Preoperative PDW levels predict pulmonary metastasis in patients with hepatocellular carcinoma

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Abstract

Background: In hepatocellular carcinoma (HCC), pulmonary metastasis (PM) after hepatectomy is associated with poor clinical outcomes. The crucial phases of tumour cell proliferation, angiogenesis, and metastasis all entail platelet activation. In HCC, platelet distribution width (PDW) suggests platelet size changes and predicts a worse prognosis. The aim of this study was to assess the association between PDW and PMs in HCC patients receiving hepatectomy.

Material/methods: From January 2013 to December 2015, a cohort of patients who underwent hepatectomy for HCC at the Harbin Medical University Cancer Hospital in China were retrospectively evaluated. The relationship between PDW levels and clinical and demographic parameters was examined. To investigate the relationships between predicted factors and PM, a competing risk model was used. From January 2016 to December 2018, a validation cohort of 109 patients from the First Affiliated Hospital of Harbin Medical University was studied independently.

Results: In the primary cohort, 19 out of 214 patients had postoperative PMs. In HCC patients with PM, PDW levels were lower than in those without PM. There was a significant difference in the cumulative incidence of 2-year PM between the high-PDW and low-PDW groups after controlling for competing risk events (death prior to the development of PM) (p < 0.001). In addition, PDW was also found to be an independent predictor for PM in a multivariable competing risk analysis. The results were externally validated in another cohort.

Conclusions: In HCC, preoperative PDW is significantly associated with PM. PDW could be a biomarker for post-operative PM in HCC patients.

Keywords: Hepatocellular carcinoma, Pulmonary metastases, Platelet distribution width, Prognosis

Introduction

Hepatocellular carcinoma (HCC) is the third most common cause of malignancy-related death [1, 2]. Curative hepatectomy remains the most common treatment for HCC patients. However, there is a substantial risk of recurrence after curative hepatectomy. Despite the fact that intrahepatic recurrence is more common, extrahepatic metastases (EHMs) represent 14.0% to 25.5% of all recurrences. After curative hepatectomy, pulmonary metastasis (PM) accounts for roughly half of all EHMs [3, 4].

The presence of PM after hepatectomy indicates a poor prognosis. Despite advances in PM therapy, strategies for accurately predicting the incidence of PM following curative hepatectomy remain inadequate [4]. Identifying

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high-risk patients for PM before surgery is helpful in early detection and early intervention. Thus, investigation of novel biomarkers for PM is urgently needed.

Recently, abundant evidence shows that platelet activation is involved in tumor proliferation, angiogenesis, and metastasis [5]. Through direct signal transduction with hepatocytes and liver parenchymal cells, platelets have been demonstrated to increase HCC cell proliferation and infiltration, as well as liver regeneration. Moreover, antiplatelet therapy has also been demonstrated to reduce liver damage and improve patient outcomes [6]. Platelet distribution width (PDW) reveals variations in platelet size and is considered a hallmark of platelet morphology [7, 8]. At present, PDW has been proven to be critical in the prediction of liver metastasis in colorectal cancer and distant metastasis in gastric cancer [9]. PDW levels were also found to predict poor survival in HCC in our previous study [10]. However, no study has investigated the association between PDW and PM following hepatectomy for HCC.

The aim of this study was to assess the association between PDW and PMs in HCC patients receiving hepatectomy.

Materials and methods

Patients

The clinical data of 214 patients with histologically diagnosed HCC at the Harbin Medical University Cancer Hospital in China were reviewed retrospectively from January 2013 to December 2015. All of the patients were subjected to radical surgical resection. They exhibited no signs of substantial portal vein/hepatic vein invasion and had not received any adjuvant therapy prior to surgery. This study excluded participants with other malignancies, haematological illness, infectious disease, and cardiovascular disease. The subjects who had treatment with anticoagulants, statins, or acetylic salicylic acid were also excluded. Information from another independent cohort of patients who underwent hepatectomy for HCC at the First Affiliated Hospital of Harbin Medical University, from January 2016 to December 2018, was retrospectively collected. Two hospitals’ ethics committees gave their approval for the study. An informed consent form was signed by all participants.

