Can preoperative neutrophil lymphocyte ratio predict malignancy in patients undergoing partial nephrectomy because of renal mass?

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ABSTRACT

Purpose: To evaluate the importance of preoperative neutrophil lymphocyte ratio (NLR) predicting malignancy in patients who undergo partial nephrectomy due to renal mass.

Materials and Methods: Seventy nine patients who underwent open partial nephrectomy for renal masses were included in this retrospective study. In preoperative routine blood tests, renal ultrasonography and contrast-enhanced computed tomography were performed for all patients. Preoperative neutrophil lymphocyte ratio were compared in patients with clear cell renal cell carcinoma (Group 1, 65 patients) and benign lesions (Group 2, 14 patients). The predictive ability of NLR was analyzed by ROC curves and Youden Index method was used to identify the cut-off value for NLR.

Results: The mean age of patients was 59.8±11.7 years in Group 1 and 57.4±12.6 years in Group 2 (p=0.493). The mean tumor size was 3.8±1.2 cm in Group 1 and 3.3±1.0 cm in Group 2 (p=0.07). The median NLR was 2.48 (1.04) in Group 1 and 1.63 (0.96) in Group 2 (p<0.001). The area under a ROC curve was 0.799 (p<0.001).

Conclusions: Preoperative neutrophil lymphocyte ratio may predict renal masses that can not be distinguished radiologically. Our results must be confirmed by large and properly designed prospective, randomized trials.
flammation markers have been validated as predictive in various types of cancer (15-17).

The neutrophil to lymphocyte ratio (NLR) is also a widely used inflammatory marker that is defined as the absolute neutrophil count divided by the absolute lymphocyte count, and can be easily determined from complete blood cell parameters (18).

Unfortunately, radiological methods are still not sufficient for predicting malignancy. This can lead to unnecessary surgery in patients with benign renal masses. In this study, we investigated the importance of preoperative neutrophil lymphocyte ratio predicting malignancy in undistinguished radiological renal masses. This is the first study in the literature.

MATERIALS AND METHODS

Seventy nine patients who underwent open partial nephrectomy for renal masses were included in the study between 2006 and 2015. Patient data were analyzed retrospectively. In preoperative routine blood tests, renal ultrasonography and contrast-enhanced computed tomography were performed in all patients. NLR was compared in patients with clear cell RCC (Group 1, 65 patients) and benign lesions (Group 2, 14 patients). The predictive ability of NLR was analyzed by ROC curves and Youden Index method was used to identify the cut-off value for NLR.

Statistical Method

Normality distribution was investigated for all numeric variables. Categorical variables were described by frequencies and percentages and numeric variables were described by means and standard deviations or medians and interquartile ranges. The relationship between two categorical variables was tested by Chi-square test. Two independent means was compared by Student t test and two independent medians were compared by Mann Whitney U test. The predictive ability of NLR was analyzed by ROC curves and Youden Index method was used to identify the cut-off value for NLR. A p value less than 0.05 was accepted as statistically significant.

RESULTS

Mean age of patients was 59.8±11.7 years in Group 1 and 57.4±12.6 years in Group 2 (p=0.493). Mean tumor size was 3.8±1.2cm in Group 1 and 3.3±1.0cm in Group 2 (p=0.07). The median NLR was 2.48 (1.04) in group 1 and 1.63 (0.96) in group 2 (p<0.001). Both groups were similar in terms of sex and tumor side (Table-1) 14 patients had benign lesions. Eight patients had oncocytoma, 3 patients had calcified cyst, 2 patients had osseous metaplasia and 1 patient had angiomylipoma.

Forty three (66.2%) of 65 patients had pT1a tumor and 22 (33.8%) of 65 patients had pT1b tumor 15 patients had grade 1 tumor, 46 patients had grade 2 tumor and 4 patients had grade 3 tumor. Optimal cut-off value of NLR was 1.725, with sensitivity of 93.8% and specificity 64.3% (Table-2).

The area under the ROC curve was 0.799 (p<0.001) (Figure-1). Predictive probability of NLR for tumor stage and grade were statistically insignificant (p=0.852) (Figures 2 and 3).

