

High systemic immune–inflammation index represents an unfavorable prognosis of malignant pleural mesothelioma

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Background: Malignant pleural mesothelioma (MPM) represents a fatal disease with high aggressiveness, and limited biomarkers have yet been identified for MPM. The present study aims to explore potential serum prognostic factors of MPM.

Materials and methods: A retrospective analysis of 97 pathologically diagnosed MPM was performed. The optimal cutoff value of pretreatment systemic immune–inflammation index (SII) was determined by receiver operating characteristic curve. Kaplan–Meier curves and Cox regression analysis were performed to assess the potential prognostic roles of parameters.

Results: A total of 59.8% (n=58) patients are male, with a median age of 56.0 years (range 18–77). The optimal cutoff value of SII was $988.6 \times 10^9/L$. High and low SII were found in 44 (45.4%) and 53 (54.6%) patients, respectively. Median survival time for total 97 cases was 18.5 months. The median overall survival for patients with low and high SII was 47.0 and 13.0 months, respectively. The 1-, 2- and 3-year survival rates for patients with low SII were 85.8%, 57.8% and 52.0% compared to that of 53.9%, 23.6% and 13.8% in patients with high SII. On univariate analysis, Eastern Cooperative Oncology Group performance status (ECOG PS) < 2 points, low SII and adjuvant treatment ($P < 0.05$) were found to be closely correlated with a better prognosis of MPM. Only ECOG PS ($P = 0.036$) and SII ($P = 0.009$) held statistical significance on multivariate analysis.

Conclusion: Pretreatment SII is easy to access to, and it represents an efficiency and noninvasive biomarker of MPM. High SII represents an unfavorable independent prognostic factor of MPM, and this needs to be validated in further studies.

Keywords: malignant pleural mesothelioma, systemic immune-inflammation index, prognosis

Introduction

Malignant mesothelioma represents a rare but fatal disease, and 80% mesothelioma cases have a pleural origin, which is called malignant pleural mesothelioma (MPM).^{1–3} In recent years, with the aggravation of environmental pollution, occupational exposure and long latency of 20–40 years between asbestos exposure and mesothelioma onset, the incidence of MPM will still be increasing.^{3,4} MPM shows an insidious characteristics and the diagnosis of MPM is hardly made due to the non-specific clinical presentations and noncontributory radiological characteristics in an early stage.

In addition to high aggressivity, MPM also shows a treatment-resistant characteristic, with a median overall survival (OS) time of 9–17 months regardless of tumor stage.³ With the development of diagnostic strategies and antitumor drugs, prognosis of

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some mesothelioma patients has been greatly improved. Recently, Serio et al report one case of malignant peritoneal mesothelioma with environmental asbestos exposure treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, who has survived over 17 years.⁵ Folate receptor 1 (FOLR1) and epidermal growth factor receptor (EGFR) have been demonstrated to be highly expressed in MPM. Preclinical investigation shows that folate-porphyrins-based photodynamic therapy (PDT) can induce selective destruction of MPM cells based on FOLR1 targeting, and the combination of pretreatment EGFR-TKI and PDT significantly enhance the therapeutic response, which provides a new treatment option for MPM.⁶ However, no uniform treatment strategy has been established for MPM at present, and combined modality treatment remains the recommended strategy for MPM.^{7–10} Surgery-based combined modality treatment seems to confer a prolonged survival for selected MPM patients.

A series of studies have been performed to evaluate the potential prognostic factors of MPM at present. Female gender, high estrogen receptor beta expression level, younger age at diagnosis, epithelial pathology, earlier tumor stage, low pretreatment platelet counts, and low soluble mesothelin-related peptide have been demonstrated to be positive prognostic factors of MPM in previous studies.^{11–13} However, the uniform established prognostic factors mainly involve tumor stage and epithelial histology.⁴ Given the negative prognosis of MPM, it is urgently needed to identify ideal prognostic factors of MPM, which is of great value for prognosis predicting and treatment decision-making.

