SCINDEKS
Serbian Citation Index
J Med Biochem 2026; 45 DOI: 10.5937/jomb0-66038

UDK 577.1 : 61 **ISSN 1452-8258**

J Med Biochem 45: 1–10, 2026

Original paper
Originalni naučni rad

ASSOCIATION BETWEEN QUANTITATIVE DISCOVERED ON DOG1 AND TYROSINE-PROTEIN KINASE KIT MRNA EXPRESSION AND SERUM INFLAMMATORY BIOMARKERS IN GASTROINTESTINAL STROMAL TUMORS

ASOCIJACIJA IZMEĐU KVANTITATIVNE EKSPRESIJE MRNK OTKRIVENE NA DOG1 I TIROZIN-PROTEIN KINAZNOM KOMPLETU I SERUMSKIH INFLAMATORNIH BIOMARKERA U GASTROINTESTINALNIM STROMALNIM TUMORIMA

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Summary

Background: To investigate the quantitative mRNA expression levels of DOG1 and CD117, two key diagnostic markers in gastrointestinal stromal tumors (GIST), and to assess their correlations with Serum Inflammatory Biomarkers measured by standardized laboratory assays, so as to clarify their value in laboratory-based risk stratification of GIST and provide a quantitative basis for improving the biomarker evaluation system for this disease.
Methods: This was a single-center prospective observational study conducted between January 2024 and December 2024, with approval from the institutional ethics committee and written informed consent obtained from all enrolled patients. A total of 110 patients with primary GIST who were scheduled to undergo radical surgery were enrolled. Tumor tissues and matched adjacent tissues obtained during surgery were analyzed by qRT-PCR to quantify DOG1 and CD117 mRNA expression. Serum levels of CRP, IL-6, TNF-α, and SAA were also measured, and the correlations between gene expression and inflammatory markers were assessed. Receiver operating characteristic (ROC) curve analysis and the Kaplan-Meier method were then used to evaluate the predictive value of gene expression for 1-year all-cause mortality.

Kratak sadržaj

Uvod: Cilj je bio ispitivanje kvantitativnih nivoa ekspresije mRNK DOG1 i CD117, dva ključna dijagnostička markera kod gastrointestinalnih stromalnih tumora (GIST), i procena njihovih korelacija sa serumskim inflamatornim biomarkerima merenim standardizovanim laboratorijskim testovima, kako bi se razjasnila njihova vrednost u laboratorijskoj stratifikaciji rizika GIST-a i pružila kvantitativna osnova za poboljšanje sistema procene biomarkera za ovu bolest.
Metode: Ovo je bila prospektivna opservaciona studija u jednom centru sprovedena između januara 2024. i decembra 2024. godine, uz odobrenje institucionalnog etičkog komiteta i pisani informisani pristanak dobijen od svih uključenih pacijenata. Ukupno je uključeno 110 pacijenata sa primarnim GIST-om koji su bili zakazani za radikalnu operaciju. Tumorska tkiva i uparena susedna tkiva dobijena tokom operacije analizirana su qRT-PCR-om kako bi se kvantifikovala ekspresija DOG1 i CD117 mRNA. Takođe su mereni serumski nivoi CRP, IL-6, TNF-a i SAA, a procenjene su korelacije između ekspresije gena i inflamatornih markera. Analiza ROC krive (Receiver Operating Characteristic) i Kaplan-Majerova metoda su zatim korišćene za procenu prediktivne vrednosti ekspresije gena za mortalitet od svih uzroka u roku od 1 godine.
Rezultati: U poređenju sa uparenim susednim normalnim tkivima, tkiva GIST-a su pokazala značajno veću ekspresiju

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Results: Compared with matched adjacent normal tissues, GIST tissues showed significantly higher DOG1 mRNA expression (2.67±0.69 vs 1.23±0.37) and CD117 mRNA expression (2.06±0.61 vs 1.14±0.31) (P<0.01). Serum Inflammatory Biomarkers were consistently higher in the high-expression groups than in the low-expression groups (P<0.05). The 1-year all-cause mortality rate after surgery was 20.00%. The areas under the curve for DOG1 and CD117 in predicting 1-year all-cause mortality were 0.7991 and 0.7546, respectively. For both markers, the 1-year overall survival rate was significantly lower in the high-expression group than in the low-expression group (P<0.001).

