

THE PROGNOSTIC VALUE OF PROSTATE SPECIFIC ANTIGEN AND TIME TO PSA NADIR IN CASTRATION-RESISTANT PROSTATE CANCER

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ABSTRACT

High mortality rates was often found in castration-resistant prostate cancer (CRPC). Our aim on this research 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 marker 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. There was significant difference found of initial PSA level between survivor (445,7 + 165,6 ng/mL) and non-survivor (200.7 + 144.9 ng/mL). There were no significant differences were also found in PSA nadir level, TTN and TTC between survivor and non-survivor groups. This study revealed that there was association between initial PSA level on 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

1. INTRODUCTION

From all male cancers worldwide, prostate cancer was accounted 15% and became the second most common malignancy in men [1]. The study showed that 1 from 25 men will be most likely to develop prostate cancer in his life time [2]. The gold standard therapy for metastatic prostate cancer was primary androgen deprivation therapy (ADT). However, even after ADT, disease progression may occur in some cases [3]. This progression is known as castrate-resistant prostate cancer (CRPC) [4]. Few is currently understood about the factors influencing the survival of CRPC patients. 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 [5]. Recent studies have reported the utilization of initial PSA level, time to PSA nadir (TTN), PSA nadir level, and time to CRPC (TTC) among other parameters for predicting the prognosis of CRPC patients [6]. Therefore, this study aimed to evaluate PSA level and time to PSA nadir as a prognostic marker for survival in CRPC patients.

2. MATERIAL AND METHODS

This is descriptive study evaluating the characteristic of prostate cancer patients based on the medical record date from Dr. Soetomo General-Academic hospital from January 2013 to December 2020. On treatment prostate cancer patients 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 [7]. Initial PSA level of the patients is defined as the 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 of both times between the surviving and non-surviving groups of patients; otherwise a Mann-Whitney U test would be used. This study has been approved by the ethical committee of Dr. Soetomo General Academic Hospital with the ethical number: 0392/129/XI/2020.

3. RESULTS

3.1 Baseline Characteristics

In this study, 24 patients with CRPC were included. The average age of the samples were 65.54 ± 7.5 years old. The patients' initial PSA was 388.57 ± 596.7 ng/mL. Four patients were performed medical castration, meanwhile 20 patients were performed surgical castration. It took approximately 308.4 ± 293.7 days for the 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.

3.2. 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 $445,7 \pm 165,6$ 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 is a significant difference in initial PSA level between the groups ($p < 0.05$).

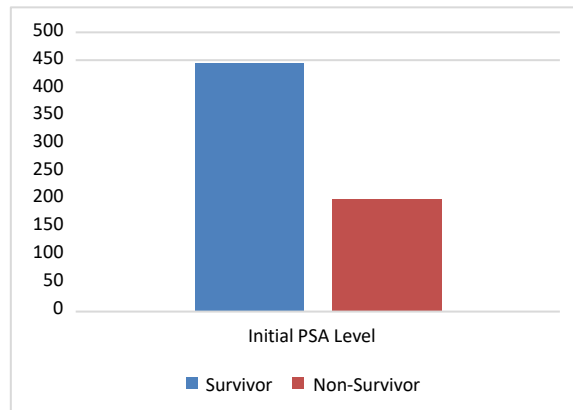


Figure 1. Initial PSA Level Differences between Surviving and Non-surviving Patients

3.3. PSA Nadir and Patient Survival

The average PSA nadir level among patients who survived was $42,8 \pm 131,9$ ng/dL, while the average PSA nadir level among patients who died was $42,7 \pm 48,7$ ng/dL. To compare both groups we used Mann-Whitney test, due to the abnormal data distribution ($p < 0.05$). The difference between both groups in figure 2 was insignificant ($p > 0.05$).

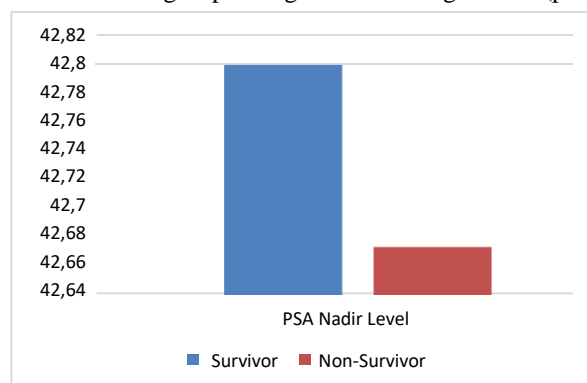


Figure 2. PSA Nadir Level Differences between Surviving and Non-surviving Patients

3.4. TTN and Patient Survival

The average TTN of the surviving patients was $318,5 \pm 176,9$ day, whereas the TTN of patients who died was $284,1 + 510,5$ days. Because of the 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 ($p > 0.05$).

