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Predictive value of neutrophil-to-lymphocyte ratio in diagnosis of early prostate cancer among men who underwent robotic transperineal prostate biopsy

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Abstract

To evaluate the predicted value of neutrophil-to-lymphocyte ratio (NLR) in the diagnosis of early prostate cancer by using standardized Full blood count (FBC) performed within 4 weeks before biopsy and histology results from transperineal prostate biopsy (RTPB).

Patients who underwent RTPB under general anesthesia (GA), at Urology Department, Singapore General Hospital between September 2006 and Febuary 2016 were retrospectively reviewed.

NLR was calculated using full blood count (FBC) that was done as a pre-admission test before GA within 4 weeks before the biopsy. Statistical analyses were done to establish the correlation of NLR and different clinical parameters such as biopsy histology, pre-biopsy PSA, and prostate volume.

A total of 652 patients who underwent RTPB for diagnostic purposes with a valid PSA level were included in this study. There was total of 409 (62.7%) benign histology and 243 (37.3%) prostate cancer. There was no significant difference in median NLR between the benign and prostate cancer group (2.00 vs 1.99; $P = .29$).

In the subgroups analysis, there was also no significant difference of median NLR value in clinical significant cancer (defined as Gleason 3+4 and above) and benign histology group (NLR 2.00 vs 2.01, $P = .41$), as well as prostate cancer and benign group according to different pre-biopsy PSA levels: PSA (ug/l) < 4, 4 to 10, 10 to 20, and >20, respectively. (Median NLR 1.34 vs 1.76; 1.97 vs 1.97; 1.97 vs 2.18; 2.18 vs 1.98, $P > .05$). NLR is neither associated with prostate cancer using logestic regression model nor a strong predictor of the Gleason grade group and D'Amico risk stratification group using ordinal regression model. ($P > .05$)

There was no statistically significant difference of NLR between the benign and prostate cancer group as a whole or in the subgroup analyses for patients who underwent robotic transperineal prostate biopsy. NLR may have a limited role in predicting early-stage prostate cancer.

Abbreviations: CBC = complete blood count, GA = general anesthesia, NLR = neutrophil-lymphocyte ratio, RTPB = robotic assisted transperineal prostate biopsy, TRUS biopsy = Transrectal ultrasound guided biopsy.

Keywords: neutrophil-to-lymphocyte ratio, prostate biopsy, prostate cancer, transperineal prostate biopsy

1. Introduction

The neutrophil-lymphocyte ratio (NLR), a measure of the proportion of systemic neutrophils and lymphocytes, has been proven to be associated with many types of cancer.[1,2] In the field of prostate cancer, NLR is known to have prognostic value for metastatic prostate cancer.[3,4] However, for early-localized prostate cancer due to lack of systemic response; the role of NLR is not conclusive. Published data revealed conflicting results. We hope this study could add more information to this area.

The objective of the study is to investigate how was the NLR value related to transperineal prostate biopsy histology and Gleason grade group and assess the predictive value of NLR in diagnosis of early prostate cancer.

2. Methods

A total of 652 patients who underwent RTPB under general anesthesia (GA) for diagnostic purposes with valid pre-procedure PSA level were included in this study with the ethical approval from the institutional review board. Indications for RTPB were as

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The authors have no conflicts of interests to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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follows: Biopsy naïve patients with raised PSA > 4 ng/mL; rising PSA > 4 ng/mL with previous negative Transrectal ultrasound guided biopsy (TRUS biopsy) patients; abnormal DRE with any PSA level; suspicious lesions on multiparametric magnetic resonance imaging examination defined as prostate imaging report and data system (PIRADS) 3 and above.

2.1. Inclusion criteria

Patients who underwent RTPB at the Department of Urology, Singapore General Hospital between Sep 2006 and Feb 2016 were recruited into the study.

2.2. Exclusion criteria

Patients with missing NLR and/or PSA parameters or known metastatic diseases; patients with biopsy results of high-grade prostatic intraepithelial neoplasia and chronic inflammation or who underwent biopsy for non-diagnostic purposes (e.g., Brachytherapy, active surveillance) were excluded from the study. Patients with symptomatic prostatitis or urinary tract infection or systemic inflammatory disease were also excluded. For patients who had multiple times of biopsies, only the last histology results were included in this study.

