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

Du Jingzeng (pkudujz@gmail.com)
Singapore General Hospital
Ee Jean Lim
Singapore General Hospital
Hong Hong Hong Huang
Singapore General Hospital
Kam On Weber Kam On Lau
Singapore General Hospital

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Abstract

Background NLR is known to have prognostic value for metastatic prostate cancer (PCa). However for early PCa due to lack of systemic response; the role of NLR is not conclusive. In this study we aim to evaluate the predictive value of NLR for early clinical PCa in patients who underwent robotic transperineal prostate biopsy (RTPB). Methods Patients who underwent RTPB under general anesthesia (GA), at the Department of Urology, Singapore General Hospital between Sep 2006 and Feb 2016 were retrospectively reviewed. Exclusion criteria includes: 1. Patients with missing value of PSA NLR 2. Patients who underwent biopsy for non-diagnostic purposes. 3. Patients with chronic inflammation or high grade prostatic intraepithelial neoplasia. Patients who had more than one biopsies and only the last histology results were included in this study. NLR was calculated for all patients using Complete blood count that was done as pre-admission test before GA within 4 weeks before operation. NLR values were compared between PCa; clinical significant PCa and benign group. Patients were divided further into different groups according to PSA level for subgroup analysis. Results A total 652 patients who underwent RTPB for diagnostic purpose with valid pre-procedure PSA level were included in this study. There were total 409 (62.7%) benign histology and 243 (37.3%) PCa cases. Median NLR in the benign histology group and PCa group were 2.00 and 1.99. There was no statistically significant (P=0.29). In the subgroups analysis, there were also no significant difference of median NLR value in clinical significant cancer group (defined as Gleason 3 + 4 and above) when compared to benign group (NLR 2.00 vs. 2.01, P=0.41) as well as in prostate cancer group and benign group according to different pre-biopsy PSA levels (PSA < 4, 4-10, 10-20 and > 20 ug/L), respectively. (P>0.05). NLR is not a significant predictor for Gleason grade group and D'Amico risk stratification group. (P>0.05) Conclusion There were no statistical significant difference of NLR between benign and prostate cancer group as a whole or in the subgroup analyses for patients who underwent RTPB. NLR may have a limited role in predicting early prostate cancer.

Background

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 in this area.

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 taken from a standardized complete blood count (CBC) reading 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.

Methods

A total 652 patients who underwent RTPB for diagnostic purpose with valid pre-procedure PSA level were included in this study. Indications for RTPB were as follows: Biopsy naïve patients with raised PSA > 4 ng /ml; rising PSA > 4 ng/ml with previous negative TRUS biopsy patients; abnormal DRE with any PSA level; abnormal signal in B ultrasound or computed tomography or magnetic resonance imaging examination.

Patients with symptomatic prostatitis or urinary tract infection or systemic inflammatory disease were excluded. Besides, patients with high-grade prostatic intraepithelial neoplasia were also excluded. Patients who underwent multiple times of biopsy only the last histology were included in this study.

Clinical and laboratory assessment:

Method of biopsy:

In this study all patients underwent RTPB using Mona Lisa robotic device, 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 allow us to merge MRI prostate images with real-time prostate ultrasound for targeted biopsy.

CBC value:

As transperineal prostate biopsy is performed under GA, so all patients underwent standard pre-admission tests including CBC within 4 weeks before operation. All clinical and pathological data were extracted retrospectively from the electronic records and pathology reports in our institution and included serum PSA, hematological, and biochemistry testing with the permission of the ethical committee of the hospital. NLR was calculated by dividing the neutrophil count by the lymphocyte count.

Clinical parameters like age of diagnosis, number of biopsy cores, and histopathology biopsy results were collected. For patients who were diagnosed with PCa, Gleason score was also gathered.

In terms of subgroups analyses: Patients were categorized into groups of clinical significant cancer (Defined as Gleason Score (GS) $\geq$ 7 based on the pathology of the transperineal biopsies) as well as according to serum PSA levels.

