Predictable Resistance and Overall Survival of Gemcitabine/Cisplatin by Platelet Activation Index in Non-Small Cell Lung Cancer

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Author’s Contribution:

- Study Design: A
- Data Collection: B
- Statistical Analysis: C
- Data Interpretation: D
- Manuscript Preparation: E
- Literature Search: F
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Source of support:
This research was financially supported by the National Key Research and Development Program of China (2017YFC0908602) and Fundamental Research Funds for the Central University, the National Natural Science Foundation of China (81403026 and 81430081), the Zhejiang Provincial Natural Science Foundation of China (Q18H290004 and LY17H310001), Zhejiang Province Medicine Health General Research Program (2015KYB071, 2017KY258, and 2018KY314), Zhejiang Pharmaceutical Association (2017ZY14), Scientific Research Fund Project of Integrated Chinese and Western Medicine Institute in Zhejiang Province (2014LYZD017), the Zhejiang Provincial Program for the Cultivation of 151 Talents (Ping Huang), and the Zhejiang Provincial Program for the Cultivation of High-Level Innovative Health Talents (Ping Huang), the 102 Talent Training Program of Zhenjiang Cancer Hospital (Zeng Wang).

Background:
Gemcitabine/cisplatin (GP) resistance displays a negative role in treating advanced and metastatic non-small cell lung cancer (NSCLC). Several studies found that the association existed between platelets and cancer antigen 125 (CA125) with anticancer drugs. But the exact correlation between GP resistance and platelet activation index remains poorly understood.

Material/Methods:
Pre-chemotherapy platelet activation index and CA125 were retrospectively evaluated in 169 advanced and metastatic NSCLC patients. All variables were screened by chi-square test and then evaluated by log-rank test. Survival curves were generated by Kaplan-Meier analysis. Univariate and multivariate survival analysis were performed by using Cox proportional hazards model.

Results:
The overall rate of GP resistance for NSCLC patients was 72.19%. Mean platelet volume (MPV) and plateletcrit (PCT) are negative predictors of GP resistance adenocarcinoma [Odds ratio (OR): 5.81, 95% confidence interval (CI): 1.082–31.195, P=0.004] and squamous cell carcinoma (PCT: OR: 3.517, 95% CI: 1.087–11.387, P=0.036), respectively. But both were an independent factor associated with overall survival (OS). Moreover, only CA125 was a dependent factor associated with OS for squamous cell carcinoma [OS: hazard ratio (HR): 1.741, 95% CI: 1.002–3.024, P=0.049; GP resistance: OR: 4.862, 95% CI: 1.437–16.448, P=0.011].

Conclusions:
Platelet activation index will be a potential marker for predicting GP resistance. Besides, CA125 ≥16.9 could be used as a potential marker for predicting GP resistance and OS, which was more sensitive than CA125 ≥35 for squamous cell carcinoma.

MeSH Keywords:
Blood Platelets • Carcinoma, Non-Small-Cell Lung • Drug Resistance • Mean Platelet Volume

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/911125
Background

Non-small cell lung cancer (NSCLC) continues to be the cancer with the highest incidence and cancer-related mortality among malignant tumors, accounting for approximately 80% of all diagnosed lung cancer cases. The main reason for poor prognosis is that the great majority of NSCLC patients are diagnosed at an advanced stage [1]. With the development of technology, many methods have been used to treat NSCLC [2–6]. Chemotherapy has become the standard approach in the treatment of advanced NSCLC [7]. Gemcitabine/cisplatin (GP) serves as first-line doublet chemotherapy for treating advanced NSCLC, with an objective response rate of 20%, median progression-free-survival of 6.1 months, and median overall survival (OS) time of 13.1 months [8]. Unfortunately, not all the sufferers receive clinical benefits from GP chemotherapy [8]. The majority of patients treated with GP who are GP resistance will eventually become deceased, which suggests that we need to find a suitable marker to predict GP resistance before its use.

Platelets count is commonly used to evaluate whether chemotherapy can be used for patients. Recently, several studies found complex interactions between platelets and tumor cells resulting in tumor progression and metastases [9,10]. Clinical studies reported that platelet activation index including platelet count (PLC), mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT) were associated with poor prognosis in solid tumors [11–15]. Theoretically, platelets display an anti-proliferative effect role through releasing various growth factors during chemotherapy [16]. In fact, laboratory research demonstrated that platelets increase the survival of tumor cells challenged with anticancer drugs [16]. Furthermore, a few researchers found that some anti-platelet drugs enhanced the effect of anticancer drugs, including gemcitabine, paclitaxel, and 5-fluorouracil, by a complicated mechanism that downregulates the phosphorylation of DNA repair proteins and epithelialization in cancer cells, while enhancing drug-induced cell cycle arrest [16–18]. It might imply an important link between platelet activation index and GP resistance for NSCLC patients.

Additionally, cancer antigen 125 (CA125) ≥35 is commonly considered a marker of disease progression and sometimes also a sign of ineffective chemotherapy by oncologists. In this study, we focused on the evaluation of GP resistance and prognosis via platelet activation index such as PLT, MPV, PCT, and PDW in NSCLC patients. The potential value of CA125 in predicting both GP resistance and OS time were also discussed.

