Prognostic value of Onodera’s Nutritional Index for intermediate and high risk gastrointestinal stromal tumors treated with or without TKIs

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Research

Keywords: Gastrointestinal stromal tumor, Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, Onodera’s prognostic nutritional index, propensity score matching, prognostic marker

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Abstract

Background

Immunoinflammatory and nutritional markers such as peripheral blood neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and onodera’s prognostic nutritional index (OPNI) have gained considerable attention and revealed preliminarily as prognostic markers in gastrointestinal stromal tumor (GIST).

Methods

In this study, we firstly investigated the prognostic value of OPNI in GIST treated with or without TKIs based on the propensity score matching (PSM) method. All of the patients had received surgical resection for primary GIST, The data from 2010 to 2018 were initially and retrospectively identified from our gastrointestinal center. Recurrence-free survival (RFS) was calculated by the Kaplan-Meier method and compared by the log-rank test.

Results

These patients who were treated with TKIs and those who did not were divided into two groups, and we used propensity score matching method to make them have more unified baseline data. Multivariate Cox proportional hazard regression models were applied to identify associations with outcome variables. A total of 563 GISTs were initially chosen and 280 of them were included for analysis under an inclusion criteria. After PSM, there were 200 patients included. Multivariate analyses identified OPNI was an independent prognostic marker, and was associated with primary site, tumor size, mitotic index, tumor rupture, necrosis, and modified NIH risk classification. Low OPNI (< 44.05; HR 0.433; 95% CI 0.236–0.794; P = 0.007) were associated with worse RFS.

Conclusions

Preoperative OPNI is a novel and useful prognostic marker for GISTs both treated with or without TKIs.

Background

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tissue neoplasms of digestive system. It often occurs in stomach and small intestine, accidentally found in abdominal and pelvic, omentum, colorectal, esophagus, pancreas, etc [1]. According to literatures, the incidence of GIST is about 0.001%~0.0015%[2], which only accounts for a small part of gastrointestinal tumors. And the elderly suffer more. GIST is now considered to originate in the interstitial cell of Cajal, and the most common cause is mutations in receptor tyrosine kinases, especially among adults with proto-oncogene c-kit and platelet-derived growth factor receptor A (PDGFRα) [3]. Treatment methods for GIST are relatively limited because it is
not sensitive to radiotherapy and chemotherapy, so surgical resection is the first choice, and is the only potentially curative therapy. Tyrosine kinase inhibitors (TKIs) are used as routine clinical drugs for GIST patients of medium to high risk due to their significant effects [4]. Despite the availability of TKIs such as imatinib mesylate (IM), which greatly promoted the disease-free survival (DFS), the relapse of GIST is common, even the tumors are R0 resected. So GIST is not easy to manage, let alone the prevalent side effects (fatigue, diarrhea, nausea, periorbital edema, muscle spasm, rash, etc) and resistance to IM. There are also approximately 15% of GIST patients are innately resistant or intolerant to first-line imatinib treatment[5–7].Therefore, accurate risk classification schemes are becoming increasingly significant for screening out patients who are most possibly to benefit from systematic IM therapy. Nowadays, four widely accepted factors which can reflect the prognosis of GIST patients are tumor location, size, mitotic index and tumor rupture as suggested by National Institutes of Health (NIH) consensus criteria[8], Armed Forces Institute of Pathology (AFIP) criteria [9], and modified NIH consensus criteria [10]. As time goes by, more and more independent prognostic factors are proposed, such as antigen identified by monoclonal antibody Ki-67 index and surgery options[11, 12],