Conclusion: DOG1 and CD117 were consistently up-regulated at the transcriptional level in GIST tissues. Their expression levels were positively correlated with serum inflammatory biomarkers measured by standardized laboratory testing, and both markers showed good predictive value for short-term postoperative prognosis in patients with GIST.

Keywords: gastrointestinal stromal tumor, DOG1, CD117, inflammatory biomarkers, quantitative real-time polymerase chain reaction, prognosis, laboratory diagnostics

DOG1 mRNA (2,67±0,69 naspram 1,23±0,37) i ekspresiju CD117 mRNA (2,06±0,61 naspram 1,14±0,31) (P<0,01). Serumski inflamatorni biomarkeri bili su konstantno viši u grupama sa visokom ekspresijom nego u grupama sa niskom ekspresijom (P<0,05). Stopa mortaliteta od svih uzroka nakon jednogodišnje operacije bila je 20,00%. Površine ispod krive za DOG1 i CD117 u predviđanju mortaliteta od svih uzroka tokom jednogodišnje operacije bile su 0,7991 i 0,7546, respektivno. Za oba markera, stopa ukupnog preživljavanja nakon 1 godine bila je značajno niža u grupi sa visokom ekspresijom nego u grupi sa niskom ekspresijom (P<0,001).

Zaključak: DOG1 i CD117 su bili konstantno pojačani na transkripcionom nivou u tkivima GIST-a. Njihovi nivoi ekspresije su bili pozitivno korelirani sa serumskim inflamatornim biomarkerima merenim standardizovanim laboratorijskim testiranjem, a oba markera su pokazala dobru prediktivnu vrednost za kratkoročnu postoperativnu prognozu kod pacijenata sa GIST-om.

Ključne reči: gastrointestinalni stromalni tumor, DOG1, CD117, inflamatorni biomarkeri, kvantitativna lančana reakcija polimeraze u realnom vremenu, prognoza, laboratorijska dijagnostika

Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor arising from the interstitial cells of Cajal in the gastrointestinal tract. Its annual incidence worldwide is approximately 10–20 per million, and it accounts for 1%–3% of gastrointestinal malignancies (1). The biological behavior of GIST is highly heterogeneous, ranging from relatively indolent growth to highly aggressive malignant progression (2). For this reason, identifying quantifiable biochemical markers that can improve prediction of its biological behavior has remained a major concern in laboratory diagnosis and medical biochemistry.

CD117 is a type III tyrosine kinase receptor encoded by the c-KIT proto-oncogene. Its overall positive expression rate in GIST can reach 95%, which is why it has long been regarded as a first-line laboratory diagnostic marker (3). DOG1 is a calcium-activated chloride channel protein encoded by the ANO1 gene (4). It shows better tissue detection specificity and can identify 70%–80% of CD117-negative GIST cases, making it an important complementary marker in diagnostically difficult cases (5). Even so, most previous studies have concentrated mainly on the qualitative diagnostic significance of these two markers and have largely been confined to a binary positive-or-negative interpretation (6, 7). Their expression levels, especially in relation to the tumor biochemical microenvironment, have not been explored in a sufficiently systematic way.

Inflammation is a key component of the tumor microenvironment and plays an important part in tumor initiation and progression. In GIST, oncogenic tyrosine kinase signaling drives inflammatory microenvironment remodeling, and core inflammatory cytokines (IL-6, TNF-α) and acute-phase proteins (CRP, SAA) are validated as objective indicators reflecting GIST-related inflammatory activation (8). Serum inflammatory biomarkers such as C-reactive protein (CRP) and interleukin-6 (IL-6) can be quantified reliably by routine biochemical testing, and they reflect inflammatory activation in both the host and the local tumor milieu in an objective manner (9–11). Increasing evidence has shown that these markers are closely linked to major biochemical processes in a range of solid tumors, including cell proliferation, invasion, and angiogenesis (12, 13). In the field of GIST, however, systematic biochemical studies addressing the relationship between these inflammatory markers and the core diagnostic markers of the tumor remain limited.