Material and Methods

Enrolled population

This work was approved by Zhejiang Cancer Hospital Ethic Committee. Based on the patient enrollment criteria, 169 NSCLC patients were enrolled by a medical team at our hospital (to reduce the subjective differences in the treatment groups) from January 2008 to December 2010. The information about patient gender, age, smoking status, histology, tumor-node-metastasis (TNM) stage, PLT, MPV, PCT, PDW, and CA125 were collected based on the original patient records.

Cancer staging was assessed by the TNM classification criteria issued by the International Union Against Cancer (UIACC) in 2007. Peripheral blood was collected with EDTA tubes at 1 week before chemotherapy. The routine full blood test was performed by our hospital Clinical Laboratory Department.

Patient enrollment criteria were as follows: 1) without any treatment before GP chemotherapy; ≥2 cycles of GP chemotherapy (gemcitabine (GEM) 1000 mg/m² day 1 and 8 + cisplatin (DDP) 35–45 mg/m² day 1 and 2). 2) 18 years < age <75 years, life expectancy ≥3 months (90 days); pathological diagnosis of squamous cell carcinoma or adenocarcinoma. 3) Systemic functional status score (WHO ECOG) 0–2 or KPS score ≥70. 4) Bone marrow hematopoietic function is basically normal: peripheral blood leukocyte count ≥1.5×10³/L, neutrophil absolute value number ≥1.5×10³/L, hemoglobin ≥9.0 g/L, platelet count ≥100×10³/L. 5) Liver and kidney function test: serum aminotransferase ≤2 times the upper limit of normal, total bilirubin ≤1.5 times the upper limit of normal, serum creatinine ≤1.5 times the upper limit of normal or serum creatinine clearance ≥50 mL/min. 6) No previous history of malignancy, organ function was normal, without serious complications, or died from lung cancer and related complications.

Exclusion criteria were as follows: 1) allergy and allergy to many drugs, 2) suffers from mental disorders, 3) severe infection or organic disease, 4) for women, pregnancy and lactation.

To determine OS, follow-up was conducted by telephone and during hospitalization from April 6, 2011. The survival time was calculated until the last follow-up (April 24, 2012).

Response evaluation

The primary drug resistance with GP chemotherapy were assessed after 2 cycles of chemotherapy, based on the rules established the Response by Evaluation Criteria in Solid Tumors (RECIST) [19]. The standard with GP chemotherapy resistance follows the principles described by Altan et al. [20].
PLR measurement

The PLC, MPV, PDW, PCT, and CA125 of peripheral blood were measured with an automatic hematology analyzer 1 week before GP chemotherapy.

Statistical analysis

Inter-group differences in categorical variables were assessed for significance using the chi-square test; differences in continuous variables were assessed using the Mann-Whitney U test or t-test. The optimal cutoff value for age, PLC, MPV, PDW, PCT, and CA125 were determined by receiver operating characteristic (ROC) curve analysis. All variables were screened by chi-square test and then evaluated by log-rank test to confirm the risk factors eventually. Survival curves were generated by Kaplan-Meier analysis. Univariate and multivariate survival analysis were performed using Cox proportional hazards model. All data were analyzed by SPSS 16.0 software. (Version 16.0, purchase by SPSS software package). P<0.05 was considered as statistical significance.

Results

Patient characteristics

The characteristics of the patients according to histology are summarized in Table 1. Only 31 patients (24.627%) were alive after the last follow-up (April 24, 2012) among the 169 patients who were enrolled in our study. In total, 72.19% of NSCLC patients (122 out of 169) developed GP resistance. According to

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Table 1. Different variables according to histology with NSCLC.

| Variable     | ADC (n=90)     | SqCC (n=79)     | P value |
|--------------|---------------|----------------|---------|
| Gender       |               |                |         |
| Female       | 35 (38.889)   | 12 (15.190)    | 0.001   |
| Male         | 55 (61.111)   | 67 (84.810)    |         |
| Age (yr)     |               |                |         |
| Median (range)| 53.311±10.211 (27–73) | 57.038±6.991 (44–72) | 0.007   |
| TNM stage    |               |                |         |
| IIIA         | 8 (8.889)     | 12 (15.190)    |         |
| IIIB         | 28 (31.111)   | 26 (32.911)    | 0.378   |
| IV           | 54 (60.000)   | 41 (51.899)    |         |
| Smoking      |               |                |         |
| Never smoker | 41 (45.556)   | 21 (26.582)    | 0.011   |
| Current or former smoker | 49 (54.444) | 58 (73.418) |         |
| GP resistance|               |                |         |
| PD+SD        | 71 (78.89)    | 51 (64.557)    | 0.038   |
| PR+CR        | 19 (21.111)   | 28 (35.443)    |         |
| State        |               |                |         |
| Alive        | 15            | 16             | 0.548   |
| Death        | 75            | 63             |         |
| Median survival time [MST] | 505 days         | 434 days       |         |
| PLT (10^9/L) | Median (range)| 249.689±77.664 (123–484) | 260.430±87.46 (120–483) | 0.402   |
| MPV (fl)     | Median (range)| 10.639±1.594 (7.1–18.5) | 10.162±1.708 (6.5–14.7) | 0.064   |
| PCT (%)      | Median (range)| 0.263±0.079 (0.15–0.62) | 0.257±0.070 (0.13–0.46) | 0.586   |
| PDW (%)      | Median (range)| 13.662±2.826 (8.1–22.7) | 13.585±3.033 (8.5–23.7) | 0.88    |
| CA125 (U/mL) | Median (range)| 93.451 (6.4–509.2) | 59.713 (6.5–677.3) | 0.001   |

NSCLC – non-small cell lung cancer; ADC – adenocarcinoma; SqCC – squamous cell carcinoma; GP – gemcitabine + cisplatin; PD – progressive disease; SD – stable disease; PR – partial response’s; CR – complete response; PLC – platelet count; MPV – mean platelet volume; PDW – platelet distribution width; PCT – plateletcrit, OS – overall survival time.

