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The prognostic value of the neutrophil/lymphocytes ratio (NLR) in renal oncology : a review

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ABSTRACT (100 words)

The neutrophils/lymphocytes ratio (NLR) is a biological marker of inflammation with a demonstrated prognostic value in the field of oncology. In this review we discussed the prognostic value of the NLR in renal cell carcinomas (RCC), where several multiparametric nomograms already existed. For localized RCC, a NLR <3 was predictive of a reduced risk of recurrence. In metastatic or locally advanced RCC, a NLR <3 predicted an increased overall survival, progression-free survivals and response to systemic treatment. In current practice the NLR is a simple costless prognostic factor with potential improvement in the prognostic performance of nomograms used in renal oncology.

1. INTRODUCTION

The neutrophils/lymphocytes ratio (NLR) is a marker of inflammation and an independent prognostic factor for many cancers [1]. For these cancers, the NLR has been identified as a poor prognostic factor of overall survival, disease-specific survival, and free-progression survival for metastatic cancer [1]. For the colorectal cancer, Walsh et al reported in 2005 that a RNL > 5 at the diagnosis was an independent prognostic factor of decreased overall survival and specific survival [2]. For small cells lung cancer, a NLR > 4 at the diagnosis was associated with a poor performance status, a locally advance disease and a poor response to systemic treatment [3]. The prognostic value of the NLR was also confirmed for gastric, liver and ovaric cancer [4–6].

The NLR may also have a prognostic value for urological cancers [7,8]. To date, the prognostic systems validated for renal cell carcinoma (RCC), such as the score UISS for localized RCC and the MSKCC score (Memorial Sloan Kettering cancer Center) modified by Heng for metastatic RCC, took into account a combination of clinical criteria (ECOG or Karnofsky), biological criteria (LDH, calcium, haemoglobin, neutrophils), histological criteria (Fuhrman) and imaging parameters (tumor size) but excluded the NLR [9,10]

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The objective of this work was to conduct a review of the literature evaluating the prognostic impact of the NLR in RCC and to compare the relevance of this single biological ratio with the multifactorial nomograms.

2. MATERIAL AND METHODS

2.1. *Search strategy and eligibility criteria*

We conducted a literature review in March 2016 in the PubMed database. The search algorithm was "Kidney Neoplasms" [MeSH] AND"neutrophil lymphocyte ratio" (all fields). Studies evaluating the prognostic value of the NLR in kidney cancer were included. We excluded the references dealing with others cancers than RCC. The language restriction was limited to articles in French and English. We excluded case reports, editorial, conference abstracts and reviews. A first screening of the articles was performed with the titles and the abstracts. A second screening was performed with the full texts to definitely include/exclude the studies for this review.

2.2. Extraction and analysis of data

In the included studies, we took into account the following datas: the type and level of evidence of the study, the number of patients, the age at the diagnosis, the NLR and the time of its dosage (NLR pretreatment vs. post -treatment), the initial staging of the RCC (localized vs metastatic), the type of treatment and the oncological outcomes. The primary endpoint was the overall survival for metastatic disease and the recurrence free-survival for localized disease. Secondary outcomes were the specific survival and the progression-free survival. A synthesis of the datas was performed with Review Manager 5.2 software (Informatics and Knowledge Management Department, Cochrane, London, UK).

3. RESULTS

3.1. Search results

The PRISMA diagram of the literature search is presented in Figure 1. The initial research identified 31 publications. Twenty five references matched the inclusion criteria.

According to the full text screening, 15 studies were finally included. One study was excluded for a lack of datas. We included 7 studies concerning metastatic or locally advance renal cancer, and 6 studies dealing with localized renal cancer. Two articles evaluated the NLR in renal cancer whatever the status of the disease (metastatic or localized). The characteristics of the included studies are summarized in Table 1.

3.2. NLR and localized renal cancer (Table 2)

In the 6 studies included in the review, a high NLR at the time of the diagnosis was significantly associated with an increased risk of recurrence compared with a low NLR (Hazard ratio 1.63 [1.15-2.29]). The NLR was not significant for the overall survival (Figure 2 A, B).