In addition, tumor-associated inflammatory cells, which consist tumor microenvironment, promote the proliferation, invasion and metastasis of tumor cells. Thus enhance the development and progression of tumor[13]. As many studies shown, GIST is also affected by immunoinflammatory factors such as peripheral blood neutrophil-to-lymphocyte ratio (NLR), as well as platelet-to-lymphocyte ratio (PLR)[14], which are readily measurable, reproducible and inexpensive systemic inflammatory marker. The that high level of NLR or PLR were reported to associate with poor prognosis of various solid tumors. However, investigations on the prognostic value of NLR and PLR for GISTs are lacking and the results remain controversial[15–17].Onodera's prognostic nutritional index (OPNI) was initially used to evaluate the immune-nutritional state of patients who are given gastrointestinal surgery [18]. Several studies have shown that the OPNI is a crucial prognostic factor in some specific human cancers such as gastric cancer [19], pancreatic cancer [20], colorectal cancer [21] and esophageal cancer [22]. Recently, an article about OPNI and GIST illustrated that OPNI plays a crucial role in prediction for GISTs that were not treated with medicine[23]. However, whether OPNI is a prognostic marker for GIST treated with TKIs has not been expounded, and the predictability difference between GIST treated with or without TKIs remains unknown. In this study, we investigate this firstly.

**Methods**

**Patients**

We retrospectively retrieved the 563 cases of GIST ranging from the lowest to high risk according to the modified NIH risk classification, in Nanjing Drum Tower Hospital from January 2010 to December 2018. Among them, 349 cases were not treated with TKIs, and the other 214 cases received TKIs therapy. In this study, we selected patients classified as the intermediate and high risk, and divided them into two groups: TKIs-using group and TKIs-unused group. We intended to investigate whether OPNI can be a prognostic marker to these two groups. The inclusion criteria was set as follows: (1)Classified as intermediate and high risk according to modified NIH risk classification; (2) primary localized GISTs with R0 resection; (3) no other
synchronous primary tumors; (4) complete medical records; (5) patients whose follow-up was done. Eventually, 280 GISTs were enrolled in this investigation. Among them, 102 patients received no therapies of imatinib, while 178 patients were treated by imatinib after operation. This study was approved by the Ethics Committee of Nanjing Drum Tower Hospital. And written informed consent was acquired from all the patients in this program.

**Preoperative peripheral blood routine tests and OPNI evaluation**

All the results of preoperative peripheral blood routine and blood biochemistry were obtained within 5 days before surgery. The NLR value was calculated as neutrophil count \((10^9/L)\) divided by the lymphocyte count \((10^9/L)\). The value of platelet-to-lymphocyte ratio (PLR) was calculated same as NLR. The OPNI was calculated as serum albumin (g/L) + 5×total lymphocyte count \((10^9/L)\).

**Clinicopathological features**

All GISTs were initially diagnosed as gastrointestinal mesenchymal tumors by pathological ways based on a combination of histopathological evaluation and immunohistochemistry for CD117 or Discovered On GIST 1 (DOG1). They are further confirmed by CD34, desmin, SMA, S-100 expression. DNA mutation analysis of PDGFRA gene exons 12 and 18 or c-kit gene exons 9, 11, 13 and 17 were also made to determine the application of TKIs. In this study, clinical data and histopathological parameters are all collected from medical records. Clinical data includes age, gender, initial complaint, primary tumor site, tumor size, surgery options, tumor rupture (preoperative or intraoperative) , whether the TKIs were used and hospitalization time. Tumor size was accurately measured by pathologists after surgery. Histopathological factors include predominant cell type (spindle, epithelioid, or mixed), mitotic index (per 50 randomly selected high power fields [HPFs]), tumor necrosis and Ki-67 index. Risk stratification of each case was determined by modified NIH consensus criteria covering tumor size, mitotic index, tumor site, and rupture.

**Follow-up**

The patients after surgery were followed up through routine peripheral blood tests, abdominal ultrasonography, endoscopy and computed tomography (CT) every 6 months in the first 5 years, and then annually after 5 years to evaluate tumor recurrence or distant metastasis. Follow-up information was obtained by outpatient or hospitalized records , or direct contact with patients or their family. Relapse-free survival (RFS) is more suitable to evaluate patients’ survival than overall survival (OS). RFS was calculated from the date of surgery to the date of GIST relapse, metastasize or to the last follow-up date.