PLR measurement

The PLC, MPV, PDW, PCT, and CA125 of peripheral blood were measured with an automatic hematology analyzer 1 week before GP chemotherapy.
pathological histology, we divided the 169 cases into 2 groups: 90 cases (53.254%) had adenocarcinoma (ADC group) and 79 cases (46.746%) had squamous cell carcinoma (SqCC group). Among all the variables, gender, age (years), smoking status, CA125 (U/mL), and GP resistance were significantly different between the 2 groups, especially the factor of GP resistance. However, between the two groups, gender, age, smoking status, and CA12 were not the influence factors for GP resistance according to non-conditional logistic regression analysis (Table 2). Therefore, the study result that showed the incidence of GP resistance in the ADC group was higher than that in the SqCC group was reliable (71 out of 90 cases versus 51 out of 79 cases, \(P=0.038\) at <0.05, Table 1).

### Subgroup analysis for OS according to histology

First, we used ROC curve analysis to determine the optimal cutoff value for age, PLC, MPV, PCT, and CA125 for prediction of survival status, which was 44.5, 166.5, 11.05, 0.255, 13.15, and 19.8, respectively (Table 3, Figure 1). Second, we investigated the OS value of pathological histology type relative to gender, age, TNM stage, GP resistance, smoking status, PLC, MPV, PCT, PDW, and CA125 (Table 4). There was no significant correlation between the OS value and histology irrespective of parameters (gender, age, TNM stage, smoking status, PLC, MPV, PCT, PDW, and CA125). We found that the SqCC group had

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**Table 2.** The correlation between the parameters and GP resistance.

| Variable       | B     | OR   | 95% CI          | \(P\) value |
|----------------|-------|------|-----------------|-------------|
| Gender         | 0.476 | 0.4  | 0.588–3.792     | 0.4         |
| Age (yr)       | 0.02  | 0.169| 0.988–1.071     | 0.169       |
| Smoking        | 0.425 | 0.387| 0.628–3.324     | 0.387       |
| CA125 (U/mL)   | 0.002 | 0.197| 0.994–1.001     | 0.197       |

GP – gemcitabine+cisplatin; OR – odds ratio; CI – confidence interval.

**Table 3.** The Age, PLT, MPV, PCT, PDW, CA125 markers for prediction of survival status.

| Variable       | AUC (95% CI)       | SN, %  | SP, %  | Cut-off value |
|----------------|--------------------|--------|--------|---------------|
| Age (yr)       | 0.503 (0.395–0.611)| 0.877  | 0.968  | 44.5          |
| PLT (10^9/L)   | 0.517 (0.404–0.63) | 0.899  | 0.806  | 166.5         |
| MPV (fl)       | 0.504 (0.396–0.613)| 0.312  | 0.194  | 11.05         |
| PCT (%)        | 0.544 (0.436–0.653)| 0.464  | 0.323  | 0.255         |
| PDW (%)        | 0.54 (0.43–0.649)  | 0.543  | 0.355  | 13.15         |
| CA125 (U/mL)   | 0.652 (0.548–0.757)| 0.746  | 0.419  | 19.8          |

AUC – area under the curve; CI – confidence interval; SN – sensitivity; SP – specificity; PLC – platelet count; MPV – mean platelet volume; PDW – platelet distribution width; PCT – plateletcrit.

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**Figure 1.** Overall survival in NSCLC group. ROC curve analysis was performed to analyze the optimal cutoff values of age, PLC, MPV, PCT, PDW, and CA125 for survival status prediction. NSCLC – non-small cell lung cancer; ROC – receiver operating characteristic; PLC – platelet count; MPV – mean platelet volume; PCT – plateletcrit; PDW – platelet distribution width; CA125 – cancer antigen 125.
Table 4. Subgroup analysis for OS according to histology.