The pre-treatment NLR was determined on a preoperative blood test. The threshold of NLR among the 6 included studies ranged from 2.7 to 5. All the patients had a surgical treatment with total or partial nephrectomy. The mean follow-up was from 3.3 to 9.3 years.

The NLR was an independent prognostic factor for recurrence in three studies. A high NLR was associated with a risk of recurrence ranging from 1.17 to 3.12 (1 excluded) in multivariate analysis.

The post-nephrectomy NLR was evaluated in one study and was associated with an increased risk of recurrence (Table 2).

For Grivas and al and De Martino and al, a NLR superior to 2.7 was a predictive factor of a metastatic lymph node disease on the final histology ($p = 0.04$)[11,12]. In multivariate analysis, a preoperative NLR superior to 2.7 was a prognostic factor for recurrence but not for the overall survival.

Ohno et al analysed the kinetics of the NLR at different timelines : before nephrectomy, after nephrectomy and at the recurrence[13]. In this study including 250 nephrectomies for localized

conventional cells renal carcinoma, the 10 years recurrence free survival was significantly higher for patients with a NLR inferior to 2.7 at the diagnosis (64.4% vs 83.7%, p = 0.0004). The patients who had a high NLR prior to nephrectomy and normalized the NLR after nephrectomy were at greater risk of recurrence: disease free survival at 10 years 52% vs 83.5% (p=0.0487). For these patients, the recurrence corresponded to a re-rise of the NLR above 2.7 (p = 0.009)[13].

3.3. NLR and locally advanced or metastatic renal cancer (Table 3)

We included 7 studies dealing with the NLR in metastatic or locally advanced RCC. The mean follow-up was 15 to 46.9 months. These studies demonstrated that a high NLR was an independent prognostic factor of decreased overall survival and progression-free survival. The NLR at the diagnosis was significantly associated with symptomatic tumors, the presence of lymph node metastasis, and a high inflammatory syndrome. The NLR was an independent predictor of the benefit of a cytoreductive nephrectomy in metastatic disease.

(Figure 2 C, D).

Ohno et al observed that the median overall survival was significantly better in the nephrectomy group (28.3 vs 6.1 months p <0.0001)[14]. In the nephrectomy group, a sub group of patients with a high RNL had a median survival similar to the non-nephrectomized patients. For the patients who had a cytoreductive nephrectomy, the overall survival was significantly decreased when the preoperative NLR was above 4 before the treatment (p = 0.002)[14].

Keizman and al demonstrated a correlation between the pre-treatment NLR and the response to systemic therapy (Sunitinib), the progression free survival and the overall survival. In their series of 133 metastatic patients, a NLR below 3 at the diagnosis was associated with a better

progression-free survival: 15 months vs 4 months (p <0.001) and a better overall survival: 29 months vs 14 months (p = 0.04)[15].

3.4. NLR and renal cancer regardless metastatic status

Two recent studies evaluated the NLR regardless of the status of the disease (localized or metastatic). In a retrospective study Keskin et al determined that the NLR was a prognostic factor of mortality OR = 3.21 95% CI (1.26 to 8.16) p = 0.014, in the same way with the age, the haemoglobin and creatinine levels [16].

4. DISCUSSION

In this review, we found that the NLR was a simple and cheap biomarker with a prognostic value in all stages of renal cell carcinoma, either localized or metastatic. In the localized kidney cancer, a high NLR was an independent prognostic factor of recurrence-free survival. In metastatic kidney cancer, a high NLR was an independent prognostic factor for progression-free survival, overall survival, the response to systemic treatments and the cytoreductive nephrectomy.

The NLR was a marker of inflammation and reflected the activity of the immune system. Several studies reported the key role of inflammation in carcinogenesis. The hypothesis was that chronic inflammation favoured the tumor development by preventing / suppressing any anti-tumor activity of the immune system[17–19]. A high NLR could be the marker of both a systemic and a local inflammation, which could create a favourable microenvironment for the development of the tumor and the metastases[20,21].