Against this background, the present study focused on patients with GIST and examined the expression levels of DOG1 and CD117. Different from previous studies that mostly focused on the qualitative diagnostic value of the two markers, this study adopted a full-process standardized laboratory testing and quality control system, and simultaneously analyzed the association between the quantitative transcriptional expression of the two core markers and multiple serum inflammatory biomarkers. We analyzed their associations with several serum inflammatory biomarkers and further characterized the inflammatory profiles corresponding to different expression gradients. In doing so, we sought to fill the gap in research on the relationship between core immunobiochemical markers of GIST and systemic inflammatory biochemical indicators. These findings

may help refine the laboratory evaluation system for GIST, provide a quantitative reference for combined assessment using immunohistochemical and serum biochemical indicators in risk stratification, and also lay a basis for further investigation into the inflammation-related molecular biochemical mechanisms involved in GIST development and progression.

Materials and Methods

Study subjects

This study was approved by the Institutional Ethics Committee of Northern Jiangsu People's Hospital, and all enrolled patients signed written informed consent before study enrollment. This was a single-center prospective observational study. A total of 110 consecutive patients with primary gastrointestinal stromal tumor (GIST) who were scheduled for surgical treatment at our hospital between January 2024 and December 2024 were enrolled. The inclusion criteria were as follows: primary GIST was suspected on preoperative imaging, radical surgical resection was planned, and postoperative histopathology confirmed the diagnosis of GIST (14); the patient agreed to participate and comply with follow-up, and qualified tumor tissue together with matched adjacent normal tissue could be obtained after resection for nucleic acid extraction and qRT-PCR testing; fasting peripheral venous blood could be collected within 7 days before surgery, with complete laboratory data available; and the clinical records were complete, allowing full follow-up; all included patients underwent preoperative biopsy, with 100% diagnostic consistency between preoperative biopsy and postoperative histopathology. The exclusion criteria were as follows: any antitumor treatment before surgery, including targeted therapy, radiotherapy, or chemotherapy; concurrent acute or chronic infectious disease, autoimmune disease, hematologic disease, or malignant tumors in other organ systems; severe nucleic acid degradation in the specimens that prevented reliable qRT-PCR amplification; failure to achieve radical resection as confirmed intraoperatively, or postoperative pathology indicating a non-primary GIST; refusal to cooperate with follow-up or loss to follow-up during the study period.

Sample size calculation

Sample size estimation was performed using G-Power 3.1 software. The primary endpoint was the difference in 1-year survival between patients stratified by DOG1 and CD117 expression levels, and the Log-rank test was used for between-group comparison. The significance level was set at $\alpha=0.05$ (two-sided), and the statistical power at $1-\beta=0.85$. Based on previous studies of GIST, the 1-year all-cause mortality rate was assumed to be 24% in the DOG1 high-expression group and 7% in the low-expression group, corresponding to a hazard ratio (HR) of 2.2, as reported in a previous GIST prognostic study (15). The minimum required sample size was therefore estimated to be 103 cases. After allowing for a 7% loss-to-follow-up rate, the final sample size was set at 110 cases, which satisfied the prespecified power requirement.

Collection and preservation of tumor and matched adjacent tissues

Resected GIST tissues and matched adjacent normal gastrointestinal tissues were collected within 30 min after removal. The adjacent tissue was taken at least 5 cm from the tumor margin, and rapid intraoperative pathology confirmed the absence of tumor infiltration. After rinsing with pre-cooled normal saline to remove blood and necrotic material, the tissues were immediately placed in RNAlater tissue preservation solution (Takara, Dalian, China), kept at 4 °C overnight, and then transferred to a -80 °C ultra-low-temperature freezer until use.