| Histology | Gender | N (%) | Median (SD) | 95%CI | P value |
|-----------|--------|-------|-------------|-------|---------|
| ADC       | Female | 35 (74.468) | 626 (84.373) | 460.629–791.371 | 0.419 |
|           | SqCC   | 12 (25.532) | 357 (175.604) | 12.817–701.183 | |
| ADC       | Male   | 55 (45.082) | 460 (76.106) | 310.832–609.168 | 0.842 |
|           | SqCC   | 67 (59.181) | 437 (65.476) | 308.668–565.332 | |
| Age (yr)  | <44.5  | 11 (61.111) | 405 (125.51) | 159.001–650.999 | 0.487 |
|           | >44.5  | 79 (52.318) | 562 (56.302) | 451.649–672.351 | 0.214 |
| TNM stage | IIIA   | 8 (40) | 867 (166.651) | 540.364–1193.636 | 0.932 |
|           | IIIB   | 28 (51.852) | 697 (97.404) | 506.089–887.911 | 0.058 |
|           | IV     | 54 (56.842) | 436 (35.63) | 366.165–505.835 | 0.735 |
| GP resistance | PD+SD | ADC | 71 (58.197) | 554 (62.722) | 431.065–676.935 | 0.047 |
|           | SqCC   | 51 (41.803) | 356 (17.068) | 322.546–389.454 | |
|           | PR+CR  | ADC | 19 (40.426) | 544 (156.353) | 237.548–850.452 | 0.618 |
|           | SqCC   | 28 (59.574) | 480 (101.273) | 281.504–678.496 | |
| Smoking   | Never smoker | ADC | 41 (66.129) | 606 (48.649) | 510.647–701.353 | 0.304 |
|           | SqCC   | 21 (33.871) | 343 (166.587) | 16.489–669.511 | |
|           | Current or former smoker | ADC | 49 (45.794) | 460 (36.052) | 389.339–530.661 | 0.667 |
|           | SqCC   | 58 (54.206) | 437 (71.081) | 297.682–576.318 | |
| PLT (10⁹/L) | <166.5 | ADC | 11 (55) | 455 (107.894) | 243.527–666.473 | 0.491 |
|           | SqCC   | 9 (45) | 476 (58.138) | 362.05–589.95 | |
|           | ≥166.5 | ADC | 79 (53.02) | 554 (65.425) | 425.768–682.232 | 0.214 |
|           | SqCC   | 70 (46.98) | 429 (59.315) | 312.743–545.257 | |
significantly shorter OS than the ADC group once the GP resistance occurred (ADC: median survival time (MST)=554 days vs. SqCC: MST=356 days, P=0.047, Table 4, Figure 2).

**The impact of various factors on GP resistance to OS in the ADC group**

First, the optimal cutoff value with GP resistance for age, PLT, MPV, PCT, PDW, and CA125 were determined by ROC curve analysis. Then, we assessed risk factors with GP resistance for the ADC group by univariate analysis and multivariate analysis. We found that the presence of GP resistance was an independent factor associated with MPV (³10.85) factors [odds ratio (OR): 5.81, 95% confidence interval (CI): 1.082–31.195, P=0.004] eventually (Tables 6, 7). In addition, we found that there was no significant link between GP resistance and CA125, whether we used 35 or 29.55 as the optimal cutoff value for CA125 (Tables 6, 7).

Finally, we found there was no significant correlation between OS and MPV, with using 10.85 as the optimal cutoff value for MPV [hazard ratio (HR): 1.025, 95%CI: 0.321–3.271, P=0.967, Table 8].

**The impact of various factors on GP resistance to OS in the SqCC group**

First, we determined the optimal cutoff value with GP resistance for age, PLT, MPV, PCT, PDW, and CA125 were 58.5, 229.5, 11.85, 0.255, 13.15, and 19.8 U/mL, respectively (Table 5, Figure 3). Then, we assessed risk factors with GP resistance for the ADC group by univariate analysis and multivariate analysis. We found that the presence of GP resistance was an independent factor associated with MPV (³10.85) factors [odds ratio (OR): 5.81, 95% confidence interval (CI): 1.082–31.195, P=0.004] eventually (Tables 6, 7). In addition, we found that there was no significant link between GP resistance and CA125, whether we used 35 or 29.55 as the optimal cutoff value for CA125 (Tables 6, 7).

**Table 4 continued. Subgroup analysis for OS according to histology.**

| Histology | N (%) | OS, days | 95%CI | P value |
|-----------|-------|----------|------|---------|
| **MPV (fl)** | | | | |
| <11.05     | ADC   | 61 (50.833) | 481 (68.456) | 346.827–615.173 | 0.64 |
|            | SqCC  | 59 (49.167) | 474 (71.315) | 334.223–613.777 | |
| ≥11.05     | ADC   | 29 (59.184) | 606 (100.463) | 409.092–802.908 | 0.095 |
|            | SqCC  | 20 (40.816) | 289 (105.654) | 81.917–496.083 | |
| **PCT (%)** | | | | |
| <0.255     | ADC   | 46 (48.421) | 544 (77.432) | 392.234–695.766 | 0.826 |
|            | SqCC  | 49 (51.579) | 474 (29.408) | 416.361–531.639 | |
| ≥0.255     | ADC   | 44 (59.459) | 505 (90.89) | 326.855–683.145 | 0.209 |
|            | SqCC  | 30 (40.541) | 356 (19.855) | 317.084–394.916 | |
| **PDW (%)** | | | | |
| >13.15     | ADC   | 44 (53.488) | 481 (75.528) | 332.964–629.036 | 0.204 |
|            | SqCC  | 39 (46.988) | 429 (67.809) | 296.095–561.905 | |
| ≤13.15     | ADC   | 46 (53.459) | 570 (85.344) | 402.725–737.275 | 0.966 |
|            | SqCC  | 40 (46.512) | 437 (88.544) | 263.454–610.546 | |
| **CA125 (U/mL)** | | | | |
| <19.8      | ADC   | 19 (35.549) | 744 (156.327) | 437.599–1050.401 | 0.527 |
|            | SqCC  | 34 (64.151) | 695 (129.722) | 440.744–949.256 | |
| ≥19.8      | ADC   | 71 (61.207) | 455 (37.323) | 381.848–528.152 | 0.07 |
|            | SqCC  | 45 (38.793) | 357 (9.389) | 338.597–375.403 | |
9.3, 0.235, 14.95, and 16.9 respectively, by ROC curve analysis (Table 9, Figure 4). Then, using 35 as the CA125 (U/mL) standard cutoff value, we confirmed PCT (%) (≥0.235) and CA125 (U/mL) (≥16.9) were dependent predictors of GP resistance in the lung SqCC group by chi-square test and log-rank test. At the same time, by comparison, we found GP resistance evaluated at a cutoff value of 16.9 for CA125 was more sensitive than using 35 as a cutoff value for CA125.

