

PROGNOSTIC SIGNIFICANCE OF THE COMBINATION OF PREOPERATIVE HEMOGLOBIN AND ALBUMIN LEVELS AND LYMPHOCYTE AND PLATELET COUNTS (HALP) IN PATIENTS WITH RENAL CELL CARCINOMA AFTER RADICAL NEPHRECTOMY: A FACT OR FALLACY ?

Urology

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ABSTRACT

AIMS & OBJECTIVE: Renal cancer accounts for 2% to 3% of all cancers, approximately 90% of renal cancer is RCC, and surgery is the only curative treatment. About 20% of RCC patients have advanced stage disease, and for those with localized RCC, nearly 30% show recurrence after tumor resection. Therefore, we need better prognostic models to improve prognosis. Hence we conducted a study to evaluate the prognostic significance of the novel index combining preoperative hemoglobin and albumin levels and lymphocyte and platelet counts (HALP) in renal cell carcinoma (RCC) patients.

METHOD: We included 203 patients retrospectively with histologically confirmed RCC who had undergone radical nephrectomy in the Department of Urology, Institute of Nephrourology between 2007 and 2020. The cut-off values for HALP were determined by using X-tile v3.6.1. Various statistical analysis were done with SPSS v27 software. Multivariate Cox proportional-hazards model was used to evaluate the prognostic significance of HALP for RCC.

RESULTS: In a sample of 203 patients, 144 were male and mean age was 55 (45-65 IQR). 189 patients had clear cell RCC and right sided (118) was the mostly affected. 11 patients had hypoalbuminemia & 38 patients had anemia. 30 patients had lymphocytosis, 12 patients had thrombocytosis, 8 patients had metastasis. HALP score was calculated and stratified into high (>33.4) and low (<33.4) which included 98 & 105 patients respectively. Kaplan-Meier and log-rank tests revealed that HALP was strongly correlated with cancer specific survival ($P < 0.001$) and Cox multivariate analysis demonstrated that preoperative HALP was independent prognostic factor for cancer specific survival (HR=1.838, 95%CI: 1.260-2.681, $P=0.002$).

CONCLUSIONS: Low HALP was closely associated with worse clinicopathologic features and was an independent prognostic factor of cancer-specific survival for RCC patients undergoing radical nephrectomy. A nomogram based on HALP independently & accurately predict prognosis of RCC.

KEYWORDS

INTRODUCTION

Renal cell carcinoma (RCC) encompasses a heterogeneous group of cancers derived from renal tubular epithelial cells. Renal cancer accounts for 2% to 3% of all cancers, and the rate of renal cell carcinoma (RCC) has increased by 1.6% per year for the past 10 years. [1] Approximately 90% of renal cancer is RCC, and surgery is the only curative treatment. About 20% of RCC patients have advanced stage disease, and for those with localized RCC, nearly 30% show recurrence after tumor resection [2, 3]. Therefore, we need better prognostic models to improve prognosis. The TNM stage, reflecting tumor invasion, lymph node metastasis and distant metastasis, is the most widely used system for predicting RCC prognosis [2]. However, because of heterogeneous prognoses, the outcomes of some patients with the same stage of cancer may be completely different. Therefore, we need useful biomarkers to increase the prognostic accuracy in RCC. Increasing evidence supports that inflammation and nutrition are involved in the initiation and progression of various cancers, including RCC [4]. Hematologic parameters including albumin and hemoglobin levels and lymphocytes, neutrophils and platelets counts are easily acquired laboratory data reflecting inflammation and nutrition status and have been extensively studied. Numerous studies have reported the prognostic value of serum albumin and hemoglobin levels and lymphocyte and platelet counts for various cancers, including RCC [5-8]. However, the disadvantage of these indicators is that each reflects only one respect of inflammation or nutrition. Further studies found that the combination of those factors in an index such as the prognostic nutritional index (PNI), combining albumin level and lymphocyte count, or the neutrophil-to lymphocyte ratio (NLR), or platelet-to-lymphocyte ratio (PLR) could more accurately predict prognosis than a single index [9-12].

A novel index combining hemoglobin and albumin levels and lymphocyte and platelet counts (HALP) has been found significantly associated with outcomes in colorectal and gastric cancer [13, 14]. In this study, we investigated the clinical value of this index in RCC patients undergoing nephrectomy.