2.3. Protocol of biopsy

Oral antibiotics were given 5 to 7 days before the procedure and it was done under general anesthesia and lithotomy position. Real-time transrectal ultrasound was performed and 3D reconstruction of the prostate was processed by computer. Biopsy template including the number of cores and locations of cores were planned using software which acts as interact phase between robotic biopsy device and surgeon. During the procedure, all biopsy tracts were accurately projected by the robotic device according to the pre-set biopsy template.

2.4. Method of biopsy

In this study, all patients underwent RTPB using iSR'obot Mona Lisa robotic device (Serial No: iSR265001; n230 V, 50–60 Hz,1.8A), which was developed by our medical group. It contains a Robot arm and a connected computer with build-in software that enables the surgeon to perform template sampling for the biopsy. The software also allows us to merge MRI prostate images with real-time prostate ultrasound for targeted biopsy.

2.5. CBC value

Transperineal prostate biopsy is performed under GA, so all patients underwent standard pre-admission tests including complete blood count (CBC) within 4 weeks before the operation.

2.6. Histology report

All histology slides were processed with Hematoxylin and Eosin staining and reported by senior pathologists. Gleason scores were assigned according to WHO colleague of American pathologist prostate cancer.[5] One to three percent of the histology slides were reviewed by second independent senior pathologists according to department quality control protocol.

2.7. Data management

NLR was calculated by dividing the neutrophil count by the lymphocyte count. Prostate volumes were measured by intra-operative ultrasound. Clinical significant cancer was defined as Gleason Score ≥7 based on the pathology of the transperineal biopsies. Gleason grade system of the biopsy histology was classified as grade 0 to 5 based on WHO 2016 edition of Pathology and Genetics: Tumors of the Urinary System and Male Genital Organs.[6] AJCC TNM staging 8th edition[7] was used for histologic grade group /upgrading and T stage. Risk group was divided into benign, low risk, intermediate risk and high risk groups according to D'Amico risk stratification system.[8] The latest PSA levels before transperineal biopsy were used for one of the criteria of D'Amico classification and the comparison of NLR at different PSA levels. Clinical data such as PSA, CBC, age of diagnosis, number of biopsy cores, prostate volume, histopathology biopsy results, and clinical T stage were obtained from prospective Uro-oncology registry and/or the institution's electronic medical systems.

2.8. Statistical analysis

Mann–Whitney *U* test was carried out to compare the NLR difference between the groups. Univariate and multivariate logestic regression model was used to assess the correlation between NLR and prostate cancer. Ordinal regression model with negative log-log link function was used to access categorical outcomes such as Gleason grade group and D'Amico risk stratification system in the association with NLR and prostate volume.

All statistical analyses were conducted in Statistical Package for Social Sciences (SPSS) version 25.0 (SPSS Inc., Armonk, NY). Two-sided P value of $<.05$ was considered statistically significant.

3. Results

There were a total of 944 transperineal biopsies were performed in the Department of Urology, Singapore General Hospital between Sep 2006 and Feb 2016 (Fig. 1). Among these 44 cases that had more than one biopsy, only the last histology results were included in this study. Additionally, 93 were excluded due to missing NLR and PSA parameters. Fourteen patients with biopsy results of high-grade prostatic intraepithelial neoplasia and chronic inflammation were also excluded. In addition, 141 patients who underwent biopsy for non-diagnostic purposes (brachytherapy 5 cases, active surveillance 103 cases, and other indications 33 cases) were also excluded.

A total of 652 patients who underwent RTPB for diagnostic purposes with valid pre-procedure PSA levels were included in this study. Clinical demographics were shown in Table 1. Median PSA before the biopsy was 8.9 ng/mL and the median number of cores taken was 29 and the overall mean NLR was 2.22.

NLR was calculated as shown in Table 2, and there was no statistically significant difference in NLR between the benign and prostate cancer group ($P = .29$) (Fig. 2).