Data collection

The following demographic and clinicopathological information were collected: age, sex, body mass index (BMI), hepatitis B virus surface antigen (HBsAg), antibodies to hepatitis C virus (anti-HCV), the presence of liver cirrhosis, Child–Pugh’s grade, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transferase (γ-GGT), albumin, total bilirubin, creatinine, alphafetoprotein (AFP), international normalized ratio (INR), tumor size, tumor number, capsule, tumor differentiation, macrovascular invasion, model of end-stage liver disease score (MELD score), fibrosis-4 index (FIB-4), aspartate aminotransferase to platelet ratio index (APRI), platelet-albumin-bilirubin (PALBI), and albumin-bilirubin (ALBI) score. White blood cell count (WBC), platelet count, PDW, mean platelet volume (MPV), and haemoglobin were directly obtained by an automated hematological analyzer. PDW had a normal range of 11–17%.

Follow-up

After hepatectomy, patients were followed up every three months. At each appointment, a routine abdomen and chest computed tomography (CT) was conducted.

Liver function and serum AFP were measured. When tumor recurrence or metastasis is suspected, abdominal contrast-enhanced CT and/or magnetic resonance imaging (MRI) are performed every 6 months or earlier. The following criteria were used to diagnose PM: (a) A dynamic chest CT scan revealed freshly emerging lesions, particularly many round nodules around the lungs; and (b) AFP levels were increased. The CT findings were confirmed by at least two independent radiologists. Response Evaluation Criteria in Solid Tumors (RECIST) (version 1.1) was used to define the response. A bronchial perfusate examination and sputum cytological test were used to differentiate other pulmonary lesions. All of the patients were tracked for up to two years. Patients who were diagnosed with PM less than a month after hepatectomy were excluded.

Statistical analysis

Statistical analyses were completed using SPSS software (version 26.0), and R software (version 4.1.2). Categorical and continuous variables were analyzed using Chi-squared test and Student’s t-test, respectively. Receiver operating characteristic (ROC) curve was constructed to define the optimal cut-off value of PDW using MedCalc software (version 15.0). Among these survival outcomes, PM was the interest event, while death was considered a competing risk. Survival analyses were performed using univariable and multivariable competing risk models. Variables were included in the multivariable competing risk analysis if the P value on univariable competing risk analysis was < 0.10. The cumulative incidence of PM was estimated using the cumulative incidence function (CIF) curves and intergroup comparison was analyzed using the Gray’s test. The results were presented as sub-distribution hazard ratios (sHR) with 95% CI. P < 0.05 was regarded as significant.
Results

The clinicopathological characteristics of HCC patients in the derivation set and validation set are summarized in Table 1. There were 214 patients (mean age, 52.6±9.2 years; range, 26.0 to 74.0 years) in the derivation cohort, including 162 males (75.7%) and 52 females (24.3%). However, no statistically significant differences were detected between the derivation and validation cohorts with regard to age, sex, hepatitis C, vascular invasion, tumor number, MELD score, APRI score, FIB-4 score,AFP levels, platelet count, and ALT levels.

Table 2 displays the characteristics of HCC patients stratified by PM status. In the derivation cohort, over a median follow-up period of 27.0 (range 4.0–82.0) months, 19 (8.88%) patients had PM events. Moreover, statistical significance was found in vascular invasion, capsule, tumor size, AFP, and PDW levels between the PM and non-PM groups (Table 2). Other clinical parameters were not in correlation with PM. In the validation set, the median follow-up time was 25.0 (range 4.0–46.0) months. Cirrhosis, Child Pugh score, AFP, hemoglobin, platelet count, and tumor size were not in correlation with PM. In the validation cohort, including 162 males (75.7%) and 52 females (24.3%) had PDW ≤ 14.1. Over a median follow-up of 27.0 months, 7 patients were classified into two parts by the same cut-off value (low-PDW (PDW ≤ 14.1) and PDW > 14.1). During the follow-up of 25.0 months, 1 patient in high-PDW group and 10 patients in low-PDW group developed PM. In the validation cohort, the HCC patients were classified into two parts by the same cut-off value of PDW. During the follow-up of 25.0 months, 1 patient in high-PDW group and 10 patients in low-PDW group developed PM. In the validation cohort, the HCC patients were classified into two parts by the same cut-off value of PDW. During the follow-up of 25.0 months, 1 patient in high-PDW group and 10 patients in low-PDW group developed PM. In the validation cohort, the HCC patients were classified into two parts by the same cut-off value of PDW. During the follow-up of 25.0 months, 1 patient in high-PDW group and 10 patients in low-PDW group developed PM.

