The influence of transarterial chemoembolization on serum levels of soluble programed cell death protein-1 in advanced hepatocellular carcinoma patients

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Research Article

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Abstract

Aims

To investigate the implications of soluble programmed cell death protein 1 (sPD-1) in hepatocellular carcinoma (HCC) patients treated with transarterial chemoembolization (TACE) and to evaluate the potential value of sPD-1 to guide selection of the optimal time to begin combination therapy of TACE and immune checkpoint inhibitors (ICIs).

Materials and methods

Forty-four HCC patients suitable for TACE and fifty-five healthy volunteers were enrolled in this study. Three milliliters of peripheral venous blood of patients were collected on 1 day before TACE and 3, 7, and 30 days after TACE respectively for assay of sPD-1 using enzyme-linked immunosorbent assay. The associations of the sPD-1 level with the clinical features, outcomes, and the fluctuation of sPD-1 during the treatment were analyzed.

Results

The initial sPD-1 level of patients was significantly higher than that of the control group. Although the initial level of sPD-1 showed a decreasing trend with the increase of BCLC stage, there were no significant differences among patients with different BCLC stages. The sPD-1 level of 3 and 7 days after TACE was significantly lower than the initial level. The sPD-1 level of 30 days after TACE was significantly higher than that of 7 days after TACE and nearly elevated to the initial level before TACE. The level of sPD-1 of CR and PD patients was lower than that of PR, SD patients, but the differences were not significant.

Conclusion

The level of sPD-1 was significantly elevated in patients with HCC but further research is necessary to better understand the value of sPD-1 in onset, development, and prognosis of HCC as a potential biomarker. The decreases in sPD-1 after TACE suggested that TACE could probably reduce immune effector cells as well as weaken immune function, which indicated that the ICIs shouldn't be administered shortly after TACE.

Introduction

Primary liver cancer is the sixth most commonly diagnosed cancer and the fourth most leading cause of cancer deaths globally. Hepatocellular carcinoma (HCC) accounts for 75–95% of all primary liver cancer [1]. Usually, a large part of HCC patients are diagnosed in the intermediate or advanced stages and are not candidates for curative treatments [2]. What is worse, HCC is easy to recur even after curative

treatments [3]. It is crucial to find more effective treatment for advanced stage HCC to prolong patients' survival. Nowadays systemic therapies are normally indicated for those patients at the advanced stage [4], such as tyrosine kinase inhibitors (TKIs), immune checkpoint inhibitors (ICIs) and combination of ICI and TKI.

The ICIs therapy targeting programmed cell death protein-1(PD-1), programmed cell death ligand-1(PD-L1) and cytotoxic T-lymphocyte antigen-4 (CTLA-4) is progressing at rapid pace in HCC [5]. These ICIs have proved their effectiveness in solid and hematologic malignancies and have already been approved for use in patients [6–9]. However, the efficacy of ICIs monotherapy is limited in HCC [10,11]. Results of the ImBrave150 study emphasize the necessity of combined treatments to improve patient outcome [12]. In addition to combination of ICIs and anti-vascular agents, there are many clinical trials to explore the efficacy of other combination strategy, such as regional and systemic therapies and the preliminary results are promising [13]. But the identification of the optimal treatment for a specific patient is still an unanswered question because of lacking the ideal biomarkers.

According to 2022 Edition of China Liver Cancer Staging(CNLC), transarterial chemoembolization (TACE) is the first-line treatment for intermediate and advanced stages of HCC. It has been demonstrated to have a positive effect on improving survivals and the efficacy has been supported by large cohorts [14]. Theoretically, TACE has the pleiotropic effects on modulating the tumoral microenvironment which may be suitable for combination with ICIs. Embolization agents can obstruct the tumor feeding arteries, resulting in ischemic necrosis of the tumor [15]. It is possible that the acute inflammation and the liberation of antigens caused by the necrosis greatly enhance the response of immune system which was previously inhibited. However, the immune response affected by TACE to HCC remain to be fully elucidated.

We hypothesized that TACE could be one potential combination candidate with ICIs in HCC patients. In this study we investigated the influence of TACE on tumoral microenvironment(TME) of HCC by analyzing the changes of the soluble programmed cell death protein 1 (sPD-1) level during the period of TACE.

