Influence of SLCO1B1 in gastric cancer patients treated with EOF chemotherapy

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Abstract. Cytochrome-P450 enzymes, ATP-binding cassette transporters, and solute carriers mediate drug metabolism as metabolic enzymes and membrane transporters, respectively. The present study investigated whether single nucleotide polymorphisms (SNPs) in genes encoding these proteins were predictive or prognostic factors in patients with metastatic gastric cancer (MGC) undergoing chemotherapy. A retrospective study of 108 MGC patients who received epirubicin, oxaliplatin, and 5-fluorouracil (EOF) as first-line treatment was performed. A total of 13 SNPs were genotyped, including SLCO1B1 (rs4149056), SLC2A9 (rs16890979, rs6449213, rs734553), ABCG2 (rs2231142), CYP2C9 (rs1057910, rs1799853), CYP2C19 (rs72552267, rs28399504, rs56337013, rs41291556) and CYP1A2 (rs12720461, rs56107638). The associations between these genotypes and disease-control rate (DCR), progression-free survival (PFS) and overall survival (OS) were analyzed. Patients with SLCO1B1 rs4149056 TT genotype had a significantly shorter OS compared with those with a C allele (CC + CT; 312 vs. 565 days, P=0.039). Multivariate analysis revealed that the rs4149056 TT homozygous genotype was an independent prognostic factor for shorter OS (hazard ratio: 2.565, 95% confidence interval: 1.215 -5.415, P=0.014). However, no significant associations were observed, between the other 12 SNPs and PFS or OS, or between any of the 13 SNPs and DCR. In conclusion, SLCO1B1 rs4149056 TT may be an independent predictor of survival in patients with MGC treated with EOF chemotherapy.

Introduction

Gastric cancer (GC) represents the fourth most common malignant neoplasm and the second leading cause of cancer-related death worldwide. More than 40% of all GC cases diagnosed annually occur in China, of whom almost 50% are diagnosed at an advanced stage and cannot be cured. Treatment of advanced GC is challenging. Epirubicin, cisplatin, and fluorouracil (ECF) and its modified regimens, such as EOF (epirubicin, oxaliplatin, and fluorouracil) and EOX (epirubicin, oxaliplatin, and capecitabine), are widely used to treat GC patients based on the results of phase III clinical trials. However, although these regimens are common first-line treatments, their response rates remain <50%. Biomarkers able to predict chemotherapeutic efficacy are therefore urgently needed.

Both membrane transporters and metabolic enzymes affect cytotoxic-drug metabolism. Solute carrier (SLC) superfamily proteins and ATP-binding cassette (ABC)-transporters are vital membrane transporters. SLCO1B1 encodes the transporter protein, organic anion-transporting polypeptide-1 (OATP1B1), which mediates liver uptake of a wide variety of drugs, and its role in the efficacy of cytotoxic drugs, including 5-fluorouracil (5FU) (1,2), methotrexate (MTX) (3-5), irinotecan (6,7), and paclitaxel (8) has been widely reported. MTX was the first cytotoxic drug reported to be associated with SLCO1B1, and SLCO1B1 SNPs were shown to affect MTX pharmacokinetics in children with acute lymphoblastic leukemia, particularly in terms of deposition and toxicity (5). These findings have been validated in several later studies (9-11). The breast cancer resistance protein (BCRP/ABCG2) has been reported to affect drug resistance in many cancer types, including colorectal cancer, lymphoblastic leukemia, and breast cancer (12-15), and ABCG2 polymorphisms are prognostic factors in breast cancer patients treated with anthracycline-based neoadjuvant chemotherapy (16). Expression levels of glucose transporters (GLUT/SLC1A) were also shown to be related to response to 5FU chemotherapy in GC cells (17), and glucose transporters were reported to be independent prognostic factors in patients with GC (18,19).
Among metabolic enzymes, the cytochrome-P450 (CYP) enzyme family plays an important role in the metabolism of various anticancer drugs (20). Several studies have shown that SNPs in CYP2C9 influence disease-free survival in breast cancer patients treated with tamoxifen (21,22). Moreover, CYP2C9 polymorphism was related to response to fluorouracil-based neoadjuvant chemotherapy in breast cancer (23). CYP2C9 is involved in the metabolism of cyclophosphamide (24,25) and tamoxifen (26,27), and P450 enzymes in human liver microsomes, including CYP1A2 have also been reported to catalyze tegafur into 5FU (28).