Death was treated as an event competing with PM. Table 3 shows the results of the competing-risk analysis. In the univariable analysis, sex, vascular invasion, capsule, PDW (continuous variable) and tumor size (continuous variable) were significant prognostic factors for PM in the derivation cohort (p<0.05). All these factors were included in the multivariable model. The multivariable competing-risk analysis revealed that PDW (sHR = 0.850, 95%CI [0.736–0.983]) and tumor size (sHR = 1.240, 95%CI [1.045–1.481]) were the independent predictive factors for PM. The same results were externally validated in another cohort.

Table 1 Baseline characteristics of patients with HCC

| Variables           | Derivation set | Validation set | P-value |
|---------------------|----------------|----------------|---------|
| N                   | 214            | 109            |         |
| Age (years)         | 52.6±9.2       | 52.7±10.1      | 0.966   |
| BMI (kg/m²)         | 24.2±5.8       | 22.0±2.6       | <0.001  |
| Sex (male, %)       | 162 (75.7)     | 82 (75.2)      | 0.926   |
| HBsAg (%)           | 190 (88.8)     | 65 (59.6)      | <0.001  |
| Hepatitis C (%)     | 11 (5.1)       | 2 (1.8)        | 0.153   |
| Cirrhosis (%)       | 196 (91.6)     | 41 (37.6)      | <0.001  |
| Child Pugh score    |                |                | <0.001  |
| A                   | 205 (95.8)     | 85 (78.0)      |         |
| B                   | 9 (4.2)        | 24 (22.0)      |         |
| Vascular invasion   |                |                | 0.631   |
| No                  | 186 (86.9)     | 24 (22.0)      |         |
| Yes                 | 28 (13.1)      | 85 (78.0)      |         |
| Tumor number        |                |                | 0.631   |
| Single              | 183 (85.5)     | 91 (83.5)      |         |
| Multiple            | 31 (14.5)      | 18 (16.5)      |         |
| Tumor differentiation|               |                | <0.001  |
| Poor                | 38 (17.8)      | 50 (45.9)      |         |
| Moderate/well       | 176 (82.2)     | 59 (54.1)      |         |
| Capsule             |                |                | 0.001   |
| Complete            | 183 (85.5)     | 77 (70.6)      |         |
| Incomplete          | 31 (14.5)      | 32 (29.4)      |         |
| Tumor size (cm)     | 4.9±2.9        | 6.3±4.2        | 0.002   |
| MELD score          | -1.84 (-3.58 to -0.02) | 1.57 (-4.20 to 0.90) | 0.451  |
| FIB-4               | 1.9 (1.4–3.2)  | 1.9 (1.1–3.2)  | 0.417   |
| APRI                | 0.6 (0.4–0.9)  | 0.7 (0.4–1.2)  | 0.439   |
| PALBI               | -3.3 (-3.6 to -3.1) | -4.8 (-5.2 to -4.2) | <0.001  |
| ALBI                | -2.6 (-2.9 to -2.3) | -2.0 (-2.4 to -1.7) | <0.001  |
| AFP (ng/mL)         | 14.8 (4.1–227.5) | 23.7 (4.7–471.2) | 0.390   |
| WBC (x 10⁹/L)       | 5.84±2.10      | 8.39±3.98      | <0.001  |
| Haemoglobin (g/L)   | 142.0±17.3     | 122.2±23.7     | <0.001  |
| Platelet count (x 10¹²/L) | 161.5±63.2  | 177.9±90.6  | 0.093  |
| MPV (fl)            | 10.6±1.4       | 11.1±1.1       | <0.001  |
| PDW (%)             | 15.2±2.4       | 13.2±2.2       | <0.001  |
| INR                 | 1.06±0.09      | 1.21±0.26      | <0.001  |
| Albumin (g/L)       | 39.5±4.6       | 34.3±5.8       | <0.001  |
| Creatinine (µmol/L) | 76.8±15.0      | 60.6±15.5      | <0.001  |
| AST (U/L)           | 35 (28–47)     | 51 (31–88)     | <0.001  |
| ALT (U/L)           | 39 (28–52)     | 39 (26–60)     | 0.589   |
| γ-GGT (U/L)         | 49 (32–84)     | 78 (44–135)    | <0.001  |
| Total bilirubin (µmol/L) | 13.9 (10.4–18.7) | 18.2 (14.1–25.6) | <0.001 |