Collection and pretreatment of peripheral venous blood samples

Fasting peripheral venous blood was collected from all patients in the early morning within 7 days before surgery. Samples were placed separately into EDTA-K2 anticoagulant vacuum tubes and procoagulant vacuum tubes without anticoagulant. Routine blood testing was completed within 2 h after collection of the anticoagulated whole blood. For the procoagulant samples, the blood was left at room temperature for 30 min to allow complete clotting and was then centrifuged at 3000 r/min for 10 min at 4 °C using a 5424R high-speed refrigerated centrifuge (Eppendorf, China). The upper serum layer was separated, aliquoted, and stored at -80 °C. All samples were thawed only once before testing to minimize degradation of the target markers caused by repeated freeze-thaw cycles.

Detection of target gene mRNA expression levels

Approximately 50 mg of frozen tissue was fully ground into powder in liquid nitrogen, and total RNA was extracted using the RNAiso Plus total RNA extraction kit (Takara, Dalian, China). The purity and concentration of the extracted total RNA were detected by a NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific, USA), and only RNA samples with an OD260/280 ratio of 1.8–2.1 were

Table I Primer sequences used for qRT-PCR analysis of DOG1, CD117, and GAPDH.

	F (5′-3′)	R (5′-3′)	bp
DOG1	TGGATGAGAACCGCAACTAC	GATGACGAAGCCGATGAAG	142
CD117	ATGGATTTGCTGGAGAAGGA	TCCAAGGCACAGTGGAAGTA	168
GAPDH	GAAGGTGAAGGTCGGAGTC	GAAGATGGTGATGGGATTTC	226

included for subsequent experiments. Reverse transcription was then performed with the PrimeScript reverse transcription kit (Takara, Dalian, China) to synthesize cDNA. The reaction conditions were 37 °C for 15 min and 85 °C for 5 s to inactivate the reverse transcriptase, after which the products were stored at -20 °C in the dark. The qRT-PCR was performed in a 20 μL total reaction system, with 2 μL cDNA template and 10 μmol/L final primer concentration. The amplification protocol was as follows: pre-denaturation at 95 °C for 30 s, followed by 40 cycles of 95 °C for 5 s and 60 °C for 34 s. All qRT-PCR reactions were performed on the ABI 7500 Fast Real-Time PCR System (Applied Biosystems, USA). After amplification, melting curve analysis was carried out to verify product specificity and exclude interference from primer dimers and nonspecific amplification. Only results with a coefficient of variation in Ct values of <5% between replicate wells were included in the final analysis. Primers for DOG1, CD117, and GAPDH were designed with Primer Premier 5.0 software and synthesized by Sangon Biotech (Shanghai) Co., Ltd. (*Table I*). Relative mRNA expression levels of DOG1 and CD117 were calculated by the $2^{-\Delta\Delta}$Ct method, using matched adjacent tissues as the reference.

Laboratory measurement of serum inflammatory biomarkers

All measurements were performed in an ISO 15189-accredited clinical laboratory. Serum concentrations of C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and serum amyloid A (SAA) were measured with a cobas e 602 fully automated chemiluminescence immunoassay analyzer (Roche Diagnostics, Shanghai, China), together with the same batch of original reagents, calibrators, and quality-control materials, with inter-batch quality control performed for each test batch. For each batch, internal quality-control materials at both high and low concentration levels were included to ensure an intra-assay coefficient of variation of <5% and an inter-assay coefficient of variation of <8%. Only results obtained when internal quality control was within the acceptable range were entered into the final statistical analysis.

Prognostic assessment

Follow-up started on the day of surgery and ended 12 months after the operation. The primary endpoint was 1-year all-cause mortality (including all-cause death occurring within 30 days after surgery and during the 12-month follow-up period). The secondary endpoint was 1-year recurrence-free survival (RFS), defined as the time from surgery to the first confirmed tumor recurrence/metastasis or all-cause death. Patients were followed through regular postoperative outpatient visits and telephone calls, with one follow-up conducted every 3 months. No patients were lost to follow-up during the study period; for any potential lost-to-follow-up cases, the last valid follow-up data would be used for survival analysis, and sensitivity analysis would be performed to evaluate the impact of lost-to-follow-up on the results. Receiver operating characteristic (ROC) curves were used to determine the optimal cutoff values of DOG1 and CD117 expression levels for predicting 1-year all-cause mortality, with the maximum Youden index as the selection criterion for the optimal cutoff value, and patients were then divided into high-expression and low-expression groups accordingly.