Statistical analysis:

NLR values in different groups were compared using Mann-Whitney U test, respectively. Ordinal regression model was used to assess co-relation between NLR and Gleason score; NLR and D'Amico classification. All statistical analyses were conducted in Statistical Package for Social Sciences (SPSS) version 25.0 (SPSS Inc., Armonk, NY). Two-sided P value of <0.05 was considered statistically significant.

Results

There were a total of 944 patients who underwent RTPB at the Department of Urology, Singapore General Hospital between Sep 2006 and Feb 2016 (Figure 1). Among these patients 93 were excluded due to missing NLR and PSA parameters. Fourteen patients with biopsy results of HGPIN and chronic inflammation were also excluded. In addition, 141 patients who underwent biopsy for non diagnostic purposes (eg. Brachytherapy, active surveillance) were also excluded.

Among 44 cases who had more than one biopsies, only the last histology results were included in this study.

A total 652 patients who underwent RTPB for diagnostic purpose with valid pre-procedure PSA level were included in this study. Clinical demographics were shown in Table 1. Median PSA before biopsy was 8.9 ng/ml and median number of cores taken was 29 and overall median NLR was 2.00.

As shown in Table 2, there was no statistically significant difference of NLR between the benign and prostate cancer group (P = 0.29).

If defined Gleason 3 + 4 and above as clinical significant prostate cancer, there was no statistically significant difference of median NLR value in the clinical significant cancer group compare to benign histology group (Table 3, figure 2). We also compared NLR value in prostate cancer group and benign group according to different pre-biopsy PSA level. However, there was no statistically significant difference in the various PSA levels (Table 4, figure 3).

Of all 243 cases of prostate cancer, 93 patients underwent robotic radical prostatectomy. We compared the biopsy histology to prostatectomy histology and found 25 cases of upgraded histology. (According to AJCC 8^{th} edition histologic grade group). And we compared the NLR in these two groups of patients; there was no statistically significant different. (Table 5)

Gleason score and D'Amico risk stratification distribution as shown in Table 7–8. Ordinal regression model was used to assess correlation between NLR and Gleason score; NLR and risk stratification groups. NLR was not a significant predictor for Gleason grade groups (P = 0.27) and D'Amico risk stratification groups (P = 0.27). WHO 2016 edition of Pathology and Genetics: Tumours of the Urinary System and Male Genital Organs was used for Gleason score grading system.

Discussion

Previous articles had described the association of NLR and localized prostate cancer. Raised NLR was associated with higher incidence of prostate cancer. Kawahara's paper [5] first demonstrated NLR was significantly higher in localized prostate cancer patients. Total 810 patients who underwent TRUS biopsy with PSA 4–10 ng/ml were included in this study. Results revealed NLR was significantly higher in prostate cancer group compared to benign group. Conversely, Huang TB et al [6] 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. [7,8] 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. [9–11]

On the contrary, Yuksel et al [12] studied 873 cases who underwent TRUS biopsy. They divided histology into benign prostatic hyperplasia (BPH), prostatitis and prostate cancer and found out there was no significant difference of NLR between cancer and BPH group.

This study showed that there was no statistically significant difference of 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, Figure 3–4]

To assess the cancer detection yield and proportion of clinical significant prostate cancer disease of current series; we used published reference in this field. There was 54.3% of high-grade cancer patients in current series which was significantly higher than 3 of the studies except for one. And in terms of cancer cases load: in this study 34.2% of patients with PSA 4–10 ng/ml were cancer cases which was not significantly lower than published data. In summary current series contained more clinical 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:

1. Standardized samples of CBC

In this study all CBC were done as pre-admission test. This would be strictly done within 4 weeks of biopsy. Also this would ensure patients were in generally well condition and no systemic infective disease which can affect NLR significantly. If we compare this to other studies, 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.

2. Methods of prostate biopsy

All the previous publications regarding NLR in the diagnosis of prostate cancer were based on results of template TRUS biopsy. However non-targeted TRUS biopsy do have chance of missing cancer. Furthermore in articles that demonstrated positive predictive value of NLR; majority of the patients had

PSA between 4–10 ng/L indicated relatively low disease burden and higher chance of getting a false negative biopsy.

