HALP Score and Albumin Levels in Men with Prostate Cancer and Benign Prostate Hyperplasia

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Abstract

Aims: To evaluate the diagnostic significance of the novel index combining preoperative hemoglobin, albumin levels, lymphocyte and platelet counts (HALP) in prostate cancer (PCa) patients. Methods: Between January 1, 2015 to December 31, 2018 at the Hitit University Erol Olçok Education and Research Hospital 225 patients who had undergone transrectal ultrasound guided prostate biopsy or prostate surgery were analyzed retrospectively. A total of patients; 155 had benign prostate hyperplasia (group 1) and 70 had PCa (group 2). The preoperative serum levels of hemoglobin, albumin, lymphocyte counts, and platelet counts were recorded. The HALP scores and the sub parameters of this index for each of the two groups were compared. Results: The total Prostate Specific Antigen (PSA), albumin and lymphocyte differences between the groups were statistically significant (p=0.0002, p=0.0001, p= 0.005). The median value of HALP scores in Group 1 and 2 were 49.43 and 51.2 respectively, and this was not statistically significant between groups (p=0.737). The HALP score had the least Area Under Curve (AUC) value compared to the others (0.514). the AUC of Albumin was larger than PSA for diagnostic efficacy in PCa patients (0.696-0.656). However, albumin levels were statistically significant compared to platelet count and the HALP score (p=0.0033, p=0.0068), except PSA and lymphocyte (p=0.4580, p=0.1717). Conclusion:Further prospective clinical studies that include more patients from multiple centers are needed to show the diagnostic role of the HALP score and its compounds on the patients with PCa.

Introduction

The prevalence of all cancer types, including prostate cancer (PCa), have increased with the more extensive usage of the cancer screening program. PCa has been the second most observed cancer type, while it is the fifth most common cause of death in men. 1.3 million new cases were diagnosed in the world in 2018.[1] After the discovery of the prostate-specific antigen (PSA), most of the patients with PCa have been detected at an early stage. However, a digital rectal examination (DRE) or high level of PSA may be insufficient in finding the index patient. A false positive PSA level in patients with benign prostatic hyperplasia (BPH), and/or prostatitis, result in an unnecessary biopsy. The multiparametric magnetic resonance imaging (mpMRI) with a standardized reporting system (Prostate Imaging Reporting and Data System [PI-RADS] has begun being used as a clinical parameter for PCa diagnosis.[2,3] Despite these improvements on the technology, the results are still controversial, and the total cost of these tests could still be a large burden on the economy of the health system. Therefore, a new diagnostic method or scoring system, which is readily available in clinical practice, is still needed for the correct decision of prostate biopsy.

The initiation, progression, and metastasis of cancer does not only depend on the type of tumor cells, but systemic inflammation and nutritional status play important roles in the development of the cancer.[4-6] Recent studies have identified a new inflammation index called HALP, a combination of hemoglobin, albumin,

lymphocytes, and platelets, which could show the status of both the immune system and the nutrition status of the patient. This novel score system has proven to be a good prognostic indicator in gastric, colorectal, renal, bladder, and prostate cancers.[7-11]However, there have been no studies which have been performed an assessment on the HALP score as a diagnostic marker of PCa. In this study we aimed to investigate if there was any statistically significant difference of the HALP score between patients with PCa or BPH.

Materials and Methods

The database of 225 patients who had undergone transrectal ultrasound guided prostate biopsy or prostate surgery, performed between January 1, 2015 to December 31, 2018 at the Hitit University Erol Olçok Education and Research Hospital, was analyzed retrospectively. A local ethics committee confirmed our study, and all patients signed consent forms. Our study also complied with the principles of the Declaration of Helsinki.

PSA, free PSA (fPSA), hemoglobin, albumin, lymphocyte, and platelet levels were measured before the prostate biopsy or transurethral resection. Prostate biopsies were performed by an 18-gauge tru-cut biopsy needle under local anesthesia at twelve cores, while transurethral prostate resection was performed under general or spinal anesthesia using bipolar system.

Patients with the level of PSA above 20 ng/ml, with a history of acute or chronic prostatitis, dutasteride therapy, urethral instrumentation in the last month leading up to the biopsy, a pathological report of high grade prostatic intraepithelial neoplasia, and/or atypical small acinar proliferation, were excluded from the study.

The HALP score was calculated as hemoglobin level (g/L) $\times$ albumin level (g/L) $\times$ lymphocyte (/L) / platelet count (/L) (17). The patients were then divided into two groups; Group 1 had benign prostate hyperplasia (BPH), and Group 2 consisted of patients with prostate cancer (PCa).

The statistical analyses were performed using MedCalc Statistical Software demo version 16.2.0 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016). The data of the groups were compared with the independent sample t test, expressed as mean $\pm$ standard error, and $p < 0.05$ was considered as statistically significant. The receiver operating characteristic (ROC) curve analysis was performed to compare the ability of PSA, hemoglobin, albumin level, lymphocyte, platelet count and the HALP score to identify prostate cancer patients.