Metabolism-related genes, including SLCO1B1, ABCG2, SLC2A9, CYP2C9, CYP2C19, and CYP1A2, might thus influence the efficacy of EOF regimens. In the present study, we investigated the associations between metabolism-related genes and the clinical outcomes of GC patients treated with first-line EOF regimens, in terms of disease-control rate (DCR), progression-free survival (PFS), and overall survival (OS).

Materials and methods

Study population. This retrospective study enrolled 108 consecutive Chinese Han patients with metastatic GC (MGC) treated with EOF regimens as first-line chemotherapy at Fudan University Shanghai Cancer Center (Shanghai, China) between May 2009 and June 2012. Their diagnoses were pathologically confirmed as gastric adenocarcinoma. The study was approved by the Ethics Committee of Fudan University Shanghai Cancer and complied with the principles of the Helsinki Accord. This was a retrospective study and patient consent was therefore deemed unnecessary. However, blood samples were collected from all subjects before treatment, with patient consent, and stored in the tissue bank at Fudan University Shanghai Cancer Center.

Treatment. All patients in this study were treated with first-line chemotherapy using an EOF regimen, consisting of epirubicin infusion (50 mg/m\(^2\))/day) for 5 days, over a 21-day treatment cycle. Tumor responses were evaluated every 6 weeks in accordance to the Response Evaluation Criteria in Solid Tumors 1.0 (RECIST 1.0). Treatment was terminated in the event of disease progression or unacceptable toxicity. If the lesions continued to shrink after six cycles, with no unacceptable toxicity, a further one or two EOF cycles were recommended; otherwise, oral FU was recommended as follow-up treatment.

SNP selection and genotyping. We selected and genotyped 13 drug-metabolism-related genetic polymorphisms located at SLCO1B1 (rs4149056), SLC2A9 (rs16890979, rs6449213, rs734553), ABCG2 (rs2231142), CYP2C9 (rs1057910, rs1799853), CYP2C19 (rs72552267, rs28399504, rs56337013, rs41291556), and CYP1A2 (rs12720461, rs56107638) in the 108 patients (data not shown).

Statistical analysis. The allelic and genotypic distributions and Hardy-Weinberg equilibrium were analyzed using the online analysis tool, SHEsis. Differences in clinical characteristics among the 108 GC patients were analyzed by \(\chi^2\) tests, and differences in allelic and genotypic frequencies between the controlled-disease and progressive-disease groups were compared with \(\chi^2\) or Fisher’s exact probability tests. Genetic power was calculated using the G’Power program (29). Survival curves were analyzed using the Kaplan-Meier method. Differences in PFS and OS between genotype groups were estimated by log-rank tests. Multivariate analysis of prognostic predictors was carried out using a Cox proportional hazards model. A two-sided P-value <0.05 was considered significant. P-values for association analysis were corrected by a false-discovery rate (FDR) procedure (30). To be detailed, FDR \(p = \alpha/n\). In this formula, n is the number of SNPs in the same gene, and \(\alpha\) is the rank of the P-value among the SNPs in the same gene.

Results

Patient characteristics. Most of the 108 GC patients enrolled in the study had ≥3 tumor sites, with the most common metastatic organs being the liver and retroperitoneal lymph nodes. Among the clinicopathological features, liver metastasis and pleural effusion were significantly associated with OS, whereas histological grade, number of tumor sites, retroperitoneal lymph node involvement, and ascites were significantly associated with PFS (Table II).

The responses to EOF chemotherapy were CR, n=1; PR, n=41; SD, n=47; and PD, n=19. The 89 patients with CR, PR, or SD were classified as the disease-control group and the 19 patients with PD were classified as the disease-progression group.

Genotype frequency and disease control. There was no significant relationship between genotype frequency and disease-control rate for any of the 13 SNPs analyzed in the present study (Table III). There was only one genotype distribution each for CYP2C9 (rs72552267, rs28399504, rs56337013, rs41291556) and CYP1A2 (rs12720461, rs56107638) in the 108 patients (data not shown).

Genotype frequency and survival analysis. Univariate analysis of the 13 SNPs in relation to survival (Table IV) showed that patients with SLCO1B1 rs4149056 CC and CT genotypes had significantly longer median OS than patients with the TT genotype (565 vs. 312 days, log-rank \(P=0.039\); Fig. 1). However, there was no significant association between PFS and SLCO1B1 rs4149056 (log-rank \(P=0.956\); Fig. 2), or between any of the other 12 SNPs and OS or PFS (Table IV).

