Systemic inflammation score predicts postoperative prognosis of patients with clear-cell renal cell carcinoma

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Background: Growing evidence indicates that inflammation has a crucial role in the development and progression of cancer. We developed a novel systemic inflammation score (SIS) based on preoperative serum albumin and lymphocyte-to-monocyte ratio (LMR), and examined its prognostic value for patients with clear-cell renal cell carcinoma (ccRCC) after surgery.

Methods: The study comprised 441 ccRCC patients undergoing nephrectomy between 2008 and 2009 in a single centre. The SIS was developed and its associations with clinicopathological features and overall survival (OS) were evaluated.

Results: The SIS consisted of serum albumin and LMR that were both retained as independent indicators adjusting for other haematological and laboratory markers of systemic inflammation responses and traditional clinicopathological features. A high SIS was significantly associated with aggressive tumour behaviours and served as an independent prognostic factor of reduced OS. Furthermore, the SIS could significantly stratify patient prognosis in different tumour stages and Mayo Clinic stage, size, grade and necrosis scores. Incorporation of the SIS into a prognostic model including TNM stage, Fuhrman grade and lymphovascular invasion generated a nomogram, which predicted accurately 3- and 5-year survival for ccRCC patients.

Conclusions: The SIS as a potentially powerful prognostic biomarker might improve traditional clinicopathological analysis to refine clinical outcome prediction for ccRCC patients after surgery.
albumin levels (Chechlinska et al, 2010). Thus, several circulating blood cell-based prognostic biomarkers have been developed to predict patient outcome in various tumours, such as neutrophil-to-lymphocyte ratio (NLR) (Pichler et al, 2013; Hermanns et al, 2014), platelet-to-lymphocyte ratio (PLR) (Fox et al, 2013; Krenn-Pilko et al, 2014) and lymphocyte-to-monocyte ratio (LMR) (Hutterer et al, 2014; Szkandera et al, 2014). Preoperative haemoglobin and serum albumin levels are also reported as prognostic indicators for cancer clinical prognosis (Karakiwicz et al, 2007; McMillan, 2013). These markers are inexpensive to test and routinely performed in clinical setting, and hence potentially provide readily available and objective information to help clinicians to estimate patient outcome. However, there are few reports about the values of these markers, as independent indicators analysed all together and the extent how to integrate them to refine outcome prediction for ccRCC patients.

In this study, we developed a novel prognostic score named systemic inflammation score (SIS) based on preoperative serum albumin and LMR, which were both proven to be independently associated with ccRCC patients outcome adjusting for NLR, PLR, haemoglobin and traditional clinical and pathologic variables, and investigated the correlations of SIS with clinicopathological parameters and the prognostic value of SIS in ccRCC patients. Furthermore, a nomogram-combined SIS with TNM stage, Fuhrman grade and lymphovascular invasion was established to predict 3- and 5-year survival for ccRCC patients after surgery.

### Table 1. Patient and tumour characteristics

| Characteristics | No. | % |
|-----------------|-----|---|
| **Age, years** |
| Median (IQR) | 56 (46–63) |
| **Sex** |
| Male | 318 | 72.1 |
| Female | 123 | 27.9 |
| **T stage** |
| T1 | 301 | 68.3 |
| T2 | 32 | 7.3 |
| T3 | 107 | 24.3 |
| T4 | 1 | 0.2 |
| **N stage** |
| N0 | 434 | 98.4 |
| N1 | 7 | 1.6 |
| **M stage** |
| M0 | 435 | 98.6 |
| M1 | 6 | 1.4 |
| **TNM stage** |
| I | 297 | 67.3 |
| II | 30 | 6.8 |
| III | 108 | 24.5 |
| IV | 6 | 1.4 |
| **Fuhrman grade** |
| 1 | 72 | 16.3 |
| 2 | 202 | 45.8 |
| 3 | 106 | 24.0 |
| 4 | 61 | 13.8 |
| **Tumour size, cm** |
| <5 | 299 | 67.8 |
| >5 | 142 | 32.2 |
| **Tumour necrosis** |
| Absent | 348 | 78.9 |
| Present | 93 | 21.1 |
| **Lymphovascular invasion** |
| Absent | 323 | 73.2 |
| Present | 118 | 26.8 |
| **SSIGN score** |
| 0–3 | 320 | 72.6 |
| 4–7 | 105 | 23.8 |
| >8 | 16 | 3.6 |
| **Haemoglobin, g l⁻¹** |
| Median (IQR) | 139 (126–148) |
| **Albumin, g l⁻¹** |
| Median (IQR) | 42 (39–44) |
| **NLR** |
| Median (IQR) | 2.0 (1.5–2.6) |
| **PLR** |
| Median (IQR) | 110 (84–142) |
| **LMR** |
| Median (IQR) | 4.4 (3.2–5.8) |

**Abbreviations:** IQR = interquartile range; LMR = lymphocyte to monocyte ratio; NLR = neutrophil to lymphocyte ratio; No. = number of patients; PLR = platelet to lymphocyte ratio; SSIGN = the Mayo Clinic stage, size, grade, and necrosis.