Pal RP et al studied 426 patients who underwent both TRUS biopsy and mapping transperineal prostate biopsy [13]. 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 this study all patients underwent transperineal prostate biopsy which can achieve relatively higher cancer detection rate. Due to 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 traditional 10–16 cores TRUS biopsy. Furthermore this series included 73 patients with MRI targeted biopsy which had higher cancer detection rate. Table 6 revealed that overall cancer detection rate in this series was 34.2% which was higher than two of the published NLR series. [6,8]

We did further analysis of prostate volume and biopsy histology and D'Amico risk stratification groups (Table 9–10) which revealed strong correlation (Estimate –0.025; OR = 1.026 and 1.025;$P<0.05$). This means small prostate were associated with higher cancer grade and higher cancer risk group. Similar findings were revealed in study of prostate volume and radical prostatectomy histology. [14]

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

3. Risk stratification of prostate cancer

In this 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 maybe one of the possibilities for negative results as NLR as a systemic biomarker maybe associated with more advanced disease. However none of the other NLR studies had mentioned clinical staging so 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 this 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 prostate biopsy. And since the procedure was performed under general anaesthesia, all CBC were done as pre admission blood tests, which were more controlled and standardized. In addition, this was a consecutive series with a relatively large sample size.

There are limitations as a retrospective study. We excluded patients who did not have a valid PSA before biopsy, which might introduce selection bias. Although RTPB has relatively lower cancer missing rate;

there is still chance of missing cancer in the biopsy. Large-scaled prospective study may be needed in this field.

Conclusions

There was no statistical significant difference of NLR between 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.

Declarations

Abbreviations

NLR: Neutrophil lymphocyte ratio

RTPB: Robotic transperineal prostate biopsy

HGPIN: High grade prostatic intraepithelial neoplasia

PCa: Prostate cancer

GS: Gleason Score

CBC: Complete blood count

IQR: Interquartile range

BPH: benign prostatic hyperplasia

Ethics approval and consent to participate:

This study was approved by Singhealth Centralised Institutional Review Board D. Reference number: 2018/3201

Consent for publication:

Not applicable

Availability of data and material:

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

Competing interests:

None of the contributing authors have any conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or material discussed in the manuscript.

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Authors' contributions:

Jingzeng Du: Data acquisition; manuscript written; design of the work

Ee Jean Lim: Data acquisition; manuscript written

Hong Hong Huang: Interpretation of data

Weber Kam On Lau: Concept and design of the work; manuscript modification

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Not applicable

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Tables

Table 1 Clinical characteristics

Number of patients	652
Age of biopsy (year)(IQR)	62.8 (58, 67)
Total PSA before biopsy (ng/ml) (IQR)	8.9 (6.5, 12.6)
Number of cores taken (IQR)	29 (25, 34)
NLR (IQR)	2.00 (1.55, 2.60)
Neutrophil count (IQR)	3.65 (3.01, 4.45)
Lymphocyte count (IQR)	1.89 (1.47, 2.28)
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%)
Biopsy naïve	176 (27.0%)
Previous negative biopsy	476 (73.0%)

IQR: Interquartile range

Table 2 Overall NLR in benign and prostate cancer group

	No. Patients	Median NLR (IQR)	P
Benign	409	2.00 (0.95)	0.29
Prostate cancer	243	1.99 (1.26)	

Table 3. NLR value in benign and clinical significant prostate cancer groups

	No. Patients	Median NLR (IQR)	P
Benign	409	2.00 (0.95)	0.41
Clinical significant cancer	132	2.01 (1.32)	

Table 4. NLR value in patients with different PSA levels

PSA (ug/L)	Histology	No. of Patients	Median NLR (IQR)	P
<4	Benign	7	1.34 (1.73)	0.84
	Malignant	6	1.76 (1.44)	
4-<10	Benign	239	1.97 (1.13)	0.29
	Malignant	127	1.97 (1.22)	
10-20	Benign	139	1.97 (0.83)	0.34
	Malignant	78	2.18 (1.32)	
>20	Benign	24	2.18 (0.53)	0.31
	Malignant	32	1.98 (1.08)	

Table 5 NLR and histology upgrading

	No. of patients	Median NLR (IQR)	P value
Upgraded group	25	2.21 (0.87)	0.527
Not upgraded group	68	2.04 (1.54)	