Multivariate PFS and OS analysis with cox regression. Multivariate analysis showed that SLCO1B1 rs4149056
Table I. SNPs in the SLCO1B1, SLC2A9, SLC17A1, ABCG2, CYP2C9, CYP2C19 and CYP1A2 genes analyzed in the article.

| Gene       | SNP ID   | Chromosome | Function     | Allele   | HWE test  |
|------------|----------|------------|--------------|----------|-----------|
| SLCO1B1    | rs4149056| 12:21178615| Missense     | T/C      | 0.608     |
| SLC2A9     | rs16890979| 4:9920543  | Missense     | C/T      | 0.903     |
| SLC2A9     | rs6449213 | 4:9992591  | Intron       | C/T      | 0.903     |
| SLC2A9     | rs734553  | 4:9921380  | Intron       | A/C      | 0.903     |
| ABGC2      | rs2231142 | 4:88131171 | Missense     | A/C      | 0.047     |
| CYP2C9     | rs1057910 | 10:94981296| Missense     | A/C      | 0.808     |
| CYP2C9     | rs1799853 | 10:94942290| Missense     | C/T      | 1.000     |
| CYP2C9     | rs72552267| 10:94775453| Missense     | A/G      | 1.000     |
| CYP2C9     | rs28399504| 10:94762706| Missense     | A/G/T    | 1.000     |
| CYP2C19    | rs56337013| 10:94852738| Missense     | C/T      | 1.000     |
| CYP2C19    | rs41291556| 10:94775416| Missense     | C/T      | 1.000     |
| CYP1A2     | rs12720461| 15:74749010| Intron       | C/T      | 1.000     |
| CYP1A2     | rs56107638| 15:74753271| Splice donor  | A/C/G    | 1.000     |

HWE, hardy-weinberg equilibrium; SNP, single nucleotide polymorphism.

discussion

We investigated the association between SNPs of metabolism-related genes and chemotherapy response in patients with MGC. Patients with SLCO1BI rs4149056 CC and CT genotypes had longer OS than patients with TT genotype (312 vs. 565 days, P=0.039), and SLCO1BI rs4149056 TT was confirmed as an independent prognostic factor for shorter OS in GC patients treated with EOF by Cox regression analysis (hazard ratio: 2.565, 95% confidence interval: 1.215-5.415, P=0.014).

SLCO1BI encodes the SLC family member OATP1B1, which is highly expressed in hepatocytes and associated with hepatic drug uptake and elimination (31). Among single-nucleotide variants of SLCO1B1, c.521T>C rs4149056 had the greatest effect on OATP1B1 activity in this study. SLCO1B1 c.521T>C decreases OATP1B1 transporting activity, thus increasing plasma concentrations of drugs, including cytotoxic drugs. SLCO1B1 rs4149056 has been significantly associated with exposure to SN-38, the active metabolite of irinotecan (7). In another study, OATP1B1 was responsible for SN-38 uptake from plasma into hepatocytes (6). Innocenti et al also revealed that SLCO1B1 rs4149056 increased patient exposure to CPT-11 and was associated with an increased risk of severe neutropenia (6). OATP1B1 was shown to transport paclitaxel in an in vitro ovarian cancer study, implying that it contributed to the disposition of paclitaxel (8). Huang et al reported that another SLCO1B1 variant, rs2306283, was an independent prognostic factor for longer PFS in patients with metastatic colorectal cancer treated with a fluoropyrimidine plus irinotecan (1). Overall, these studies suggest that SLCO1B1 affects the metabolism of fluoropyrimidines, CPT-11, and docetaxel, thus influencing their chemotherapeutic efficacy, consistent with the results of the current study.

To the best of our knowledge, the present study provides the first evidence for an association between SLCO1B1 and GC. A literature search of MEDLINE via PubMed found no similar reports with respect to the efficacy of first-line chemotherapy, GC risk, or prognosis.