Inflammation plays an important role in cancer development and progression.^{14,15} Serum samples are easy to access, and the identification of serum biomarkers as prognostic factors has more important meaning for clinicians. As systematic inflammatory response indicators, serum neutrophils, lymphocytes, monocytes and platelets, neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR) have been demonstrated to be closely associated with prognosis of many malignancies.^{2,16–19} Systemic immune–inflammation index (SII) ($SII=N \times P/L$), known as systemic immune–inflammation index, which is calculated on neutrophil (N), platelet (P) and lymphocyte (L) counts, has been found to be a better prognosis predicting factor.^{20–23} However, the role of pretreatment SII in MPM remains poorly understood. The present study aims to explore the potential prognostic value of pretreatment SII in MPM.

Materials and methods

Patients

A retrospective analysis of 97 pathologically diagnosed MPM between April 2003 and December 2015 in Linyi People's Hospital was performed. Our study was approved by the Ethics Committee of Linyi People's Hospital. Prior to the present study, written informed consent was obtained from each patient. Our present study was conducted in accordance with the Declaration of Helsinki.

The eligibility criteria were (1) pathologically confirmed MPM; (2) age ≥ 18 years; (3) available clinical and follow-up data; (4) no patient received the treatment of anti-tumor therapies before definitive diagnosis. Patients with inflammatory diseases or autoimmune disease were excluded. In detail, patients with any other virus infection (HBV, HCV, HIV, etc.), autoimmune diseases involving systemic lupus erythematosus, leukemia or any other blood system diseases or inflammatory diseases or organic disease (liver, spleen, etc.) were excluded, which is consistent with previous studies.^{24,25}

Serum SII examinations

Serum samples were collected and examined before the definitive diagnosis of MPM. No patients received any anti-tumor activities before. Pretreatment SII was calculated as neutrophil (N) \times platelet (P)/lymphocyte (L) counts.

Data collection

Parameters were collected as potential prognostic factors including age (<65 or ≥ 65 years), gender (male or female), smoking history (never or ever), Eastern Cooperative Oncology Group performance status (ECOG PS) scores (<2 or ≥ 2 points), primary site of tumor (left or right), pleural effusion (yes or no), weight loss (yes or no), pretreatment SII (<988.6 or $\geq 988.6 \times 10^9/L$) and treatment strategies (best supportive care [BSC] or adjuvant therapies). Adjuvant therapies included chemotherapy, radiotherapy, surgery or the combination of any treatment strategies above.

Statistical analysis

Chi-squared test was performed to assess the relationships between pretreatment SII and clinicopathological characteristics enrolled in the present study. Survival outcomes were dichotomized by survival status in the ROC curve analysis. OS was defined from a definitive diagnosis to the date of

death or the last follow-up. The survival curves were obtained using the Kaplan–Meier method, and survival difference in variable groups was evaluated by the log-rank test. Multivariate analysis was performed using the Cox proportional hazard model, and all variables assessed on univariate analysis were included in the last multivariate analysis. SPSS 20.0 statistical software was used for statistical analysis. A P -value < 0.05 were considered statistically significant.

Results

Patient characteristics

Ninety-seven MPM patients were enrolled in our study, and the detailed information of MPM patients is shown in Table 1. Fifty-eight patients (59.8%) were male, and 39 patients were female (40.2%), with a male-to-female ratio of 1.49:1. The median age for total cases was 56.0 years

(range 18–77 years). Among the cases, 33 (34.0%) patients had a positive smoking history. Patients with ECOG PS 0–1 and ≥ 2 points were seen in 91 (93.8%) and 6 (6.2%) cases, respectively. Median OS for all cases was 18.5 months. At the diagnosis of MPM, 83 (85.6%) and 18 (18.6%) patients showed positive pleural effusion and weight loss, respectively.

Treatment strategy

After the definition of MPM diagnosis, 15 (15.5%) patients were treated with best supportive care and they did not receive any positive anti-tumor therapies. The rest 82 (84.5%) cases received the adjuvant treatment of single chemotherapy, radiotherapy, surgery or the combination of therapies above. The number of patients treated with single chemotherapy was 11 (11.3%); single pemetrexed