Materials And Methods

2.1 Patient selection

HCC patients who were candidates of TACE were prospectively recruited between May 2019 and February 2022. The HCC diagnosis was based on the diagnostic criteria outlined in Diagnostic and Treatment Practices for Hepatocellular Carcinoma (2019 edition, People's Republic of China). The eligibility criteria included TACE candidate, no history of other antitumor therapies, measurable lesions, an ECOG score 0–2; and Child–Pugh's level A or B. Exclusion criteria included significant shunt of the hepatic artery-portal vein or hepatic artery-hepatic vein, lack of blood supply to the tumor, widespread metastatic tumor with estimated survival of less than 3 months, Child-Pugh level C, occlusion of the second hepatic hilum or

inferior vena cava, severe anemia, cachexia, or multiple organ failure. Fifty-five healthy volunteers were recruited as control group. The study was approved by the ethics committee of Qilu Hospital of Shandong University. Informed consents were obtained from all the participants.

Clinicopathological characteristics including age, sex, Child-Pugh score, Barcelona clinic liver cancer (BCLC) stage, hepatitis B history, HBV DNA level, alpha-fetoprotein (AFP) level, baseline imaging features such as maximum diameter of tumor, numbers of foci, monolobar or bilobar lesion, and vascular invasion and the curative effect on 30 days after TACE based on mRECIST criteria, were obtained from the electronic medical record.

2.2 Blood Sampling And Spd-1 Measurement

Peripheral venous blood samples were collected from healthy volunteers. The samples of patients were collected on 1 day before TACE and 3, 7, and 30 days after TACE. Blood samples were collected in Vacutainer tubes (BD Biosciences, Franklin Lakes, NJ, USA) containing EDTA, by use of aseptic measures and were centrifuged at 3,000 rpm for 5min at 4℃ to separate the buffy coats and plasma. Additional centrifugation for 10min was performed to produce cell-free plasma, after which the plasma aliquots were immediately frozen at − 80℃ until analysis.

Serum sPD-1 was measured with a commercially available enzyme linked immunosorbent assay (ELISA) Kit(Abcam Plc, Cambridge, UK)according to the recommendation of the manufacturer. Detection limit for ELISA was 9.6pg/ml. Detection range was between 25 to 1600 pg/ml.

2.3 TACE

All the procedures were performed using GE3100 digital angiographic system. Drug eluting beads, Callispheres (Jiangsu Hengrui Medicine Co. Ltd., Jiangsu, China) were used to load doxorubicin and embolize the feeding arteries. The size of the Callispheres was 100–300 or 300–500μm, depending on the tumor size and blood supply. Thirty minutes were required to load doxorubicin with a dosage of 60–80mg prior to the beginning of the TACE procedure. 4F RH catheter was selectively catheterized into superior mesenteric artery, celiac trunk, and common hepatic artery, then an angiography was performed to make it clear the location, size, and feeding arteries of the tumor. After getting all of the information, a microcatheter was superselectively catheterized into the feeding artery. Then, the Callispheres was injected slowly under fluoroscopic monitoring. Subsequent angiography was performed to evaluate the efficacy of embolization.

2.4 Statistical Analysis

Continuous variables were shown as mean ± standard deviation and categorical variables are presented as rates. The sPD-1 levels at each time point were compared using the Wilcoxon signed-rank test or

repeated measure analysis of variance. And that between the different groups were analyzed by the Wilcoxon–Mann–Whitney or Kruskal–Wallis test. Correlations between the sPD-1 and clinical factors were analyzed using the Pearson or Spearman correlation analysis for continuous variables and Pearson's chi-squared test or Fisher's exact test for categorical variables. All statistical tests were two-sided, with significance defined as $P < 0.05$. All data were analyzed using IBM SPSS software version 26.0 (SPSS Inc., Chicago, IL, USA).