In addition, although PDW (%) (<14.95) and CA125 (≥16.9) were not dependent factors of GP resistance, we found they were both significantly associated with GP resistance (Table 10). Then, we assessed risk factors with GP resistance for the SqCC group by univariate analysis and multivariate analysis. We found the presence of GP resistance was an independent factor associated with PCT MPV (≥0.235) factors (OR: 3.517, 95% CI: 1.087–11.387, P=0.036), and CA125 (≥16.9) factors (OR: 4.862, 95% CI: 1.437–16.448, P=0.011) (Table 11).

Finally, we found no difference in the OS of PCT (≥0.235) group and PCT (<0.235) group by Cox proportional regression model (P=0.439, Table 12). Therefore, the data presented in Table 12 for multivariate analysis were the results that incorporated PDW, TNM stage, and CA125 (not PDW, TNM stage, CA125, and GP resistance) into the Cox proportional regression model together. On the other hand, predicting GP resistance and OS evaluated at a cutoff value of 16.9 for CA125 was more sensitive than using 35 as a cutoff value for CA125 (cutoff =16.9: HR: 1.741, CI: 1.014–2.988, P=0.044; cutoff=35: HR: 1.365, CI: 0.816–2.284, P=0.236, Table 12). Additionally, the data analyzed from the Cox proportional regression model, which included GP resistance and TNM stage, showed that GP resistance was a prognostic factor independent of stage (HR: 1.858, 0.0 1000.00 2000.00

Figure 2. Kaplan-Meier analysis of the overall survival of histology difference in non-small cell lung cancer patients with gemcitabine/cisplatin resistance (P=0.047, n=122).

Figure 3. Gemcitabine/cisplatin resistance for adenocarcinoma. ROC curve analysis was used to measure the optimal cutoff values for gemcitabine/cisplatin resistance for age, PLT, MPV, PCT, PDW, and CA125. ROC – receiver operating characteristic; PLC – platelet count; MPV – mean platelet volume; PCT – plateletcrit; PDW – platelet distribution width; CA125 – cancer antigen 125.

Table 5. The age, PLT, MPV, PCT, PDW, CA125 markers for prediction of GP resistance for ADC.

| Variable          | AUC (95% CI) | SN, % | SP, % | Cut-off value |
|-------------------|-------------|------|------|--------------|
| Age (yr)          | 0.504 (0.353–0.656) | 0.085 | 0.211 | 65.5         |
| PLT (10^9/L)      | 0.463 (0.321–0.604) | 0.437 | 0.632 | 235.5        |
| MPV (fl)          | 0.616 (0.488–0.745) | 0.451 | 0.106 | 10.85        |
| PCT (%)           | 0.499 (0.35–0.648)  | 0.099 | 0.211 | 0.355        |
| PDW (%)           | 0.579 (0.423–0.734) | 0.676 | 0.421 | 12.2         |
| CA125 (U/mL)      | 0.459 (0.324–0.594) | 0.549 | 0.737 | 29.55        |

AUC – area under the curve; CI – confidence interval; SN – sensitivity; SP – specificity; PLC – platelet count; MPV – mean platelet volume; PDW – platelet distribution width; PCT – plateletcrit.
Table 6. Univariate analysis of risk factors for GP resistance in ADC.

| Variable           | PD+SD (n, %) | PR+CR (n, %) | P value |
|--------------------|--------------|--------------|---------|
| **Gender**         |              |              |         |
| Female             | 28 (80)      | 7 (20)       | 0.837   |
| Male               | 43 (78.182)  | 12 (21.818)  |         |
| **Age (yr)**       |              |              |         |
| <65.5              | 65 (81.25)   | 15 (18.75)   | 0.121   |
| ≥65.5              | 6 (60)       | 4 (40)       |         |
| **TNM stage**      |              |              |         |
| IIIA               | 6 (75)       | 2 (25)       |         |
| IIIB               | 20 (71.429)  | 8 (28.571)   | 0.438   |
| IV                 | 45 (83.333)  | 9 (16.667)   |         |
| **Smoking**        |              |              |         |
| Never smoker       | 32 (78.049)  | 9 (21.951)   | 0.0858  |
| Current or former smoker | 39 (79.592) | 10 (20.408) |         |
| **PLT (10^9/L)**   |              |              |         |
| ≥235.5             | 31 (72.093)  | 12 (27.907)  | 0.131   |
| <235.5             | 40 (85.106)  | 7 (14.894)   |         |
| **MPV (fl)**       |              |              |         |
| <10.85             | 39 (69.643)  | 17 (30.357)  | 0.006   |
| ≥10.85             | 32 (94.118)  | 2 (5.882)    |         |
| **PCT (%)**        |              |              |         |
| ≥0.355             | 7 (63.636)   | 4 (36.364)   | 0.186   |
| <0.355             | 64 (81.013)  | 15 (18.987)  |         |
| **PDW (%)**        |              |              |         |
| <12.2              | 23 (67.647)  | 11 (32.353)  | 0.042   |
| ≥12.2              | 48 (85.714)  | 8 (14.286)   |         |
| **CA125 (U/mL)**   |              |              |         |
| ≥29.55             | 39 (73.585)  | 14 (26.415)  | 0.14    |
| <29.55             | 32 (86.486)  | 5 (13.514)   |         |
| **CA125 (U/mL) - standard** |        |              |         |
| <35                | 34 (85)      | 6 (15)       | 0.204   |
| ≥35                | 37 (74)      | 13 (26)      |         |