Table 6

Studies	Rate for high grade disease[1]	P Value	Parentage of cancer cases[2]	P Value
Current series	54.3% (132/243)	-	125/366 (34.2%)	-
Kawahara T et al [5]	20.6% (71/344)	0.00	357/810 (44.1%)	0.00
Huang TB et al [6]	65.9% (209/317)	0.01	30.5% (50/164)	0.43
Oh JJ et al [7]	15% (166/1106)	0.00	No data available	-
Gokce MI et al [8]	31.7% (194/611)	0.00	28.3% (1106/3913)	0.02

1. High grade disease definition: Gleason 7 and above
2. Only calculated for patients with PSA between 4 to 10 ng/ml.

Table 7 NLR in different Gleason score grade groups

Gleason grade Group	N	Mean NLR
0 (Benign)	409	2.18
1	111	2.29
2	65	2.27
3	34	2.28
4	26	2.35
5	7	2.31
Total	652	2.22

Table 8 NLR in different D’ Amico risk stratification groups

D’Amico risk classification	N	Mean NLR
Benign	409	2.18
Low risk	73	2.32
Intermediate risk	91	2.20
High risk	79	2.36
Total	652	2.22

Table 9 Prostate volume and Gleason grade group

Gleason grade Group	N	Prostate Volume
0 (Benign)	399	41.3
1	109	37.3
2	62	32.7
3	33	30.0
4	25	33.4
5	6	33.7
Total	634	38.8

Table 10 Prostate volume and D’Amico risk classification

D’Amico risk classification	N	Prostate Volume (ml)
Benign	399	41.3
Low risk	72	35.5
Intermediate risk	88	32.8
High risk	75	35.6
Total	634	38.8