In the context of a locally advance advanced renal cell carcinoma, Sejima et al demonstrated a connection between the value of the NLR, and the level of activity of the immune system measured by the rate of Fas ligand (FasL). The Fas ligand was a surface receptor involved in

the cell apoptosis by the action of cytotoxic T Cell[22]. The level of expression of FasL was significantly associated with the appearance of metastasis, the risk of recurrence and the value of the NLR. For locally advanced disease, a low NLR was correlated with a high level of FasL and an increased overall survival. The patients with a metastatic disease at the time of diagnosis had a significantly higher NLR, and a decreased level of expression of FasL ($p = 0.0004$). This study suggested the existence of an association between the NLR and the local expression of the FasL for the prognosis of locally advanced renal carcinomas[22].

Among the studies referenced in this review, the mean threshold of NLR was 3.3 and ranged from 2.7 to 5. For localized kidney cancer, only 2 studies (Viers et al Forget et al) did not show a significant correlation between a high NLR and an increased risk of recurrence ($p = 0.09$ and $p = 0.07$)[23,24]. Both studies considered a higher threshold of NLR than the others references, with respectively 4 and 5. These thresholds corresponded to the thresholds used in thoracic and colorectal oncology, and were probably too high for kidney cancer [1]. However these two studies confirmed in multivariate analysis the prognostic value of the NLR for overall and specific survivals. For kidney cancer, it would be reasonable to consider an RNL threshold of 3, which is lower than for colorectal and lung cancer[1].

To this date, we didn't find a study comparing the NLR to prognostic scores currently validated in renal oncology. However Cetin et al demonstrated in a multivariate analysis, that a low NLR at the diagnosis in metastatic kidney cancer was as strong as a low MSKCC score to predict the overall survival [27]. After six months of follow up, the NLR was the only independent predictor of progression-free survival.

The study by Fox et al, including 362 patients was a multicenter prospective randomized phase III trial, whose objective was to study the biological markers of inflammation (albumin, neutrophils, lymphocytes, platelets, and report RNL platelets / cell) as oncological prognostic factors[28]. Among the biological factors, only the NLR with a threshold of 3 was predictive of

a decreased overall survival (p = 0.008), as well as the isolated elevation of neutrophils (P = 0.01) or platelets (p = 0.01). When these independent prognostic factors were associated with the MSKCC score, the prognostic performance of the MSKCC nomogram was improved from 0.654 to 0.673 (p = 0.002) and 25% of the patients were better classified in the prognostic groups [32]. Grivas et al shew that the NLR was the only biological parameter significantly correlated with the overall survival among the haemoglobin, the blood levels of calcium and sodium, or the rate of alkaline phosphatase [11]. For Ramsey et al, the C-reactive protein (CRP) is an other marker of inflammation strongly correlated to the survival rate (p = 0.028)[25]. Ohno and al also demonstrated that there was a correlation between the NLR and the CRP (p= 0.0001)[26]. In daily practice, the NLR is extremely simple to use. It can be calculated systematically on pre and post-operative standard blood tests.

Currently there are no recommendations on the use of RNL renal oncology. The studies reported on this subject were few, mainly retrospective and low numbered. It would be interesting to confirm these data in a prospective study, comparing the NLR to the referring scores in renal cancer (UISS, MSKCC score changed by Heng).

5. CONCLUSIONS

In conclusion, this review demonstrated that a high NLR indicated with a poorer prognosis for patients with RCC. For localized kidney cancer, a NLR <3 was predictive of a reduced risk of recurrence. In metastatic or locally advanced kidney cancer, a RNL <3 predicted a better overall survival and progression-free survival. In metastatic kidney cancer, the NLR was independent from the MSKCC score in multivariate analysis. Currently there are no recommendations on the use of RNL renal oncology. Further investigations are needed to clearly validate the inclusion of the NLR in a score or nomogram.

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Figure 1: PRISMA flow diagram

Figure 2: (A) Effect of NLR on recurrence in localized renal cancer; (B) Effect of NLR on overall survival in localized renal cancer; (C) Effect of NLR on overall survival in locally advanced/metastatic renal cancer; (D) Effect of NLR on progression free survival in locally advanced/metastatic renal cancer. Mean values with 95% confidence intervals.

Table 1. Characteristics of included studies

RFS=Recurrence Free Survival, NP=Not Precised, DFS=Disease Free Survival, PFS=Progression Free Survival, OS=Overall Survival

Table 2. Oncological outcomes of NLR in localized RCC.

