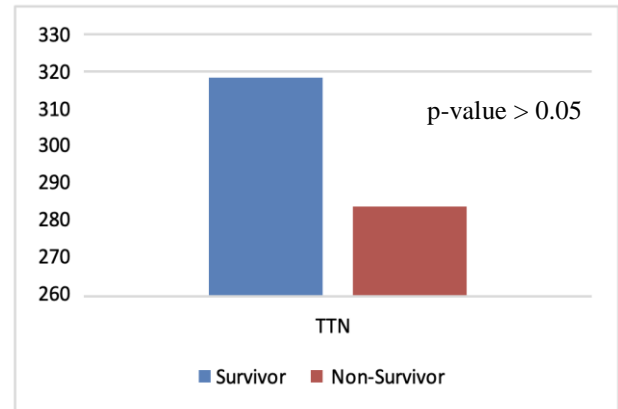


Figure 3. Time to PSA Nadir level difference between surviving and non-surviving patients

TTC and patient survival

The average TTC of patients who survived was 598.9 + 431.1 days, while the TTC of patients who did not survive was 445.2+499.2 days. Mann-Whitney test showed an insignificant difference between the two groups shown in figure 4 ($p < 0.095$) as shown in Table 2.

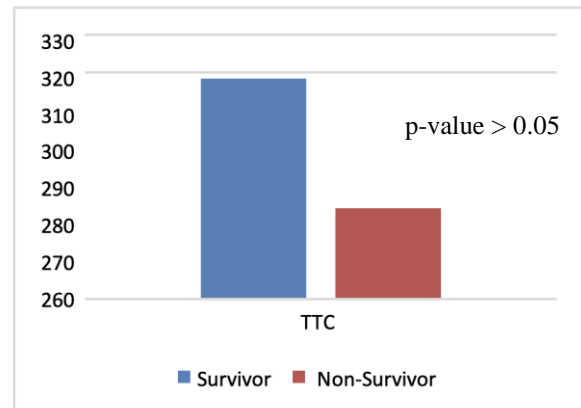


Figure 4. Time to castration-resistant progression between surviving and non-surviving patients

TTN and TTC

Correlation test analysis was performed using Pearson Correlation test to determine the correlation between TTN and TTC. Our result revealed that there was significant positive correlation ($p < 0.05$) between TTN and TTC with correlation coefficient of 0.737 as described in Figure 5.



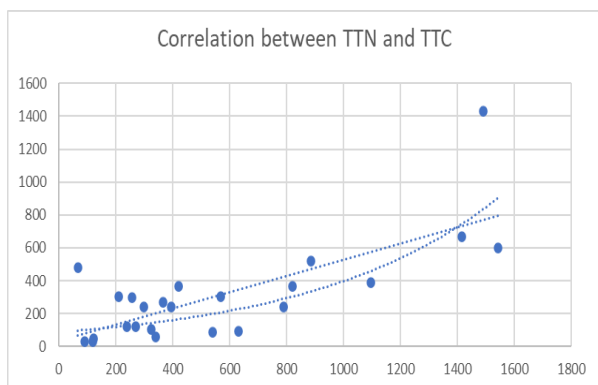


Figure 5. Correlation between TTN and TTC

DISCUSSION

PSA tests are used on a regular basis to screen prostate cancer and monitor progression (Ilic et al. 2018). PSA monitoring is important for evaluating treatment response during androgen deprivation therapy (ADT). In the first month following ADT treatment, most patients had a decrease in PSA levels (Sasaki & Sugimura 2018). In this study, there were 24 evaluated patients with CRPC. Our results found that initial PSA level was significantly associated with patient survival. Moreover, time to PSA nadir (TTN) and time to CRPC progression (TTC) was also significantly correlated. However, there was no significant association between nadir PSA level, time to PSA nadir (TTN) and time to CRPC progression (TTC) to patient survival.