Table 1 Prognostic analysis of MPM patients

| Variables | O/N* | Univariate | Analysis | P-value | Multivariate | Analysis |
|-----------------------|-------|--------------|---------------|------------------|----------------------|--------------|
| | | MST (months) | 95% CI | | HR (95% CI) | P-value |
| Age (years) | | | | 0.062 | | 0.926 |
| <65 | 41/76 | 21.5 | 15.336–27.664 | | 1.00 (reference) | |
| ≥ 65 | 17/21 | 13.7 | 8.549–18.851 | | 0.959 (0.400–2.301) | |
| Gender | | | | 0.832 | | 0.773 |
| Male | 36/58 | 21.5 | 16.595–26.405 | | 1.00 (reference) | |
| Female | 22/39 | 16.0 | 12.785–19.215 | | 1.099 (0.580–2.081) | |
| Smoking | | | | 0.967 | | 0.747 |
| Never | 39/64 | 17.5 | 13.229–21.771 | | 1.00 (reference) | |
| Ever | 19/33 | 24.0 | 11.779–36.221 | | 1.117 (0.570–2.187) | |
| PS | | | | <0.001 | | 0.036 |
| <2 | 52/91 | 21.5 | 15.020–27.980 | | 1.00 (reference) | |
| ≥ 2 | 6/6 | 1.5 | 0.000–5.305 | | 3.573 (1.085–11.765) | |
| Primary site of tumor | | | | 0.777 | | 0.892 |
| Left | 25/44 | 19.0 | 10.316–27.684 | | 1.00 (reference) | |
| Right | 33/53 | 18.5 | 9.850–27.150 | | 1.039 (0.594–1.817) | |
| Pleural effusion | | | | 0.996 | | 0.710 |
| Absence | 8/14 | 14.0 | 1.781–26.219 | | 1.00 (reference) | |
| Presence | 50/83 | 18.5 | 12.052–24.948 | | 0.858 (0.384–1.921) | |
| Weight loss | | | | 0.629 | | 0.580 |
| No | 49/79 | 17.3 | 13.262–21.738 | | 1.00 (reference) | |
| Yes | 9/18 | 23.0 | 10.253–35.747 | | 1.237 (0.582–2.630) | |
| SII | | | | <0.001 | | 0.009 |
| <988.6 | 17/44 | 47.0 | 15.020–27.980 | | 1.00 (reference) | |
| ≥ 988.6 | 41/53 | 13.0 | 0.000–5.305 | | 2.298 (1.232–4.289) | |
| Treatment | | | | 0.003 | | 0.077 |
| BSC | 12/15 | 2.3 | 0.028–4.572 | | 1.00 (reference) | |
| Adjuvant therapies | 46/82 | 21.5 | 16.007–26.993 | | 0.467 (0.201–1.085) | |

Notes: *O/N=observed death number/total patient number in each group. Bold values indicate statistical significance, $P < 0.05$.

Abbreviations: BSC, best supportive care; MPM, malignant pleural mesothelioma; MST, median survival time; PS, performance status; HR, hazard ratio; SII, systemic immune–inflammation index.

($n=4$, 4.1%) and the rest 7 patients were treated with platinum-based chemotherapy or other anti-tumor drugs. Another 3 (3.1%) patients were treated with the combined management of surgery, immunotherapy and radiotherapy with chemotherapeutic drugs. In addition, 67 (69.1%) patients were treated with pemetrexed and platinum-based chemotherapy. Eight patients (6.6%) received the treatment of surgery and adjuvant therapies. The number of patients treated with single radiotherapy or radiotherapy plus other treatment strategies were 1 (1.0%) and 8 (6.6%), respectively.

The optimal cutoff value of SII

The mean pretreatment SII level of 97 cases was $1275.4 \pm 955.9 \times 10^9/L$ (range 247.5–6725.1). According to the result of ROC analysis, the optimal cut-off value of pretreatment SII was $988.6 \times 10^9/L$ (Figure 1, AUC, 0.700; 95% CI, 0.594–0.805; $P=0.001$). High and low pretreatment SII could be seen in 53 (54.6%) and 44 (45.4%) cases, respectively. The median OS for patients with low and high pretreatment SII was 47.0 and 13.0 months, respectively. The 1-, 2- and 3-year survival rates for patients with low SII were 85.8%, 57.8% and 52.0% compared to that of 53.9%, 23.6% and 13.8%, respectively, in patients with high SII (Figure 2B).