Abbreviations : HR=Hazard Ratio, OS = Overall Survival, IC = Confidence Interval, DFS = Disease Free Survival, PFS = Progression Free Survival, NA = Not Analysed

Table 3. Oncological outcomes of NLR in locally advanced/metastatic RCC.

Abbreviations : HR=Hazard Ratio, OS = Overall Survival, CI = Confidence Interval. NA = Not Analyzed

Table 1. Characteristics of included studies

Author	Year	Journal	Type of study	Stade	NLR Threshold	patients (low NLR vs high NLR)	Treatment	Follow up (months)	Outcomes
Viers et al[23]	2014	Urol Oncol	Retrospective	Localized	4	827 (476 vs 351)	Nephrectomy	Median 111 (72-144)	RFS,DFS, OS
Forget et al[24]	2013	Ann Surg	Retrospective	Localized	5	227 (175 vs 52)	Nephrectomy	Median 74,5 (31-112)	DFS, OS
De Martino et al[12]	2013	J urol	Retrospective	Localized	3,6	352 (NP)	Partial or total Nephrectomy	Meann 49 (15-71)	DFS
Grivas et al[11]	2014	Urol Ann	Retrospective	Localized	2,7	114 (NS)	Partial or total Nephrectomy	Median 69 (1-179)	DFS, OS
Ohno et al[13]	2012	J Urol	Retrospective	Localized	2,7	250 (166 vs 84)	Partial or total Nephrectomy	Mean 75 (+/- 54)	DFS
Ohno et al [13]	2010	J Urol	Retrospective	Localized	2,7	192 (NS)	Néphrectomy	Mean 93 (6-232)	DFS
Hatakeyama et al[30]	2013	BMC Urol	Retrospective	Locally advanced /Metastatic (53%)	NP	85	Nephrectomy + thrombectomy vs immunotherapy or Interferon α	Median - surgery 26 - Imm or INF α 5	OS
Ohno et al[14]	2014	Int J Clin Oncol	Retrospective	Metastatic	4	73 (NS)	Néphrectomy+/- Interferon α +/- interleleukin-2	Mean 20,6 (1-114)	OS
Cetin et al[27]	2013	Clin. Genitourin. Cancer	Retrospective	Metastatic	3,04	100 (50 vs 50)	INF α + VEGF (Sunitinib, Sorafenid,	Median 15 (1-53)	PFS, OS

Table 1. Characteristics of included studies

							pazopanib)		
Keizman et al[15]	2012	Eur. J. Cancer	Retrospective	Metastatic	3	109 (54 vs 55)	Sunitinib vs other	Median 37 (5-85)	PFS, OS
Santoni et al[31]	2013	Br. J. Cancer	Retrospective	Metastatic	3	97 (59 vs 38)	Everolimus (2nd or 3rd ligne)	Median 46,9 (39,9-53,9)	SSP, OS
Fox et al[28]	2013	Br. J. Cancer	Phase III Randomized Control Trial	Locally advanced /Metastatic	3	362 (174 vs 188)	Trial EGF20001 lapatinib vs antiangiogenic	NS	OS
Keskin et al[16]	2014	BMC Urology	Retrospective	Locally advanced	NP	211	nephrectomy	Mean 24	OS
Sejima et al[22]	2013	Urol Onco	Retrospective	Locally advanced	NP	35	nephrectomy	Mean 16,8 (6 – 29,6)	PFS
Koo et al[32]	2016	Int Urol Nephrol	Retrospective	Metastatic	2,5	478	Immunotherapy, antiangiogenic +/- cytoreductive nephrectomy	NS	OS

RFS=Recurrence Free Survival, NP=Not Precised, DFS=Disease Free Survival, PFS=Progression Free Survival, OS=Overall Survival

Table 2. Oncological outcomes of NLR in localized RCC.