Notably, although we identified SLCO1B1 rs4149056 as a prognostic factor for OS in MGC patients treated with first-line EOF, we failed to detect any correlation between SLCO1B1 rs4149056 and PFS. There are two possible reasons for this apparent discrepancy. First, SLCO1B1 rs4149056 may only be a prognostic factor in GC patients, and may not affect the short-term efficacy of first-line chemotherapy. Second, CPT-11 or paclitaxel were administered as the main second- or third-line chemotherapy regimens in the present study; as noted above, SLCO1B1 rs4149056 has been associated with the metabolism
of CPT-11 and paclitaxel, and rs4149056 may thus affect OS by influencing the efficacy of the second- or third-line regimens. In our study, \textit{ABCG2} (BCRP2) C421A rs2231142 was borderline-significantly associated with PFS (P=0.083), though multivariate analysis did not identify it as an independent predictor in GC patients treated with EOF regimen. However, several previous studies reported significant relationships between \textit{ABCG2} (BCRP2) C421A rs2231142 and the toxicity or efficacy of oxaliplatin or anthracyclines. Custodio \textit{et al} revealed that \textit{ABCG2} rs3114018 was associated with oxaliplatin-induced peripheral neuropathy in patients with stage II-III colon cancer (32), while breast cancer patients with an \textit{ABCG2} rs2231142 A allele reportedly showed better responses to anthracycline-based neoadjuvant chemotherapy (16). Ghafouri \textit{et al} also showed that the \textit{ABCG2} rs22311442 A allele was associated with stronger responses to anthracyclines and paclitaxel (33). Overall, these three studies indicated that patients with an \textit{ABCG2} rs22311442 A allele showed better responses to anthracyclines and paclitaxel. Although the current univariate analysis failed to find an association between \textit{ABCG} rs22311442 and PFS, there was a nonsignificant tendency towards longer PFS among rs22311442 AA/AC compared with rs22311442 CC patients. There are three possible reasons for this apparent discrepancy. First, it is possible that the sample-size was too small to demonstrate any significant difference between the survival trends of patients with rs22311442 A and C alleles, respectively. Second, the previous studies involved patients with colon cancer or breast cancer, rather than GC, and the results may thus have been affected by this tumor heterogeneity. Third, the EOF regimen contains epirubicin, oxaliplatin, and 5FU.

Table II. Associations between patient characteristics and survival.

| Characteristics                      | Number of patients (%) | Median OS | P-value | Median PFS | P-value |
|--------------------------------------|------------------------|-----------|---------|------------|---------|
| Age (years)                          |                        |           |         |            |         |
| ≤60                                  | 80 (74.1)              | 465       | 0.916   | 159        | 0.176   |
| >60                                  | 28 (25.9)              | 403       |         | 187        |         |
| Sex                                  |                        |           |         |            |         |
| Male                                 | 64 (59.3)              | 534       | 0.359   | 166        | 0.163   |
| Female                               | 44 (40.7)              | 372       |         | 182        |         |
| ECOG performance status              |                        |           |         |            |         |
| 0                                    | 14 (13.0)              | 704       | 0.153   | 240        | 0.768   |
| 1                                    | 89 (82.4)              | 367       |         | 167        |         |
| 2                                    | 5 (4.6)                | 299       |         | 237        |         |
| Histological grade                   |                        |           |         |            |         |
| Moderate and high                    | 13 (12.0)              | 403       | 0.226   | 156        | 0.004   |
| Low/undifferentiated                 | 66 (61.2)              | 875       |         | 380        |         |
| Unclassified                         | 29 (26.8)              | 367       |         | 180        |         |
| Number of tumor sites                |                        |           |         |            |         |
| 1                                    | 5 (4.6)                | 984       | 0.076   | 545        | 0.038   |
| 2                                    | 8 (7.4)                | 570       |         | 411        |         |
| ≥3                                   | 95 (88.0)              | 372       |         | 167        |         |
| Metastasis sites                     |                        |           |         |            |         |
| Liver                                |                        |           |         |            |         |
| Yes                                  | 36 (33.3)              | 281       | 0.004   | 169        | 0.232   |
| No                                   | 72 (66.7)              | 570       |         | 178        |         |
| Lung                                 |                        |           |         |            |         |
| Yes                                  | 7 (6.5)                | 252       | 0.997   | 169        | 0.885   |
| No                                   | 101 (93.5)             | 444       |         | 187        |         |
| Retroperitoneal lymph node           |                        |           |         |            |         |
| Yes                                  | 45                    | 372       | 0.710   | 156        | 0.033   |
| No                                   | 63                    | 534       |         | 192        |         |
| Ascites                              |                        |           |         |            |         |
| Yes                                  | 32                    | 312       | 0.101   | 126        | 0.015   |
| No                                   | 76                    | 534       |         | 192        |         |
| Pleural effusion                     |                        |           |         |            |         |
| Yes                                  | 9                     | 211       | 0.001   | 144        | 0.054   |
| No                                   | 99                    | 475       |         | 178        |         |

