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Comparative Usefulness of High-frequency Doppler Ultrasonography, Serum PSA Density, and Free to Total Serum PSA Ratio in the Prediction of Prostate Cancer

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Abstract

Objective: In this study, we tried to assess whether power Doppler ultrasonography (PDU) evaluation along with transrectal ultrasound (TRUS) has an additional benefit in the diagnosis of prostate cancer in patients with prostate-specific antigen (PSA) levels of 4-10 ng/mL, when combined with the other methods proposed for this range of PSA.

Materials and Methods: Fifty-six patients with PSA values of 4-10 ng/mL were included in the study. Digital rectal examinations, evaluation of total and free PSA, and PDU assessments were done simultaneously with TRUS and eight-core systematic prostate biopsies. Along with the latter, additional biopsies were taken from the suspicious areas detected on PDU. The free/total PSA ratios, PSA density values, TRUS, PDU findings, and biopsy results of 56 patients were recorded and evaluated.

Results: Specificity and positive predictive values in detecting prostate cancer in patients with PSA range of 4-10 ng/mL, calculated using the criteria of free/total PSA values <15%, PSA density values >15%, and PDU findings, were 94.87% and 75%, respectively. These values were significantly higher than those of 89.75% and 69.73%, respectively, defined for the criteria of free/total PSA values <15% and PSA density values >15%.

Conclusion: The results of this study highlighted that PDU may be useful to detect prostate cancer, and decrease the number of unnecessary biopsy recommendations in patients with PSA values of 4-10 ng/mL, when used in combination with free/total PSA ratio and PSA density.

Keywords: Power Doppler ultrasonography, prostate cancer, prostate specisific antigen, PSA density

Introduction

Worldwide, prostate cancer is the second most common malignancy seen in men, and the fifth most common cause for their mortality; responsible for 3.8% of all cancer related deaths (1,2).

It develops more gradually than the other cancer types. In localized cancers with Gleason grade 2-4, the risk of cancer-related mortality within 15 years is around 4%-7% percent and biochemical recurrence free survival for Gleason scores < =6 is 96.6% for six years (3,4).

However, in non-localized, advanced-staged prostate cancers, mortality rates rise up to 70%-80%, and overall survival rates range from 26% to 30% at 5 years (5). These findings show that early diagnosis is important in prostate cancer.

The definitive diagnosis of prostate cancer is made by histopathological examination (6). Biopsy is indicated based on the results of prostate-specific antigen (PSA) test, digital rectal examination (DRE), and transrectal ultrasound (TRUS) (7). Among these, the most frequently used and useful method is PSA measurement (8,9,10,11,12). Since the chance of a malignancy is 25% when DRE reveals an abnormality, even with PSA levels <4 ng/mL, it is absolutely necessary to perform a prostate biopsy (13,14).

PSA measurements and DRE are recommended for the risk adopted prostate cancer screening along with counseling the patients on the potential risks and benefits (15).

The main problem in prostate cancer screening is experienced in patients whose PSA levels are between 4 and 10 ng/mL (16). In

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this range; defined as the gray zone, the specificity of PSA value alone is very low and the financial and psychosocial costs of a prostate biopsy are very high (12). Although, many methods have been developed to avoid unnecessary biopsies [free PSA measurement, free/total PSA ratio (f/t PSA)]; PSA density (PSAD), PSA velocity, etc; a satisfactory method that increases the diagnostic specificity, prevents unnecessary biopsies, and ensures the detection of greater number of cases with clinical cancer, is not available yet (17,18).

Although, increased blood flow in cancerous tissue is also observed in prostate examinations performed with color Doppler ultrasound, this method has not been found to be specific because increased blood flow can also be seen in prostatitis and benign prostatic hyperplasia (BPH). In recent years, high-frequency color Doppler ultrasound [power Doppler ultrasound - (PDU)] has been used with to increase the diagnostic specificity. PDU has shown to be more sensitive than the color Doppler US and less dependent on the probe in showing blood flow, number of vessels, and their distribution (16).

In this study, we tried to determine whether the TRUS-guided PDU examination performed in patients with PSA levels between 4 and 10 ng/mL will provide additional benefits when compared with other auxiliary methods used to increase the specificity of the PSA test.