The majority of patients with high initial PSA level reflected severity of tumor characteristics or an asymptomatic tumor for a long period of time, indicating the possibility that the patient is neglectful of his condition (Kan et al. 2017). A high PSA level also indicates a high androgen receptor activity of prostate cancer cells (Iwamoto et al. 2019). Previous studies also highlighted the mortality risk of a high PSA level. On the contrary, patients with lower PSA levels in this study had significantly higher mortality rate compared to patients with relatively higher PSA levels ($p < 0.05$). The difference in findings was possible possibly due to the bias of PSA measurement and age variation among patients. The evaluation of age difference is often not assessed in measuring initial PSA (Heidegger et al. 2015). The sensitivity and specificity of PSA measurement was low due to several factors affecting PSA level, such as catheterization, post-coitus, benign prostatic enlargement (BPE), and prostate infection (McAninch & Lue 2020).

Our result also found that there was no correlation between TTN and survival ($p > 0.05$). Patients with TTN of less than 9 months had a considerably greater overall survival rate than those with TTN of more than 9 months, according to the study. A previous large scale retrospective study analyzing 89 patients conducted between 2000 and 2009 found a significant association between TTN and survival. Also, the study also indicated that patients with TTN of less than 9 months had a considerably better overall survival rate than those with TTN of more than 9 months as well as discovering that a PSA nadir level of less than 0.2 ng/mL was associated with a better prognosis (Sasaki et al. 2011). Number of studies suggested that TTN and survival rate may be due to nature of some prostate cancer cells which can adapt to castration by utilizing intracrine androgens. During castration, androgen-sensitive cells would perish, while cells which can produce intracrine androgen (Sasaki & Sugimura 2018).

Our finding also revealed that the TTC was not associated with the patients' survival rate. These findings were different compared to a previous retrospective study evaluating 287 patients from 1996 to 2009, which reported that TTC was an independent factor to predict overall survival and progression-free survival. The study claimed that TTC less than two years was associated with a worse prognosis (Frees et al. 2018). Another retrospective study evaluating 289 patients from 2008 to 2015 reported a positive association between TTC and survival. Interestingly, the study also reported a positive association between hormone sensitive prostate cancer (HSPC) and patient survival (Bournakis et al. 2011). The differences of the findings in this study compared to previous studies may be due to the small number of samples in this study. Several studies suggested that a low TTC was due to PSA volume and PSA doubling time difference (Iwamoto et al. 2019).

Finally, in this study, the positive significant correlation between TTN and TTC highlighted intriguing implications. This finding was according to previous study which reported that the ability to reach an undetectable PSA level such as nadir was the most significant predictor for the time to CRPC progression in metastatic advanced prostate cancer (Benaim et al. 2002). Previous studies also stated that patients with short TTN were faster to develop castration-resistant (Hamano et al. 2019). The oncogene retinoblastoma protein (pRB) is reduced during castration level, resulting in a reduction of cyclin dependent kinase (CDK).

The prostatic cancer cell replication is halted due to this reduction. In a terminal proliferation phase, there are two possibilities for prostatic cancer cells, apoptosis or continually producing intracranial testosterone at a certain level of castration (Sasaki & Sugimura 2018). The mechanism of dependent androgen receptors has a role in castration-resistant progression. In some cases, androgen is still available at a low concentration even though the ADT has been given. This condition could lead to an adaptation of prostate cancer cells by amplification and an increase of AR expression via a mutation.

The amplification and mutation of AR involve several co-activators and co-repressors. Several studies reported the increase of FKBP51 co-activator in castrated rats. Co-repressor proteins are lower in CRPC patients. Based on the mechanism, several studies concluded that castration which leads to a short TTN would increase the activity of co-activators, while decreasing the activity of co-repressors, inducing the amplification and mutation of AR (Choueiri et al. 2009).

Strength and limitation

This study was limited due to its retrospective design and small sample size. The patients' follow-up period could also be extended to assess additional factors that might impact survival rate. The diagnostic modality used to evaluate metastasis was also limited in this study.

CONCLUSION

The initial PSA level differed significantly between survivors and non-survivors. However, there were no significant variations in PSA nadir level, time to PSA nadir, or time to CRPC progression. Our finding also revealed that there was an association between the time to PSA nadir and CRPC progression.