Figures

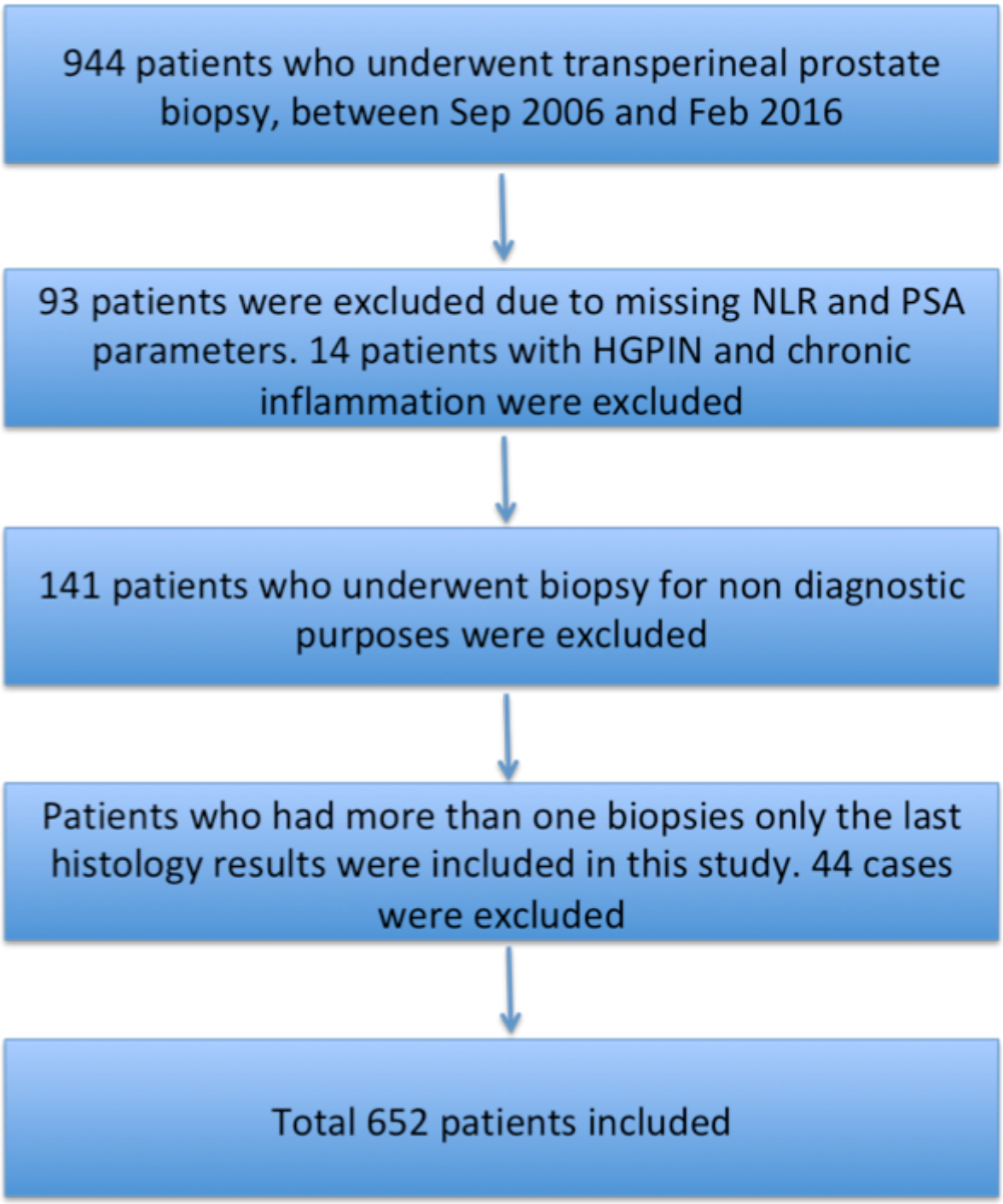

Figure 1

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