Results

Forty-four patients with HCC were prospectively enrolled in this study, including 36 males and 8 females with an average age of 58 (range 40–81) years. Among them, 61.4% (27/44) had an elevated AFP and 54.5% (24/44) had a high level of HBV-DNA (≥ 500 IU/ml). According to Child-Pugh's score, most patients were classified as Child–Pugh score A (31/44, 70.5%) and thirteen of them were classified as Child–Pugh score B (29.5%). The maximum diameter of tumor ranged from 1.3 to 20 cm with an average of 8.86cm. Patients with monolobar tumors accounted for 59.1% (26/44). Portal vein invasion was detected in 52.3% of the cases (23/44). Nine patients were classified as BCLC stage A (20.4%). Eight patients were classified as BCLC stage B (18.2%). Twenty-seven patients were classified as BCLC C (61.4%). The detailed patient characteristics are shown in Table 1.

Table 1
clinical characteristics of HCC patients

	No.	Mean sPD-1	P Value
Sex			0.421
Male	36	279.37 ± 191.94	
Female	8	339.73 ± 180.35	
Age			0.798
≥ 60yrs	15	280.00 ± 162.35	
60yrs	29	295.70 ± 204.38	
BCLC stage			0.551
A stage	9	350.74 ± 145.30	
B stage	8	291.46 ± 136.55	0.909
C stage	27	269.88 ± 214.60	
Portal venous invasion	23	293.53 ± 222.75	
Yes	21	286.86 ± 149.82	
No			
Child-Pugh score			0.846
A	31	286.70 ± 182.52	
B	13	299.03 ± 212.17	
AFP (ng/ml)			0.405
≤ 20	17	320.72 ± 156.27	
20	27	271.22 ± 207.98	
HBV-DNA(IU/ml)			0.574
500	20	308.18 ± 149.87	
≥ 500	24	275.48 ± 218.95	

	No.	Mean sPD-1	P Value
Tumor location	26	291.62 ± 182.31	0.958
Monolobar	18	288.51 ± 204.35	0.191
Bilobar	9	364.44 ± 184.78	
Up to 7 criteria	35	271.29 ± 188.32	
≤ 7			
7			

3.1 Comparison of sPD-1 level between experimental and control group and association of initial sPD-1 levels with clinical factors

The sPD-1 level of 55 healthy people was 221.26 ± 94.35pg/ml. That of the patients was 290.34 ± 189.31pg/ml, which was significantly higher than the control group (P = 0.031; Fig. 1). Although the level of sPD-1 showed a decreasing trend with the increasing of BCLC stage, there were no significant difference (BCLC stage A, B, C: 350.74 ± 145.30, 291.46 ± 136.55, 269.88 ± 214.60, P = 0.551; Fig. 2). There were no other significant relationships between the sPD-1 level and other factors, including sex, age, Child-Pugh's score, portal vein invasion, up to seven criteria, HBV-DNA, and AFP level.

3.2 Comparative analysis between the level of sPD-1 pre-TACE and post-TACE in patients with HCC

The fluctuation of sPD-1 level of seven HCC patients during the treatment period of TACE was explored. The sPD-1 level of 3 days after TACE was 112.48 ± 91.91pg/ml, which was significantly lower than that before TACE (P = 0.032, Fig. 3). The sPD-1 level of 7 days after TACE was 123.32 ± 100.96pg/ml, which showed a slightly increasing compared to that of 3 days after TACE but still lower than the initial level of sPD-1. The differences were not significant (P = 0.541; P = 0.059). Then the level of sPD-1 showed an increasing trend and on 30 days after TACE the sPD-1 level was 174.45 ± 116.35pg/ml, which was higher than that of 7 days after TACE significantly(P = 0.002) and nearly recovered to the level before TACE (P = 0.920).

In addition, the influence on sPD-1 level of the embolic beads with different diameters was also analyzed. There were no significant differences between 100–300μm and 300–500μm drug eluting beads in the data 3 days after TACE (260.24 ± 167.78 vs.253.70 ± 181.15, P = 0.914). However, concerning about 7 days after TACE, the result had significant differences (100–300μm vs. 300–500μm: 310.86 ± 127.91 vs. 158.66 ± 107.06, P = 0.017).

The tumoral response to TACE in 1 month of 35 patients was analyzed according to mRECIST criteria. There were 3 CR, 8 PR, 20 SD, and 4 PD patients. Interestingly, the sPD-1 level of 1 day before TACE in CR and PD patients was lower than that of PR, SD patients, but the differences were not significant (P = 0.707; Figs. 4).