Materials and Methods

Fifty-six patients who reported to our clinic with total PSA values between 4 and 10 ng/mL, as detected during the prostate cancer screening tests, also underwent free PSA evaluation (fPSA), DRE, TRUS-guided biopsy, and PDU examinations. Patients were informed about the study and a written informed consent were signed by the patients. PSA and fPSA values were determined using the Hybritech Tandem-R® test kit. TRUS and PDU findings were evaluated by the same radiologist in our radiology department by considering the presence (+) or absence (-) of malignancy that was based on the increased neo-vascularity of the tumor tissue seen in the color map generated by the amplitude or power of Doppler signal, specific to this Doppler ultrasonography (USG) method.

Eight quadrant TRUS-guided biopsies were performed in all patients by the radiologist and an additional biopsy specimen was obtained from a suspicious lesion seen in the PDU. Prostate sizes of the patients and number of biopsy quadrants were convenient with the least number of core biopsies recommended by The European Association of Urology (EAU) guidelines for these prostate sizes (15,19).

During this process, Toshiba power 7000® ultrasound device and 6.5 mHz endocavitary probe was used. All biopsies were evaluated by the same pathologist at our hospital. The f/t PSA ratios and PSA densities of the patients were calculated and recorded.

Statistical Analyses

SPSS (Statistical Package for Social Sciences) for Windows 10.0 program was used for statistical analysis of the study data. While evaluating the study data, Mc Nemar test was used to compare the qualitative data in addition to the descriptive statistical methods (mean, standard deviation, frequency). Results were evaluated within 95% confidence interval and the level of statistical significance was set at $p<0.05$.

Results

In 16 of 56 patients with a mean age of 68±15 (range: 51-88), biopsy results revealed the presence of prostate adenocarcinoma.

Prostate cancer (+) patients had Gleason scores of 6 (3+3, n=6), 7 (3+4, n=7), 9 (4+5, n=1), and 7 (4+3, n=2). When patients were evaluated according to TRUS findings, 10 of 15 patients with suspicious findings in TRUS contracted cancer. Of the remaining 41 patients with negative TRUS findings, 6 had cancer. According to these values, the positive predictive value of this test in detecting prostate cancer was 66%, while its sensitivity and specificity were calculated as 62% and 87%, respectively (Figure 1: Sensitivity, specificity, and positive predictive values of TRUS).

In PSAD evaluation, calculated according to the ratio of patients' PSA values to prostate volumes detected in TRUS, 13 of 31 patients with PSA densities (PSADs) >0.15 ng/mL and 3 of 25 patients with PSA densities <0.15 ng/mL contracted cancer, respectively. Per these values, the positive predictive value of this test in detecting prostate cancer was 41%; while its sensitivity and specificity were 81% and 55%, respectively (Figure 2: PSAD's sensitivity, specificity, and positive predictive value).

A cut-off value of 15% was used for f/t PSA ratio. While, cancer was detected in 11 of 18 patients below this value, only 6 of 38 patients with a ratio above this value had cancer. The positive predictive value, sensitivity, and specificity of f/t PSA ratio were 61%, 62%, and 82%, respectively (Figure 3: Sensitivity, specificity, and positive predictive value of f/t PSA ratio).

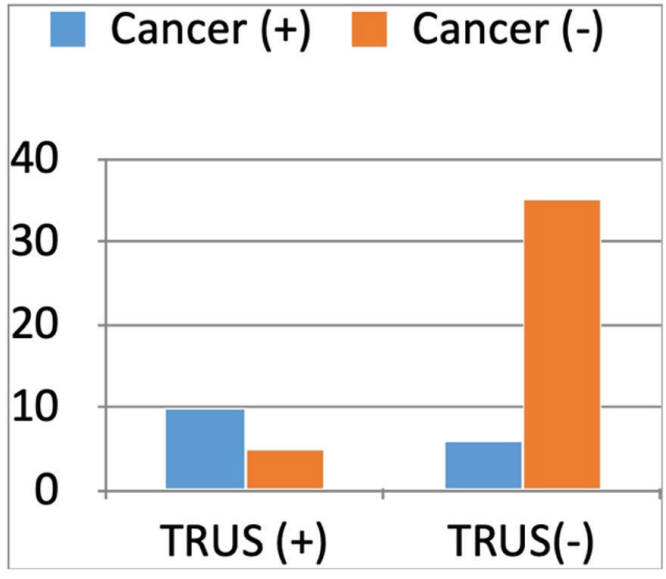

Figure 1. Sensitivity, specificity, and positive predictive values of TRUS
TRUS: Transrectal ultrasonography

While, cancer was detected in 8 of 17 patients with positive findings on PDU, 8 of 39 patients with negative findings were diagnosed on histopathology after their biopsy. Positive predictive value, sensitivity, and specificity of PDU were 47%, 50% and 79%, respectively (Figure 4: Sensitivity, specificity and positive predictive value of PDU).