**Statistical analysis**

All statistical analyses were calculated by using IBM SPSS Statistics, version 22.0 (IBM, New York, USA). The ranked and unordered categorical variables were respectively assessed by Mann–Whitney U and Chi-square test. The correlation of continuous variables was calculated by Pearson correlation coefficient, while discrete variables by Spearman’s correlation coefficient. Cox’s regression model was used to perform multivariate survival analyses. The log-rank test and Kaplan–Meier method were utilized to calculate univariate survival. The PLR, NLR, OPNI cut-off value was determined according to the receiver operating characteristic (ROC)
curve analysis, which was performed based on the recurrence state at 9-year follow-up. The Youden index was estimated to determine the optimal cutoff value for PLR, NLR and OPNI, calculated as sensitivity - (1 – specificity). A P-value <0.05 was indicated to be statistical significant, and confidence intervals (CI) were calculated at the 95 % level.

In this study, we applied 1:1 propensity score matching to adjust patients for gender, age, primary tumor site, tumor size, mitotic index and risk stratification in order to reduce the effect of potential confounding factors and selection bias, such as patients’ baseline clinicopathologic factors or unequal patients distribution between the TKIs-used and TKIs-unused groups. A 0.05-width caliper of the standard deviation of the logit was set to match the two groups.

Results

Clinicopathological parameters

The median age of 280 patients was 60 years old (range 26 to 83 years old), with 114 patients (40.7%) aged >60 years. Among them, there were 143 men and 137 women. Primary manifestations of GISTs were as follows: abdominal discomfort or pain (n = 65), GI bleeding (n = 56), obstruction (n = 17), tumor perforation or rupture (n = 24), medical examination reported (n = 104), and other symptoms (n = 14). The primary tumor sites were mainly stomach (n = 182), secondly small intestine (n = 84), and colorectum or intraperitoneally with unknown origin in the next place (n = 14). The tumor size varied from 1.0 to 30.0 cm (median, 7.5 cm). Histologically, the spindle cell type was most common (n = 162), followed by epithelioid cell type (n = 12) and mixed type (n = 6). The mitotic index, necrosis, and more detailed clinicopathological variables of our patients before and after PSM are summarized in Table 1.

ROC analysis

According to the recent study, OPNI is a prognostic marker to GIST[23]. We used the continuous variable NLR, PLR and OPNI of 349 patients who did not receive any preoperative or postoperative therapies of imatinib as test variables, and RFS as the state variable. The cut-off point of OPNI is 44.05 (P<0.001). Areas under the ROC curve (AUC), cut-off points, sensitivity, specificity, and Youden indexes of NLR, PLR and OPNI were summarized in Table 2, Figure 1.

Correlation analysis

Lower OPNI was associated with primary tumor site (P=0.004), tumor size (P<0.017), mitotic index (P<0.001), and modified NIH risk classification (P<0.001). A strong correlation was observed between NLR, PLR, Ki-67 and tumor size (Pearson correlation coefficient \( r_{\text{NLR}} = 0.06, P_{\text{NLR}} = 0.002; r_{\text{PLR}} = 0.28, P_{\text{PLR}} = 0.003; r_{\text{Ki-67}} = 0.35, P_{\text{Ki-67}} = 0.047\). (Table 3, Figure 2)

Evaluation of the PS Model

The Hosmer-Lemeshow test and the value of c-statistic (0.71) showed fairly excellent calibration (p = 0.08) and discrimination, respectively, between the 2 groups. The ASD values after matching ranged from 0
Follow-up

Patients were followed for a median of 48 months (Range: 8 months– 103 months). 62 patients experienced tumor relapse during the follow-up period. Metastasis to the lymph nodes was not spotted.