Discussion

HCC is one of the leading causes of tumor deaths worldwide. Despite systemic treatments which have showed promising effect in other tumors are wildly used in patients of the advanced HCC, a substantial part of patients responds poorly to these treatments. The combination of local and systemic therapy may have tremendous talent to improve the patient's outcome. Although, there are several ongoing clinical trials evaluating the efficacy of such kind of combination therapy, only a few have investigated the potential impact of TACE on HCC immune profiles from the point of view of soluble molecule, such as the expression of sPD-L1 and sPD-1, especially fewer studies on the early changes of immune microenvironment after TACE [16–18]. Interestingly, we observed a significantly lower sPD-1 expression in 3 days after TACE.Activation of PD-1/PD-L1 pathway was one of the most critical mechanisms of tumor evasion, inhibiting T-cell proliferation, inducing T-cell exhaustion, and enhancing the activity of regulatory T cells [19]. PD-1/PD-L1 pathway molecules have two forms: membranous PD1/PD-L1 (mPD-1/mPD-L1) and soluble PD-1/PD-L1 (sPD-1/sPD-L1). All these molecules play important roles in tumor immune response but the specific roles of mPD-1/mPD-L1 and sPD-1/sPD-L1 in tumor environment are different [20,21]. Molecules on cell membrane mediate costimulatory signals through direct receptor–ligand interactions; on the other hand, soluble molecules not only affect near-end cells, but also bind receptors on the far-end cell surface. These features make them participate in occurrence and development of diseases, with a far more important role than membranous molecules [22]. Recent findings have shown that expression of membranous molecules was associated with tumor staging, prognosis, and could be potential biomarker to guide ICIs therapy [23,24]. But in clinical practice, most of the patients with HCC are in advanced stage when being diagnosed and they have little chance to receive radical therapy, such as RFA, surgical resection, and liver transplantation. So, it is difficult to acquire the tumor tissue for analyzing mPD-1/mPD-L1 expression. On the contrary, it is easier and less traumatic to test sPD-1/sPD-L1 expression in the peripheral blood. Furthermore, we could collect peripheral blood repeatedly to dynamically monitor the changing of sPD-1/sPD-L1 expression during the whole treatment procedure.

Our study showed that sPD-1 level was significantly elevated in HCC patients compared to control group. These results are consistent with the previous findings showing that sPD-1 is associated with risks of HCC [25]. Although our study showed that the sPD-1 level decreased with the increasing of BCLC stage, the results showed no significant differences among them. And there were no significant relationships between sPD-1 level and portal vein invasion, up to seven criteria. Further research is necessary to explore the value of sPD-1 in onset, development, and prognosis of HCC as a potential biomarker.

The embolization of tumoral feeding artery and chemotherapeutic drugs used in TACE could cause necrosis and local inflammation of the tumor. The disruption of tumor cells could lead to the release of tumor antigens, which could be taken up by antigen-presenting cells, and induce tumor-associated antigen-specific responses [26,27], which was thought to be a positive influence on ICIs therapy. However, TACE can induce sudden hypoxia in tumor microenvironment and produce numerous hypoxia-related factors, which can influence components of cancer-immunity in a short time [17]. There are few studies that investigate the early influence of TACE on sPD-1 in advanced HCC patients. We found that the sPD-1

levels 3 and 7 days after TACE were both much lower than that before TACE. However, the sPD-1 level of 30 days after TACE was significantly higher than that 7 days after TACE and nearly elevated to the initial level before TACE. As we all know, PD-1 are mainly expressed in activated CD8+, CD4 + lymphocytes and NK cells [28,29]. sPD-1 could be produced from the cleavage of their extracellular domains or from alternative splicing of the pre-mRNA coding for the membrane form [30], it could partially reflect the expression of mPD-1. So our finding suggests that TACE could decrease the level of immune effector cells in a short period of time. Previous studies showed that 1–2 weeks after Gelatin Sponge Microparticles TACE(GSMs-TACE), the CD8 + T cells were significantly lower than that before the GSMs-TACE [31] and Doxorubicin which is the most used chemotherapy drugs in TACE can induce immunogenic cell death [32]. So the low level of immune effector cells suggests that at least within 1 week after TACE is not a suitable for ICIs therapy. Some studies also found that sPD-1 could be used as a blockade of PD-1/PD-L1 interactions to restore the inhibited immune response [33,34]. While the decreasing of sPD-1 1 week after TACE may weaken this effect. So it is another clue that suggests it may be less effective to begin the administration of ICIs early after TACE.