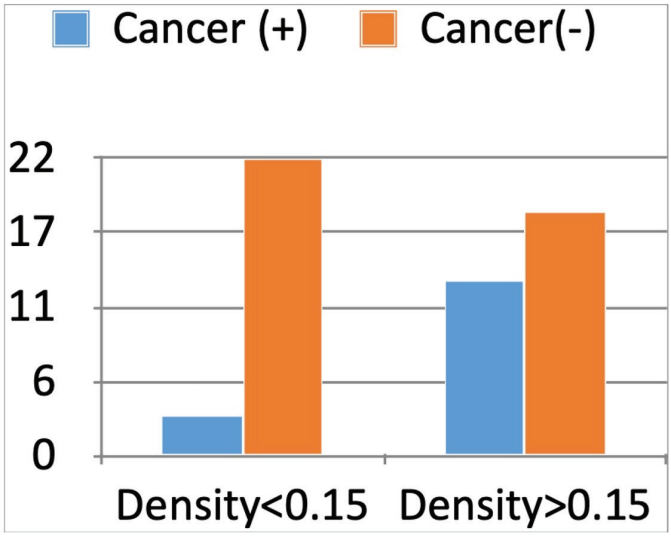

Figure 2. PSAD's sensitivity, specificity, and positive predictive value
PSAD: Prostate-specific antigen density

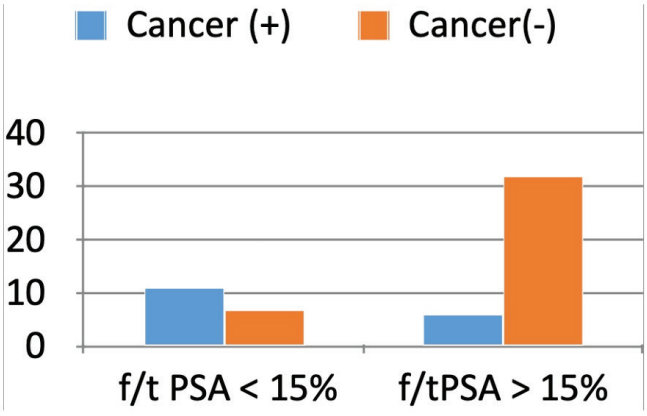

Figure 3. Sensitivity, specificity, and positive predictive value of f/t PSA ratio
f/t PSA: Free/total PSA ratio, PSA: Prostate-specific antigen

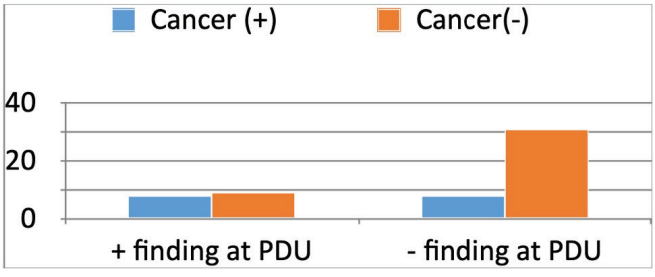

Figure 4. Sensitivity, specificity and positive predictive value of PDU
PDU: Power Doppler ultrasonography

PDU findings were positive for prostate cancer in only 3 of 18 patients without prostate cancer in those with PSADs >0.15 ng/mL, while the remaining 15 patients had negative PDU findings (Figure 5: PDU and PSAD).

When the cut-off value for f/t PSA ratio was taken as 15%, 7 patients with a f/t PSA ratio <15% did not have prostate cancer, and among them 3 patients had positive PDU findings (Figure 6). PDU findings of 2 out of 5 patients with the diagnosis of prostate cancer and f/t PSA ratios >15% had PDU findings favoring prostate cancer (Figure 6: PDU and f/t PSA ratios).