If defined Gleason 3 + 4 and above as clinically significant prostate cancer, there was no statistically significant difference in NLR value in the clinically significant cancer group compared to the benign histology group (Table 2). Of all 243 cases of prostate cancer, 93 patients underwent robotic radical prostatectomy. We

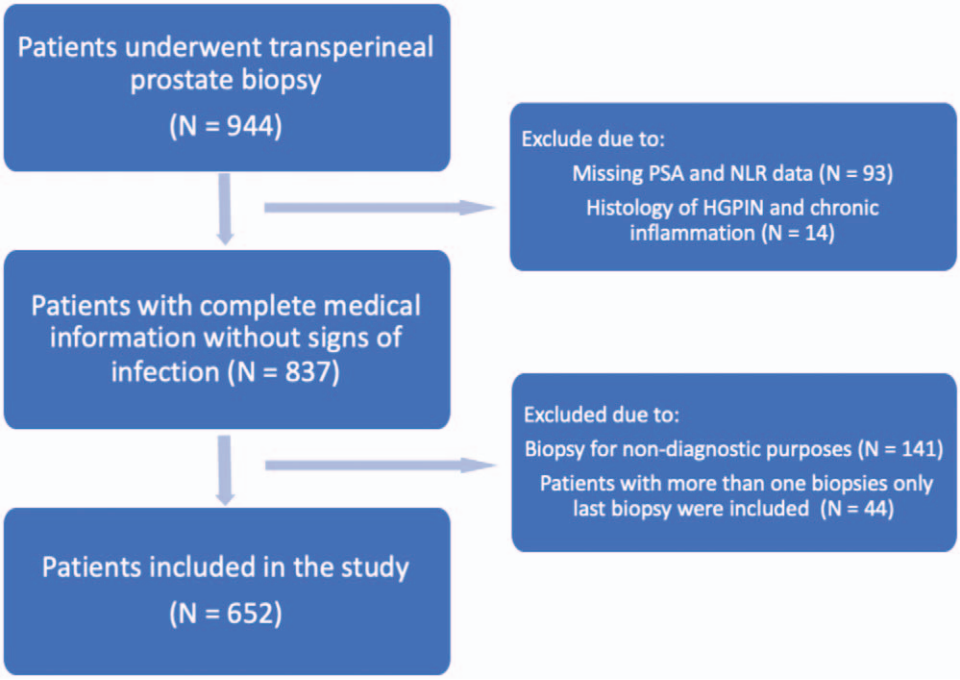

Figure 1. Patients selection.

compared the biopsy histology to prostatectomy histology and found 25 cases in which prostatectomy histology revealed a higher Gleason grade group compare to biopsy histology (upgraded group). And the remaining 68 patients had the same Gleason grade group in the prostatectomy histology and biopsy specimen (not upgraded group). We compared the NLR in these 2 groups of patients; there was no statistically significant difference ($P = .53$) in NLR between the upgraded group and the not-upgraded group. (Table 2)

We also compared NLR values in the prostate cancer group and benign group according to different pre-biopsy PSA levels. However, there was no statistically significant difference in the various PSA levels (Table 3, Fig. 3). The correlation of total PSA and NLR was calculated using Pearson Correlation Coefficient method; there was no statistically significant correlation ($r = -0.039$, $P = .32$) (Fig. 4)

In univariate logestic regression analysis (Table 4) NLR was not statistically significant ($P = .248$) between benign and prostate cancer group. While age (OR = 1.068; 95% C.I. = 1.043–1.093), tPSA (OR = 1.033; 95% C.I. = 1.013–1.054), prostate volume (OR = 0.971; 95% C.I. = 0.960–0.982) were statistically significant different. Multivariate logestic regression analysis revealed similar results: NLR was not significant ($P = .472$) between 2 groups while age (OR = 1.087; 95% C.I. = 1.060–1.015), tPSA (OR = 1.043; 95% C.I. = 1.019–1.068) and prostate volume (OR = 0.957; 95% C.I. = 0.945–0.969)

Table 1

Clinical characteristics.

Number of patients	652
Median Age at biopsy (yr)(IQR)	62.8 (58, 67)
Median total PSA before biopsy (ng/mL) (IQR)	8.9 (6.5, 12.6)
Median Number of cores taken (IQR)	29 (25, 34)
Mean NLR (SD)	2.22 (1.13)
Median Neutrophil count (IQR)	3.65 (3.01, 4.45)
Median Lymphocyte count (IQR)	1.89 (1.47, 2.28)
Prostate volume (ml; Mean ± SD)	
Overall	38.8 ± 15.8
Benign	41.3 ± 0.80
Prostate cancer	34.6 ± 0.97
Histology:	
Benign	409
Prostate cancer	243
Gleason score 6 and below (Grade 1)	111 (45.7%)
Gleason score 7 (3 + 4) (Grade 2)	65 (26.7%)
Gleason score 7 (4 + 3) (Grade 3)	34 (14.0%)
Gleason score 8 (Grade 4)	26 (10.7%)
Gleason score 9 (Grade 5)	7 (2.9%)
Clinical staging:	
cT1-T2	229 (94.2%)
cT3	14 (5.8%)
D'Amico risk classification	
Low risk	73 (30.0%)
Intermediate risk	91 (37.4%)
High risk	79 (32.6%)
Biopsy naïve	176 (27.0%)
Previous negative biopsy	476 (73.0%)