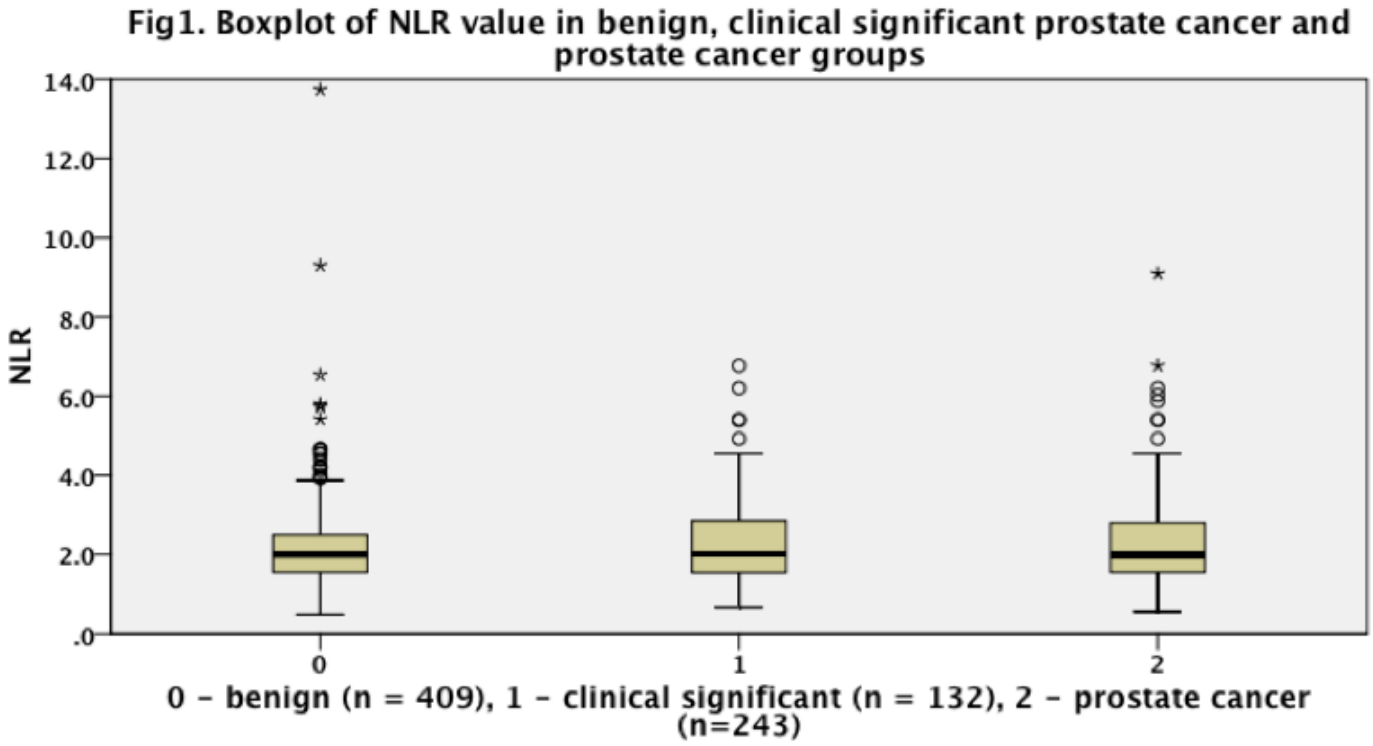

Figure 2

Boxplot of NLR value in patients with different PSA levels

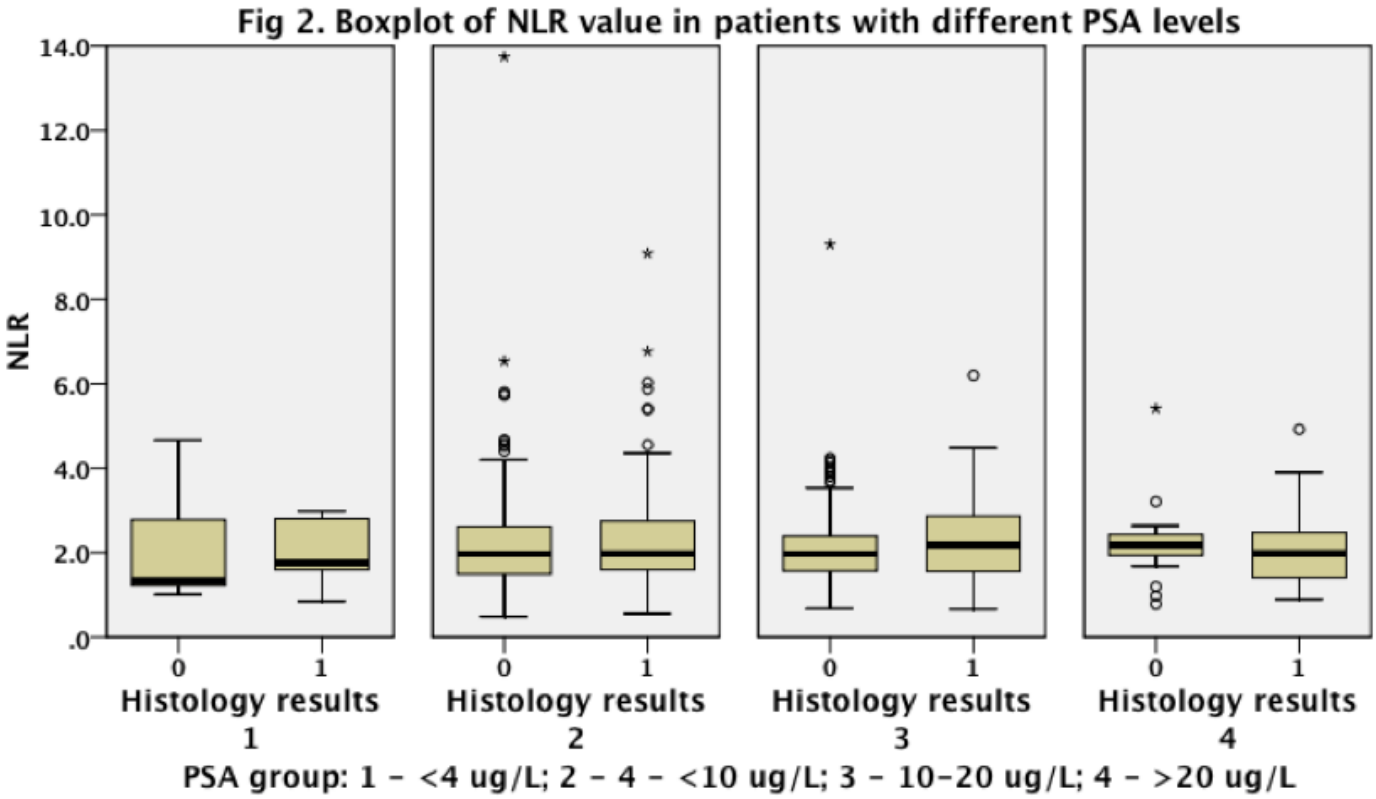