Results

Of the total of 225 patients included in the study, 155 had BPH and 70 had PCa with pathology confirmation . The mean age of the patients was 66.54+ 8.19 years, and 67.8+ 6.85 years in Group 1 and Group 2, respectively. As seen in Table 1, the mean total PSA levels of the patients in Group 1 was 6.37+ 3.98 and Group 2 was 8.62+ 4.25. The total PSA, albumin, and lymphocyte differences between the groups were statistically significant (p=0.0002, p=0.0001, p= 0.005). The median value of the HALP scores in Group 1 and 2 were 49.43 and 51.2 respectively, and this was not statistically significant between two groups (p=0.737).

The HALP score had the least Area Under Curve (AUC) value compared to the others (0.514). Surprisingly, the AUC of Albumin was larger than PSA for diagnostic efficacy in PCa patients (0.696-0.656) (Figure 1), but this was not statistically significant (p=0.4580) (Table 2).

When comparing the different parameters with each other with the ROC analysis; the PSA levels were not statistically significant to hemoglobin, albumin level, lymphocyte, platelet count, or the HALP score. However, the albumin levels were statistically significant compared to the platelet count and HALP score (p=0.0033, p=0.0068), except PSA and lymphocyte (p=0.4580, p=0.1717) (Table 2).

Discussion

PSA is a glycoprotein, from the family of human kallikrein proteins and encoded by the KLK3 gene. PSA was approved by the FDA in 1986 and a high level of PSA together with positive findings of DRE have

been strongly linked as diagnostic markers for PCa.[12] Despite being organ-specific, PSA is not cancer-specific. PSA levels might be increased in some non-malignant diseases such as benign enlargement and prostatitis.[13] Furthermore, much laboratory data, which could easily be obtained, has not shown PSA as having a predictive value in the diagnosis of PCa. Recently, prostate cancer antigen 3 (PCA 3), a urine-based assay, was approved by the FDA. PCA3 can prevent unnecessary prostate biopsies but predicting the presence of PCa still lacks clinical validation.[13] The Mi-Prostate score (MiPS) screens for the presence of the PCA3 gene and an RNA biomarker has been found to be more specific than PSA alone, but it needs to be validated.[14] Urokinase plasminogen activation (uPA and uPAR) is involved in PCa progression, however it seems to be helpful in predicting poor pathologic characteristics rather than diagnosis of PCa.[15] There have also been a number of studies about the diagnostic role of the platelet-to-lymphocyte ratio (PLR)[16-19]; the neutrophil-to-lymphocyte ratio (NLR)[20] and the combined use of PSA, mean platelet volume (MPV), and platelet distribution width (PDW).[21]These studies found these values to be associated with a poor prognosis in PCa patients.

In this study, we investigated a novel index, the HALP score, which consists of the hemoglobin, albumin, lymphocytes, and platelets levels, to predict PCa. As known, while hemoglobin and albumin levels are associated with the nutrition status of the body, lymphocytes and platelets are related to the immune system. This score system has been usually used to predict the prognosis of some types of cancers by using the character of showing the two main roles (inflammation and nutrition status) in the prognosis of cancer. Chen et al. firstly described this score system to predict the prognosis of gastric cancer.[10] Then it was used in esophageal squamous cell carcinoma [22], renal cell carcinoma[8], bladder cancer [9], prostate cancer[7], lung cancer [23], colorectal cancer[11] ,and pancreatic cancer [24] for predicingt the prognosis of the above-mentioned cancer types in the literature. Guo et al. showed that the HALP score was an independent prognostic factor for PSA-progression free survival in patients with metastatic PCa or oligometastatic PCa after cytoreductive radical prostatectomy. Guo et al. also reported that NLR and PLR had no statistically significant association and their predictive ability was lower than the HALP score.(7) However, there were no reports that the HALP score has any role in diagnosing any type of cancer.

In our study, the mean HALP scores of patients with BPH and PCa were 49.43 and 51.2 points, respectively. However, this difference was not statistically significance (p= 0.737). Guo et al. mentioned the importance of a low HALP score and its association with a poor clinical outcome. In comparison to their work, we found that the HALP scores were higher in Group 2. After observing the low diagnostic efficacy of the HALP score in prostate cancer, we examined each of the components of the scoring system to see if they would predict PCa separately.

There was no difference in hemoglobin or platelet levels between the two groups (Table 1). No significant difference in hemoglobin level between the groups was an expected result, because the PCa patients in our study were almost all in the early stage of cancer and cancer related anemia is associated with advanced stages of cancer, due to the chronic blood loss, iron deficiency, and vitamin B12 or folate nutritional deficiency.(8, 25) It was shown that natural killer cells attack the tumor cells to defend the vessels, but these tumor cells are protected from natural killer cells by platelets.[22, 26] But, there was no difference between the two groups in our study in the hemoglobin levels, because the patients with PCa were in the early stages of cancer, so no tumor growth or metastasis would be evidence by high platelet levels.