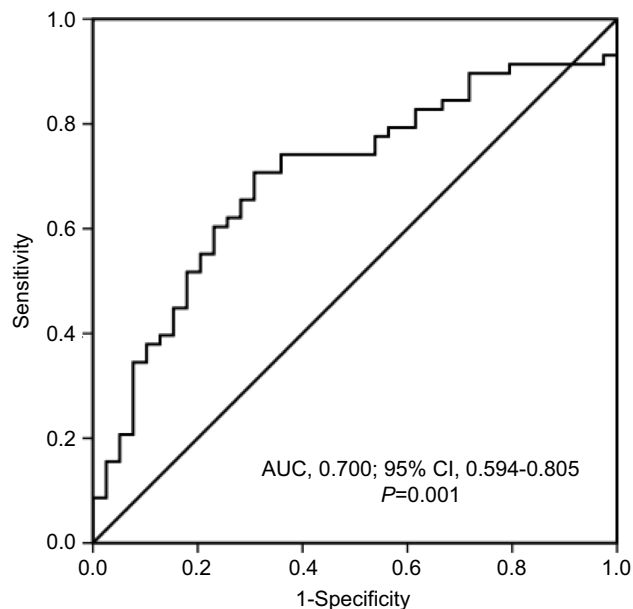


Figure 1 The optimal cutoff value of pretreatment SII of malignant pleural mesothelioma patients based on ROC curve.

Abbreviations: ROC, receiver operating characteristic; SII, systemic immune-inflammation index.

Univariate analysis

On univariate analysis, ECOG PS (Figure 2A; <2 vs ≥ 2 points; 21.5 vs 1.5 months; $P<0.001$), pretreatment SII (Figure 2B; <988.6 vs $\geq 988.6 \times 10^9/L$; 47.0 vs 13.0 months; $P<0.001$) and treatment strategy (Figure 2C; BSC vs adjuvant therapies; 2.3 vs 21.5 months; $P=0.003$) were shown to be closely correlated with the prognosis of MPM. No significant survival difference was found in age, gender, smoking history, primary site of tumor, pleural effusion and weight loss ($P>0.05$). ECOG PS 0–1 points, low pretreatment SII and adjuvant therapies were closely correlated with a prolonged survival.

Multivariate analysis

All variables enrolled were examined on multivariate analysis. The results showed ECOG PS scores (HR=3.573; 95% CI=1.085–11.765; $P=0.036$) and pretreatment SII (HR=2.298; 95% CI=1.232–4.289; $P=0.009$) were independent prognostic factors of MPM. Compared with ECOG PS score 0–1 point and low pretreatment SII, the risk of death for patients with ECOG PS ≥ 2 points and pretreatment SII $\geq 988.6 \times 10^9/L$ increased 257.3% and 129.8%, respectively. ECOG PS 0–1 point and low pretreatment SII were independent positive prognostic factors of MPM.

Relationship between pretreatment SII and clinicopathological characteristics

We also evaluated the relationships between pretreatment SII levels (high and low) and clinicopathological characteristics. Low SII was found to be closely correlated with weight loss (no vs yes, 40.5% vs 66.7%, $P=0.044$). However, no significant correlation was found in age, gender, smoking history, ECOG PS scores, primary site of tumor and pleural effusion ($P>0.05$, Table 2).

Discussion

Our present study shows that high pretreatment SII is easily accessible and is closely associated with a poorer prognosis of MPM. SII represents a powerful noninvasive, inexpensive and reproducible prognostic factor for MPM. These results are of great value for clinics, and it may help clinicians better understand the natural history of this lethal disease and make the best treatment decisions.

Inflammation plays a critical role in cancer development and progression. As key inflammatory factors, serum neutrophils, lymphocytes, monocytes and platelets, NLR,