DISCUSSION

Increasing evidences support the involvement of systemic inflammation in cancer development and progression (9). It has been shown that, among the leukocytes in circulation, neutrophils increase and lymphocytes decrease as a systemic inflammatory response develops against the tumor. NLR has been used as an indicator of systemic inflammatory response (18).

An elevated NLR reflects both a decreased lymphocyte mediated antitumor immune response and a increased neutrophil dependent inflammatory reaction. Both of these factors may contribute to aggressive tumor biology, cancer progression, and poor prognosis (19, 20).

Despite recent progress in the identification of genetic, epigenetic and common molecular alterations in RCC (21), routine diagnostic and prognostic assessment of RCC currently relies on pathological tissue examination and traditional clinicopathological prognostic variables (22). The complexity of these molecular changes, as well as
Table 1 - Descriptive characteristics of the patients.

|                    | Group 1 (n=65) | Group 2 (n=14) | p       |
|--------------------|----------------|----------------|---------|
| Age (Mean±SD)      | 59.8±11.7      | 57.4±12.6      | 0.493   |
| Sex (n, %)         |                |                |         |
| Male               | 35 (53.8)      | 6 (42.9)       | 0.455   |
| Female             | 30 (46.2)      | 8 (57.1)       |         |
| Side (n, %)        |                |                |         |
| Right              | 35 (53.8)      | 7 (50)         | 0.794   |
| Left               | 30 (46.2)      | 7 (50)         |         |
| Size (cm) (Mean±SD)| 3.8±1.2        | 3.3±1.0        | 0.077   |
| NLR (Median, IQR)  | 2.48 (1.04)    | 1.63 (0.96)    | <0.001  |

RCC = Renal cell carcinoma; SD = Standard deviation; IQR = Interquartile range

Table 2 - Cut-off values of NLR for malignancy.

|                | Cut-off values | Sensitivity % | Specificity % |
|----------------|----------------|---------------|---------------|
| Optimal        | 1.725          | 93.8          | 64.3          |
| Max Sensitivity| 1.275          | 100           | 7.1           |
| Max Specificity| 3.035          | 29.2          | 100           |

NLR = neutrophil lymphocyte ratio

Figure 1 - NLR predictive probability of the malignancy.

Figure 2 - NLR predictive probability of tumor stage.

NLR = neutrophil lymphocyte ratio
high costs of analyses, time-consuming preparation required and lack of evidence demonstrating how these newly discovered molecular markers influence diagnostic or therapeutic decisions, have rendered none of the markers available for routine testing.

Recently, several serum biomarkers and hematological indices representative of inflammatory response, notably C reactive protein (CRP), fibrinogen, lymphocyte-monocyte ratio, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio, have been demonstrated to be closely related to poor prognosis of patients with RCC (23-25). Therefore, NLR, defined as neutrophil counts divided by lymphocyte counts, is particularly noteworthy. Emerging evidences demonstrated that NLR showed its prognostic value in patients with colorectal cancer (26) and hepatocellular carcinoma (27). Patients with RCC with elevated levels of pretreatment NLR may be more likely to present a poorer clinical outcome (28).

There are other laboratory markers of systemic inflammation reaction besides NLR, such as CRP (29) and modified Glasgow prognostic score (30, 31), with a prognostic role in patients with RCC. Also, gene polymorphisms (32) and biological markers (33, 34) are suggested to be predictors of prognosis in patients with RCC. Although NLR is easy to measure, conditions such as active infection, inflammatory diseases, smoking behavior or stress at the time of blood collection may affect it (35).

In previous studies, it was demonstrated a relationship between poor prognosis and NLR. Unlike previous studies, we investigated the role of NLR in the malign-benign distinction. In the present study, we found that preoperative neutrophil lymphocyte ratio may predict renal masses that cannot be distinguished radiologically.

This study has several limitations. First, the study was retrospective. Second, NLR could be affected by different conditions, especially undetected diseases such as chronic infection, chronic disease, and autoimmune disorders, such as rheumatic disease. Third, the number of patients was especially low in the benign group. Our results should be confirmed by prospective randomized studies with large population patients. If confirmed, preoperative NLR will be an important tool to prevent unnecessary surgeries.

