Measurement of serum PSA: Is it a good predictor of the severity of symptoms scored on the International Prostate Symptom Score (IPSS) for patients with benign prostatic hyperplasia?

Calvin FJ Lim
Trainee Intern
Christchurch School of Medicine
University of Otago

Calvin is currently a Trainee Intern at the University of Otago, Christchurch campus. His future plans include non-invasive surgery and ideas on how to broaden the appeal of contributing to medicine from the radiology perspective. He is a massive supporter of Wikipedia, with other non-medicine related interests in modern history, finance and good classic rock.

INTRODUCTION

Prostate specific antigen (PSA) measurements are done in almost all health care practices in New Zealand as an indicator of prostatic disease. Prostatic diseases are the main causes of lower urinary tract symptoms in men (LUTS). Lower urinary tract symptoms are divided into two broad categories: storage symptoms (urinary frequency, urgency, dysuria, and nocturia) and voiding symptoms (terminal dribbling, poor stream, hesitancy, incomplete voiding and overflow incontinence). Benign prostatic hyperplasia (BPH) is thought to account for almost all the pathologies of prostatic diseases that cause LUTS. BPH affected approximately 90% of men over the age of 80.[1] In a random population cross sectional study done on 515 New Zealand men from Porirua, it was found that BPH affected approximately 10% of men over the age of 40 and almost 34% of men over the age of 60. There has been no difference in prevalence amongst Caucasian, Māori and Pacific Island populations although there is some evidence to suggest that Māori and Pacific Island men seek less help for their condition.[2] Although benign, symptoms caused by BPH have significant effects on the quality of life for men worldwide.

PSA is used as a measure of prostate growth hence is a potential tool to detect prostate malignancy early. PSA is produced solely in the epithelial cells of the prostate gland, initially as a proenzyme (proPSA) by the secretory cells. Then it undergoes removal of its pro-peptide and becomes proteolysed within the lumen of the prostate to form the structure that is measureable in blood test. However, in addition to growth of prostatic tissue, inflammation of the prostate, urinary tract infections, trauma to the perineal area and male ejaculation have been shown to increase serum PSA levels.[3] Therefore, clinical context and knowledge of the patients' background have to be taken into account when interpreting the results.

Due to the fact that serum PSA level was shown to be a good measure of the amount of glandular epithelium of the prostate, it was therefore seen as a good indicator for the size of the prostate gland in BPH patient.[4] There was a study done in 1999 which analysed placebo-controlled multicentre trial data collected on 4627 patients with BPH under the age of 80. This study showed a statistically significant strong correlation between serum PSA level and age as well as the size of prostate. In essence, as age increases, prostate volume increases and the growth rate of the prostate increases as the PSA level increases.[5] Similar findings were shown in a 2003 Korean multicentre study of 5717 patients with benign prostatic disease where this strong correlation was demonstrated as well.[6] Traditionally it has been thought that an increase in prostate volume precipitates the development of lower urinary tract symptoms (LUTS), due to the bladder outlet obstruction caused by the prostate exerting pressure on the urethra.

The International Prostate Symptom Score (IPSS) was developed in 1992 following the previous use of the American Urological Association (AUA) score, with an intention to quantify the symptoms experienced by patients. The questionnaire is divided into seven parts where symptoms of incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia are quantified on a scale of 0 (not at all) to 5 (almost always) to give a total score out of 35. The score is then further categorised into ranges where 0-7 is termed mildly symptomatic; 8-19 moderately symptomatic; 20-35 severely symptomatic. There is a further 8th question which requests patient to state and rate it on a scale of 0 (delighted) to 6 (terrible): "If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?". Severity of symptoms, reported on IPSS in addition to the quality of life question score provide important information which are factored in to decide on management of the prostate : to manage it conservatively with medication or proceed to surgery.