METHODS

We included 203 patients retrospectively with histologically

confirmed RCC who had undergone radical nephrectomy in the Department of Urology, Institute of Nephrourology between 2007 and 2020. Clinicopathologic characteristics and laboratory data were collected. Follow-up care including abdominal ultrasonography or abdominal CT, chest X-ray, and laboratory tests was performed at regular intervals (3-month intervals in years 1 to 3, 6-month intervals in years 4 to 5, and 12-month intervals in years 6 to 10 after diagnosis).

STATISTICAL ANALYSIS

Data are presented as number (percentage) for categorical variables and median (interquartile range [IQR]) for continuous variables. HALP was calculated as hemoglobin level (g/L) \times albumin level (g/L) \times lymphocyte (/L)/platelet count (/L), NLR as neutrophil-to-lymphocyte count and PLR as platelet-to lymphocyte count. The cut-off values for NLR, PLR and HALP were determined by using X-tile v3.6.1 (Yale University) [15]. The X-tile software was able to compare the P values of different cut-off values for a continuous variable and determine the best cut-off value with the most significant P value. Chi-square test was used to analyze an association of clinicopathologic data with HALP. The Kaplan-Meier survival method was used to estimate cancer-specific survival (CSS), with log-rank test used to test significant differences. The significant variables in the univariate analysis were included in the Cox proportional hazards regression multivariate survival analyses by Forward LR method. Statistical analyses involved use of SPSS v27 (SPSS Inc., Chicago, IL, USA) and $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

We included 203 patients 144 were males, median age 55 years (45-65 IQR). (Table 1).

Characteristics	Total, n=203
Age	55(45-65)
Female	59
Histology subtype	
CCRCC	189
Non-CCRCC	14
Location	

Left	83
Right	118
Fuhrman grade	
1	51
2	115
3	31
4	06
T-stage	
1	145
2	25
3	30
4	3
N status	
Negative	186
Positive	17
ASA Grade	
1	37
2	158
3	8
Sarcomatoid transformation	10
Metastasis	8
Necrosis	7
Hypoalbuminemia	11
Anemia	38
NLR, median (IQR)	2.26[1.78-2.97]
PLR, median (IQR)	128.9[98.3-265.6]
HALP	48.13[32.4-63.5]

The median follow-up was 64 months (IQR 27-80), and 8.4% patients died due to RCC during follow-up. The 5-year estimated CSS was 91.4% for all patients.

Association of HALP and clinicopathologic features

We detected cut-off values for HALP, 33.4; NLR, 2.89; and PLR, 218 for dividing patients into low and high HALP, NLR and PLR groups. Decreased HALP level was associated with being female, older age, high Fuhrman grade and high T stage and N and M positive status, sarcomatoid transformation, tumor necrosis, lymphovascular invasion and low NLR or PLR (Table 2).

Table-2 [association Of Baseline Clinicopathologic Characteristics And Halp]

Variable	n[%]	HALP		p-value
		Low(%)	High (%)	
All patients	203	45	158	
Gender				<0.001
Male	144	25	119	
Female	59	19	40	
Age, years				<0.001
<65	149	28	121	
>65	54	16	38	
Histology subtype				0.756
cc-RCC	189	40	149	
Non-cc RCC	14	3	11	
ASA grade				0.423
1 & 2	189	40	149	
3 & 4	14	4	10	
Fuhrman grade				<0.001
1 & 2	166	26	140	
3 & 4	37	17	20	
T- stage				<0.001
1 & 2	170	26	144	
3 & 4	37	17	20	
N status				<0.001
Negative	196	40	156	
Positive	8	5	3	
Metastasis				<0.001
Negative	195	39	156	
Positive	7	5	2	
Sarcomatoid				<0.001
Absent	188	37	151	
Present	15	7	8	
PLR				<0.001

High	30	27	3	
Low	173	17	156	

Association of HALP with patient outcomes

On univariate analysis, all included clinicopathologic features except for age (P = 0.281), gender (P = 0.310), histology subtype (P = 0.364) and American Society of Anesthesiologists grade (P = 0.934) were significantly related to survival outcomes (Table 3). Anemia and hypoalbuminemia, high PLR and low HALP were all significantly associated with worse survival. On multivariate analyses, prognostic factors for CSS with RCC were Fuhrman grade (HR 1.737, 95% CI 1.177– 2.652, P = 0.006), T stage (3.890, 2.510–6.030, P < 0.001), N stage (2.480, 1.526–4.032, P < 0.001), M stage (4.728, 3.090–7.233, P < 0.001) and HALP (1.838, 1.260–2.681, P = 0.002) (Table 3).