In patients with total PSA values between 4 and 10 ng/mL, combined use of f/t PSA ratios <15% with PSAD at the cut-off value of 0.15 ng/mL demonstrated 56.25% sensitivity, 89.75% specificity, and a predictive value of 69.23. When PDU, f/t PSA, and PSAD were used in combination, the sensitivity, specificity, and positive predictive values were 37.50%, 94.87%, and 75%, respectively. (Table 1: Sensitivity, specificity, and positive predictive values of combined PSADs and f/t PSA ratios; Table 2: Sensitivity, specificity, and positive predictive values of PDU, f/t PSA, and PSAD combination).

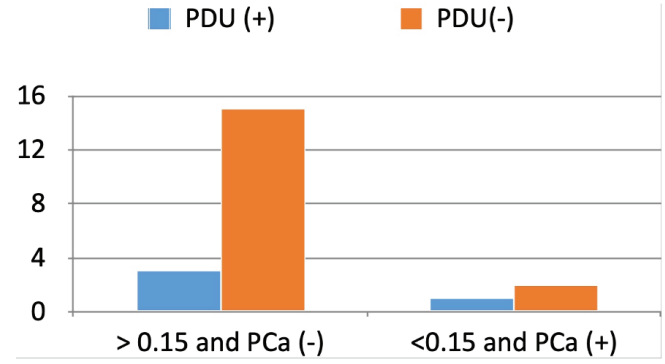

Figure 5. PDU and PSAD
PDU: Power Doppler ultrasonography, PSAD: Prostate-specific antigen density, PCa: Prostate cancer

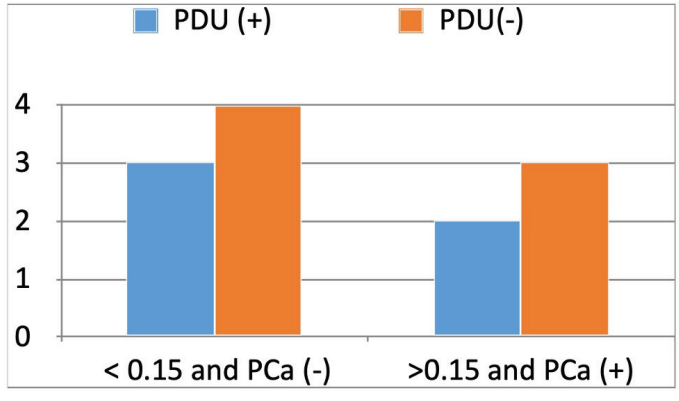

Figure 6. PDU and f/t PSA ratios
PDU: Power Doppler ultrasonography, f/t PSA: Free/total PSA ratio, PSA: Prostate-specific antigen, PCa: Prostate cancer

Table 1. Sensitivity, specificity, and positive predictive values of combined PSADs and f/t PSA ratios

Method	Sensitivity	Specificity	Positive predictive value
TRUS	62%	87%	66%
PSAD >0.15 ng/mL	81%	55%	41%
f/t PSA <15%	62%	82%	67%
PDU	50%	79%	47%

PSA: Prostate-specific antigen, PSAD: Prostate-specific antigen density, TRUS: Transrectal ultrasonography, PDU: Power Doppler ultrasonography, f/t PSA: Free/total PSA ratio

Table 2. Sensitivity, specificity, and positive predictive values of PDU, f/t PSA, and PSAD combination

Combined method	Sensitivity	Specificity	Positive predictive value
PSA density (>0.15 ng/mL + f/t PSA <15%)	56.25%	89.75%	69.23%
PSA density (>0.15 ng/mL + f/t PSA <15%) Power Doppler USG	37.50%	94.87%	75%

PSA: Prostate-specific antigen, PSAD: Prostate-specific antigen density, PDU: Power Doppler ultrasonography, USG: Ultrasonography, f/t PSA: Free/total PSA ratio