Statistical analysis

All statistical analyses were performed using SPSS 26.0. The Shapiro-Wilk test was used to assess the normality of continuous variables. Measurement data with a normal distribution are expressed as $\bar{x}\pm s$. Comparisons between two groups were made with the independent-samples t test, whereas comparisons between tumor tissues and adjacent tissues were performed with the paired t test. Pearson correlation analysis or Spearman rank correlation analysis was selected for bivariate analysis according to the data distribution. ROC curves were used to determine the optimal cutoff values of gene expression for predicting 1-year all-cause mortality, and the area under the curve (AUC) was calculated, the best cut-off value was determined by the maximum Youden index. Kaplan-Meier analysis was applied to generate the 1-year overall survival and recurrence-free survival curves, and differences between groups were evaluated with the Log-rank test. A P value <0.05 was considered statistically significant.

Results

Baseline characteristics of the study population

All enrolled patients completed the standardized 12-month postoperative follow-up, and no patient was lost during the study period. Clinical and laboratory data were complete in all cases. The median age of the patients was 61 years (range, 41–77 years), and 62 were male, accounting for 56.4%. The stomach was the most common primary site, with 68 cases (61.82%), followed by the small intestine with 35 cases (31.82%); the remaining 7 cases (6.36%) arose in less common locations such as the colorectum and esophagus. The mean tumor diameter was 5.15±2.18 cm, and patients with a mitotic count of <5/50 HPF constituted the largest subgroup (52 cases, 47.3%, *Table II*).

Table II Baseline characteristics of the study population.

Projects	n (or $\bar{x}\pm s$)	Percentage (or min-max)
Age	61.84±8.05	41–77
Sex		
Male	62	56.36%
Female	48	43.64%
Primary site of tumor		
Stomach	68	61.82%
Small intestine	35	31.82%
Others	7	6.36%
Tumor diameter (cm)	5.15±2.18	0.7–10.1
Mitotic count		
<5/50HPF	52	47.27
5–10/50HPF	38	34.55
≥10/50HPF	20	18.18
Family history of GISTs		
Yes	11	10.00
No	99	90.00

Note: This item only includes family history of GIST, not other tumor family histories.

Comparison of DOG1 and CD117 mRNA expression levels between tumor tissues and matched adjacent tissues

Compared with adjacent tissues, both DOG1 (2.67±0.69 vs 1.23±0.37; paired t=21.48, 95%CI: 1.30–1.58, P<0.01) and CD117 (2.06±0.61 vs 1.14±0.31; paired t=16.75, 95%CI: 0.81–1.03, P<0.01) were significantly increased in tumor tissues (*Figure 1*).

Differences in serum inflammatory biomarker levels stratified by DOG1 and CD117 mRNA expression

All included serum inflammatory biomarkers (CRP, IL-6, TNF-α, and SAA) were significantly higher in the DOG1 and CD117 high-expression groups than in the corresponding low-expression groups (P<0.05). A similar pattern was observed again when the analysis was stratified by CD117 expression, indicating that the expression levels of these two core coding genes in GIST were stably associated with the degree of systemic inflammatory activation in patients (*Table III*).