Until now, many studies have explored the combination therapy of TACE and ICIs [27]. However, there are still many problems need to be solved in this field. For example, the mechanism how TACE influence the immunological microenvironment has not been elucidated clearly and the best time to begin the immunotherapy needs further research, and which kind of TACE is a better choice to combine with immunotherapy also requires further exploration.

As far as we know, this is the first study showing that TACE could induce the decreasing of sPD-1 expression in HCC patients. However, there were obvious limitations in the study. First, this study analyzed a limited sample size. Second, the blood sampling time points were not enough, which made it impossible to observe the changing of sPD-1 between 7 and 30 days after TACE.In conclusion, sPD-1 level was significantly elevated in patients with HCC but further research is necessary to explore the value of sPD-1 in onset, development, and prognosis of HCC as a potential biomarker. TACE could probably reduce immune effector cells as well as weaken immune function, which suggests that the ICIs shouldn’t be administrated shortly after TACE.

Declarations

Acknowledgement

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Conflict of interest: none

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Figures

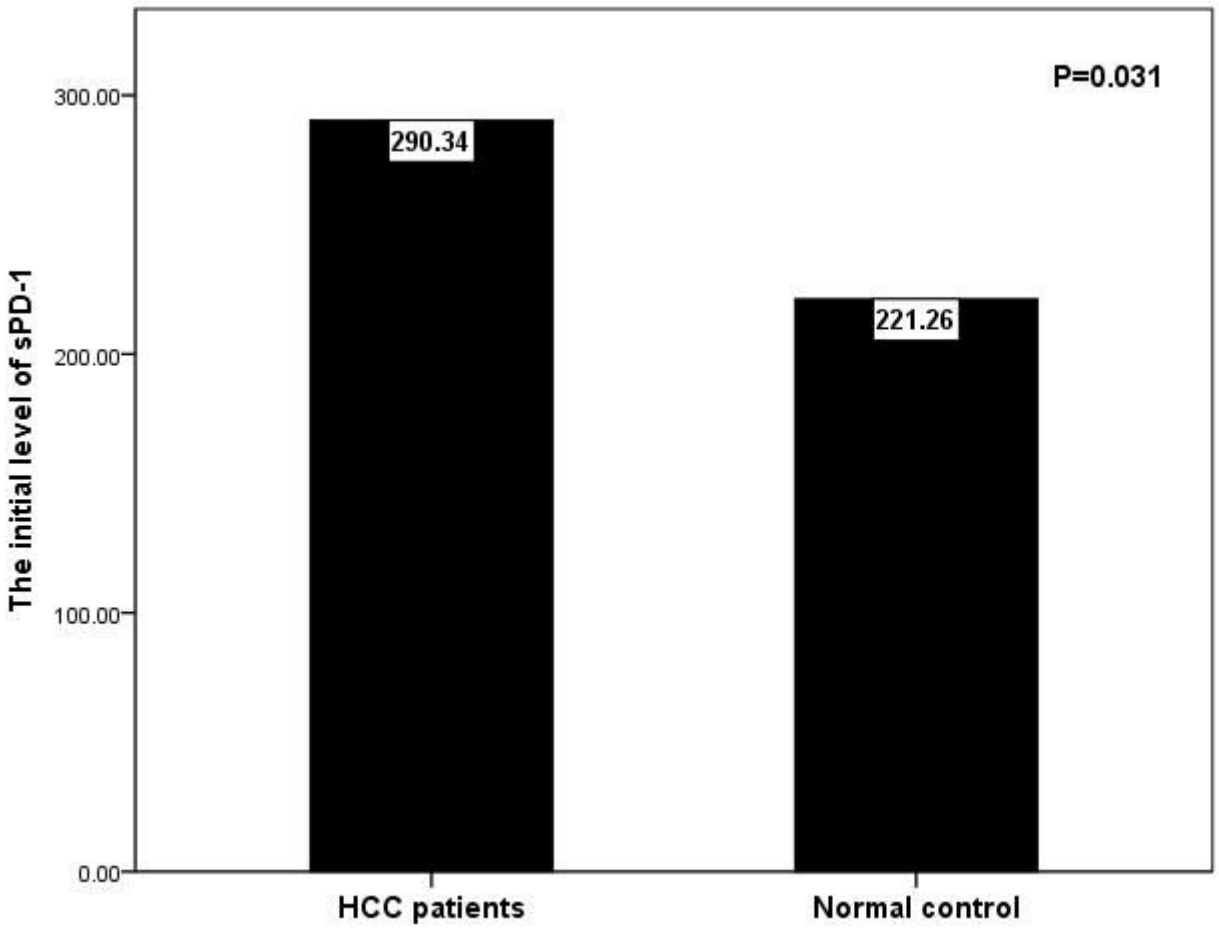

Figure 1

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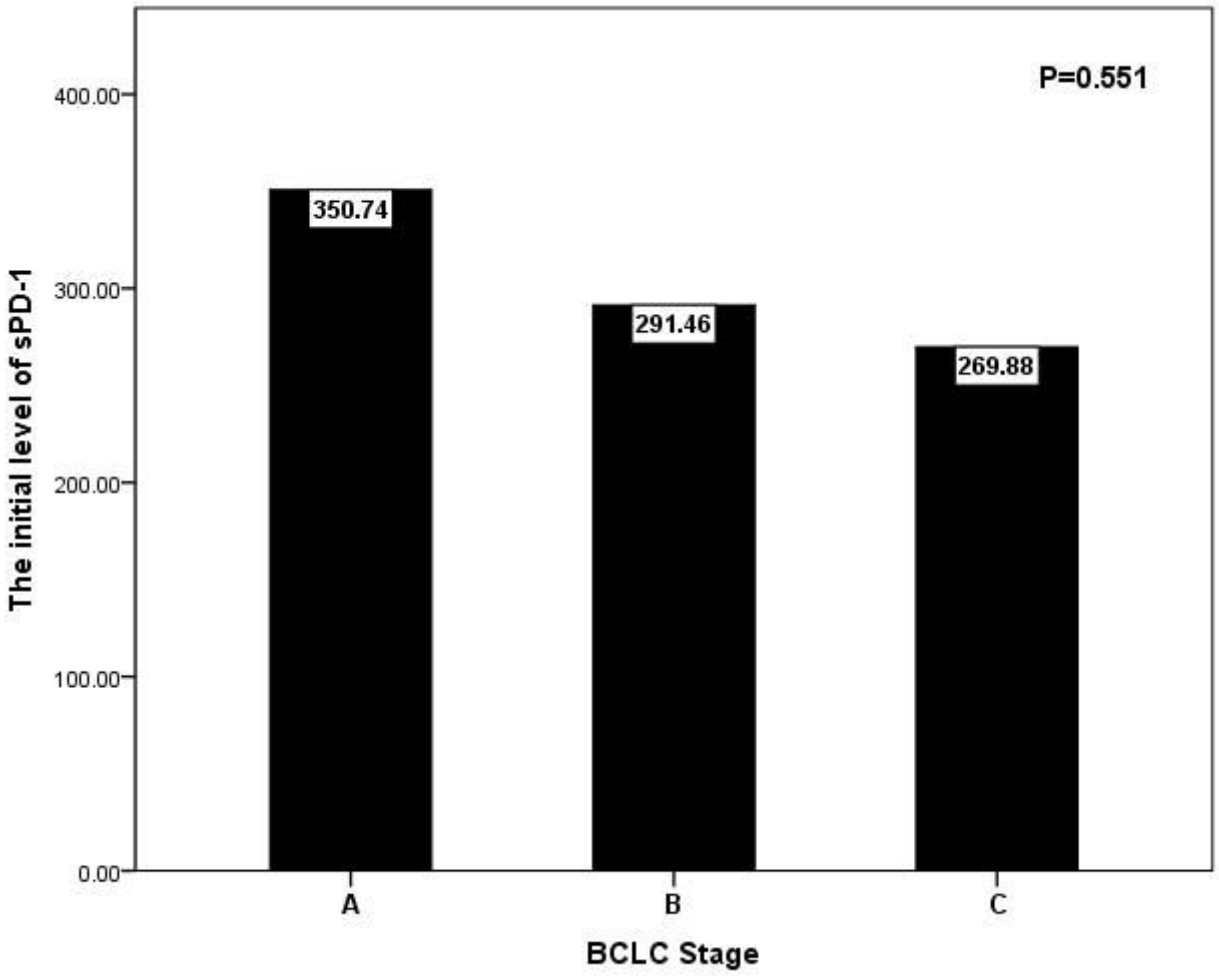