AFP Alpha fetoprotein, ALB Albumin-bilirubin, APRI Aspartate aminotransferase to platelet count ratio index, AST Aspartate aminotransferase, ALT Alanine aminotransferase, BMI Body mass index, FIB-4 Fibrosis-4 index, γ-GGT γ-glutamyl transferase, INR International normalized ratio, MPV Mean platelet volume, MELD score model of end-stage liver disease score, PDW Platelet distribution width, PALBI Platelet-albumin-bilirubin, WBC White blood cell
In the derivation cohort, Fig. 2 showed the cumulative incidence of PMs in the high-PDW and low-PDW groups. PM was the interest event, while death was considered a competing risk. After controlling for competing risk event, there was a significant difference in the incidence of PM between the high-PDW and low-PDW groups ($p<0.001$). We found that individuals with low PDW levels tended to develop PM more than individuals

### Table 2 The characteristics of HCC patients stratified by PM status (continued)

| Variables | Without PM | With PM | $P$-value |
|-----------|------------|---------|------------|
| Development set | | | |
| N | 195 | 19 | 0.855 |
| Age (years) | 52.6 ± 9.2 | 53.0 ± 9.1 | 0.780 |
| BMI (kg/m²) | 24.2 ± 3.8 | 24.4 ± 3.5 | 0.058 |
| Sex (male, %) | 151 (77.4) | 11 (57.9) | 0.980 |
| HBsAg (%) | 173 (88.7) | 17 (89.5) | 0.921 |
| Cirrhosis (%) | 5 (10.5) | 1 (5.3) | 0.728 |
| Child Pugh score | | | |
| A | 187 (95.9) | 18 (94.7) | 0.810 |
| B | 8 (4.1) | 1 (5.3) | 0.810 |
| Vascular invasion | | | <0.001 |
| No | 176 (90.3) | 10 (52.6) | 0.058 |
| Yes | 19 (9.7) | 9 (47.4) | 0.058 |
| Tumor number | | | 0.060 |
| Single | 164 (84.1) | 19 (100.0) | |
| Multiple | 31 (15.9) | 0 (0.0) | |
| Tumor differentiation | | | 0.099 |
| Poor | 32 (16.4) | 6 (31.6) | 0.533 |
| Moderate/well | 163 (83.6) | 13 (68.4) | 0.533 |
| Capsule | | | 0.004 |
| Complete | 171 (87.7) | 12 (63.2) | 0.099 |
| Incomplete | 24 (12.3) | 7 (36.8) | 0.099 |
| Tumor size (cm) | | | <0.001 |
| MELD score | -1.8 (-3.6 to -0.0) | -2.0 (-2.9 to -1.2) | 0.422 |
| FIB-4 | 1.9 (1.3–3.1) | 2.3 (1.6–3.3) | 0.327 |
| APRI | 0.6 (0.4–0.9) | 0.7 (0.4–0.9) | 0.533 |
| PALBI | -3.3 (-3.6 to -3.0) | -3.3 (-3.7 to -3.2) | 0.021 |
| ALBI | -2.6 (-2.9 to -2.3) | -2.7 (-3.0 to -2.4) | 0.021 |
| AFP (ng/mL) | 123 (3.9–174.3) | 231 (22.6–1189.4) | 0.001 |
| WBC (x 10⁹/L) | 5.82 ± 1.92 | 6.05 ± 3.48 | 0.634 |
| Haemoglobin (g/L) | 142.5 ± 16.3 | 137.4 ± 25.7 | 0.404 |
| Platelet count (x 10⁹/L) | 160.3 ± 64.3 | 174.0 ± 50.5 | 0.367 |
| MPV (fL) | 10.7 ± 1.5 | 10.2 ± 1.1 | 0.175 |
| PDW (%) | 15.4 ± 23 | 13.3 ± 23 | <0.001 |
| INR | 1.05 ± 0.08 | 1.08 ± 0.17 | 0.255 |
| Albumin (g/L) | 39.4 ± 4.6 | 40.9 ± 4.7 | 0.158 |
| AST (U/L) | 35 (28–47) | 38 (34–56) | 0.137 |
| ALT (U/L) | 40 (28–53) | 31 (26–50) | 0.250 |
| γ-GGT (U/L) | 49 (32–84) | 48 (34–76) | 0.927 |
| Total bilirubin (µmol/L) | 139 (104–187) | 146 (104–212) | 0.423 |
| Creatinine (µmol/L) | 76.8 ± 15.1 | 76.6 ± 14.2 | 0.967 |
| Validation set | | | |
| N | 98 | 11 | 0.099 |
| Age (years) | 53.2 ± 9.8 | 47.9 ± 11.9 | |
| BMI (kg/m²) | 22.1 ± 2.6 | 210 ± 2.3 | 0.193 |