Correlations between DOG1 and CD117 mRNA expression and serum inflammatory biomarkers

Pearson correlation analysis was further used to quantify the strength of the associations between

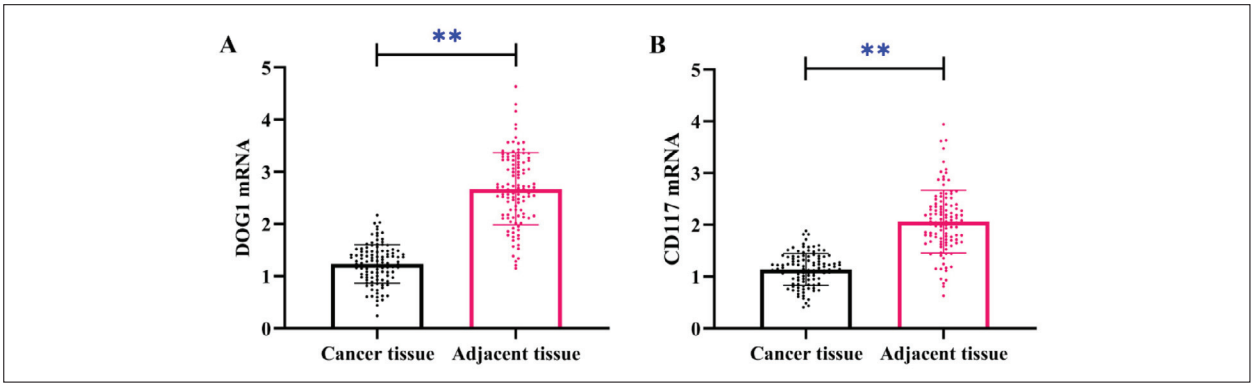

Figure 1 Relative mRNA expression of DOG1 and CD117 in GIST tissues and matched adjacent tissues.

(A) Relative DOG1 mRNA expression in GIST tissues and matched adjacent tissues. (B) Relative CD117 mRNA expression in GIST tissues and matched adjacent tissues. **P<0.01.

Table III Serum inflammatory biochemical marker levels stratified by DOG1 and CD117 mRNA expression.

Groups	n	CRP (mg/L)	IL-6 (pg/mL)	TNF-α (pg/mL)	SAA (mg/L)
DOG1 low-expression (<2.674)	54	7.79±1.57	8.15±1.92	9.01±2.30	10.61±2.44
DOG1 high-expression (≥2.674)	56	8.57±1.50	9.49±1.48	11.28±2.24	12.43±2.54
t		2.666	4.131	5.267	3.830
P		0.009	<0.001	<0.001	<0.001
CD117 low-expression (<2.063)	55	7.67±1.46	8.27±1.65	9.32±2.05	10.77±2.25
CD117 high-expression (≥2.063)	55	8.70±1.54	9.40±1.84	11.01±2.70	12.31±2.80
t		3.610	3.388	3.715	3.203
P		<0.001	0.001	<0.001	0.002

Note: Cutoff: Median.