Currently, there are conflicting evidence for the relationships between size of the prostate and severity of symptoms reported by patients: One study implicating a positive relationship by observing an increase in LUTS due to a measured increase in prostate volume when a group of patients were monitored over time.[7] Another study, a Chinese survey, which showed statistically significant results based on data from 1295 local prostate patients in the seven national urological centres, also supports this argument.[8] On the other hand, other studies showed that prostate volume is a weak determinant of symptom scores.[9,10,11] A small Japanese study on 67 men with BPH which compared all three parameters of interest: PSA, prostate volume and IPSS scores - showed statistically significant correlation between PSA and prostate volume but a statistically non-

significant relationship between PSA and IPSS symptom score.[11]

The aim of this study was to evaluate the use of PSA as a proxy to the prostate volume to be used as a predictor for LUTS given that we have convincing evidence showing a relationship between PSA levels and prostate size[5,6] and some evidence showing a positive correlation between prostate size and LUTS.[7,8,11]

METHOD

A retrospective analysis of cross sectional data collected within the Canterbury urology database was performed. The data was collected from patients at the point of clinic attendance. Patients included in the study were males who attended the prostate clinic in Christchurch Public Hospital, who had no previous diagnosis of prostate cancer and lived within the Canterbury DHB from the period of Jan 2007 to 24 Jan 2012. Excluded from the study were patients with histological evidence of malignancy; either prostatic intraepithelial neoplasia (PIN) on biopsy or by evidence of malignancy noted in clinical records. If there was no record of biopsy or note in the patients discharge summary, it was assumed that there was no evidence of malignant growth. Patients with current infection or chronic prostatitis were also excluded. Data about patients age at the time of presentation to the clinic, serum PSA level, IPSS score (0-35) and quality of life score (0-6) were collected. Obtained data were then graphed on a scatter plot and correlated using a Pearson product moment correlation analysis (reflected as the r-value) to illustrate any trends. Also, a coefficient of determination (R2 value) was calculated in order to estimate the extent of one of the variable to directly influence the other hence demonstrating the degree of its clinical significance.

RESULTS

3545 patients' entries from prostate clinics were included in the Canterbury urological database. Of those, only 1346 (38%) were found to have completed data sets to be analysed (serum PSA, IPSS, QoL score). Out of those 1346 patients, 833 (62%) were ultimately diagnosed with benign prostatic disease resulting in a response rate of 23%. The mean age of men who attended the prostate clinic was 68 years old (range: 28 years to 107 years). A summary of the results is shown in *Table 1:*

Relationships	*r* - value	R^2 Value	*P*-value
Serum PSA vs IPSS	0.1375	0.0189	0.00003
Serum PSA vs QoL	0.2070	0.0430	0.00001
IPSS vs QoL	0.6805	0.4632	0.00001
Age vs PSA	0.2404	0.0602	0.00001
Age vs IPSS	0.0710	0.0051	0.02145

Table 1*: Summary of the correlation findings*

[Note: r- values can be positive or negative. A positive value shows a direct trend (i.e a relationship where one variable increases the other increases) and a negative value showing an indirect trend (i.e when one variable increases, the other decreases). An r-value of (0.09 to 0) indicates no correlation, (0.1 to 0.3) a small correlation, (0.3-0.5) a moderate correlation and (0.5 to 1.0) a strong correlation. An R2 value >0.5 generally indicates the measure to be a significant potential influence on the outcome of interest. Cut-off values are variable depending on the type of research however for purposes of this study a value of < 0.5 is deemed insignificant]

An analysis using a scatter plot of the individual patient data points for PSA in relation to the IPSS showed a mild trend (Figure 1), with a Pearson product-moment correlation coefficient (*r* -value) of 0.1375 (p = 0.00003): this demonstrates a mild statistically significant correlation between these two parameters. However, the coefficient of determination (R2 value) was only 0.0189. This means that, each unit increase of serum PSA only influences 1.89% of the change in the symptom score. Similarly, for PSA vs QoL scores, there was a mild correlation found with the r-value of 0.207 (p=0.00001) (Figure 2). However the R2 value was only 0.043, showing a mild 4.3% influence by PSA on QoL.

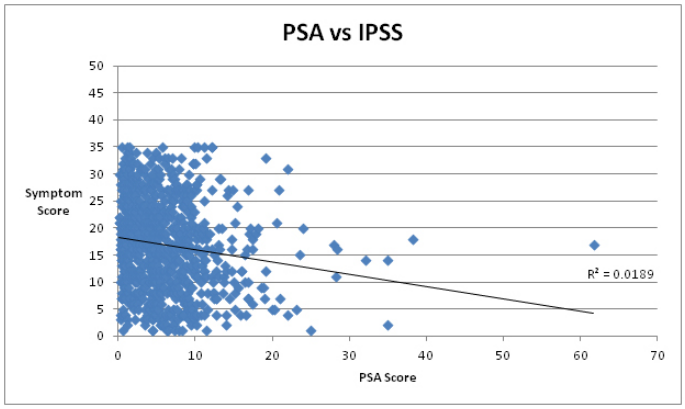

Figure 1: *A scatter plot illustrating the relationship between PSA and IPSS symptom scores. N= 833; r =-0.1375; R^2 = 0.0189.*