Authors	Journal	Year	NLR Timeline	Patients	NlR Threshold	Multivariate analysis					
						DFS (HR)	IC 95%	p	OS (HR)	IC 95%	p
Viers et al[23]	Urol Oncol	2014	pre op	827	4	1,01	1 - 1,03	0,001	1,02	1,01-1,04	**0,001**
Forget et al[24]	Ann Surg Oncol	2013	pre op	227	5	1,56	0,94-2,61	0,07	1,67	1,00-2,81	**0,05**
De Martino et al[12]	J Urol	2013	pre op	352	3.6	3,07	1,37-6,88	**0,02**	NA	NA	NA
Grivas et al[11]	Urol Ann	2014	pre op	114	2.7	(SSP) 1,23	0,95-1,59	0,113	2,87	1,08-7,59	**0,034**
Ohno et al[29]	J Urol	2012	Pre and Post-op	250	2.7	3.12	1.61-6.05	**0.001**	_	_	_
Ohno et al[26]	J Urol	2010	Pre-op	192	2.7	2.16	1.10-4.27	**0.02**	_	_	_

Table 2. Oncological outcomes of NLR in localized RCC.

Abbreviations : HR=Hazard Ratio, OS = Overall Survival, IC = Confidence Interval, DFS = Disease Free Survival, PFS = Progression Free Survival, NA = Not Analysed

Table 3. Oncological outcomes of NLR in locally advanced/metastatic RCC.

Authors	Journal	Year	Patients	NLR Threshold	Multivariate analysis		
					OS HR	IC 95%	p
Hatakeyama et al[30]	BMC Urology	2013	85	**NA**	1.250	1.034-1.513	**0.021**
Ohno et al[14]	Int J Clin Oncol	2014	73	**4**	3.425	1.549-7.232	**0.001**
Cetin et al[27]	Clin. Genitourin. Cancer	2013	100	**3.04**	2.406	1.327-4.361	**0.004**
Keizman et al[15]	Eu J Cancer	2014	109	**<3**	2,95	1,71 – 5,09	**0.043**
Santoni et al[31]	BJC	2013	97	**3**	2.27	1.16-4.30	**0.003**
Fox et al[28]	BJC	2013	362	**3**	1.42	1.10-1.84	**0.008**
Koo et al[32]	Int Urol Nephrol	2016	478	**2.5**	1.907	1.353-2.690	**0.015**

Abbreviations : HR=Hazard Ratio, OS = Overall Survival, CI = Confidence Interval. NA = Not Analyzed