Table-3{ Univariate And Multivariate Analyses Of Factors Associated With Cancer-specific Survival For Rcc Patients}

Variable	univariate analysis	multivariate analysis	p-value
		HR(95% ci)	
Age (>65 vs ≤65)	0.267		
Gender (female vs male)	0.223		
Histology subtype (non-ccRCC vs ccRCC)	0.364		
ASA grade (3 + 4 vs 1 + 2)	0.924		
Fuhrman grade (3 + 4 vs 1 + 2)	< 0.001	1.737 (1.177–2.652)	0.006
T stage (3 + 4 vs 1 + 2)	< 0.001	3.890 (2.510–6.030)	< 0.001
N status (positive/negative)	< 0.001	2.480 (1.526–4.032)	< 0.001
M status (positive vs negative)	< 0.001	4.728 (3.090–7.233)	< 0.001
Sarcomatous differentiation (present vs absent)	< 0.001		
Lymphovascular invasion (present vs absent)	< 0.001		
Necrosis (present vs absent)	< 0.001		
Hypoalbuminemia (present vs absent)	< 0.001		
Anemia (present vs absent)	< 0.001		
PLR (high vs low)	< 0.001		
HALP (low vs high)	< 0.001	1.838 (1.260–2.681)	0.002

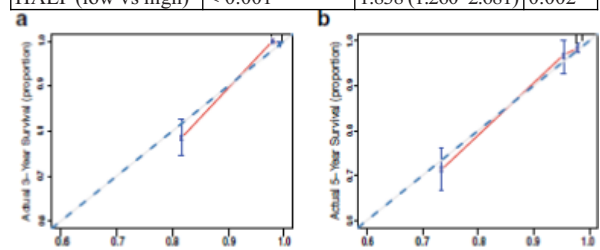


Fig-1 calibration curves for 3year(a) and 5-year(b) survival

Nomogram-predicted probability of 3 year survival

Nomogram of HALP-based risk model for RCC

We used nomogram to predict 3- and 5-year CSS for individual patients. Independent prognostic factors in the multivariate analysis including Fuhrman grade, TNM status and HALP were included in the nomogram. Similar to multivariate findings, with nomogram, high Fuhrman grade and advanced TNM status were associated with poor prognosis and high HALP with favorable prognosis. The calibration curves of the nomogram showed that the predictive probability of 3- and 5-year survival was closely related to the actual 3- and 5-year survival (Fig. 1). The C-index was 0.873 (95% CI: 0.833–0.904) by this nomogram compared with 0.846 (0.812–0.880) with the TNM staging system. Hence, the risk model including TNM stage, Fuhrman grade and HALP had better prognostic prediction accuracy than the only TNM system.

DISCUSSION

In this study, we evaluated the prognostic significance of the novel index HALP combining hemoglobin and albumin levels and lymphocyte and platelet counts in RCC patients undergoing nephrectomy. HALP was closely associated with clinicopathologic features. Univariate and multivariate analyses demonstrated that HALP was an independent predictor of CSS for RCC patients undergoing nephrectomy. Furthermore, the nomogram based on HALP could predict prognosis more accurately than the TNM system.

There are several known predictive models of RCC such as TNM stage and the Stage, Size, Grading and Necrosis (SSIGN) model [16]. Inflammatory and nutritional indicators based on hematologic parameters such as albumin and hemoglobin levels and lymphocyte, neutrophil and platelet counts were also associated with outcomes with RCC. Moreover, several indicators combined with hematologic parameters, including NLR, LMR, and PLR, were more accurate predictors [6, 9, 10, 12]. Recently, indicators combining albumin level with LMR or NLR were found significantly associated with outcomes [17, 18], which suggests better prediction of outcomes by combining inflammatory and nutritional indicators.

Accumulating evidence suggests the important role of the inflammatory response and nutritional status in cancer progression and metastasis. Overall, 30% of cancer patients were found with cancer-related anemia (CRA) at the time of diagnosis and CRA was associated with more advanced cancer stage [19]. Serum albumin is synthesized specially in the liver and known as a negative acute-phase protein. In addition, systemic factors such as inflammation and stress could affect serum albumin level. Therefore, decreased serum albumin level represents a malnutrition status and also a sustained systemic inflammation response. As important indicators of nutrition and inflammation, anemia and hypoalbuminemia are widely reported to be associated with worse outcomes in various cancers including RCC [7, 8]. Morgan et al. [21] reported that for locoregional RCC patients undergoing nephrectomy, 25% of patients have anemia and 5.1% have hypoalbuminemia. The authors also found hypoalbuminemia (< 35 g/L), unintentional preoperative weight loss $\geq 5\%$ and preoperative BMI < 18.5 kg/m² as reflecting nutritional deficiency (ND) and that anemia and ND were independent predictors of overall mortality and disease-specific mortality. We observed 5.41% hypoalbuminemia and 18.7% anemia in our patients, which is consistent with previous study. On univariate analysis, both anemia and hypoalbuminemia were associated with worse survival.