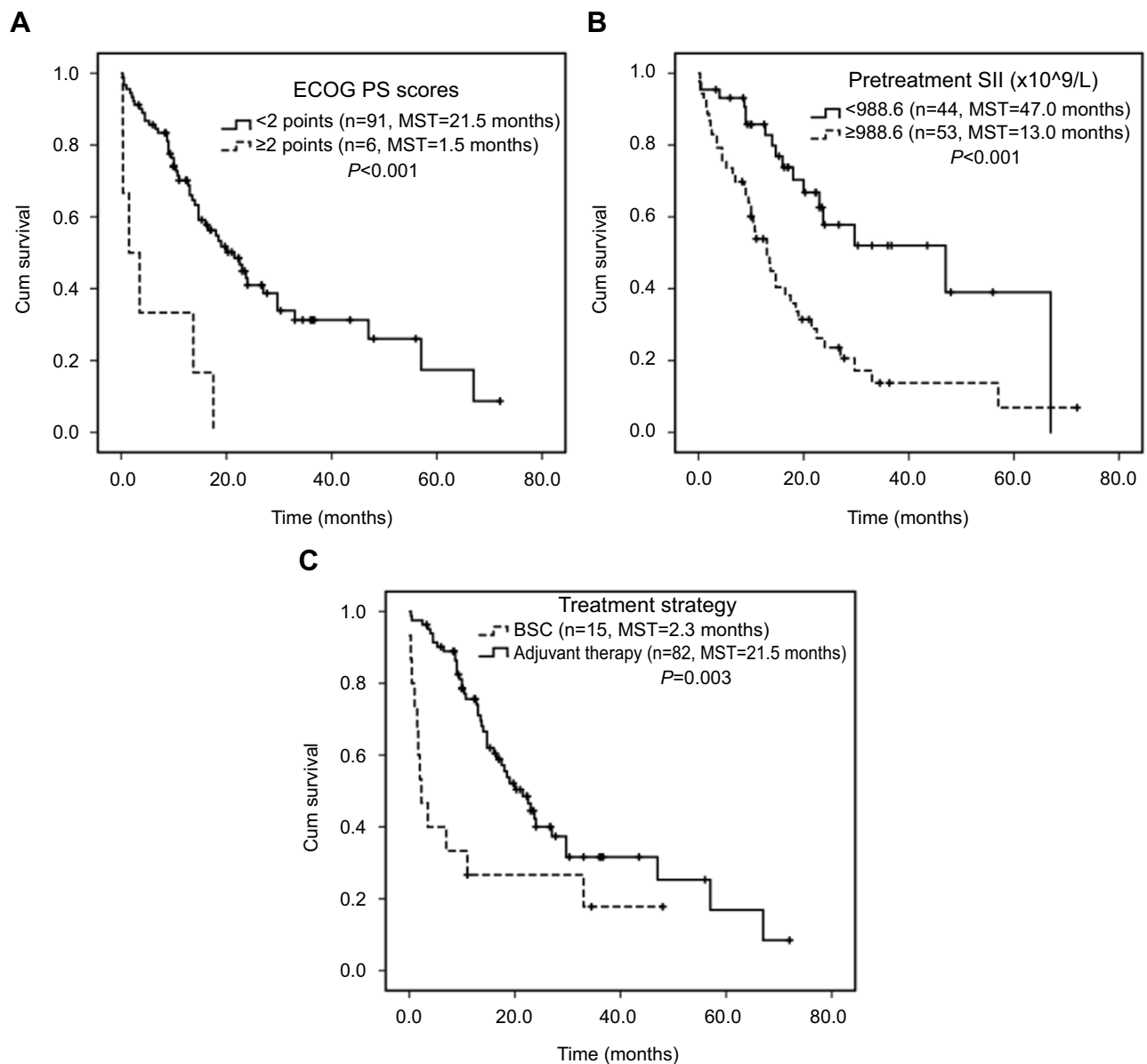


Figure 2 Kaplan–Meier survival curves of ECOG PS, pretreatment SII and treatment strategy for malignant pleural mesothelioma patients.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MST, median survival time; SII, systemic immune–inflammation index.

LMR and PLR have been demonstrated to be independent prognostic factors of many malignancies.^{2,16–19} However, the factors mentioned above are most calculated by one or two inflammatory cells. In some studies, these results cannot be repeated and their prognosis predicting ability may not be so powerful.^{17,26}

Pretreatment SII is a novel systematic inflammatory response indicator, which is calculated by neutrophil (N) \times platelet (P)/lymphocyte (L) counts. Pretreatment SII can better reflect body immune and inflammatory status. Previous studies have demonstrated that pretreatment SII can be a powerful prognosis predicting factor in a series of

malignancies including lung, gastric, metastatic renal cell cancer, esophageal squamous cell carcinoma, etc.^{20,21,23,27} However, the prognostic role of pretreatment SII in MPM remains poorly understood. Fortunately, high pretreatment SII is also found to be closely correlated with a negative prognosis of MPM in our study.