Abbreviations: see to Table 1

In the derivation cohort, Fig. 2 showed the cumulative incidence of PMs in the high-PDW and low-PDW groups. PM was the interest event, while death was considered a competing risk. After controlling for competing risk event, there was a significant difference in the incidence of PM between the high-PDW and low-PDW groups ($p<0.001$). We found that individuals with low PDW levels tended to develop PM more than individuals
Table 3  The predictors of PM in HCC patients

| Variables                                      | Univariable | Multivariable |
|------------------------------------------------|-------------|---------------|
| Development set                                |             |               |
| Sex (male vs female)                           | 0.405 (0.164–0.997) | 0.443 (0.170–1.153) | 0.095 |
| Vascular invasion (Yes vs No)                  | 5.360 (2.200–13.100) | <0.001 | 2.610 (0.898–7.596) | 0.078 |
| Tumor number (Multiple vs Single)              | 0.712 (0.209–2.430) | 0.590 |               |     |
| Tumor differentiation (Poor vs Moderate/well)  | 1.310 (0.498–3.450) | 0.580 |               |     |
| Capsule (Incomplete vs Complete)               | 3.110 (1.230–7.850) | 0.017 | 1.490 (0.534–4.181) | 0.440 |
| Tumor size (cm)                                | 1.330 (1.200–1.460) | <0.001 | 1.240 (1.045–1.481) | 0.014 |
| AFP (ng/mL)                                    | 1.000 (1.000–1.000) | 0.090 |               |     |
| PDW (%)                                        | 0.798 (0.706–0.901) | <0.001 | 0.850 (0.736–0.983) | 0.028 |
| Validation set                                 |             |               |
| Cirrhosis (Yes vs No)                          | 0.089 (0.011–0.703) | 0.022 | 0.376 (0.028–4.970) | 0.460 |
| Child Pugh score (B vs A)                      | 6.270 (1.970–19.900) | 0.001 | 2.587 (0.378–17.682) | 0.330 |
| Tumor size (cm)                                | 1.530 (1.350–1.730) | <0.001 | 1.940 (1.291–2.915) | 0.001 |
| MELD score                                     | 0.944 (0.686–1.300) | 0.720 |               |     |
| PALBI                                           | 0.400 (0.146–1.100) | 0.070 |               |     |
| AFP (ng/mL)                                    | 1.000 (1.000–1.000) | 0.630 |               |     |
| Haemoglobin (g/L)                              | 0.972 (0.961–0.983) | <0.001 | 1.046 (0.988–1.107) | 0.120 |
| Platelet count (× 10^9/L)                      | 1.010 (1.000–1.010) | 0.016 | 1.001 (0.990–1.011) | 0.920 |
| PDW (%)                                        | 0.764 (0.645–0.904) | 0.001 | 0.523 (0.304–0.898) | 0.019 |

sHR Subdistribution hazard ratio, CI Confidence interval Abbreviations: see to Table 1
with high PDW levels, with 2-year cumulative incidence of 21.0% and 4.5%, respectively. In the validation cohort, the cumulative incidence of 2-year PM in HCC patients was 21.3% in the high-PDW group and 1.6% in the low-PDW group \((p<0.001)\) (Fig. 3).

**Discussion**

This study observed that in HCC patients with PM, PDW levels were lower than in those without PM. In addition, multivariable analysis found that PDW was the independent predictor of PM after HCC resection. And an external validation cohort came to the same conclusion.