CONCLUSIONS

Preoperative neutrophil lymphocyte ratio might predict renal masses that cannot be distinguished radiologically. Our results must be confirmed by large and properly designed prospective, randomized trials.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. European Network of Cancer Registries. Eurocim version 4.0. European incidence database V2.3, 730 entity dictionary (2001), Lyon, 2001.
2. Lindblad P. Epidemiology of renal cell carcinoma. Scand J Surg. 2004;93:88-96.
3. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JW, Comber H, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49:1374-403.
4. Levi F, Ferlay J, Galeone C, Lucchini F, Negri E, Boyle P, et al. The changing pattern of kidney cancer incidence and mortality in Europe. BJU Int. 2008;101:949-58.

5. Patard JJ, Rodriguez A, Rioux-Leclercq N, Guillé F, Lobel B. Prognostic significance of the mode of detection in renal tumours. BJU Int. 2002;90:358-63.

6. Kato M, Suzuki T, Suzuki Y, Terasawa Y, Sasano H, Arai Y. Natural history of small renal cell carcinoma: evaluation of growth rate, histological grade, cell proliferation and apoptosis. J Urol. 2004;172:863-6.

7. Tsui KH, Shvarts O, Smith RB, Figlin R, de Kernion JB, Belldegrun A. Renal cell carcinoma: prognostic significance of incidentally detected tumors. J Urol. 2000;163:426-30.

8. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420:860-7.

9. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454:436-44.

10. Steffens S, Köhler A, Rudolph R, Eggers H, Seidel C, Janssen M, et al. Validation of CRP as prognostic marker for renal cell carcinoma in a large series of patients. BMC Cancer. 2012;12:399.

11. Dai J, Tang K, Xiao W, Yu G, Zeng J, Li W, et al. Prognostic significance of C-reactive protein in urolological cancers: a systematic review and meta-analysis. Asian Pac J Cancer Prev. 2014;15:3369-75.

12. de Martino M, Klatte T, Seemann C, Waldert M, Haitel A, Pichler M, Hutterer GC, Stojakovic T, Mannweiler J, Endesfelder D, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med. 2012;366:883-92. Erratum in: N Engl J Med. 2012;367:976.

13. Hu Q, Gou Y, Sun C, Ding W, Xu K, Gu B, et al. The prognostic value of C-reactive protein in renal cell carcinoma: a systematic review and meta-analysis. Urol Oncol. 2014;32:50.e1-8.

14. Tanaka N, Kikuchi E, Shiratoke S, Kanao K, Matsumoto K, Kobayashi H, et al. The predictive value of C-reactive protein for prognosis in patients with upper tract urothelial carcinoma treated with radical nephroureterectomy: a multi-institutional study. Eur Urol. 2014;65:227-34.

15. Wu Y, Fu X, Zhu X, He X, Zou C, Han Y, et al. Prognostic role of systemic inflammatory response in renal cell carcinoma: a systematic review and meta-analysis. J Cancer Res Clin Oncol. 2011;137:887-96.

16. Poole EM, Lee IM, Ridker PM, Buring JE, Hankinson SE, Tworoger SS. A prospective study of circulating C-reactive protein, interleukin-6, and tumor necrosis factor α receptor 2 levels and risk of ovarian cancer. Am J Epidemiol. 2013;178:1256-64.

17. Tanaka N, Kikuchi E, Matsumoto K, Hayakawa N, Ide H, Miyajima A, et al. Prognostic value of plasma fibrinogen levels in patients with localized upper tract urothelial carcinoma. BJU Int. 2013;111:857-64.

18. Zahorec R. Ratio of neutrophil to lymphocyte count—rapid and simple parameter of systemic inflammation and stress in critically ill. Bratisl Lek Listy. 2001;102:5-14.

19. Proctor MJ, Morrison DS, Taiwai D, Balmer SM, Fletcher CD, O’Reilly DS, et al. A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study. Eur J Cancer. 2011;47:2633-41.