PD – progressive disease; SD – stable disease; PR – partial responses; CR – complete response; PLC – platelet count; MPV – mean platelet volume; PDW – platelet distribution width; PCT – plateletcrit.
Table 7. Multivariate analysis of risk factors for GP resistance in ADC.

| Factors           | OR   | 95%CI          | P value |
|-------------------|------|----------------|---------|
| MPV(fl) (≥10.85) | 5.81 | 1.082–31.195   | 0.04    |
| PDW (%) (≥12.2)  | 1.377| 0.431–4.403    | 0.589   |

GP – gemcitabine+cisplatin; ADC – adenocarcinoma; OR – odds ratio; CI – confidence interval; MPV – mean platelet volume; PDW – platelet distribution width.

Table 8. Cox proportional regression model for OS with ADC.

| Variables                                      | OS, days |               |               |
|------------------------------------------------|----------|---------------|---------------|
|                                                | Univariate| Multivariate  |               |
|                                                | HR (95%CI)| P value       | HR (95%CI)    | P value       |
| GP resistance (PD+SD vs. PR+CR)                | 1.081 (0.604–1.935) | 0.793       |               |               |
| Gender (Male vs. Female)                       | 1.447 (0.897–2.334) | 0.13        |               |               |
| Age (yr) (<65.5 vs. ≥65.5)                     | 0.522 (0.235–1.159) | 0.11        |               |               |
| TNM stage (IIIA, IIIB, IV)                     | 2.015 (1.351–3.007) | 0.001       | 2.198 (1.458–3.313) | <0.001 |
| Smoking (Never smoker vs. current or former smoker) | 1.106 (0.701–1.744) | 0.665     |               |               |
| PLT (10⁹/L) (<235.5 vs. ≥235.5)                | 0.949 (0.602–1.496) | 0.821      |               |               |
| MPV (fl) (<10.85 vs. ≥10.85)                   | 1.025 (0.321–3.271) | 0.967      |               |               |
| PCT (%) (<0.355 vs. ≥0.355)                    | 0.835 (0.399–1.747) | 0.64       |               |               |
| PDW (%) (<12.2 vs. ≥12.2)                      | 1.106 (0.685–1.747) | 0.707      |               |               |
| CA125 (U/mL) (<29.55 vs. ≥29.55)               | 0.53 (0.33–0.853) | 0.009       | 0.459 (0.282–0.749) | 0.002 |
| CA125 (U/mL)–standard (<35 vs. ≥35)            | 1.757 (1.103–2.797) | 0.018      | 2.117 (1.311–3.418) | 0.002 |

OS – overall survival time; HR – hazard ratio; CI – confidence interval; GP – gemcitabine+cisplatin; PD – progressive disease; SD – stable disease; PR – partial responses; CR – complete response; PLC – platelet count; MPV – mean platelet volume; PDW – platelet distribution width; PCT – plateletcrit.

Table 9. The Age, PLT, MPV, PCT, PDW, CA125 markers for prediction of GP resistance for SqCC.

| Variable | AUC (95% CI) | SN, % | SP, % | Cut-off value |
|----------|--------------|-------|-------|---------------|
| Age (yr) | 0.377 (0.253–0.502) | 0.314 | 0.571 | 58.5          |
| PLT (10⁹/L) | 0.578 (0.442–0.715) | 0.647 | 0.393 | 229.5         |
| MPV (fl) | 0.593 (0.454–0.733) | 0.804 | 0.571 | 9.3           |
| PCT (%) | 0.675 (0.549–0.802) | 0.667 | 0.286 | 0.235         |
| PDW (%) | 0.329 (0.206–0.452) | 0.235 | 0.571 | 14.95         |
| CA125 (U/mL) | 0.669 (0.539–0.798) | 0.765 | 0.429 | 16.9          |

AUC – area under the curve; CI – confidence interval; SN – sensitivity; SP – specificity; PLC – platelet count; MPV – mean platelet volume; PDW – platelet distribution width; PCT – plateletcrit.
Table 10. Univariate analysis of risk factors for GP resistance in SqCC.