After a median follow-up of 66 months (interquartile range, 63–69 months), 65 patients (14.7%) had died from all causes. This study was approved by the Zhongshan hospital's Ethics Committee and informed consent was obtained from each patient.

### Statistical analysis

Analysis was performed with SPSS 21.0 (IBM Corporation, Armonk, NY, USA) and R software version 3.0.2 and the 'rms' package (R Foundation for Statistical Computing, Vienna, Austria). Pearson χ²-test or Fisher’s exact test was used to compare the differences of categorical variables. A log-rank test was used to compare the differences in survival among the groups. Univariable and multivariable analyses were performed using the Cox proportional hazards regression model. The statistical package ‘rms’ in R was used to develop the nomogram. The discriminative ability of the nomogram was assessed using the concordance index (C-index). A p-value < 0.05 was considered statistically significant.
test was used to compare categorical variables and continuous variables were analysed by Wilcoxon rank-sum test or Kruskal–Wallis test. The Kaplan–Meier method with log-rank test was used to compare survival curves. The Cox proportional hazards regression model was applied to perform univariate and multivariate analyses, and those variables that achieved statistical significance in the univariate analysis were entered into the multivariable analysis. We first evaluated these haematological and laboratory markers including NLR, PLR, LMR, haemoglobin and serum albumin as continuous variables, together with traditional clinicopathological variables in the univariate and multivariate analyses, and identified that LMR and serum albumin were independent prognostic factors of OS. Next, the two markers were analysed as categorical variables. Dichotomisation of serum albumin was based on the lower range of normal measurement (40 g l\(^{-1}\) (normal range, 40–55 g l\(^{-1}\)). Owing to no widely accepted cutpoint of LMR, we used the median value at 4.44 as the cutoff for dichotomisation. The SIS was established based on the combination of different serum albumin and LMR levels. The accepted cutpoint of LMR, we used the median value at 4.44 as the cutoff for dichotomisation. The SIS was established based on the combination of different serum albumin and LMR levels. The Harrell’s Concordance index (C-index) was used to quantify the predictive accuracy (Harrell et al., 1996), which ranges from 0.5 (no predictive power) to 1 (perfect prediction). All statistical tests were two-sided and were performed at a significance level of 0.05.

**RESULTS**

**Associations of LMR, serum albumin and SIS with OS.** Results from the univariate analysis indicated that NLR, PLR, LMR, haemoglobin and serum albumin as continuous variables were prognostic factors of OS as well as TNM stage, Fuhrman grade, tumour size, tumour necrosis and lymphovascular invasion (Table 2), whereas age at surgery and gender had no prognostic significance for OS. Based on our multivariate analysis, the serum albumin and LMR were independent prognostic factors for OS (HR, 0.909; 95% CI, 0.840–0.985; P = 0.019; HR, 0.839; 95% CI, 0.705–0.998; P = 0.047, respectively), together with TNM stage, Fuhrman grade and lymphovascular invasion (Table 2).

As mentioned above, the continuously coded serum albumin was stratified into < 40 or ≥ 40 g l\(^{-1}\) and the continuously coded LMR was stratified into < 4.44 or ≥ 4.44 for subsequent analyses. Kaplan–Meier analysis indicated that the decreased serum albumin and LMR were both associated with shorter OS (P < 0.001 for both) (Figures 1A and B). To further discriminate patients with different