Platelets are traditionally considered the principal cells active in thrombosis and hemostasis. Extensive research has demonstrated that platelets make a substantial contribution to cancer growth and dissemination. Platelet activation is caused by tumor cells interacting with platelets, which promotes tumor development and metastasis [11]. Although the functions of
platelets in tumor metastasis have been widely studied in other malignancies, the exact effects of platelets on HCC metastasis are unknown [12–14]. Compared with HCC patients without metastases, the patients with extrahepatic metastases had a higher platelet count. Moreover, platelet count is a valuable diagnostic tool for predicting extrahepatic metastasis in patients with early-stage HCC receiving curative therapy [15]. In a metastatic HCC mouse model, pharmacological inhibition of platelet activation prevents platelets from adhering to tumor cells and reduces metastasis [16]. Krüppel-like factor 6 (KLF6), a tumor suppressive gene, inhibits tumor growth and invasion in HCC. Previous studies revealed that platelet release down-regulates KLF6 expression in vivo and in vitro in HCC cells [17]. In addition, platelet extracts may also be able to counteract sorafenib or regorafenib-mediated inhibitory effects in HCC cells [18]. According to our findings, platelet activation has a crucial role in HCC. Furthermore, our data supports the use of antiplatelet treatment in patients with HCC who have undergone hepatectomy.

The mechanisms behind the link between decreased PDW and PMs are still unknown. PDW is an early biomarker of platelet activation and indicates the average change in platelet volume. In megakaryocyte development and thrombopoiesis, platelet volume is determined. The failure of heterogenic megakaryocytic maturation is reflected in the decline in PDW levels [19]. In addition, numerous clinical studies revealed a strong link between PDW and the prognosis of various cancers such as breast cancer, colon cancer, ovarian cancer, and non-small cell lung cancer [20–23]. Meanwhile, several reports have also confirmed that PDW is an independent predictor of poor clinical outcome in HCC [10, 24, 25]. Interleukin-6 (IL-6), granulocyte colony-stimulating factor (G-CSF), and macrophage colony-stimulating factor (M-CSF) have all been found to influence megakaryocytic maturation, platelet production, and platelet volume [26]. Furthermore, tumor-derived G-CSF creates a pre-metastatic environment in distant organs, and anti-G-CSF or anti-M-CSF antibodies have been shown to significantly prevent PMs [27]. Furthermore, the presence of thrombocytopenia in HCC patients with cirrhosis indicates that the disease is in an advanced stage. Thrombocytopenia before treatment could be a low-cost and practical predictor of postoperative recurrence in HCC patients [28]. This also partly explains why PDW levels in HCC patients with PM were lower than those without PM.

In the present study, there are several limitations that deserve mention. Firstly, it was a small-sized study with a retrospective nature. Secondly, the mechanisms of PDW involved in PM were not explored and further research is needed. Lastly, participants only included Chinese people, so a larger study is needed to extrapolate our findings to other ethnic groups.

In brief, preoperative PDW may predict PM in HCC patients. Further studies are warranted.

Abbreviations

AFP: Alpha-fetoprotein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; APRI: Aspartate aminotransferase to platelet count ratio index; BMI: Body mass index; CIF: Cumulative incidence function; CT: Computed tomography; CI: Confidence interval; EHMs: Extrahepatic metastases; FIB-4: Fibrosis-4 index; γ-GGT: γ-Glutamyl transferase; G-CSF: Granulocytes colony-stimulating factor; HCC: Hepatocellular carcinoma; IL-6: Interleukin-6; INR: International normalized ratio; IQR: 25%, 75% Interquartile range; KLF6: Krüppel-like factor 6; MPV: Mean platelet volume; M-CSF: Macrophage colony-stimulating factor; NELD score: Model of end-stage liver disease score; PALBI: Platelet-albumin-bilirubin; ALBI: Albumin-bilirubin; PM: Pulmonary metastasis; PDW: Platelet distribution width; RECIST: Response evaluation criteria in solid tumors; ROC: Receiver operating characteristic; sHR: Subdistribution hazard ratios; SD: Standard deviation; WBC: White blood cell.

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Authors’ contributions

XZ and RTW conceived and designed the study; WW, and MLZ collected the data; WJH, ZYL, WW and GYW analyzed the data; WJH, GYW and ZYL wrote and edited the manuscript; WJH, GYW, ZYL, MLZ, RTW and XZ revised the manuscript; RTW and XZ participated in the quality control of the study and manuscript review. All authors read and approved the final manuscript.

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Availability of data and material

The data used in the study can be obtained from the corresponding author upon request.

Declarations

Ethics approval and consent to participate

The protocol was approved by the Harbin Medical University Cancer Hospital and the First Affiliated Hospital of Harbin Medical University Institutional Review Boards. All patients involved in the study gave written consent for this study.

Consent for publication

Not Applicable.

Competing interests

All authors declare that they have no competing interests.

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