Figure 3

Patients selection

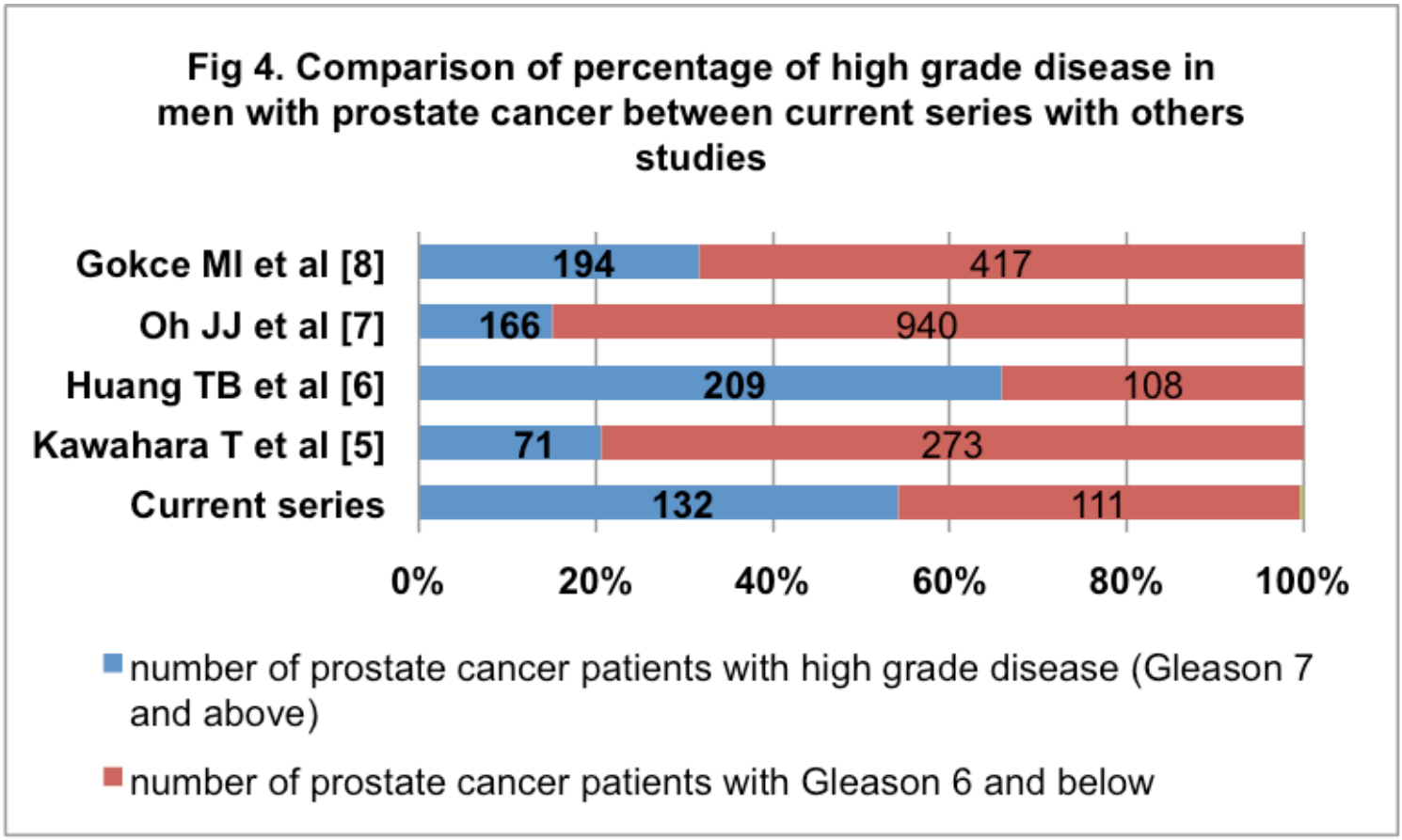

Figure 4

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