**Table 2. Univariate and multivariate Cox proportional hazards regression analysis for OS**

| Variables               | Univariate | Multivariate\(^a\) | Multivariate\(^b\) |
|-------------------------|------------|---------------------|---------------------|
|                         | P-values   | HR 95% CI           | P-values            | HR 95% CI          | P-values |
| Age                     | 0.185      | <0.001              | <0.001              | 0.017              | 0.023    |
| Sex                     | 0.236      |                     |                     |                    |          |
| TNM stage               |            |                     |                     |                    |          |
| I                       |            |                     |                     |                    |          |
| II                      | 1.331      | 0.500–3.541         | 0.567               | 1.277              | 0.472–3.458 | 0.630    |
| III                     | 2.222      | 1.232–4.008         | 0.008               | 2.348              | 1.302–4.232 | 0.005    |
| IV                      | 24.483     | 5.197–115.332       | <0.001              | 14.644             | 4.651–46.106 | <0.001   |
| Fuhrman grade           |            |                     |                     |                    |          |
| 1                       |            |                     |                     |                    |          |
| 2                       | 1.215      | 0.401–3.686         | 0.731               | 1.374              | 0.455–4.150 | 0.573    |
| 3                       | 1.263      | 0.401–3.983         | 0.690               | 1.483              | 0.477–4.613 | 0.496    |
| 4                       | 3.267      | 1.041–10.253        | 0.042               | 3.519              | 1.133–10.931 | 0.030    |
| Tumour size, cm         |            |                     |                     |                    |          |
| <5                      |            |                     |                     |                    |          |
| >5                      |            |                     |                     |                    |          |
| Absent                  |            |                     |                     |                    |          |
| Present                 | 1.255      | 0.716–2.200         | 0.428               | 1.192              | 0.680–2.091 | 0.540    |
| Tumour necrosis         |            |                     |                     |                    |          |
| Absent                  |            |                     |                     |                    |          |
| Present                 | 1.621      | 0.918–2.862         | 0.096               | 1.449              | 0.823–2.550 | 0.199    |
| LVI                     |            |                     |                     |                    |          |
| Absent                  |            |                     |                     |                    |          |
| Present                 | 2.959      | 1.657–5.286         | 1.699               | 3.033              | 1.699–5.414 |        |
| Albumin\(^f\)           |            |                     |                     |                    |          |
| Present                 | 0.909      | 0.840–0.985         | 0.019               |                    |          |
| Haemoglobin\(^f\)       |            |                     |                     |                    |          |
| Present                 | 0.993      | 0.977–1.009         | 0.406               |                    |          |
| LMR\(^f\)               |            |                     |                     |                    |          |
| Present                 | 0.839      | 0.705–0.998         | 0.047               |                    |          |
| PLR\(^f\)               |            |                     |                     |                    |          |
| Present                 | 0.997      | 0.994–1.001         | 0.138               |                    |          |
| NLR\(^f\)               |            |                     |                     |                    |          |
| Present                 | 0.971      | 0.838–1.124         | 0.691               |                    |          |
| SIS                     |            |                     |                     |                    |          |
| 0                       |            |                     |                     |                    |          |
| 1                       | 2.109      | 1.020–4.362         | 0.044               |                    |          |
| 2                       | 4.149      | 1.980–8.695         | <0.001              |                    |          |

Abbreviations: CI = confidence interval; HR = hazard ratio; LMR = lymphocyte to monocyte ratio; LVI = lymphovascular invasion; NLR = neutrophil to lymphocyte ratio; OS = overall survival; PLR = platelet to lymphocyte ratio; SIS = systemic inflammation score.

\(^a\)Adjustment for all variables listed in the table, except for age, sex and SIS.

\(^b\)Adjustment for all variables listed in the table, except for age, sex, albumin, haemoglobin, LMR, PLR and NLR.

\(^f\)Analysed as a continuous variable.
outcome, we combined serum albumin and LMR levels to generate four subgroups. We found significant differences exist among the four subgroups (Figure 1C). In subgroups of either serum albumin $\geq 40\text{g l}^{-1}$ or LMR $\geq 4.44$, the OS was quite similar (HR, 1.282; 95% CI, 0.509–3.230; $P = 0.598$). Thus, we combined the two subgroups to establish the SIS defined as follows: patients with both decreased serum albumin and decreased LMR ($< 40\text{g l}^{-1}$ and $< 4.44$, respectively) were assigned score 2; patients with either decreased serum albumin or decreased LMR were assigned score 1 and patients with both elevated serum albumin and elevated LMR ($\geq 40\text{g l}^{-1}$ and $\geq 4.44$, respectively) were assigned score 0. Kaplan–Meier curves showed that high SIS was associated with shorter OS ($P < 0.001$) (Figure 1D). To investigate further the effect of SIS in stratifying patients with different TNM stages and SSIGN scores, we considered TNM stages I and II as early-stage tumour and TNM stage III and IV as advanced-stage tumour. The SSIGN 0–3 scores, 4–7 scores and $\geq 8$ scores were grouped as low-risk, intermediate-risk and high-risk, respectively. By Kaplan–Meier analysis, we found that the three subgroups of SIS differed significantly in both early-stage and advanced-stage ($P = 0.002$ and $P < 0.001$, respectively) (Figures 2A and B), and in both SSIGN low-risk level and intermediate/high-risk level ($P = 0.021$ and $P < 0.001$, respectively) (Figures 2C and D).