| Variable             | PD+SD (n,% ) | PR+CR (n,% ) | P value |
|----------------------|--------------|--------------|---------|
| Gender               |              |              |         |
| Female               | 10 (75)      | 2 (25)       | 0.14    |
| Male                 | 41 (61.194)  | 26 (38.806)  |         |
| Age (yr)             |              |              |         |
| ≥58.5                | 16 (50)      | 16 (50)      | 0.026   |
| <58.5                | 35 (72.34)   | 12 (27.66)   |         |
| TNM stage            |              |              |         |
| IIIA                 | 7 (58.333)   | 5 (41.667)   | 0.757   |
| IIIB                 | 16 (61.538)  | 10 (38.462)  |         |
| IV                   | 28 (65.854)  | 13 (34.146)  |         |
| Smoking              |              |              |         |
| Never smoker         | 17 (76.19)   | 4 (23.81)    | 0.067   |
| Current or former smoker | 34 (58.621) | 24 (41.379)  |         |
| PLT (10⁹/L)          |              |              |         |
| <229.5               | 18 (51.429)  | 17 (48.571)  | 0.03    |
| ≥229.5               | 33 (72.727)  | 11 (27.273)  |         |
| MPV (fl)             |              |              |         |
| <9.3                 | 10 (45.455)  | 12 (54.545)  | 0.027   |
| ≥9.3                 | 41 (70.175)  | 16 (29.825)  |         |

Figure 4. Gemcitabine/cisplatin resistance for squamous cell carcinoma. ROC curve analysis was used to access the optimal cutoff values for gemcitabine/cisplatin resistance for age, PLT, MPV, PCT, PDW, and CA125. ROC – receiver operating characteristic; PLC – platelet count; MPV – mean platelet volume; PCT – plateletcrit, PDW – platelet distribution width; CA125 – cancer antigen 125.
## Table 10 continued. Univariate analysis of risk factors for GP resistance in SqCC.

| Variable | PD+SD (n,% of total) | PR+CR (n,% of total) | P value |
|----------|----------------------|----------------------|---------|
| PCT (%) |                      |                      |         |
| <0.235  | 17 (45.946)          | 20 (54.054)          | 0.001   |
| ≥0.235  | 33 (78.571)          | 9 (21.429)           |         |
| PD (%) |                      |                      |         |
| ≥14.95 | 13 (33.333)          | 17 (50.000)          | 0.002   |
| <14.95 | 38 (75.51)           | 11 (24.49)           |         |
| CA125 (U/mL) |              |                      |         |
| <16.9  | 14 (44.444)          | 16 (55.556)          | 0.005   |
| ≥16.9  | 38 (74.16% )         | 12 (25.84%)          |         |
| CA125 (U/mL)-standard |              |                      |         |
| <35    | 30 (57.692)          | 22 (42.308)          | 0.077   |
| ≥35    | 21 (77.778)          | 6 (22.222)           |         |

PD = progressive disease; SD = stable disease; PR = partial responses; CR = complete response; PLC = platelet count; MPV = mean platelet volume; PDW = platelet distribution width; PCT = plateletcrit.

## Table 11. Multivariate analysis of risk factors for GP resistance in SqCC.

| Factors | OR    | 95% CI              | P value |
|---------|-------|---------------------|---------|
| Age (yr) (<58.5) | 2.92  | 0.932–9.148         | 0.066   |
| PLT (10^9/L) (<229.5) | 0.932 | 0.161–5.389        | 0.937   |
| MPV (fl) (<9.3) | 4.258 | 0.696–26.069        | 0.117   |
| PCT (%) (<0.235) | 3.517 | 1.087–11.387       | 0.036   |
| PDW (%) (<14.95) | 1.267 | 0.282–5.689        | 0.757   |
| CA125 (U/mL) (≥16.9) | 4.862 | 1.437–16.448     | 0.011   |

OR = odds ratio; CI = confidence interval; PLC = platelet count; MPV = mean platelet volume; PDW = platelet distribution width; PCT = plateletcrit.

Cl: 1.084–3.186, P=0.024, Table 12). Overall, a cutoff value of 16.9 for CA125 was significantly associated with GP resistance and OS for the SqCC group (Figure 5).

### Discussion

According to the NCCN and European Society for Medical Oncology guidelines, GP chemotherapy is one of the recommended first-line treatment options for patients with advanced and metastatic NSCLC [21,22]. The objective response rate with GP chemotherapy for NSCLC patients is approximately 30% [23], which is close to our result of 27.81%.

A few studies have demonstrated the ascendancy of GP for squamous cell carcinoma in ORR (objective response rate) and OS [24,25]. In our study, we also found ORR with GP chemotherapy for ADC patients was significantly lower than that in SqCC patients. Strangely, we found the SqCC patients had significant shorter OS than ADC patients with the condition of GP resistance. According to the existing literature reports, few follow-up treatment options are recommended for those with squamous cell and adenocarcinoma histology once the GP resistance happens [22]. It is seldom reported that squamous cell NSCLC patients got benefit from third generation EGFR-TKI targeted drugs or immunotherapy agents compared to adenocarcinoma histology. Therefore, it is particularly important to know the risk factors with GP resistance for lung squamous cell carcinoma.
Table 12. Cox proportional regression model for OS with SqCC.