Univariate survival analysis

Our univariate survival analysis showed that tumor size (Log-rank P =0.036), mitotic index (Log-rank P <0.001), modified NIH risk stratification (Log-rank P <0.001), Ki-67 index (Log-rank P =0.053), NLR (Log-rank P =0.102), PLR (Log-rank P =0.149) and OPNI (Log-rank P =0.027) were all significant prognostic parameters for RFS. Correlations of clinicopathological factors to RFS are shown in Table 4 and Figure 3,4.

Multivariate survival analysis

Some sorted factors were analyzed in the Cox proportional hazards model in enter strategies. The results of the Cox regression analysis are listed in Table 4. High mitotic index (overall P=0.001), high NLR (P=0.033), and low OPNI (P=0.007) were statistically significant independent negative prognostic indicators for RFS.

Discussion

In this study, according to recent investigations of Sun JY’s team that showed OPNI was an independent predictive factor of RFS in GIST patients with no TKIs treatment [23]. we initially base our analysis on the 349 patients who received no TKIs therapy, and get the cut-off points of NLR, PLR, OPNI and Ki-67 index. Then we examined the univariate and multivariate survival analysis of our patients after PSM study. It was our aim to investigate the prognostic value of OPNI in intermediate and high risk gastrointestinal stromal tumors treated with or without TKIs. Eventually, analysis proved that OPNI was an independent prognostic marker for both two groups. And predictability for those patients who did not receive TKIs treatment is better than that who received TKIs.

A more precise risk classification criterion that can be applied to determine the postoperative prognosis of patients with GIST is eagerly required. Of which the items should be simply and economically detected and calculated by clinicopathological data,

Nowadays, the most widely used criterion to estimate the risk of relapse after surgery in GIST are the AFIP criteria, and modified NIH consensus criteria. Studies have proved that their prognostic accuracy is similar, by and large [24]. Moreover, Memorial Sloan-Kettering Cancer Center sarcoma team developed a nomogram that could estimate the probability of RFS at 2 and 5-year after surgery for primary GIST and was more precise than NIH criteria to a certain extent [25]. Joensuu H further demonstrated the KIT and PDGFRA mutations may have widely varying risks for recurrence, and those with KIT exon 11 duplication mutation or deletion of one codon have favorable RFS with surgery alone and are usually not candidates for adjuvant therapy[26].

OPNI is a nutrition index which is firstly raised by Onodera and his colleagues. The previous studies showed that patients with high OPNI shared a significantly better prognosis than those who had a lower value of
OPNI [22]. And similar results regarding Crohn's disease and stage III colorectal cancer have been also reported [27, 28]. In our study, the border value of the OPNI was determined to be 44.05 for TKIs-used group and TKIs-unused group according to ROC analysis. A detailed analysis demonstrated that lower OPNI was associated with primary tumor site, tumor size, mitotic index, tumor rupture and modified NIH risk classification. In multivariate survival analysis, OPNI was independent prognostic indicators. Low OPNI may result from low hypoproteinemia and/or lymphopenia, which can be explained by several potential phenomena: (1) nutritional supplementation of branched-chain amino acids can improve hypoproteinemia and reduce tumor recurrence in patient; (2) lymphocytes play an important role in the host immune response, eliminating tumor formation and progression.

There does exist limitations of this study. Firstly, it is a single-center retrospective study, therefore, a multicenter study is eagerly required to enlarge the sample to minimize the deficiency during the analysis. Secondly, the best cut-off value in this study is determined by the highest Yoden index by plotting the ROC curve. However, it is still unclear what cut-off value is the best optimal cut-off value for clinical diagnosis of GIST. In general, exploring the exact best cut-off value and studying its intrinsic molecular mechanism will be the future research direction.

**Conclusions**

We found connection among immuno-inflammatory, nutritional factors, clinico-pathological characteristics and the RFS of intermediate and high risk GIST treated with or without TKIs. OPNI is an independent indicator for RFS in GIST treated with or without TKIs, especially remarkable for TKIs-unused patients. Furthermore, OPNI also might be a ponderable factor for predicting tumor biological behavior from peripheral blood.