Log-rank test. PFS, progression free survival; OS, overall survival.
Table III. Allelic and genotypic distribution of the 15 SNPs in the disease control (CR, PR and SD) and the disease progressive (PD) to chemotherapy.

| Gene        | SNP          | Allele frequency | Chi² value | P-value | Odds ratio 95% CI | Genotype frequency | P-value |
|-------------|--------------|------------------|------------|---------|-------------------|--------------------|---------|
|             |              |                  |            |         |                   |                    |         |
| SLC01B1     | Rs4149056    | C                | 0.372      | 0.541   | 0.705 (0.229-2.168) | CC (0.000)         | 4 (0.211) |
| CR+PR+SD    | T            | 34 (0.895)       |            |         |                   | CT (0.789)         | 15 (0.789) |
| PD          |              | 24 (0.143)       |            |         |                   |                    | 0.700   |
| SLC2A9      | rs16890979   | C                | 0.185      | 0.666   | 0.606 (0.061-6.006) | CC (0.944)         | 1 (0.056) |
| CR+PR+SD    | T            | 1 (0.028)        |            |         |                   | CT (0.966)         | 3 (0.034) |
| PD          |              | 173 (0.983)      |            |         |                   |                    | 0.663   |
| SLC2A9      | rs6449213    | C                | 0.036      | 0.847   | 1.242 (0.134-11.457) | 1 (0.056)         | 17 (0.944) |
| CR+PR+SD    | T            | 35 (0.972)       |            |         |                   | CT (0.965)         | 85 (0.955) |
| PD          |              | 4 (0.022)        |            |         |                   |                    | 0.845   |
| SLC2A9      | rs734553     | A                | 0.168      | 0.681   | 0.621 (0.062-6.149) | 17 (0.944)         | 1 (0.056) |
| CR+PR+SD    | C            | 1 (0.028)        |            |         |                   | AA (0.965)         | 3 (0.035) |
| PD          |              | 169 (0.983)      |            |         |                   |                    | 0.678   |
| ABGC2       | Rs2231142    | A                | 2.081      | 0.149   | 0.525 (0.217-1.272) | 2 (0.111)         | 3 (0.167) |
| CR+PR+SD    | C            | 7 (0.194)        |            |         |                   | AC (0.124)         | 13 (0.722) |
| PD          |              | 56 (0.315)       |            |         |                   |                    | 0.175   |
| CYP2C9      | Rs1057910    | A                | 2.952      | 0.085   | 0.204 (0.027-1.500) | 17 (0.895)         | 2 (0.105) |
| CR+PR+SD    | C            | 36 (0.947)       |            |         |                   | AA (0.978)         | 2 (0.022) |
| PD          |              | 176 (0.989)      |            |         |                   |                    | 0.082   |
| CYP2C9      | rs1799853    | C                | 0.203      | 0.652   |                   | 18 (1.000)         | 0 (0.000) |
| CR+PR+SD    | T            | 36 (1.000)       |            |         |                   | 88 (0.989)         | 1 (0.011) |
| PD          |              | 177 (0.994)      |            |         |                   |                    | 0.651   |

χ² test. SNP, single nucleotide polymorphism.
Custodio showed an association between \textit{ABCG2} rs22311442 and oxaliplatin toxicity rather than oxaliplatin response, which differed from our current study.

Evidence suggests that some CYP450 enzyme family members affect 5FU metabolism (34-37). 5FU was reported to reduce the ability to metabolize a CYP2C9 probe drug (38).

Moreover, several studies have indicated that 5FU can down-regulate the expression of CYP enzymes, including CYP2C9 and CYP2C19 (39,40). However, although CYP2C9 and CYP2C19 have been shown to influence 5FU metabolism \textit{in vitro}, these results have not yet been verified in clinical studies. Furthermore, no studies have reported on the relationship between these enzymes and gastric cancer outcomes.