Systemic inflammation markers including NLR, LMR, and PLR have been found associated with survival in many solid tumors including RCC [6, 10, 30, 31]. Among those indicators, the finding of elevated NLR and PLR indicated increased neutrophil and platelet count and decreased lymphocyte count associated with worse outcomes. In our study, elevated NLR and PLR were associated with worse CSS on univariate analysis. However, on multivariate analyses, HALP rather than NLR and PLR remained an independent prognostic factor.

We used nomogram of independent prognostic factors found on multivariate analyses including HALP and evaluated their accuracy by calibration curves. The predictive accuracy was better with HALP than the TNM system. TNM stage may be an important factor in RCC, but other factors such as HALP could be included and improve the prediction of outcomes.

The major limitations of the present study are its retrospective nature and the single-center design. Additional large and prospective studies are needed to confirm these findings.

CONCLUSIONS

HALP was closely associated with clinicopathologic features of RCC patients undergoing nephrectomy and was an independent prognostic factor of CSS. A nomogram based on HALP could accurately predict prognosis with RCC. Preoperative HALP could be a novel indicator to evaluate the outcome for RCC patients after nephrectomy.

Abbreviations

CRA: cancer-related anemia; **CSS:** cancer-specific survival; **LMR:** lymphocyteto-monocyte ratio; **NLR:** neutrophil-to-lymphocyte ratio; **PLR:** platelet-to-lymphocyte