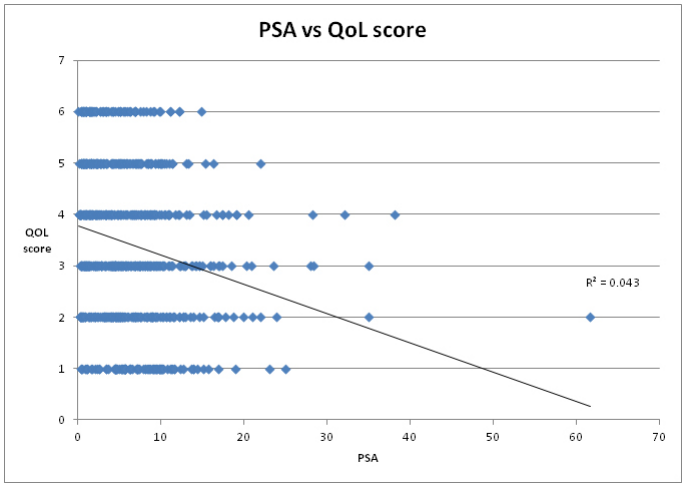

Figure 2: *A scatter plot illustrating the relationship between PSA and QoL scores. N= 833; r =0.207; R^2 = 0.04.*

There was a moderate correlation (Figure 3) found between the IPSS symptom scores and the QoL scores, with a *r*-value of 0.6805 (p=0.00001) and R^2 of 0.4632, showing a convincing evidence that an increase in symptom score affecting 46% of the QoL score.

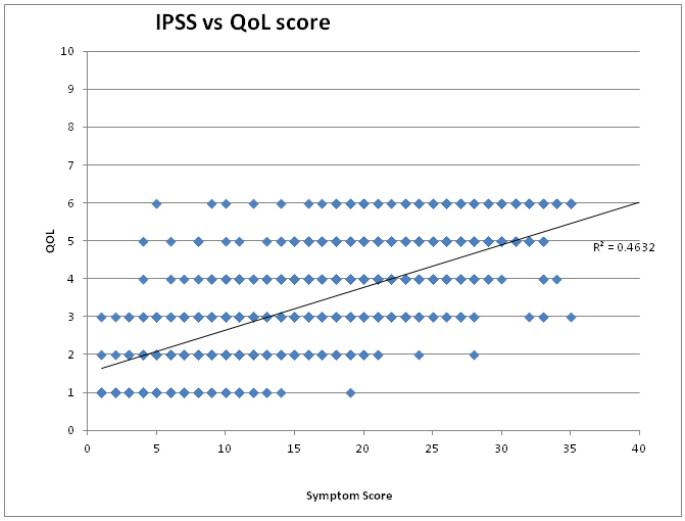

Figure 3: *Illustration of the relationship between the IPSS symptom scores measured in the population and the QoL scores. N=833; r = 0.6805; R^2 of 0.46.*

Further analysis was done to evaluate whether the age of patient at presentation to clinic was related to PSA or IPSS. It was demonstrated (Figure 4) that increasing age had a mild statistically significant relationship to increasing PSA, with r-value of 0.2404 (p = 0.00001) but a low R2 value of 0.0602. Age however (Figure 5) was not shown to correlate to the IPSS score with r value of 0.071 (p = 0.02145).

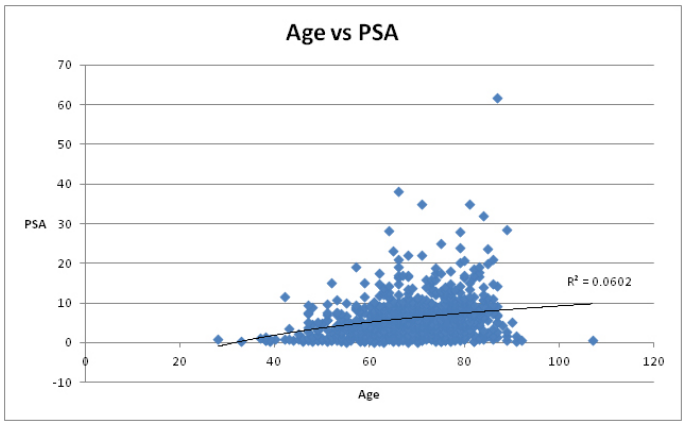

Figure 4: A scatter plot illustrating the relationship between patient age and serum PSA level. N= 833; r=0.2404, R² = 0.0602.