Lymphocyte levels were higher in the PCa group, and this was statistically significant. Lymphocytes have a role on inhibiting the tumor cells proliferation, invasion, or metastasis[8, 27] while a low level of lymphocytes is common in patients with advanced cancer. The main significant difference in the level of lymphocytes between the two groups in our study could be that the cancer was in an initial state and the immune system might be trying to defend against the tumor cells; so the level of lymphocytes were higher in group 2.

In our study the most interesting finding was the albumin level; this was significantly lower in the PCa group. The albumin level is accepted as the indicator of nutrition status and has been shown to be a valuable prognostic factor in cancer patients.[23, 28] The nutrition status would not be affected at the beginning of the cancer, and the activation of the mechanism is due to the inflammatory mediators increasing the

transcapillary escape. Another mechanism is IL-6, TNF and acute phase reactants may lead to decreased production of albumin.[29] Sejima et al. suggested that preoperative hypoalbuminemia may lead to the spread of localized prostate cancer and be associated with biochemical recurrence.[29] The ROC curve analysis in our study demonstrated a higher diagnostic efficacy of albumin to PSA, but this was not statistically significant. Albumin levels were statistically significant compared to platelet count and the HALP score, except PSA and lymphocyte as we mentioned above (Table 2). We believed that albumin levels are important in prostate cancer, as in many other cancers. Overall, the effect of testosterone on PCa is still unclear. We know that androgens can promote PCa in animal models and androgen deprivation therapy (ADT) is beneficial in PCa patients. However, after a large number of mostly retrospective studies, there remains no clear association with higher endogenous testosterone and the development or severity of PCa.(30) On the other hand, free testosterone may have an impact on PCa with its active effect on the synthesis of dihydrotestosterone in prostate tissue.[29]Serum albumin decrease reduces the level of albumin–binding testosterone and ultimately an increase in the level of free testosterone. This point may be the critical relationship between lower albumin levels and PCa. Sejima et al. also reported pre–operative low serum albumin levels as a predictor for biochemical recurrence and that lymph node metastasis may be related to increased free testosterone contributions.[29]

To our knowledge, this is the first study to assess the diagnostic value of HALP levels in patients with PCa. We acknowledge that there were some limitations in the present study. The retrospective design from single center, and the small number of patients are the main limitations.

Conclusion

We could find no diagnostic role of the HALP index which combines the factors of malnutrition (hemoglobin and albumin) with factors of the inflammatory response (counts of lymphocytes and platelets). However, albumin and lymphocytes counts were significant differences in the patients with PCa and BPH. To date, the possible diagnostic role in PCa of these two parameters have been demonstrated for the first time in the literature. With the heterogeneous character of the PCa, none of the biomarkers, screening tests or scoring systems, can provide diagnostic value but by combining prostate imaging and tissue sampling they are one piece of the whole structure. Further prospective clinical studies that include more patients from multiple centers to show the diagnostic role of the HALP score and its components on patients with PCa are needed.

Conflict of interest: Authors declared no conflict of interest

Authors' contribution:

SC: Planned and designed the study, performed the satistical analysis

MS,CA: Collected and analysed data, co-wrote the manuscript.

CK: Wrote and revised the manuscript critically.

All authors approved the final version of the article for submission.

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Legends:

Table-1: The patient characteristics and laboratory results

Table-2: Comparision of the parameters for ROC analysis

Figure-1: The ROC analysis of the parameters

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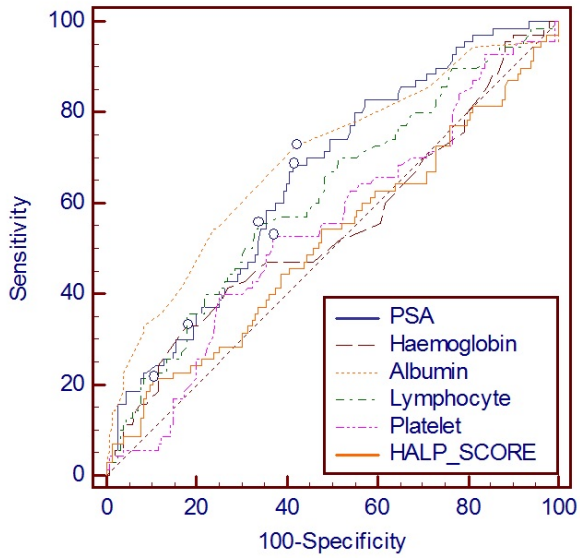

Variable	AUC	SE	95% CI
PSA	0,656	0,0381	0,590 to 0,718
Haemoglobin	0,544	0,0437	0,477 to 0,611
Albumin	0,696	0,0393	0,631 to 0,755
Lymphocyte	0,616	0,0409	0,549 to 0,680
Platelet	0,545	0,0418	0,477 to 0,611
HALP SCORE	0,514	0,0434	0,447 to 0,581

Figure-1: The ROC analysis of the parameters