20. Ishizuka M, Nagata H, Takagi K, Iwasaki Y, Kubota K. Combination of platelet count and neutrophil to lymphocyte ratio is a useful predictor of postoperative survival in patients with colorectal cancer. Br J Cancer. 2013;109:401-17.

21. Gerlinger M, Rowan AJ, Horswell S, Math M, Larkin J, Endesfelder D, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med. 2012;366:883-92. Erratum in: N Engl J Med. 2012;367:976.

22. Ficarra V, Brunelli M, Cheng L, Karki Z, Lopez-Beltran A, Martignoni G, et al. Prognostic and therapeutic impact of the histopathologic definition of parenchymal epithelial renal tumors. Eur Urol. 2010;58:655-68.

23. Hutterer GC, Stoeckigt C, Stojakovic T, Eberhard K, Pummer K, et al. Low preoperative lymphocyte-monocyte ratio (LMR) represents a potentially poor prognostic factor in nonmetastatic clear cell renal cell carcinoma. Urol Oncol. 2014;32:1041-8.

24. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncol. 2010;6:149-63.

25. Pichler M, Hutterer GC, Stojakovic T, Mannweiler S, Pummer K, Zigeuner R. High plasma fibrinogen level represents an independent negative prognostic factor regarding cancer-specific, metastasis-free, as well as overall survival in a European cohort of nonmetastatic renal cell carcinoma patients. Br J Cancer. 2013;109:1123-9.

26. Li MX, Liu XM, Zhang XF, Zhang JF, Wang WL, Zhu Y, et al. Prognostic role of neutrophil-to-lymphocyte ratio in colorectal cancer: a systematic review and meta-analysis. Int J Cancer. 2014;134:2403-13.

27. Xiao WK, Chen D, Li SQ, Fu SJ, Peng BG, Liang LJ. Prognostic significance of neutrophil-to-lymphocyte ratio in hepatocellular carcinoma: a meta-analysis. BMC Cancer. 2014;14:117.

28. Ohno Y, Nakashima J, Ohori M, Tanaka A, Hashimoto T, Gondo T, et al. Clinical variables for predicting metastatic renal cell carcinoma patients who might not benefit from cytoreductive nephrectomy: neutrophil-to-lymphocyte ratio and performance status. Int J Clin Oncol. 2014;19:139-45.
29. Jagdev SP, Gregory W, Vasudev NS, Harnden P, Sim S, Thompson D, et al. Improving the accuracy of pre-operative survival prediction in renal cell carcinoma with C-reactive protein. Br J Cancer. 2010;103:1649-56.

30. Lamb GW, Aitchison M, Ramsey S, Housley SL, McMillan DC. Clinical utility of the Glasgow Prognostic Score in patients undergoing curative nephrectomy for renal clear cell cancer: basis of new prognostic scoring systems. Br J Cancer. 2012;106:279-83.

31. Tai CG, Johnson TV, Abbasi A, Herrell L, Harris WB, Kucuk O, et al. External validation of the modified Glasgow prognostic score for renal cancer. Indian J Urol. 2014;30:33-7.

32. de Martino M, Haitel A, Schatzl G, Klatte T. The protease activated receptor 1 gene variation IVSn-14 A>T is associated with distant metastasis and cancer specific survival in renal cell carcinoma. J Urol. 2013;190:1392-7.

33. Vilella-Arias SA, Rocha RM, da Costa WH, Zequi Sde C, Guimarães GC, Verjovski-Almeida S, et al. Loss of caspase 7 expression is associated with poor prognosis in renal cell carcinoma clear cell subtype. Urology. 2013;82:974.e1-7.

34. Shi X, Jiang J, Ye X, Liu Y, Wu Q, Wang L. Prognostic prediction and diagnostic role of intercellular adhesion molecule-1 (ICAM1) expression in clear cell renal cell carcinoma. J Mol Histol. 2014;45:427-34.

35. Pedersen BK, Bruunsgaard H, Jensen M, Krzywowski K, Ostrowski K. Exercise and immune function: effect of ageing and nutrition. Proc Nutr Soc. 1999;58:733-42.

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