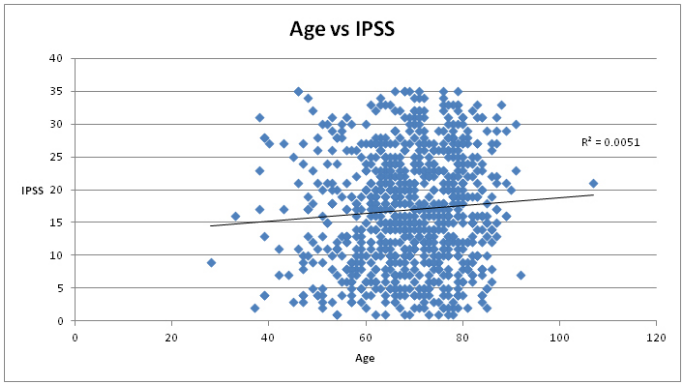

Figure 5 : A scatter plot illustrating the relationship between patient age and IPSS . N= 833; r=0.0710, R² = 0.0.0051.

DISCUSSION

The results indicate that serum PSA has only a mild association with symptom scores reported by patients with BPH, as suggested by the Tsukamoto study.[11] However, the significance of this finding is minimal as it is only able to influence <4 % of the symptoms (IPSS and QoL) reported by patients, hence making it a poor predictor.

Because this study was done retrospectively and was a cross sectional study, it is only able to provide a snapshot of the situation and cannot clearly demonstrate the trend that PSA is related to symptom scores. A further study which follows up the same BPH patients for a number of years to monitor any changes in the above study parameters would provide a stronger evidence for any relationships and/or associations. However, given the poor significance of the relationship between PSA and symptom scores, the usefulness of such a study being conducted is very much doubted.

No data on prostate volume measurements were available within the Canterbury urological database and therefore no correlation could be drawn between the patients' serum PSA and prostate volume, or prostate volumes and symptom scores. Having prostate volume measurements would have enabled the study to examine its relationship to study parameters and analyse the correlations between them, thus providing some insight into contributing factors of the symptoms experienced by the patient.

In addition, there are also some inherent weaknesses in the IPSS as a measurement. While the total score is taken into account, individual breakdown of its seven different components are not. Because of this, actual severity of symptoms could be underestimated or overestimated. Based on the results of this study showing a positive relationship between IPSS and QoL score, it could be suggested that increase in some categories of symptoms correlate more strongly with the quality of life that the patient experiences (e.g. nocturia affects the quality of life more strongly for some patients compared to having a weak stream of urine). Furthermore, as subjective as symptoms and QoL are individual patient variability in completing questionnaires and personal biases are also present. For example, patients might be inclined to rate their symptoms worse than it actually is hoping that a procedure would be done or vice versa where they report less in order to avoid treatment.

There was no correlation between age and LUTS on the IPSS score in this study, or a clinically significant increase in serum PSA as age increases. This is in conflict with previously established evidence which suggest that increase in age, LUTS or serum PSA are related to the increased development of such symptoms being reported on the IPSS.[1,5,10] This discrepancy could be attributed to the weaknesses of this study with low numbers of patient data entries and poor "response rate" of the patients (23%) , hence the skewed results towards a null correlation. Apart from the result of this study, causes other than prostatic disease have to be considered in clinical practice when there is an increase in LUTS in older men. Such causes include bladder dysfunction and/or non-prostatic bladder outlet dysfunction. Examples of bladder dysfunction pathologies are bladder hypersensitivity/over-activity, and reduced detrusor muscle contractility. Instances of bladder outlet dysfunction apart from prostatic enlargement are the development of urethral strictures, poor urethral sphincter relaxation and pseudodysenergia of the sphincter due to neuropathy.[12]

CONCLUSION

Although there was a statistically significant correlation found between PSA, IPSS and QoL scores, the influence that PSA has on IPSS and QoL are minimal. This strongly suggests that PSA would not be a good predictor for symptom scores and hence it is unable to accurately gauge the symptomatic severity in BPH patients.

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