Figure 1

Figure 1: PRISMA flow diagram

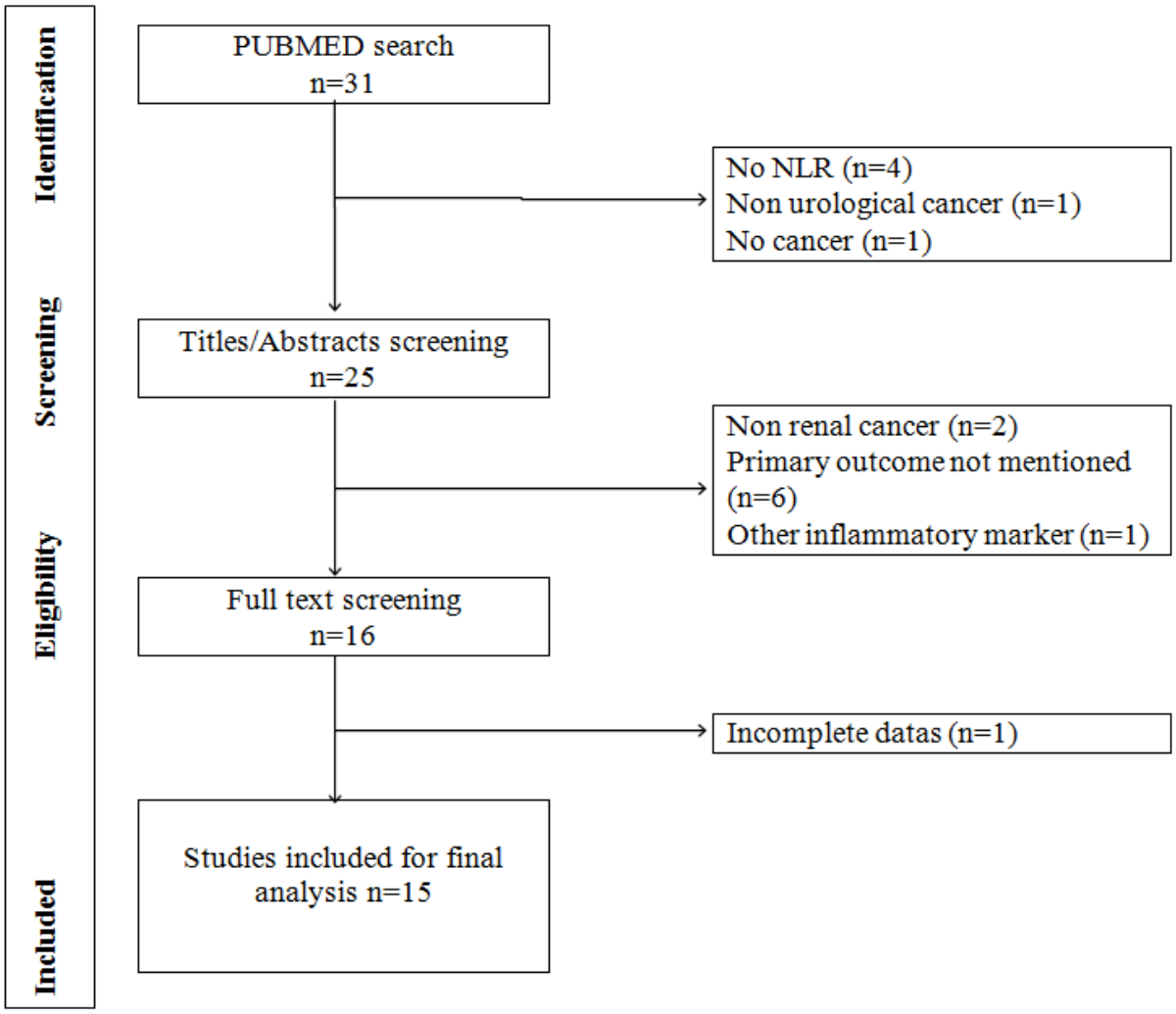
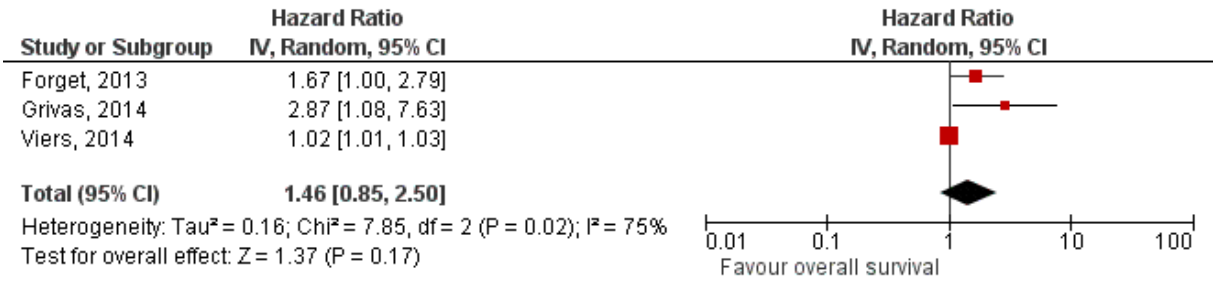
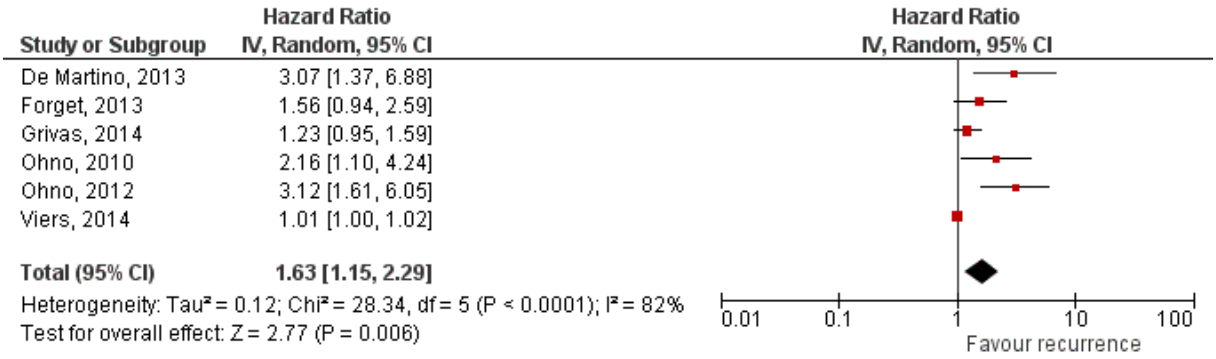


Figure 2: (A) Effect of NLR on recurrence in localized renal cancer; (B) Effect of NLR on overall survival in localized renal cancer; (C) Effect of NLR on overall survival in locally advanced/metastatic renal cancer; (D) Effect of NLR on progression free survival in locally advanced/metastatic renal cancer. Mean values with 95% confidence intervals.