Discussion

Since, PSA is not perfect in predicting prostate cancer by itself; other methods are needed to increase the cancer detection rate and to prevent unnecessary biopsies (20,21). These methods include evaluation of PSAD, f/t PSA ratio, PSA velocity, and age-specific PSA. Among them, the most accepted and commonly employed tests are PSA density and f/t PSA ratio, in that order. However, none of these additional methods have been successful in predicting cancer, and more specific methods are needed. In our study, in addition to f/t PSA ratios and PSA densities, TRUS-guided biopsies were obtained from the suspicious areas seen during the simultaneously performed PDU. The ratio obtained by dividing serum PSA value by prostate volume was defined as PSAD (22). With this measurement that was developed based on the observation of greater amount of PSA secretion from hyperplastic tissue, unnecessary biopsies were reduced by 16%-55% when PSAD >0.15 ng/mL; however, nearly 11% of cancer cases were also overlooked (22,23). These findings show that the probability of detecting higher number of cancer cases by biopsy may increase by using PSAD (22,24,25). However, other researchers have not been able to demonstrate a superiority of PSAD over the use of PSA alone. Presti et al.(26) demonstrated that when sampling errors were corrected and used in patients whose PSA levels ranged between 4 and 20 ng/mL, PSAD was superior to PSA as demonstrated by functional characteristic analyses. However, this significance was lost in patients whose PSA levels were within the gray zone i.e. 4-10 ng/mL. Most of the PSA in serum is bound to alpha1- anti-chymotrypsin (ACT). Free or non-complexed PSA is found in relatively lower concentrations in serum. It has been thought that ACT is also found in the normal or malignant prostate epithelium, but not in BPH. It has been shown that the ratio of free PSA to complex PSA may be significant in detecting malignancy in the prostate. Chen et al. (27) did not observe any differences in the mean total PSA values of two separate groups of patients with benign and malignant prostate disease with PSA values between 4 and 10 ng/mL; while they observed significant differences between the average f/t PSA values of both groups. They also investigated the diagnostic value of fPSA in patients with total PSA levels between 4 and 10 ng/mL, and demonstrated that the f/t PSA ratio had higher specificity at almost every level of sensitivity (27). When these ratios are examined in patients with f/t PSA values between 4 and 10 ng/mL and normal DRE findings, it is also found that 95% of cancers can be detected and the number of negative biopsies can decrease by 20% in patients with f/t PSA ratios <23%. The f/t PSA ratio has been suggested to be used for deciding on the need for a repeat biopsy in patients with persistent PSA elevation but without any evidence of prostate cancer in the previous biopsy (28). This finding has also proved useful in distinguishing between BPH and prostate cancer (29).

A standard imaging method that can be used reliably in the diagnosis or staging of prostate adenocarcinoma has not been reported yet (30). However, the presence of neo-vascularity in malignancies is an established fact. The use of color Doppler USG that demonstrates this increased blood flow to identify tumors has also begun to draw attention as an interesting imaging modality since the 1990's (31).

Although, increased blood flow is observed in prostate cancer using color Doppler USG, this method has not been found to be specific since hypervascularity can be seen in prostatitis and BPH (32). Recently, high-frequency PDU has been used in an attempt to increase its diagnostic specificity.

PDU has been shown to be more sensitive than color Doppler and less probe dependent in demonstrating blood flow, distribution, and number of vessels (33). In our study, sensitivity, specificity, and positive predictive values of gray scale ultrasound were higher than those of PDU. We attributed these to the fact that the radiologist who participated in our study did not have sufficient experience in performing PDU as yet. It has also been reported that PDU is less sensitive than dynamic contrast-enhanced magnetic resonance imaging (MRI) in demonstrating hypervascularity in prostate cancer (34). In addition, Frauscher et al. (35) have reported that the anomalous regions visualized by PDU contain cancerous tissue 4.7 times more frequently relative to the normal appearing area adjacent to those regions. In many studies, apart from those conducted by Kuligowska et al. (36), investigating the use of this method for prostate cancer screening, the positive predictive value of color Doppler ultrasound was found to be higher than that of the gray scale ultrasound.

However, it has been suggested that patients with higher PSA levels already have a higher chance of harboring lesions detectable with gray scale ultrasound, and this may only be valid in patients with slightly elevated PSA levels (35,36).