Figure 2

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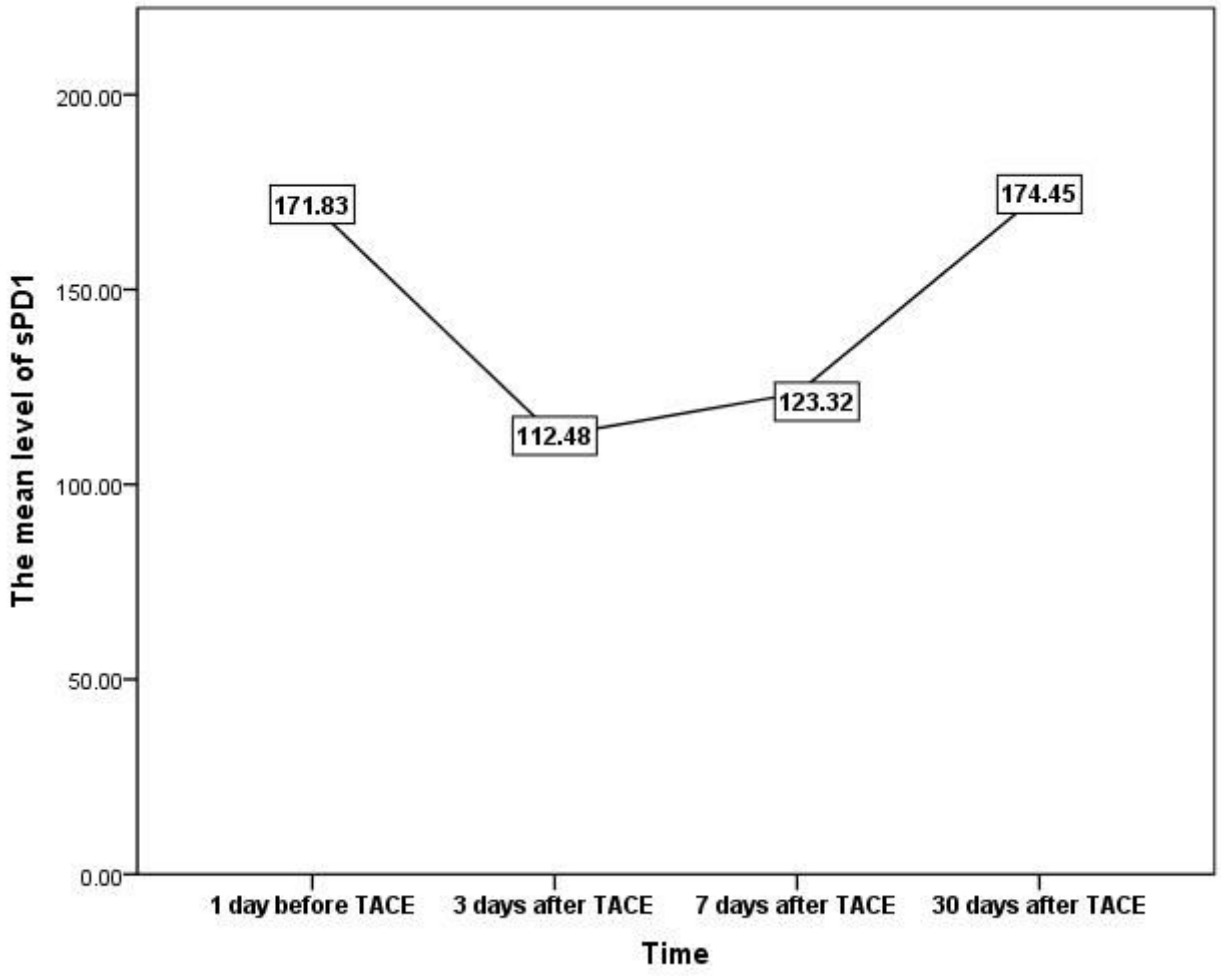