IQR = interquartile range, SD = standard deviation.

Table 2

NLR comparison in benign and prostate cancer/clinical significant cancer; upgraded and not upgraded group.

	No. Patients	Mean NLR (SD)	P^1
Benign	409	2.18 (0.06)	.29
Prostate cancer	243	2.29 (0.07)	
Benign	409	2.18 (0.06)	.40
Clinical significant cancer	132	2.29 (0.10)	
Upgraded group	25	2.50 (0.31)	.53
Not upgraded group	68	2.41 (0.17)	

P value is calculated using Mann–Whitney *U* test.

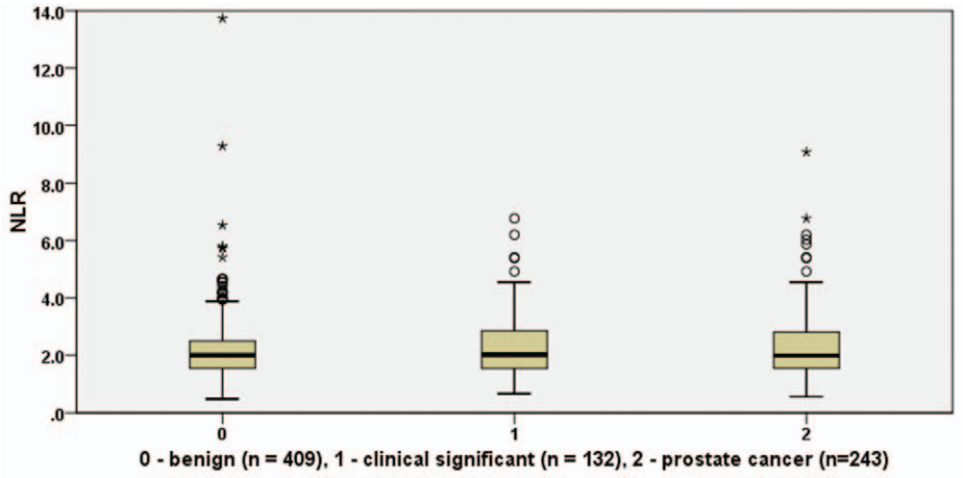

Figure 2. Boxplot of NLR value in benign, clinical significant prostate cancer and prostate cancer groups.

remained statistically significant. Older patients; higher pre-biopsy PSA and smaller prostate volume were strongly associated with prostate cancer.

Further analyses were done using ordinal regression model to assess outcomes of 1). Gleason grade groups, 2). D'Amico risk stratification groups, in the association with NLR. (Table 5) NLR was neither a significant predictor for biopsy Gleason grade groups ($P = .268$, OR [95% CI] = 1.060 (0.956–1.175)) nor D'Amico risk stratification groups ($P = .269$, OR [95% CI] = 1.060 (0.956–1.175)). On the other hand, prostate volume was strongly negative associated with biopsy Gleason grade system ($P < .001$, OR [95% CI] = 0.974 (0.965–0.983)) and D'Amico risk stratification system ($P < .001$, OR (95% CI) = 0.975 (0.967–0.984)). Negative estimate values of −0.026 and −0.025 indicated the lower the prostate volume the higher the Gleason grade group and higher D'Amico risk stratification. (Table 5)

4. Discussion

Prostate Cancer has traditionally been suspected based on a digital rectal examination (DRE) and/or prostate specific antigen (PSA) levels. PSA as a biomarker is organ specific but not cancer specific; There are many benign conditions in which PSA may also be elevated. There is a large proportion of PCa who remain latent and never progress to affect the patients' life.[9] The prognostic assessment of PCa is essential to allow the clinician to decide on the optimal management option in balancing the benefits and harms of treatment.