**Abbreviations**

NLR = neutrophil-to-lymphocyte ratio

PLR = platelet-to-lymphocyte ratio

OPNI = onodera's prognostic nutritional index

GIST = gastrointestinal stromal tumors

PSM = propensity score matching

RFS = recurrence-free survival

TKIs = Tyrosine kinase inhibitors

IM = imatinib mesylate

NCCN = National Comprehensive Cancer Network

NIH = National Institutes of Health
AFIP = Armed Forces Institute of Pathology
DFS = disease-free survival
OS = overall survival
PDGFRA = platelet-derived growth factor receptor A
HPFs = high power fields
CT = computed tomography
ROC = receiver operating characteristic
CI = confidence intervals

Declarations

Ethics approval and consent to participate
This study has been approved by the Ethics Committees of Nanjing Drum Tower Hospital.

Consent for publication
No

Availability of data and materials
Access to the data and the calculation method can be obtained from the authors by email (fengwang36@163.com).

Competing of Interests
The authors declare that they have no competing of interests.

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Authors' contributions
FW, TT and LZ contributed to the study design, drafted the manuscript. HY worked on study design and data analysis. XX and YX were involved in data collection and extraction. LZ, WG and MW revised the manuscript. All authors have read and approved the final manuscript.

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Tables

Table 1 Clinicopathological features of 280 patients with primary GIST that classified as medium and high risk.
| Characteristics                  | Before matching (n=280) | After matching (n=200) |
|--------------------------------|------------------------|-----------------------|
|                                | TKIs-using group(n=178)| TKIs-unused group(n=102)| P value | TKIs-using group(n=100)| TKIs-unused group(n=100)| P value |
|                                | Number(%) | Number(%) | P value | Number(%) | Number(%) | P value |
| Gender                         | 0.446      | 0.257      |         | 0.469      | 0.362      |         |
| Male                           | 100(56.2)  | 43(42.2)   |         | 52(52.00)  | 43(43.00)  |         |
| Female                         | 78(43.8)   | 59(57.8)   |         | 48(48.00)  | 57(57.00)  |         |
| Age (years, \( \bar{x} \pm s \)) | 0.064      |            |         | 0.064      |            |         |
| \( \leq 60 \) years           | 116(65.2)  | 50(49.0)   |         | 52(52.00)  | 50(50.00)  |         |
| >60 years                      | 62(34.8)   | 52(51.0)   |         | 48(48.00)  | 50(50.00)  |         |
| Clinical manifestation         | 0.469      | 0.362      |         | 0.469      | 0.362      |         |
| Abdominal discomfort or pain   | 41(23.03)  | 24(23.53)  |         | 36(36.00)  | 39(39.0)   |         |
| Gastrointestinal bleeding      | 36(20.22)  | 20(19.61)  |         | 17(17.00)  | 19(19.00)  |         |
| Obstruction                    | 11(6.18)   | 6(5.88)    |         | 2(2.00)    | 2(2.00)    |         |