Acknowledgment

The authors thanked the medical record staff at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

Conflict of interest

None0

Funding disclosure

Pone0

Author contribution

FHP and WD-conseptual, study design, collected data, and analysis data. FHD-write and revised the manuscript. DMS-final validation and grammar check.

REFERENCES

- Barsouk A, Padala SA, Vakiti A, et al (2020). Epidemiology, staging and management of prostate cancer. *Med. Sci* 8, 1-13.
- Benaim EA, Pace CM, Lam PM, et al (2002). Nadir prostate-specific antigen as a predictor of progression to androgen-independent prostate cancer. *Urology* 59, 73–78.
- Bournakis E, Efstathiou E, Varkaris A, et al (2011). Time to castration resistance is an independent predictor of castration-resistant prostate cancer survival. *Anticancer Res.* 31, 1475–1482.
- Bray F, Ferlay J, Soerjomataram I, et al (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. 68, 394-424.
- Choueiri TK, Xie W, D'Amico AV, et al (2009). Time to prostate-specific antigen nadir independently predicts overall survival in patients who have metastatic hormone-sensitive prostate cancer treated with androgen-deprivation therapy. *Cancer Interdiscip. Int. J. Am. Cancer Soc.* 115, 981–987.
- Frees S, Akamatsu S, Bidnur S, et al (2018). The impact of time to metastasis on overall survival in patients with prostate cancer. *World J. Urol.* 36, 1039–1046.
- Hamano I, Hatakeyama S, Narita S, et al (2019). Impact of nadir PSA level and time to nadir during initial androgen deprivation therapy on prognosis in patients with metastatic castration-resistant prostate cancer. *World J. Urol.* 37, 2365–2373.
- Heidegger I, Fritz J, Klocker H, et al (2015). Age-adjusted PSA levels in prostate cancer prediction: Updated results of the tyrol prostate cancer early detection program. *PLoS One* 10, 1-12.
- Huang S, Bao B, Wu M, et al (2011). Impact of prostate-specific antigen (PSA) nadir and time to PSA nadir on disease progression in prostate cancer treated with androgen-deprivation therapy. *Prostate* 71, 1189–1197.
- Ilic D, Djulbegovic M, Jung JH, et al (2018). Prostate cancer screening with prostate-specific antigen (PSA) test: A systematic review and meta-analysis. *BMJ* 362, 1-35.



- Iwamoto H, Izumi K, Kadono Y, et al (2019). Prognosis of patients with prostate cancer and middle range prostate-specific antigen levels of 20–100 ng/mL. *Int. Braz J Urol* 45, 61–67.
- Kan H-C, Hou C-P, Lin Y-H, et al (2017). Prognosis of prostate cancer with initial prostate-specific antigen >1,000 ng/mL at diagnosis. *Onco. Targets. Ther.* 10, 2943-2949.
- Lowrance WT, Murad MH, Oh WK, et al (2018). Castration-resistant prostate cancer: AUA guideline amendment 2018. *J. Urol.* 200, 1264–1272.
- McAninch JW, Lue TF (2020). *Smith and Tanagho's general urology*, 19th Edition. McGraw-Hill Education/Medical, New York.
- Ørsted DD, Nordestgaard BG, Jensen GB, et al (2012). Prostate-specific antigen and long-term prediction of prostate cancer incidence and mortality in the general population. *Eur. Urol.* 61, 865–874.
- Sasaki T, Onishi T, Hoshina A (2011). Nadir PSA level and time to PSA nadir following primary androgen deprivation therapy are the early survival predictors for prostate cancer patients with bone metastasis. *Prostate Cancer Prostatic Dis.* 14, 248–252.
- Sasaki T, Sugimura Y (2018). The importance of time to prostate-specific antigen (PSA) nadir after primary androgen deprivation therapy in hormone-naive prostate cancer patients. *J. Clin. Med.* 7, 1-21.
- Tomioka A, Tanaka N, Yoshikawa M, et al (2014). Nadir PSA level and time to nadir PSA are prognostic factors in patients with metastatic prostate cancer. *BMC Urol.* 14, 1–6.