Table 3

NLR value in patients with different PSA levels.

PSA (ug/L)	Histology	No. of patients	Median NLR (IQR)	*P*
<4	Benign	7 (1.7%)	1.34 (1.21–2.94)	.84
	Malignant	6 (2.5%)	1.76 (1.41–2.85)	
4- < 10	Benign	239 (58.4%)	1.97 (1.49–2.62)	.29
	Malignant	127 (52.3%)	1.97 (1.58–2.80)	
10–20	Benign	139 (34.0%)	1.97 (1.57–2.40)	.34
	Malignant	78 (32.1%)	2.18 (1.55–2.87)	
>20	Benign	24 (5.9%)	2.18 (1.93–2.46)	.31
	Malignant	32 (13.1%)	1.98 (1.39–2.47)	
Total	Benign	409 (100%)		
	Malignant	243 (100%)		

Improvements in technology in the field of genetic analysis and imaging have led to a race in the identification of novel biomarkers that can be utilized in the stratification, diagnosis and prognostication of PCa. Magnetic resonance imaging (MRI) has been increasingly used for guiding various aspects of PCa management, including detection, staging and treatment. Although there is abundant evidence demonstrating that pre-biopsy mpMRI can be used to improve the diagnostic accuracy of PCa, the results vary greatly due to the heterogeneity in interpretation and radiologic protocols.[10–12] There are early developments in exploring quantitative MR imaging metrics as noninvasive biomarkers of tumor aggressiveness to complement prostate biopsies.[13,14]

Characterization of genetic mutations in tumor tissue such as microarray and genetic sequencing are aimed to design personalized road maps to aid in clinical decision making.[15–17] Existing commercial biomarkers include Prostate Health Index (PHI), PCA3 and Polaris which are utilized with the aim to reduce the number of unnecessary biopsies.[18,19]

There is an emerging field in evaluating other preoperative markers in addition to imaging that might allow prediction of disease aggressiveness. De et al evaluated the role of Urotensin II receptor on preoperative biopsy and showed an association with upstaging and upgrading in PCa.[20] Ferro et al demonstrated that there is an association between circulating total testosterone levels and unfavorable prognosis and biochemical recurrence in low risk to intermediate to low risk prostate cancer.[21] Similarly, neutrophil-lymphocyte ratio (NLR), a cancer related systemic inflammatory marker, has been shown to predict PCa.

In this series, we investigated NLR in relation to pathology from RTPB (combined template and targeted biopsy) rather than the conventional TRUS biopsies. Additionally, to our knowledge, this study is also the first to use a consistent neutrophil and lymphocyte count reading that was taken from a standardized CBC done as part of pre-operative general anesthesia testing, as opposed to prior studies where the indication and time interval of the CBC were inconsistent.

Establish evidence have revealed raised NLR was associated with higher incidence of prostate cancer. Kawahara's paper[22]

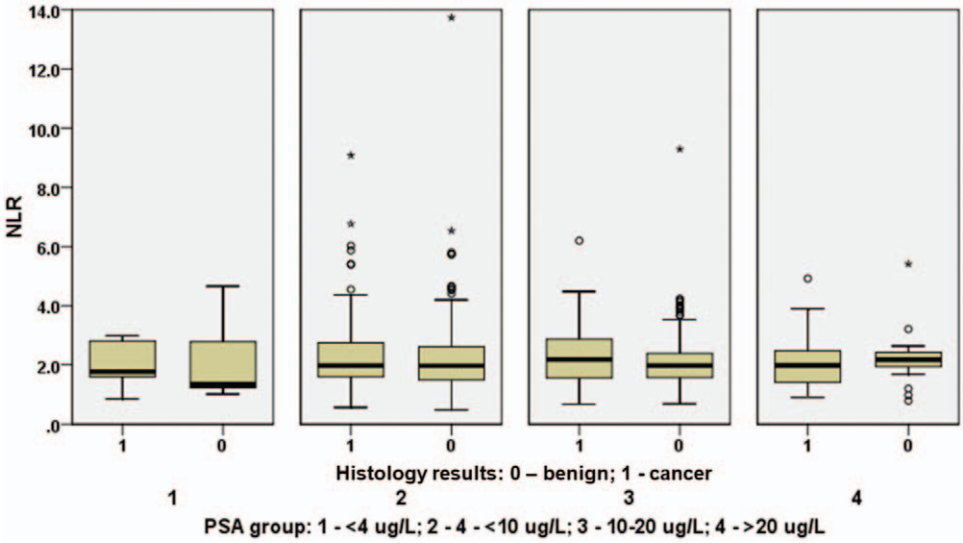

Figure 3. Boxplot of NLR value in patients with different PSA levels.