| Perforation or rupture         | 14(7.87)   | 10(9.80)   |         | 8(8.00)    | 9(9.00)    |         |
| Medical examination reported   | 68(38.20)  | 36(35.29)  |         | 32(32.00)  | 27(27.00)  |         |
| Others                         | 8(4.49)    | 6(5.88)    |         | 5(5.00)    | 4(4.00)    |         |
| Preoperative laboratory variables |            |            |         | 0.206      | 0.206      |         |
| Hemoglobin (g/L, \( \bar{x} \pm s \)) | 113.3±22.3 | 108.5±26.4 |         | 116.3±25.6 | 108.3±26.5 |         |
| White blood cell (10^9 /L, \( \bar{x} \pm s \)) | 6.4±2.5    | 6.7±4.2    |         | 6.4±2.5    | 6.7±4.2    |         |
| Neutrophil count (10^9 /L, \( \bar{x} \pm s \)) | 4.4±3.2    | 4.5±4.0    |         | 4.2±2.3    | 4.6±4.0    |         |
| Lymphocyte count (10^9 /L, \( \bar{x} \pm s \)) | 1.5±0.6    | 1.6±1.4    |         | 1.6±0.6    | 1.6±1.4    |         |
|                                |                  |                  |          |          |          |
|--------------------------------|------------------|------------------|----------|----------|----------|
| **Platelet count**             | 230.4±87.7       | 237.8±103.3      | 0.616    | 226.6±78.4 | 237.4±104.4 |
| (10^9 /L, \( \bar{x} \pm s \)) |                  |                  |          |          |          |
| **Albumin (g/L, \( \bar{x} \pm s \))** | 38.9±4.3         | 38.9±4.8         | 0.992    | 39.0±4.0   | 38.9±4.9  |
| **NLR (\( \bar{x} \pm s \))**    | 4.0±5.5          | 3.9±5.1          | 0.939    | 3.5±3.8    | 3.9±5.1  |
| **PLR (\( \bar{x} \pm s \))**    | 182.7±136.1      | 194.2±143.3      | 0.339    | 170.3±121.6 | 193.9±143.9 |
| **OPNI (\( \bar{x} \pm s \))**   | 46.4±5.7         | 46.4±8.6         | 0.015    | 47.2±5.7   | 46.4±8.6  |
| **Primary tumor site**         | <0.001           | 0.137            |
| Stomach                        | 114(64.04)       | 68(66.67)        | 75(75.00) | 66(66.00) |
| Small intestine                | 54(30.34)        | 30(29.41)        | 20(20.00) | 30(30.00) |
| Colorectum                     | 3(1.69)          | 2(1.96)          | 2(2.00)  | 2(2.00)   |
| Intraperitoneally with unknown origin | 7(3.93)        | 2(1.96)          | 3(3.00)  | 2(2.00)   |
| **Tumor size (cm, \( \bar{x} \pm s \))** | 7.75±3.64       | 7.17±4.45        | 0.051    | 6.67±2.75  | 7.16±4.49  |
| ≤ 5.0                          | 32(17.98)        | 27(26.47)        | 23(23.00) | 26(26.00) |
| 5.1-10.0                       | 112(62.92)       | 62(60.78)        | 72(72.00) | 61(61.00) |
| > 10.0                         | 34(19.10)        | 13(12.75)        | 5(5.00)  | 13(13.00) |
| **Predominant cell type**      | 0.685            | 0.795            |
| Spindle                        | 170(19.50)       | 92(90.30)        | 95(95.00) | 90(90.00) |
| Epithelioid                    | 5(2.81)          | 7(6.86)          | 4(4.00)  | 7(7.00)   |
| Mixed                          | 3(1.69)          | 3(2.94)          | 1(1.00)  | 3(3.00)   |