Despite all these promising developments, studies have reported that the biopsy specimens obtained from the regions with positive PDU findings missed a significant number of cancers

compared with the cancers detected by laterally directed modified 6 quadrant biopsy (37). Some researchers have even indicated that the increased blood flow may actually depend on the patient's position (37,38). In our study, systematic biopsies were performed in all patients; however, when an anomaly was detected on PDU, an additional biopsy material was obtained from that region. A recent study demonstrated that in the first and second biopsies performed in patients with PSA levels between 2.5-10 ng/mL, PDU could exclude most of the non-cancerous patients and had a better sensitivity, specificity, and positive predictive value compared to the gray scale ultrasound (39).

In our study, when PDU was used as an independent screening method, it was found that its sensitivity, specificity, and positive predictive value in the detection of prostate cancer were 50%, 79%, and 47%, respectively. These values were lower than the corresponding values of 82.8%, 78.8%, and 87.9% cited in the literature (39). The sensitivity, specificity, and positive predictive values calculated in patients with PSADs >0.15 ng/mL were close to those determined by Akdas et al. (40) in Turkish patients with PSA levels <10 ng/mL (85%, 55%, and 41%, respectively). Again, the sensitivity, specificity, and positive predictive values calculated for the f/t PSA ratio were 62%, 82%, and 61%, which were close to respective 76%, 77% and 52% values cited in the literature (41).

We also evaluated the success of identifying those patients with cancer who could not undergo a biopsy, since their other tests yielded prostate cancer-negative results, and subsequently were not included in the screening. PDU positivity was detected in only 2 prostate cancer patients (40%) with f/t PSA ratios >15%. PDU-positivity was detected in only one of three patients (33%) with PSADs <0.15 ng/mL (33%). However, the number of patients in our study was not sufficient to render these values statistically significant.

While, PDU was found as the test with the lowest sensitivity in comparison with f/t PSA and PSAD in detecting cancer cases, the specificity of only f/t PSA ratio of <15% was greater than that of this method. The positive predictive value of PDU in detecting prostate cancer was found to be higher than that of the other tests only when the cut-off value of PSAD was accepted as 0.15 ng/mL.

However, in patients with PSADs >0.15 ng/mL and f/t PSA ratios <15% in the presence of suspicious findings revealed by PDU; specificity and positive predictive value in detecting prostate cancer (94.87% and 75%, respectively) were significantly higher in patients with PSAD values >0.15 ng/mL and f/t PSA ratios <15% (89.75%, and 69.23%, respectively) ($p<0.05$). These findings showed that this method may be useful in detection of prostate cancer when used in combination with other methods.

Prostate cancer detection rates of PDU in patients with only PSADs >0.15 ng/mL and f/t PSA ratios <15% were not statistically significant ($p>0.05$). However, cancer detection rates were found to be statistically significant in patients with positive PDU findings in those with PSADs >0.15 ng/mL and f/t PSA ratios <15% ($p<0.05$).

Study Limitations

An important limitation of our study was the lack of comparison of our findings with the current methodology of prostate biopsy; the MRI guided fusion biopsy. However, it is important to remember that systematic biopsy is an acceptable approach in case mpMRI is unavailable as is stated in EAU guidelines (15). Utilization of multi parametric MRI fusion biopsy could be challenging due to the high cost of the procedure, access to this type of biopsy systems by all clinicians, and technical requirements that are encountered not only by radiologists but also urologists. Hence, the result of this study may be a useful guide for the patients and centers without an access to MRI evaluation. Future studies including direct comparison of different methodologies would be helpful to find out a better method for the diagnosis of prostate cancer.

Conclusion

PDU has become popular recently and is one of the more promising imaging methods whose usefulness in prostate cancer has not yet been fully demonstrated. In this study, we found that when PDU was used in combination with PSAD (>15 ng/mL) and f/t PSA ratio (<15%) in screening patients with total PSA levels ranging between 4 and 10 ng/mL, who we most frequently encountered, it can be useful in detecting higher number of prostate cancer patients.

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Contribution: There is not any contributors who may not be listed as authors.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Ethics

Ethics Committee Approval: As medical tests, evaluations and interventions were performed within the limits of routine medical practice, approval of local ethic committee, which was not present at the time period of the study, was not required.

Informed Consent: Patients were informed about the study and a written informed consent were signed by the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Critical Review: N.D.G., Concept: M.T.E., Design: M.T.E., Data Collection or Processing: M.T.E., Analysis or Interpretation: M.T.E., Literature Search: M.T.E., Writing: M.T.E.

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