first demonstrated NLR was significantly higher in localized prostate cancer patients. Total 810 patients who underwent TRUS biopsy with PSA 4 to 10 ng/mL were included in this study. Results revealed NLR was significantly higher in prostate cancer group compared to benign group. Conversely, Huang et al[23] analyzed 662 patients who underwent TRUS biopsy with valid CBC before biopsy. They found out there was no significant difference of NLR in benign and prostate cancer group; however in the subgroup analysis of patients of PSA 4-10, NLR was significantly higher in prostate cancer group. And there were other similar studies to support this conclusion.[24,25] Other studies also reported that NLR might be helpful to predict TRUS biopsy upgrading; help differentiate real Gleason > 7 cancer and stratifying low risk prostate cancer.[26–28]

On the contrary, Yuksel et al[29] studied 873 cases who underwent TRUS biopsy. They divided histology into benign prostatic hyperplasia, prostatitis and prostate cancer and found out there was no significant difference of NLR between cancer and benign prostatic hyperplasia group.

The present study revealed that there was no statistically significant difference in NLR value in patients with and without prostate cancer. Moreover, there was no significant difference in NLR ratio between patients with and without prostate cancer in the different PSA levels. These differences may be attributed to the intrinsic differences in the characteristics of each patient cohort in these studies. [Table 6, Figs. 5 and 6]

To assess the cancer detection yield and proportion of clinically significant prostate cancer disease of the current series; we used published references in this field. There were 54.3% of high-grade cancer patients in the current series which was significantly higher than 3 of the studies except for 1. And in terms of cancer caseload: in the current study, 34.2% of patients with PSA 4 to 10 ng/mL were cancer cases that were not significantly lower than published data. In summary current series contained more clinically significant cancer and overall similar cancer yield which could not be accounted for negative results.

Other possible explanations for the different findings were probably related to the variation in the methodology:

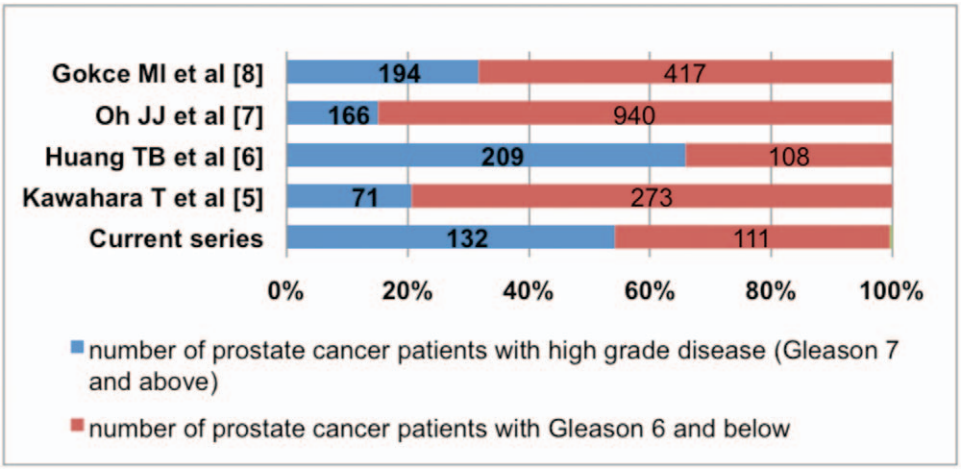

Figure 4. Pearson Correlation coefficient between total PSA and NLR.

Table 4

Univariate and Multivariate logistic regression using age, tPSA, prostate volume, previous biopsy and NLR to predict benign or malignant histology results.

	Univariate			Multivariate		
Variables	***P***	**OR**	**95% CI for EXP(B)**	***P***	**OR**	**95% CI for EXP(B)**
Age	<.001	1.068	1.043–1.093	**<.001**	1.087	1.059–1.115
tPSA	.001	1.033	1.013–1.054	**<.001**	1.046	1.022–1.071
Prostate Volume	<.001	0.971	0.960–0.982	**<.001**	0.956	0.944–0.969
NLR	.248	1.085	0.945–1.247	.493	1.054	0.906–1.227
1st* or redo bx	<.001	0.434	0.304 – 0.619	**<.001**	0.395	0.266–0.588

Table 5

Ordinal regression of NLR and prostate volume related to Gleason score and D'Amico classification stratification.