ratio; PNI: prognostic nutritional index; **RCC:** renal cell carcinoma

REFERENCES

- Motzer RJ, Jonasch E, Agarwal N, Beard C, Bhayani S, Bolger GB, et al. Kidney cancer, version 3.2015. *Journal of the National Comprehensive Cancer Network : JNCCN*. 2015;13(2):151–9.
- Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol*. 2015;67(5):913–24.
- Hsieh JJ, Purdue MP, Signoretti S, Swanton C, Albiges L, Schmidinger M, et al. Renal cell carcinoma. *Nat Rev Dis Primers*. 2017;3:17009–28.
- Senbabaoglu Y, Gejman RS, Winer AG, Liu M, Van Allen EM, de Velasco G, et al. Tumor immune microenvironment characterization in clear cell renal cell carcinoma identifies prognostic and immunotherapeutically relevant messenger RNA signatures. *Genome Biol*. 2016;17(1):231–56.
- Kim K, Seo H, Chin JH, Son HJ, Hwang JH, Kim YK. Preoperative hypoalbuminemia and anemia as predictors of transfusion in radical nephrectomy for renal cell carcinoma: a retrospective study. *BMC Anesthesiol*. 2015;15:103–10.
- Chang Y, Fu Q, Xu L, Zhou L, Liu Z, Yang Y, et al. Prognostic value of preoperative lymphocyte to monocyte ratio in patients with nonmetastatic clear cell renal cell carcinoma. *Tumour Biol*. 2016;37(4):4613–20.
- Corcoran AT, Kaffenberger SD, Clark PE, Walton J, Handorf E, Piotrowski Z, et al. Hypoalbuminaemia is associated with mortality in patients undergoing cytoreductive nephrectomy. *BJU Int*. 2015;116(3):351–7.
- Stenman M, Laurell A, Lindskog M. Prognostic significance of serum albumin in patients with metastatic renal cell carcinoma. *Med Oncol*. 2014;31(3):841–9.
- Sun J, Ning H, Sun J, Qu X. Effect of hypertension on preoperative neutrophil-lymphocyte ratio evaluation of prognosis of renal cell carcinoma. *Urol Oncol*. 2016;34(5):239. e239-215
- Gunduz S, Mutlu H, Tural D, Yildiz O, Uysal M, Coskun HS. Platelet to lymphocyte ratio as a new prognostic for patients with metastatic renal cell cancer. *Asia-Pac J Clin Oncol*. 2015;11(4):288–92.
- Ohno Y, Nakashima J, Otori M, Gondo T, Hatano T, Tachibana M. Followup of neutrophil-to-lymphocyte ratio and recurrence of clear cell renal cell carcinoma. *J Urol*. 2012;187(2):411–7.
- Hofbauer SL, Pantuck AJ, de Martino M, Lucca I, Haitel A, Shariat SF, et al. The preoperative prognostic nutritional index is an independent predictor of survival in patients with renal cell carcinoma. *Urol Oncol*. 2015;33(2):68. e61-67
- Chen XL, Xue L, Wang W, Chen HN, Zhang WH, Liu K, et al. Prognostic significance of the combination of preoperative hemoglobin, albumin, lymphocyte and platelet in patients with gastric carcinoma: a retrospective cohort study. *Oncotarget*. 2015;6(38):41370–82.
- Jiang H, Li H, Li A, Tang E, Xu D, Chen Y, et al. Preoperative combined hemoglobin, albumin, lymphocyte and platelet levels predict survival in patients with locally advanced colorectal cancer. *Oncotarget*. 2016;7:72076–83.
- Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcome-based cut-point optimization. *Clin Cancer Res*. 2004;10(21):7252–9.
- Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. An outcome prediction model for patients with clear cell renal cell carcinoma treated with radical nephrectomy based on tumor stage, size, grade and necrosis: the SSIGN score. *J Urol*. 2002;168(6):2395–400.
- Wang YQ, Jin C, Zheng HM, Zhou K, Shi BB, Zhang Q, et al. A novel prognostic inflammation score predicts outcomes in patients with ovarian cancer. *Clin Chim Acta*. 2016;456:163–9.
- Chang Y, An H, Xu L, Zhu Y, Yang Y, Lin Z, et al. Systemic inflammation score predicts postoperative prognosis of patients with clear-cell renal cell carcinoma. *Brit J Cancer*. 2015;113(4):626–33.
- Ludwig H, Van Belle S, Barrett-Lee P, Birgegard G, Bokemeyer C, Gascon P, et al. The European Cancer Anaemia survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. *Eur J Cancer*. 2004;40(15):2293–306.
- Maccio A, Madeddu C, Gramignano G, Mulas C, Tanca L, Cherchi MC, et al. The role of inflammation, iron, and nutritional status in cancer-related anemia: results of a large, prospective, observational study. *Haematologica*. 2015;100(1):124–32.
- Morgan TM, Tang D, Stratton KL, Barocas DA, Anderson CB, Gregg JR, et al. Preoperative nutritional status is an important predictor of survival in patients undergoing surgery for renal cell carcinoma. *Eur Urol*. 2011;59(6):923–8.
- Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646–74.
- Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008;454(7203):436–44.
- Hoffmann TK, Dworacki G, Tsukihito T, Meidenbauer N, Gooding W, Johnson JT, et al. Spontaneous apoptosis of circulating T lymphocytes in patients with head and neck cancer and its clinical importance. *Clin Cancer Res*. 2002;8(8):2553–62.
- Bindea G, Mlecnik B, Fridman WH, Pages F, Galon J. Natural immunity to cancer in humans. *Curr Opin Immunol*. 2010;22(2):215–22.
- Labelle M, Begum S, Hynes RO. Platelets guide the formation of early metastatic niches. *P Natl Acad Sci USA*. 2014;111(30):e3053–61.
- Suzuki K, Aiura K, Ueda M, Kitajima M. The influence of platelets on the promotion of invasion by tumor cells and inhibition by antiplatelet agents. *Pancreas*. 2004;29(2):132–40.
- Karakiewicz PI, Trinh QD, Lam JS, Tostain J, Pantuck AJ, Belldegrin AS, et al. Platelet count and preoperative haemoglobin do not significantly increase the performance of established predictors of renal cell carcinoma-specific mortality. *Eur Urology*. 2007;52(5):1428–36.
- Best MG, Sol N, Kooi I, Tannous J, Westerman BA, Rustenburg F, et al. RNAseq of tumor-educated platelets enables blood-based pan-Cancer, multiclass, and molecular pathway Cancer diagnostics. *Cancer Cell*. 2015;28(5):666–76.
- Shin JS, Suh KW, Oh SY. Preoperative neutrophil to lymphocyte ratio predicts survival in patients with T1–2N0 colorectal cancer. *J Surg Oncol*. 2015;112(6):654–7.
- Hsu JT, Liao CK, Le PH, Chen TH, Lin CJ, Chen JS, et al. Prognostic value of the preoperative neutrophil to lymphocyte ratio in Resectable gastric Cancer. *Medicine*. 2015;94(39):e1589–95.