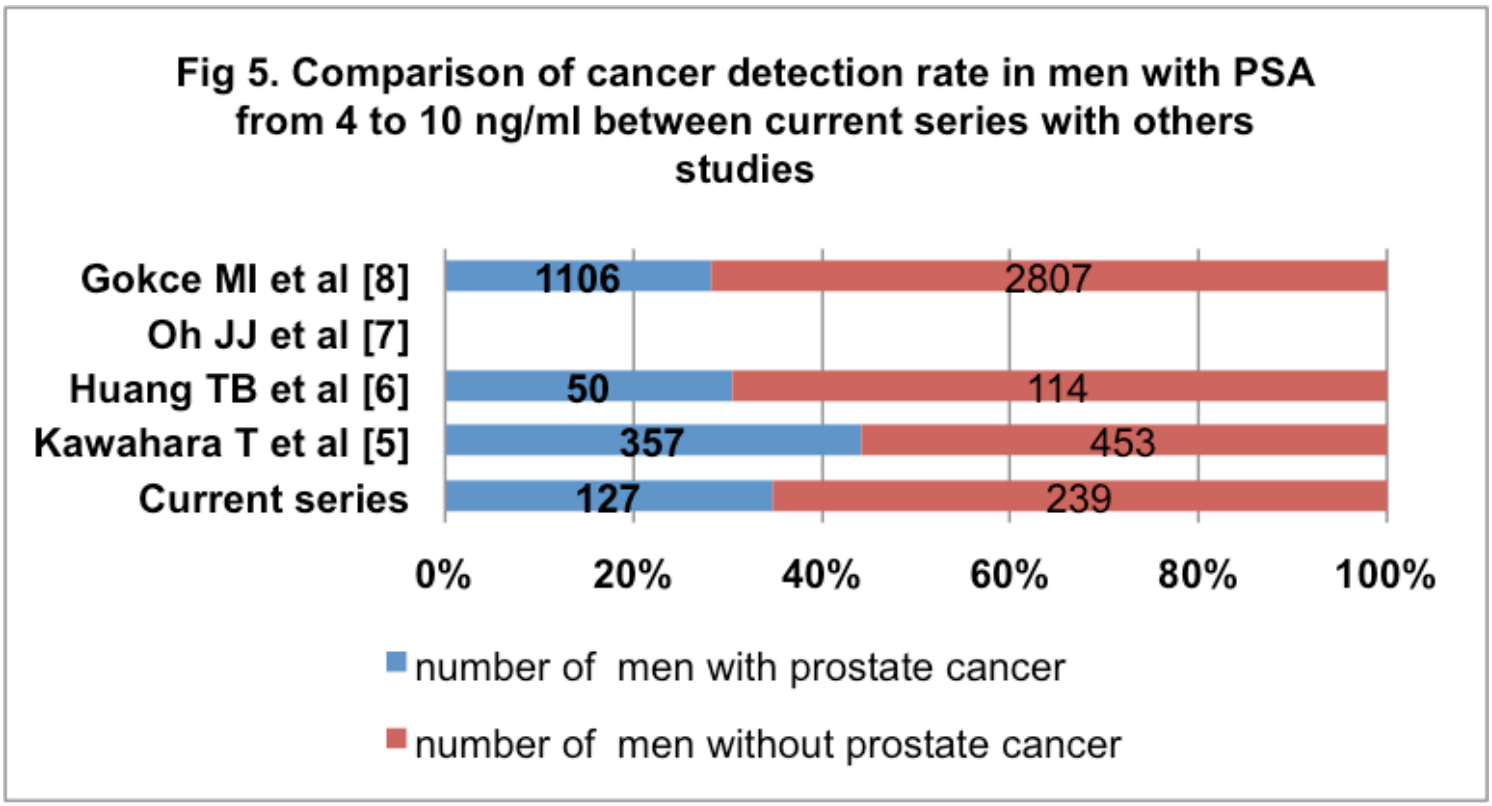

Figure 5

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