| Variables                                      | OS, days |                     |                   |                     |
|------------------------------------------------|----------|----------------------|-------------------|---------------------|
|                                                 | Univariate | Multivariate         |                   |                     |
|                                                 | HR (95%CI) | P value              | HR (95%CI)        | P value             |
| GP resistance (PD+SD vs. PR+CR)                 | 1.78      | (1.042–3.041)        | 0.035             |                     |
| Gender (Male vs. Female)                        | 1.196     | (0.569–2.515)        | 0.636             |                     |
| Age (yr) (<58.5 vs. ≥58.5)                      | 1.284     | (0.775–2.126)        | 0.332             |                     |
| TNM stage (IIIA, IIIB, IV)                      | 1.546     | (1.087–2.197)        | 0.015             | 1.502               | 0.021               |
| Smoking (Never smoker vs. current or former smoker) | 0.93      | (0.519–1.666)        | 0.807             |                     |
| PLT (10^9/L) (<229.5 vs. ≥229.5)                | 1.127     | (0.681–1.862)        | 0.642             |                     |
| MPV (fl) (<9.3 vs. ≥9.3)                        | 1.629     | (0.927–2.863)        | 0.09              |                     |
| PCT (%) (<0.235 vs. ≥0.235)                     | 1.217     | (0.74–2.004)         | 0.439             |                     |
| PDW (%) (<14.95 vs. ≥14.95)                     | 1.74      | (1.028–2.943)        | 0.039             | 1.617               | (0.952–2.748)       | 0.076               |
| CA125 (U/mL) (<16.9 vs. ≥16.9)                  | 1.741     | (1.014–2.988)        | 0.044             | 1.741               | (1.002–3.024)       | 0.049               |
| CA125 (U/mL)-standard (<35 vs. ≥35)             | 1.365     | (0.816–2.284)        | 0.236             |                     |

OS = overall survival time; HR = hazard ratio; CI = confidence interval; GP = gemcitabine+cisplatin; PD = progressive disease; SD = stable disease; PR = partial responses; CR = complete response; PLC = platelet count; MPV = mean platelet volume; PDW = platelet distribution width; PCT = plateletcrit.

PCT is the marker of platelet activation, which is obtained by multiplying PLT and MPV. Changes in the PCT have been reported in a small number of inflammatory diseases and cancer patients [33]. Higher PCT seems to be associated with tumorigenesis for epithelial ovarian cancer [34]. In this study, we found that PCT ≥0.235 had no significant link with outcomes but was a main risk factor for GP resistance for lung squamous cell carcinoma. PCT is a maker that seems to be mainly associated with platelet plaque formation [35], including tumor cell-induced platelet aggregation (TCIPA) through tumor cells and platelet-related interactions, resulting in the release of platelet cytokines to tumor cells, and finally affecting GP resistance [30,36]. Simultaneously, we found that MPV ≥10.85 was the only main risk factor with GP resistance for lung adenocarcinoma cell carcinoma. MPV level is regarded as a signal of abnormal platelet production and activation, especially for high platelet levels. Thus, larger platelets release more cytokines upon stimulation than smaller ones, and some of cytokines can hearten epithelial-mesenchymal transition (EMT) in tumor cells [26–29]. Then a variety of adhesion proteins and transcriptional factors (Snail, Slug, and EMX2) are upregulated by epithelialization resulting in GP resistance [30–32].
Generally, increasing the value of CA125 is often considered a sign of ineffective treatment after GP chemotherapy compared with before therapy. The mechanism involved may be related to enhance mesohaline-related EMT [38]. In our research, we found that CA125 ≥16.9 was more sensitive than CA125 ≥35 to predictive GP resistance for lung squamous cell carcinoma. Furthermore, we found that MPV ≥10.85 was more sensitive than CA125 ≥35 to predictive GP resistance for lung adenocarcinoma cell carcinoma, and PCT ≥0.235 was more sensitive than CA125 ≥35 to predictive GP resistance for lung squamous cell carcinoma. But we also found that CA125 ≥16.9 was more sensitive than PCT ≥0.235 to predictive GP resistance for lung squamous cell carcinoma. This suggests that GP resistance emerges at the cutoff value of 16.9 for CA125 but not 35.

Conclusions

PCT and MPV are important parameters showing platelet functions, and PCT and MPV decrease has been shown in earlier studies in colorectal cancer treated with bevacizumab [39]. In our study, MPV ≥10.85 was significantly related to GP resistance for lung adenocarcinoma cell carcinoma, and PCT ≥0.235 was significantly related to GP resistance for lung squamous cell carcinoma. Therefore, platelets and its activation index will be potential makers for predicting GP resistance. Furthermore, platelets and its activation index are likely to be used more extensively due to their low cost in comparison with serum tumor markers.

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In clinical practice, the intense surveillance for platelet-related indicators of NSCLC is conducive to early understanding of the status of GP resistant for NSCLC, which is of great significance for disease assessment, treatment guidance, and complications prevention of NSCLC. With the pervasive application of platelet-related indicators in NSCLC, we expect to be able to effectively control the risk factors to reduce the morbidity and mortality of NSCLC.

To the best of our knowledge, this is the first study to use the ROC curve replaced Bonferroni test analysis. In this study, we confirmed that the ideal cutoff value of PCT was 0.235 for predicting GP resistance in patients with advanced stage IIIA–IV lung squamous cell carcinoma, and had a significantly higher area under the curve (AUC) value than CA125 ≥16.9; MPV was 10.85 for predicting GP resistance in patients with advanced stage IIIA–IV lung adenocarcinoma cell carcinoma. Besides, CA125 ≥16.9 was a potential marker for predicting GP resistance and OS, which was more sensitive than CA125 ≥35 as well.

There were some limitations to this study. This was a single-center, small sample, retrospective study; multicentric prospective studies are needed to reduce selection bias. In future research, we will make the value of platelet activation index and CA125 with GP resistance more precise and operable by increasing the clinical cases in future research.

Conflict of interests

None.
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