In the univariate analysis, the SIS had prognostic significance for OS ($P < 0.001$). The multivariate analysis demonstrated the SIS ($P = 0.001$), TNM stage ($P < 0.001$), Fuhrman grade ($P = 0.023$) and lymphovascular invasion ($P < 0.001$) were independent prognostic factors of OS in ccRCC (Table 2).

**Associations of LMR, serum albumin and SIS with clinico-pathological characteristics.** The associations of LMR and serum albumin with clinico pathological characteristics are shown in Table 3. Decreased serum albumin and LMR were both associated with older age at surgery ($P < 0.001$ for both), high Fuhrman grade ($P = 0.049$ and $P = 0.009$, respectively), tumour size $\geq 5\text{cm}$ ($P = 0.017$ and $P = 0.002$, respectively), the presence of tumour necrosis ($P < 0.001$ and $P = 0.001$, respectively), the presence of lymphovascular invasion ($P = 0.034$ and $P = 0.025$, respectively) and high SSIGN score ($P < 0.001$ for both). In addition, decrease serum albumin was associated with high TNM stage ($P < 0.001$).

The relationships between the SIS and clinico pathological features are also summarised in Table 3. High SIS was more likely to have older age at surgery ($P < 0.001$), high TNM stage ($P < 0.001$), high Fuhrman grade ($P = 0.001$), large tumour size ($P < 0.001$), the presence of tumour necrosis and lymphovascular invasion ($P < 0.001$ and $P = 0.005$, respectively), and high SSIGN score ($P < 0.001$) (Table 3).

**Predictive nomogram for OS.** To provide a quantitative method for better outcome prediction, we constructed a nomogram that integrated the proven independent prognostic factors consisting of TNM stage, Fuhrman stage, lymphovascular invasion and SIS (Figure 3A). In this nomogram, a higher total point indicates a worse prognosis. For internal validation, calibration plots of the nomogram predicting 3- and 5-year survival performed well with the ideal model (Figures 3B and C). The $C$-index of the multivariate prognostic model based on TNM stage, Fuhrman stage and lymphovascular invasion was 0.80 and improved to 0.82 when the SIS ($C$-index 0.71) was incorporated, which showed a better predictive ability of OS than TNM stage ($C$-index 0.68) or SSIGN score ($C$-index 0.78).

**Figure 1.** Kaplan–Meier analysis for OS of ccRCC patients according to preoperative serum albumin and LMR. Kaplan–Meier analysis for OS according to (A) preoperative serum albumin, (B) preoperative LMR, (C) combination of preoperative serum albumin and LMR, and (D) SIS.
DISCUSSION

We investigated clinicopathological characteristics and prognosis of 441 ccRCC patients with haematological and laboratory markers of systemic inflammation responses. We demonstrated that decreased serum albumin and LMR levels before surgery were independent and adverse predictors of OS in multivariate analysis. Furthermore, we created a novel prognostic score named the SIS based on the combination of serum albumin and LMR after dichotomisation, and found that high SIS was associated with high TNM stage, high SSIGN risk level and poor outcome. Together with TNM stage, Fuhrman grade and lymphovascular invasion, the SIS was integrated in a prognostic nomogram that predicted OS with an accuracy of 0.82. The magnitude of the SIS was on the same order as that of Fuhrman grade system. Thus, our study serves as a proof of principle that systemic inflammatory information can provide important prognostic information that augments traditional clinicopathological analysis. It is hoped that additional, prospective and clinical validation studies will be conducted to confirm our findings and further basic research studies will be performed to identify the detailed mechanism that how inflammatory cells and mediators are involved in the pathogenesis and progression of renal cell cancer.

As Virchow originally made links between cancer and inflammation in the nineteenth century, contemporary studies have led to a general acceptance that inflammation has an important role in carcinogenesis (Balkwill and Mantovani, 2001). The hallmarks of cancer-related inflammation consist of the infiltration of inflammatory cells and the production of inflammatory mediators in tumour tissues, tissue remodelling, tissue repair and angiogenesis (Mantovani et al., 2008). Moreover, inflammation generates not only pro-tumoral microenvironment changes but also systemic changes that can facilitate tumour progression (Chechlinska et al., 2010). Therefore, the complex array of inflammatory cells and inflammatory mediators in tumour microenvironment may be reflected in the peripheral circulation.