### Table IV. Univariate survival analysis of SNPs and overall survival/progression free survival time.

| SNPs               | Median OS | 95% CI       | P-value | Median PFS | 95% CI       | P-value |
|--------------------|-----------|--------------|---------|------------|--------------|---------|
| SLCO1B1 rs4149056  |           |              |         |            |              |         |
| TT                 | 312.0     | 178.0-445.9  | 0.039   | 173.0      | 142.7-203.2  | 0.760   |
| CC+CT              | 565.0     | 108.9-1021.0 |         | 179.0      | 157.6-200.3  |         |
| SLC2A9 rs1689079   |           |              |         |            |              |         |
| CC                 | 465.0     | 303.1-626.8  | 0.301   | 176.0      | 156.7-195.2  | 0.427   |
| TC                 | 189.0     | 0.0-383.6    |         | 162.0      | 0.0-353.6    |         |
| SLC2A9 rs6449213   |           |              |         |            |              |         |
| CT                 | 265.0     | 94.0-435.9   | 0.161   | 162.0      | 55.8-268.1   | 0.257   |
| TT                 | 465.0     | 304.2-625.7  |         | 176.0      | 161.4-190.5  |         |
| SLC2A9 rs734553    |           |              |         |            |              |         |
| AA                 | 444.0     | 307.7-580.2  | 0.282   | 173.0      | 154.2-191.7  | 0.489   |
| CA                 | 189.0     | 0.0-383.6    |         | 162.0      | 0.0-353.6    |         |
| ABGC2 rs2231142    |           |              |         |            |              |         |
| CC                 | 444.0     | 293.2-594.7  | 0.750   | 167.0      | 144.1-189.8  | 0.083   |
| AA+CA              | 475.0     | 128.5-821.4  |         | 182.0      | 138.1-225.8  |         |
| CYP2C9 rs1057910   |           |              |         |            |              |         |
| AA                 | 444.0     | 289.8-598.1  | 0.382   | 176.0      | 156.8-195.1  | 0.311   |
| CA                 | 295.0     | 0.0-727.6    |         | 41         | 0.0-202.7    |         |
| CYP2C9 rs1799853   |           |              |         |            |              |         |
| CC                 | 465.0     | 272.9-657.0  | 0.711   | 173.0      | 153.6-192.3  | 0.750   |
| CT                 | 444.0     |              |         | 178.0      |              |         |

Log-rank test. PFS, progression-free survival; OS, overall survival; HR, hazards ratio; CI, confidence interval; SNP, single nucleotide polymorphism.

Figure 1. Kaplan-Meier OS curves in patients with different SLCO1B1 rs4149056 genotypes. OS, overall survival.

Figure 2. Kaplan-Meier PFS curves in patients with different SLCO1B1 rs4149056 genotypes. PFS, progression-free survival.
between 5FU efficacy and SNPs in CYP2C9 or CYP2C19. Our results showed that all 108 blood samples had the same genotypic distributions of CYP2C9 and CYP2C19 SNPs, except for CYP2C9 rs1057910, which was not significantly associated with PFS or OS. The roles of CYP2C9 and CYP2C19 in 5FU metabolism thus currently remain unclear.

There were several limitations to the present study. First, we only analyzed some of the genes related to the CYP, SLC, and ABC families, and any associations between the remaining untested genes and GC remain unknown. Second, we only detected selected polymorphisms for each target agent, and other potentially related polymorphisms may have been missed. Third, the sample size was relatively small. The conclusions of this study therefore require verification in further studies.

In conclusion, the present study identified an association between the SLCO1B1 rs4149056 SNP and clinical outcomes of MGC patients treated with EOF chemotherapy. The resulting risk model successfully divided patients into low-risk and high-risk groups, with a significant difference in OS, but not PFS. SLCO1B1 rs4149056 is therefore a prognostic, but not a predictive factor in MGC patients treated with EOF. Further studies are required to validate our results and to detect other potential prognostic sites in SLCO1B1.

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

Authors’ contributions

WF and XL performed the statistical analysis and wrote the article. XZhu and ZC designed and managed the research. XZha and MH performed the experiments. WG and JY assisted with the research design.

Ethics approval and consent to participant

Informed consent was been obtained from all participants. The study was approved by the Ethics Committee of Fudan University Shanghai Cancer.

Patient consent for publication

Not applicable.
Competing interests

The authors declare that they have no competing interests.

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