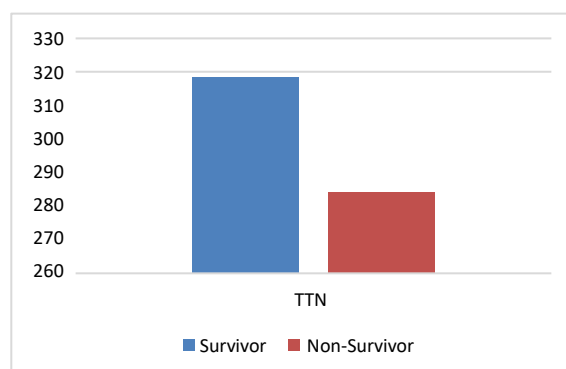


Figure 3. Time to PSA Nadir Level Difference between Surviving and Non-surviving Patients

3.5. TTC and Patient Survival

The average TTC of patients who survived was $598,9 \pm 431,1$ days, while the TTC of patients who did not survive was $445.2 \pm 499,2$ days. Mann-Whitney test showed an insignificant difference between the two groups shown in figure 4 ($p < 0.095$).

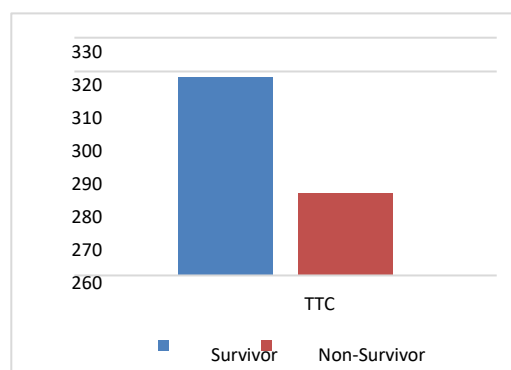


Figure 4. Time to Castration-Resistant Progression between Surviving and Non-surviving Patients

4. DISCUSSION

PSA tests are used on a regular basis to screen prostate cancer and monitor progression [8]. 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 [9]. In this study, there were 24 evaluated patients with CRPC. The majority of patients with high initial PSA level reflects the 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 [10]. A high PSA level also indicates a high androgen receptor activity of prostate cancer cells [11]. Previous studies also highlighted the mortality risk of a high PSA level [12]. On the contrary, the patients with lower PSA levels in this study have a significantly higher mortality rate compared to patients with relatively higher PSA levels ($p < 0.05$). The difference in findings is 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 [13]. The sensitivity and specificity of PSA measurement is low due to several factors affecting PSA level, such as catheterization, post-coitus, benign prostatic enlargement (BPE), and prostate infection [14].

In this study, there is 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 analysing 89 patients conducted between 2000 and 2009 found a significant association between TN and survival. Patients with TTN of less than 9 months had a considerably better overall survival rate than those with TTN of more than 9 months, according to the study. They discovered a PSA nadir level of less than 0.2 ng/mL was associated with a better prognosis [15]. A 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 [9].

The TTC in this study was not associated with the patients' survival rate. These findings are different compared to a previous retrospective study evaluating 287 patients from 1996 to 2009, which reported that TTC is an independent factor to predict overall survival and progression-free survival. The study claimed that TTC less than two years is associated with a worse prognosis [16]. 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 [17]. 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 is due to PSA volume and PSA doubling time difference [11].

In this study, the significant correlation between TTN and TTC highlighted intriguing implications. Previous studies also stated that patients with short TTB are faster to develop castration-resistant [6]. 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 as a result of this reduction. In a terminal proliferation phase, there are two possibilities for prostatic cancer cells, apoptosis or continually producing intracrine testosterone at a certain level of castration [9]. 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 [18].

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

5. CONCLUSION

The initial PSA level differs significantly between survivors and non-survivors, however there are no significant variations in PSA nadir level, time to PSA nadir, or time to CRPC progression. However, there is an association between the time time to PSA nadir and CRPC progression.

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