	Gleason grade group			D'Amico risk stratification system		
	***P* value**	**Estimate (95% CI)**	**OR (95% CI)**	***P* value**	**Estimate (95% CI)**	**OR (95% CI)**
NLR	.418	0.056 (−0.080–0.192)	1.058 (0.923–1.212)	.332	0.068 (−0.069–0.205)	1.070 (0.935–1.226)
Prostate volume	**<.001**	−0.037 (−0.049–−0.026)	0.963 (0.952–0.975)	**<.001**	−0.038 (−0.049–−0.026)	0.963 (0.952–0.974)
tPSA	**<.001**	0.052 (0.034–0.070)	1.053 (1.034–1.073)	**<.001**	0.087 (0.065–0.110)	1.091 (1.064–1.119)

CI = confidence interval.

Gleason grade group: grade 0 (reference), grade 1, grade 2, grade 3, grade 4, and grade 5.

D'Amico risk stratification system: benign (reference), low risk, intermediate risk and high risk.

Table 6

Comparison of current series with published literatures.

Studies	**Rate for high grade disease***	***P* value**	**Parentage of cancer cases†**	***P* value‡**
Current series	54.3% (132/243)	–	125/366 (34.2%)	–
Kawahara et al [22]	20.6% (71/344)	.00	357/810 (44.1%)	.00
Huang et al[23]	65.9% (209/317)	.01	30.5% (50/164)	.43
Oh et al[24]	15% (166/1106)	.00	No data available	–
Gokce et al[25]	31.7% (194/611)	.00	28.3% (1106/3913)	.02

* Number of high grade cases / total number of PCa cases in current series and listed literatures. High grade disease definition: Gleason 7 and above.

† Number of PCa cases / total number of cases with PSA between 4 to 10 ng/mL in current series and listed literatures.

‡ *P* values were calculated compared listed literatures to current series using Chi-Squared test.

4.1. Standardized samples of CBC

In the present study, all CBC were done as a pre-admission test. This would be strictly done within 4 weeks of biopsy. And patients were reviewed by anesthesiologists in the pre-admission clinic and this would ensure patients were in general good condition and no systemic infective disease which can affect NLR significantly. If we compare this to other published literature, none of them mentioned the indication of CBC done before biopsy; neither the interval between CBC and biopsy were strictly controlled. Since NLR is not a specific biomarker and many medical conditions could alter the results if this was not strictly controlled.

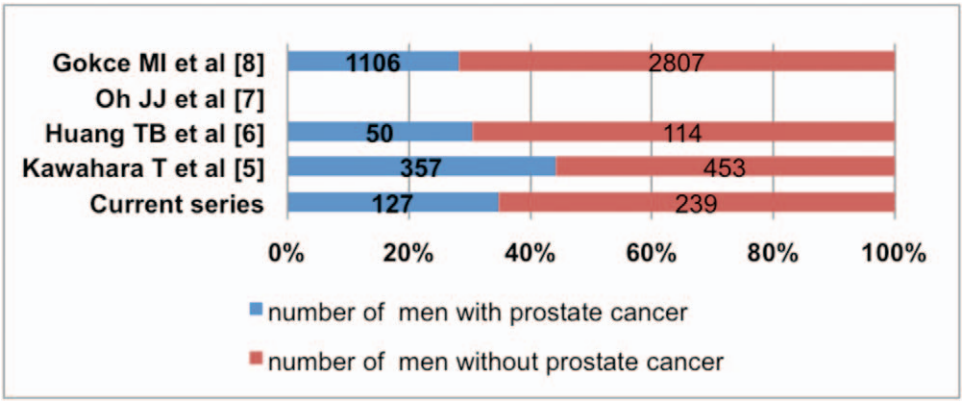

Figure 5. Comparison of percentage of high grade disease in men with prostate cancer between current series with others studies.