| **Mitotic index (per 50 HPFs)** | 0.875            | 0.250            |
| ≤ 5                            | 85(47.75)        | 47(46.08)        | 53(53.00) | 45(45.00) |
| 6-10                           | 35(19.66)        | 26(25.49)        | 21(21.00) | 26(26.00) |
| >10                            | 58(32.58)        | 29(28.43)        | 26(26.00) | 29(29.00) |
| **Necrosis**                   | 0.014            | 0.002            |
| Yes                            | 62(34.83)        | 32(31.37)        | 33(33.00) | 37(37.00) |
| No                             | 116(65.17)       | 70(68.63)        | 67(67.00) | 63(63.00) |
| **Tumor rupture**              | <0.001           | <0.001           |
|                      | Yes     | No      |                  |                  |
|----------------------|---------|---------|------------------|------------------|
|                      | 23(12.92) | 14(13.73) | 6(6.00)          | 7(7.00)          |
|                      | 155(87.08) | 88(86.27) | 94(94.00)        | 93(93.00)        |
| **Risk classification** |         |         |                  |                  |
| Intermediate risk    | 0.096   | 0.024   |                  |                  |
|                      | 59(33.15) | 44(43.14) | 58(58.00)        | 42(42.00)        |
| High risk            |         |         |                  |                  |
|                      | 119(66.85) | 58(56.86) | 42(42.00)        | 58(58.00)        |
| **CD117**            | 0.279   | 0.031   |                  |                  |
| (-)                  | 3(1.69)  | 5(4.90)  | 2(2.00)          | 5(5.00)          |
| (+)                  | 37(20.79)| 27(26.47)| 23(23.00)        | 25(25.00)        |
| (+++)                | 35(19.66)| 10(9.80) | 17(17.00)        | 11(11.00)        |
| (++++)               | 103(57.87) | 60(58.82) | 58(58.00)        | 59(59.00)        |
| **CD34**             | 0.257   | 0.531   |                  |                  |
| (-)                  | 20(11.24) | 12(11.76) | 10(10.00)        | 12(12.00)        |
| (+)                  | 33(18.54) | 36(35.29) | 15(15.00)        | 33(33.00)        |
| (+++)                | 22(12.36) | 8(7.84)  | 12(12.00)        | 8(8.00)          |
| (++++)               | 103(57.87) | 46(45.10) | 63(63.00)        | 46(46.00)        |
| **Ki-67 index (%)**  |         |         |                  |                  |
| (≤ 5)                | 7.87±7.66 | 7.31±7.59 | 7.01±6.62        | 7.35±7.69        |
| (6-10)               | 110(61.80) | 64(62.75) | 67(67.00)        | 63(63.00)        |
| (>10)                | 35(19.66) | 25(24.51) | 16(16.00)        | 24(24.00)        |
| **Follow-up time (months)** | 44.47±25.07 | 55.01±29.39 | 48.57±24.61 | 53.98±28.75 |
| (≤ 5)                | <0.001   | <0.001   |                  |                  |
| (6-10)               | 146(82.02) | 72(70.59) | 85(85.00)        | 70(70.00)        |
| (>10)                | 32(17.98) | 30(29.41) | 15(15.00)        | 30(30.00)        |