Figure 3

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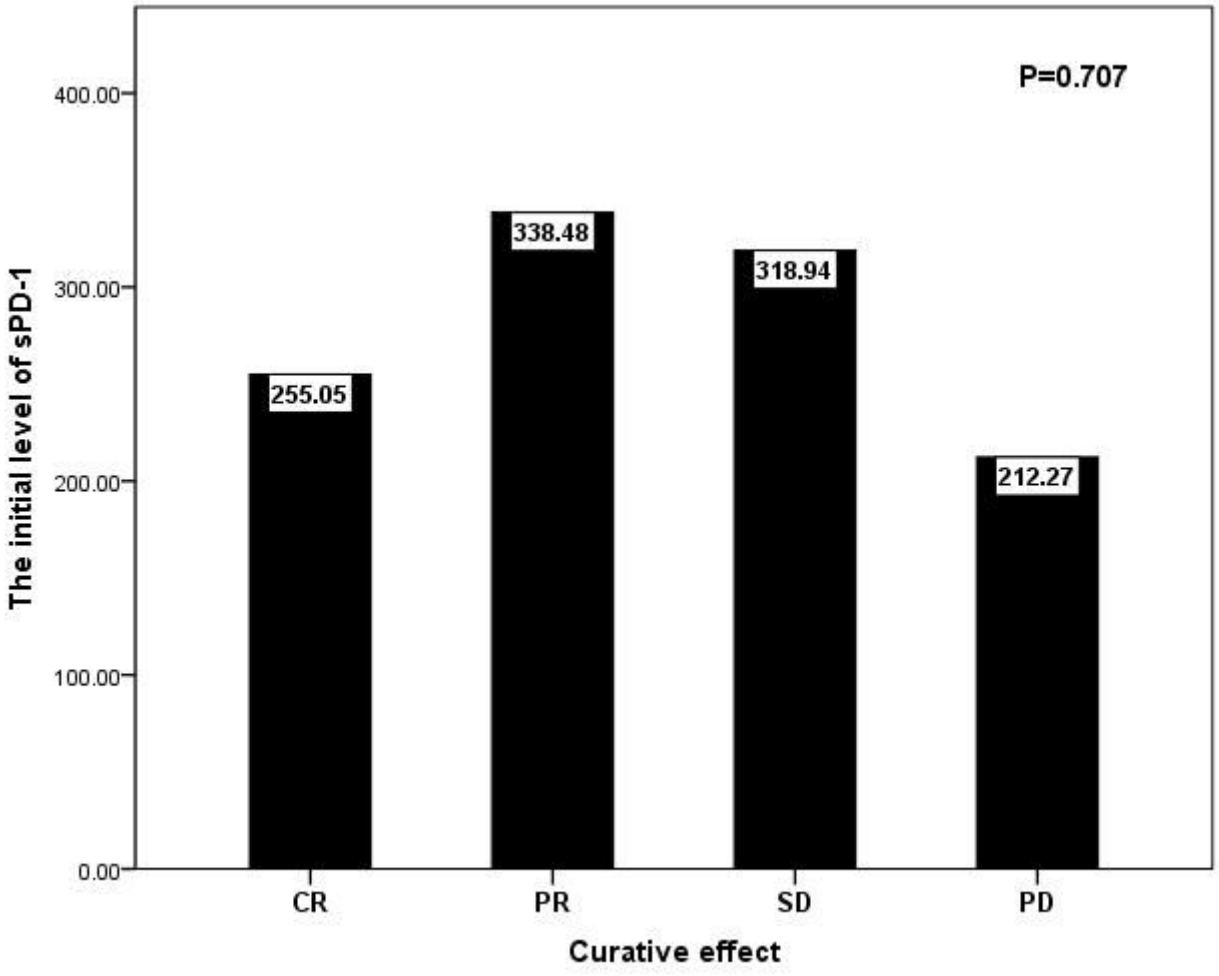

Figure 4

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