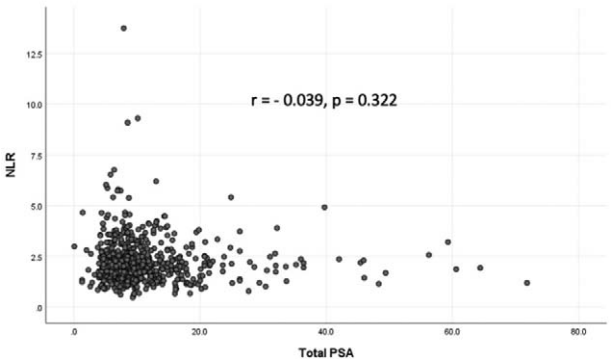

Figure 6. Comparison of cancer detection rate in men with PSA from 4 to 10 ng/mL between current series with others studies.

4.2. Methods of prostate biopsy

All the previous publications regarding NLR in the diagnosis of prostate cancer were based on the results of template TRUS biopsy. However non-targeted TRUS biopsy does have the chance of missing cancer. Furthermore in articles that demonstrated the positive predictive value of NLR; the majority of the patients who had PSA between 4 to 10 ng/L indicated a relatively low disease burden and a higher chance of getting a false negative biopsy.

Pal et al studied 426 patients who underwent both TRUS biopsy and mapping transperineal prostate biopsy.[30] They found out that up to 53% (94/179) of patients who had benign histology on TRUS biopsy actually had prostate cancer that detected by mapping transperineal biopsy.

In the current series, all patients underwent transperineal prostate biopsy which can achieve a relatively higher cancer detection rate. Due to the low risk of urosepsis and accuracy of robotic biopsy more template cores were taken and this potentially may lead to lower cancer missing rate. The median number of cores taken was 29, which is significantly higher than the traditional 10 to 16 cores TRUS biopsy. Table 6 revealed that the overall cancer detection rate in the present study was 34.2% which was higher than 2 of the published NLR series.[23,25]

According to the ordinal regression results: prostate volume had a strong negative correlation with biopsy histology grade and D'Amico risk stratification groups. This means small prostate were associated with higher cancer grade and higher cancer risk group. Similar findings were revealed in the study of prostate volume and radical prostatectomy histology.[31]

In addition, the majority of the patients (73%) in the present study already had previous negative biopsies which might further enhance the reliability of the negative biopsies being the true negatives.

4.3. Risk stratification of prostate cancer

In the current study majority of patients (94.2%) had clinically organ-confined prostate cancer cT1-T2, 94.2%. Together with PSA < 10 ng/mL (133/243 54.7%) as well as Gleason 7 and below (210/243 86.4%) which might represent a relatively more indolent disease. This may be one of the possibilities for negative results as NLR as a systemic biomarker may be associated with more advanced disease. However, none of the other NLR studies had mentioned clinical staging so the direct comparison was not possible. Therefore, more prospective studies are required for further evaluation of the diagnostic and prognostic potential of NLR in early prostate cancer.

To our knowledge, the current study was the first to evaluate NLR value in the diagnosis of prostate cancer in patients who underwent transperineal biopsy. We used RTPB, which was a consistent accurate way of doing a prostate biopsy. And since the procedure was performed under GA, all CBC were done as pre-admission blood tests, which were more controlled and standardized. In addition, this was a consecutive series with relatively large sample size.

There are limitations to a retrospective study. We excluded patients who did not have a valid PSA before a biopsy, which might introduce selection bias. Although RTPB has a relatively lower cancer missing rate; there is still the chance of missing cancer in the biopsy. A large-scaled prospective study may be needed in this field.

5. Conclusions:

There was no statistically significant difference in NLR between the benign and prostate cancer group as a whole. The same results remained in the subgroup analysis according to different PSA levels and clinically significant and insignificant cancer. NLR is not a significant predictor for Gleason grade group and D'Amico risk stratification group and may have a limited role in predicting early-stage prostate cancer.

Author contributions

Data curation: Jingzeng Du, Ee Jean Lim, Hong Hong Huang.
Formal analysis: Jingzeng Du, Hong Hong Huang.
Investigation: Weber Kam On Lau.
Methodology: Weber Kam On Lau.
Project administration: Jingzeng Du, Weber Kam On Lau.
Supervision: Weber Kam On Lau.
Validation: Weber Kam On Lau.
Writing – original draft: Jingzeng Du, Ee Jean Lim.
Writing – review & editing: Jingzeng Du.

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