**Table 2.** ROC analysis for NLR, PLR, OPNI.
|                     | NLR  | PLR  | OPNI |
|---------------------|------|------|------|
| nYouden Index       | 0.241| 0.271| 0.482|
| AUC (95% CI)        | 0.632| 0.621| 0.775|
| P-value             | 0.010| 0.018| <0.001|
| Cut-off point       | 3.65 | 208.5| 44.05|
| Sensitivities       | 0.400| 0.486| 0.755|
| Specificities       | 0.822| 0.799| 0.686|

Table 3. Correlation analysis of tumor size and mitotic index with NLR, PLR, OPNI and Ki-67 index.

| Tumor size | Pearson r | P-value |
|------------|-----------|---------|
| NLR        | 0.06      | <0.01   |
| PLR        | 0.28      | <0.01   |
| OPNI       | -0.27     | <0.01   |
| Ki-67 index| 0.35      | <0.05   |

Table 4. Univariate and multivariate analysis of the prognostic factors for recurrence-free survival of patients after PS matching.
| Characteristics          | Univariate analysis | Multivariate analysis |
|-------------------------|---------------------|-----------------------|
|                         | HR(95%CI)           | P value               | HR(95%CI)           | P value               |
| **Age/year**            |                     |                       |                     |                       |
| ≤60                     | 1                   | 0.005                 | 1                   | 0.020                 |
| >60                     | 0.230(0.091-0.583)  | 2.015(1.117-3.635)    |
| **Gender**              |                     |                       |                     |                       |
| Male                    | 1                   | 0.728                 | 1                   | 0.628                 |
| Female                  | 0.859(0.364-2.024)  | 0.855(0.454-1.612)    |
| **GI bleeding**         |                     |                       |                     |                       |
| Yes                     | 1                   | 0.054                 | 1                   | 0.699                 |
| No                      | 0.655(0.270-1.585)  | 0.883(0.471-1.657)    |
| **Primary site**        |                     |                       |                     |                       |
| Gastric                 | 1                   | 0.001                 | 1                   | 0.864                 |
| Non-gastric             | 0.513(0.189-1.389)  | 1.066(0.560-2.029)    |
| **Tumor size**          |                     |                       |                     |                       |
| ≤ 5.0 cm                | 1                   | 0.036                 | 1                   | 0.732                 |
| 5.1-10.0 cm             | 0.786(0.164-3.777)  | 0.904(0.509-1.608)    |
| > 10.0 cm               | 0.739(0.193-2.830)  | 1.034(0.576-1.965)    |
| **Predominant cell type**|                    |                       |                     |                       |
| Spindle                 | 1                   | 0.419                 | 1                   | 0.377                 |
| Epithelioid             | 0.765(0.263-3.376)  | 0.377(0.104-1.362)    |
| Mixed                   | 0.735(0.363-3.289)  | 0.678(0.226-2.973)    |
| **Mitotic index**       |                     |                       |                     |                       |
| ≤ 5 per 50 HPFs        | 1                   | <0.001                | 1                   | 0.001                 |
| 6-10 per 50 HPFs       | 0.288(0.068-1.216)  | 1.787(1.254-2.545)    |
| >10 per 50 HPFs        | 0.422(0.120-1.490)  | 2.395(1.786-4.502)    |
| **Tumor rupture**       |                     |                       |                     |                       |
| No                      | 1                   | 0.097                 | 1                   | 0.817                 |
| Yes                     | 0.477(0.092-2.488)  | 0.894(0.346-2.313)    |
| **NIH risk classification** |                 |                       |                     |                       |
| Intermediate risk | 1 | <0.001 | 1 | 0.013 |
|-------------------|---|--------|---|------|
| High risk         | 0.456(0.138-1.508) | 2.514(1.218-5.191) |

**Ki-67 index**

|       |     |        |     |      |
|-------|-----|--------|-----|------|
|       | 1   | 0.053  | 1   | 0.161|
| ≤ 5   | 1   | 0.053  | 1   | 0.161|
| 6-10  | 1.630(0.429-6.189) | 1.362(0.884-2.098) |
| >10   | 2.696(0.617-11.787) | 2.176(0.754-6.873) |

**NLR**

|       |     |        |     |      |
|-------|-----|--------|-----|------|
| <3.65 | 1   | 0.102  | 1   | 0.033|
| ≥ 3.65| 1.123(0.301-4.188) | 1.388(1.026-1.876) |

**PLR**

|       |     |        |     |      |
|-------|-----|--------|-----|------|
| < 208.50 | 1 | 0.149  | 1   | 0.165|
| ≥ 208.50 | 1.695(0.429-6.700) | 1.301(0.642-2.634) |

**OPNI**

|       |     |        |     |      |
|-------|-----|--------|-----|------|
| < 44.05 | 1 | 0.027  | 1   | 0.007|
| ≥ 44.05 | 3.320(1.146-9.621) | 0.433(0.236-0.794) |

**Figures**
Figure 1

ROC analysis of NLR (A), PLR (B) and OPNI (C) in TKIs-unused patient.

Figure 2
Correlation between tumor size and NLR (A), PLR (B), OPNI (C) and Ki-67 index (D).

Figure 3
Recurrence-free survival analysis of 200 patients after PSM divided into TKIs-using group and TKIs-unused group. Kaplan-Meier curve analysis demonstrated a worse relapse-free survival for patients presenting with larger tumor size (A,E), higher Ki-67 index (B,F), high NIH risk classification (C,G), and higher mitotic index (D,H).
Figure 4

Recurrence-free survival analysis of 200 patients after PSM. Kaplan-Meier curve analysis demonstrated a worse relapse-free survival for patients presenting with lower OPNI (A), higher PLR (B), and higher NLR (C).