High pretreatment SII always reflect a status of elevated neutrophil and platelet counts or decreased lymphocytes counts. Neutrophils play a key role in cancer progression by the secretion of proangiogenic factor vascular endothelial growth factor (VEGF).²⁸ On one hand, by the secretion of VEGF, transforming growth factor beta

Table 2 Relationship between pretreatment SII and clinicopathological characteristics

| Variables | SII<988.6 | SII≥988.6 | P-value |
|------------------|-----------|-----------|--------------|
| | n (%) | n (%) | |
| Age (years) | | | 0.795 |
| <65 | 35 (46.1) | 41 (53.9) | |
| ≥65 | 9 (42.9) | 12 (57.1) | |
| Gender | | | 0.337 |
| Male | 24 (41.4) | 34 (58.6) | |
| Female | 20 (51.3) | 19 (48.7) | |
| Smoking | | | 0.989 |
| Never | 29 (45.3) | 35 (54.7) | |
| Ever | 15 (45.5) | 18 (54.5) | |
| PS | | | 0.216* |
| <2 | 43 (47.3) | 48 (52.7) | |
| ≥2 | 1 (16.7) | 5 (83.3) | |
| Tumor location | | | 0.225 |
| Left | 17 (38.6) | 27 (61.4) | |
| Right | 27 (50.9) | 26 (49.1) | |
| Pleural effusion | | | 0.706 |
| Absence | 7 (50.0) | 7 (50.0) | |
| Presence | 37 (44.6) | 46 (55.4) | |
| Weight loss | | | 0.044 |
| No | 32 (40.5) | 47 (59.5) | |
| Yes | 12 (66.7) | 6 (33.3) | |

Notes: *Fisher's Exact test. Bold values indicate statistical significance, $P < 0.05$.

Abbreviations: PS, performance status; SII, systemic immune-inflammation index.

and platelet-derived growth factor, platelets can facilitate cancer invasion, migration and metastasis.^{29,30} On the other hand, platelets can also promote angiogenesis via the secretion of cytokine VEGF.²³ As key body immune cells, lymphocytes can induce direct and indirect anti-tumor activities, leading to the inhibition of tumor cells proliferation, invasion and migration.³¹ Low lymphocytes counts always reflect the impaired host immunosurveillance, leading to a poorer prognosis.

In our study, low SII was found to be closely correlated with weight loss, and no significant correlation was found between SII and age, gender, smoking history, ECOG PS scores, primary site of tumor and pleural effusion. This result is consistent with the previous study performed by Li et al³². The study involves patients with age ≥ 70 years, and no correlation is found between SII and clinical characteristics. However, high SII is demonstrated to be a rough indicator of tumor differentiation. The potential relationship between pretreatment SII and clinical characteristics remains to be evaluated.

MPM represents a fatal, high aggressive and treatment-resistant disease, and no uniform treatment strategy has been established at present. Although pemetrexed and

cisplatin-based chemotherapy has been approved for the first-line management of MPM, most patients died with 1 year.³³ In our study, adjuvant therapies including single chemotherapy, radiotherapy, surgery or the combination of chemo-, radio- and surgery show a prolonged survival compared with patients treated with BSC. The best treatment strategies for MPM remain to be explored.

There are some limitations of our present study. Firstly, our study is a single institution retrospective study with limited numbers of patients enrolled. Secondly, due to the retrospective characteristics of our study and the long timespan of 2003–2015, some important feature information including protein c reactive erythrocyte sedimentation rate, histological type, asbestos exposure and TNM stage cannot be reached at this time. So we do not evaluate the histological data, asbestos exposure and TNM stage in this present study. In addition, the potential correlations between pretreatment SII and histological types and asbestos exposure were also not evaluated. We will pay more attention to these questions and we will present more detailed prognostic factor information of MPM in our further study.

In conclusion, the present study is performed in pathological proved MPM and we do not set a healthy control group. Pretreatment SII is easy to access, and it represents an efficiency and noninvasive biomarker of MPM. High SII represents an unfavorable independent prognostic factor of MPM, and the results need to be validated in further studies with a larger number of patients enrolled.

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Disclosure

The authors report no conflicts of interest in this work.

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