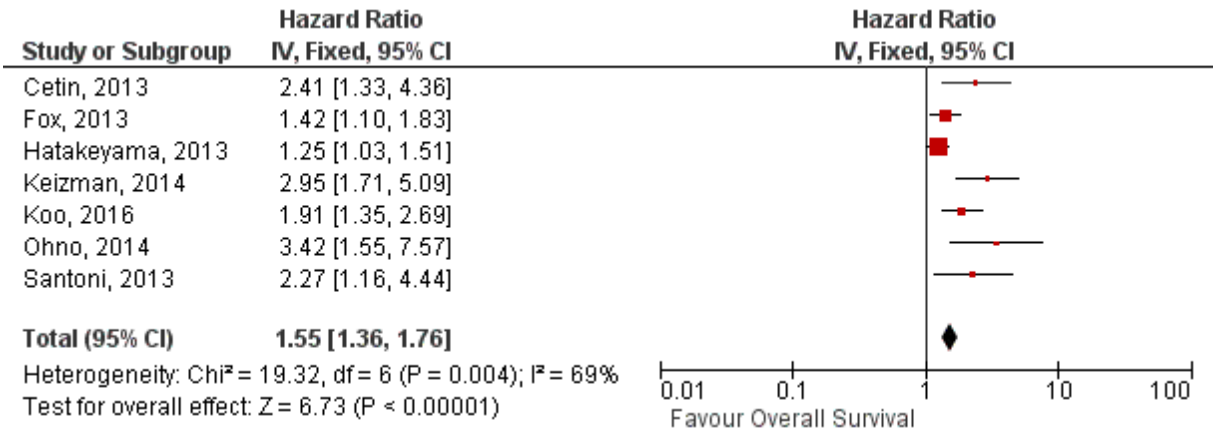
A



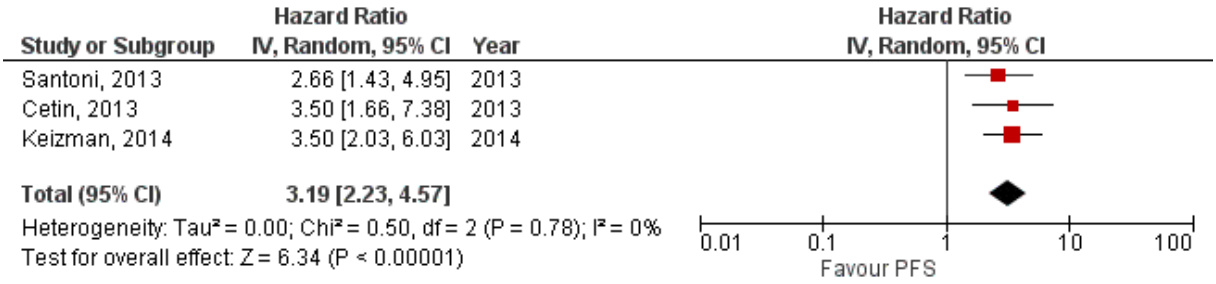
B



C



D


Hazard Ratio
Study or Subgroup
IV, Random, 95% CI
Year
Hazard Ratio
IV, Random, 95% CI
Santoni, 2013
2.66 [1.43, 4.95]
2013
Cetin, 2013
3.50 [1.66, 7.38]
2013
Keizman, 2014
3.50 [2.03, 6.03]
2014
Total (95% CI)
3.19 [2.23, 4.57]
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 2 (P = 0.78); I² = 0%
Test for overall effect: Z = 6.34 (P < 0.00001)
0.01
0.1
1
10
100
Favour PFS