Recent studies have shown the prognostic significance of NLR and LMR in postoperative patients with nonmetastatic RCC (Pichler et al., 2013; Hutterer et al., 2014) and that of PLR in patients with advanced RCC (Fox et al., 2013). Moreover, Morgan et al. (2011) found that preoperative low serum albumin was significantly associated with reduced survival for 369 locoregional RCC patients. Another study for 1828 all-stages RCC patients found that preoperative haemoglobin was a significant predictor of RCC-specific mortality (Karakiewicz et al., 2007). However, the prognostic value of integrating these frequently requested haematological and laboratory markers into the traditional clinicopathological features remains obscure in RCC. In our study, we demonstrated that serum albumin and LMR were independent prognostic factors of OS in ccRCC patients. Although NLR, PLR and haemoglobin were significantly associated with survival in univariate analysis, they were not retained as independent indicators in the multivariate model. Furthermore, we created
Table 3. Associations of albumin, LMR and SIS with clinicopathological characteristics

| Characteristics | Albumin (g/l) | LMR | SIS |
|----------------|--------------|-----|-----|
|                | < 40         | ≥ 40|     |
| Age, years     |              |     |     |
| Median         | 58           | 55  |     |
| IQR            | 51–70        | 45–62|     |
| Sex            |              |     |     |
| Male           | 83           | 235 |     |
| Female         | 34           | 89  |     |
| TNM stage      |              |     |     |
| I              | 63           | 234 |     |
| II             | 12           | 18  |     |
| III            | 37           | 71  |     |
| IV             | 5            | 1   |     |
| Fuhrman grade  |              |     |     |
| 1              | 15           | 57  |     |
| 2              | 47           | 155 |     |
| 3              | 31           | 75  |     |
| 4              | 24           | 37  |     |
| Tumour size, cm|              |     |     |
| < 5            | 69           | 230 |     |
| ≥ 5            | 48           | 94  |     |
| Tumour necrosis|              |     |     |
| Absent         | 79           | 269 |     |
| Present        | 38           | 55  |     |
| LVI            |              |     |     |
| Absent         | 77           | 246 |     |
| Present        | 40           | 78  |     |
| SSIGN score    |              |     |     |
| 0–3            | 65           | 255 |     |
| 4–7            | 40           | 65  |     |
| ≥ 8            | 12           | 4   |     |
| P-values        | < 0.001      |     |     |
| < 0.001        | 0.032        |     |     |
| 0.071          |              |     |     |
| 0.017          | 0.002        |     |     |
| 0.005          |              |     |     |
| Abbreviations: IQR = interquartile range; LMR = lymphocyte to monocyte ratio; LVI = lymphovascular invasion; SIS = systemic inflammation score; SSIGN = the Mayo Clinic stage, size, grade, and necrosis.
constructed and performed well in internal validation. When assessing OS, a higher predictive accuracy of the nomogram can be observed compared with that of TNM stage or SSIGN score. Nonetheless, it needs to be further investigated whether the predictive value of the nomogram is superior to that of SSIGN score for cancer-specific survival (CSS), because the SSIGN score is developed originally with the endpoint of CSS. Meanwhile, the magnitude of the SIS was on the same order as Fuhrman grade. Thus, our study indicates that the SIS can provide additional prognostic information to traditional clinicopathological features. These results may facilitate clinicians to better stratify patients who need adjuvant therapy, intensive postoperative follow-up or participating in clinical trials.

The strength of our study is that the measurement of SIS is based on standard laboratory tests of serum albumin, lymphocyte and monocyte counts, which are routinely applied in clinical practice. However, there are a few limitations in this study. First, owing to the retrospective nature and no external validation, the prognostic significance of the SIS in ccRCC patients remains to be investigated prospectively in other populations and larger cohorts in the future. Second, because C-reactive protein (CRP) is not routinely measured in our clinical practice, we did not add CRP in our analyses. Further studies should estimate the prognostic value of CRP in combination with SIS as well as clinicopathological parameters. Third, because of limited patients with metastasis (n = 12), we did not specially assess the relationship between the SIS and metastatic disease.

In conclusion, we developed a novel and easily obtained prognostic score named SIS, which was based on preoperative serum albumin and LMR. The SIS served as an independent prognostic factor and should be incorporated into traditional clinical and pathologic variables to complement outcome prediction of ccRCC patients after surgery.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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