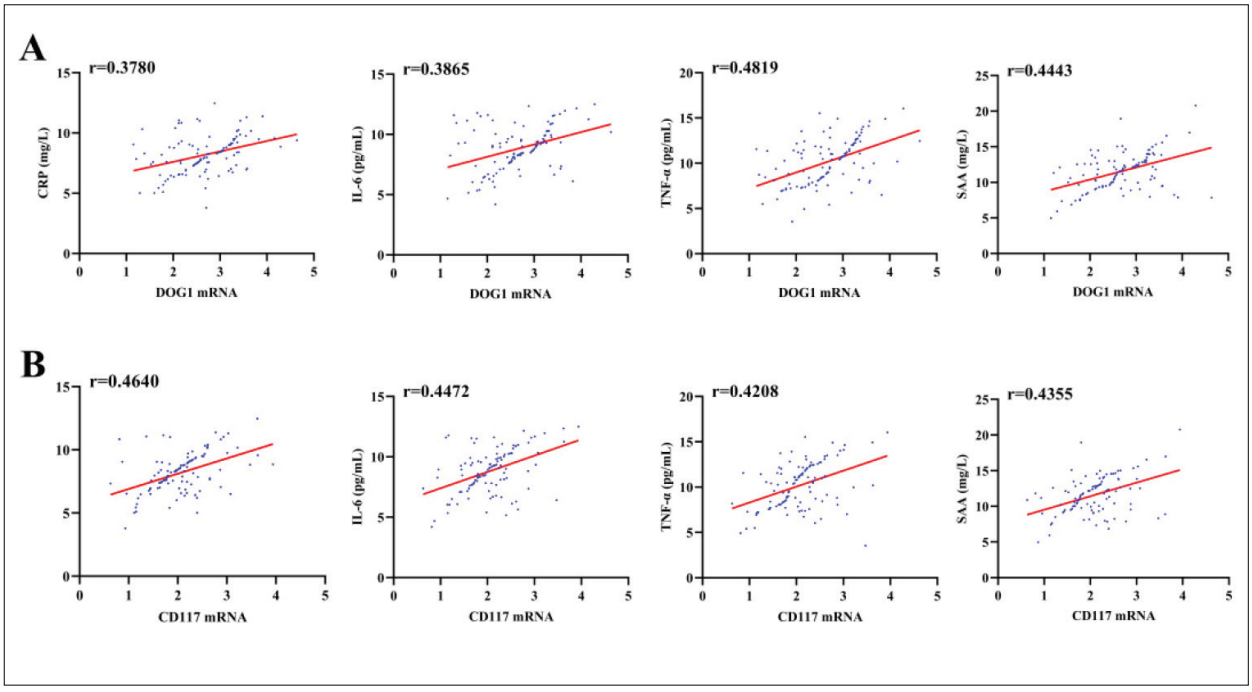

Figure 2 Correlations between DOG1/CD117 mRNA expression and serum inflammatory biomarkers.

(A) Correlations between DOG1 mRNA expression and serum CRP, IL-6, TNF- , and SAA levels. (B) Correlations between CD117 mRNA expression and serum CRP, IL-6, TNF- , and SAA levels. All correlations were statistically significant (P<0.05), with Pearson correlation coefficient r values marked in each subplot.

gene expression and inflammatory markers. The results showed that the relative mRNA expression level of DOG1 was positively correlated with all included serum inflammatory biomarkers (P<0.05). The strongest association was observed with TNF-α, with a correlation coefficient of r=0.4819, suggesting that higher DOG1 expression was accompanied by a parallel increase in systemic inflammatory response. CD117 mRNA expression showed a similar positive pattern, and the overall association was slightly stronger, with correlation coefficients ranging from 0.4208 to 0.4640 (P<0.05, *Figure 2*).

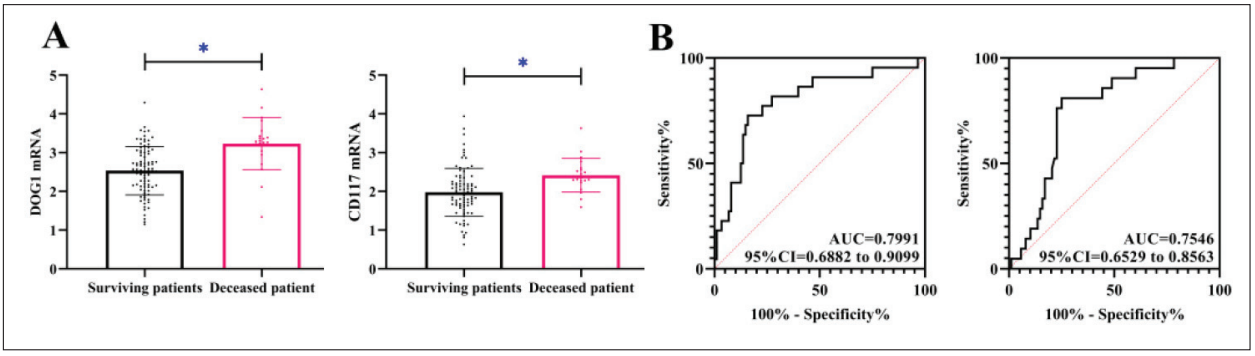

Figure 3 Comparison of DOG1 and CD117 mRNA expression between surviving and deceased patients and ROC analysis for 1-year all-cause mortality.

(A) Relative DOG1 and CD117 mRNA expression levels in surviving patients and deceased patients. (B) ROC curves of DOG1 and CD117 mRNA expression for predicting 1-year all-cause mortality.

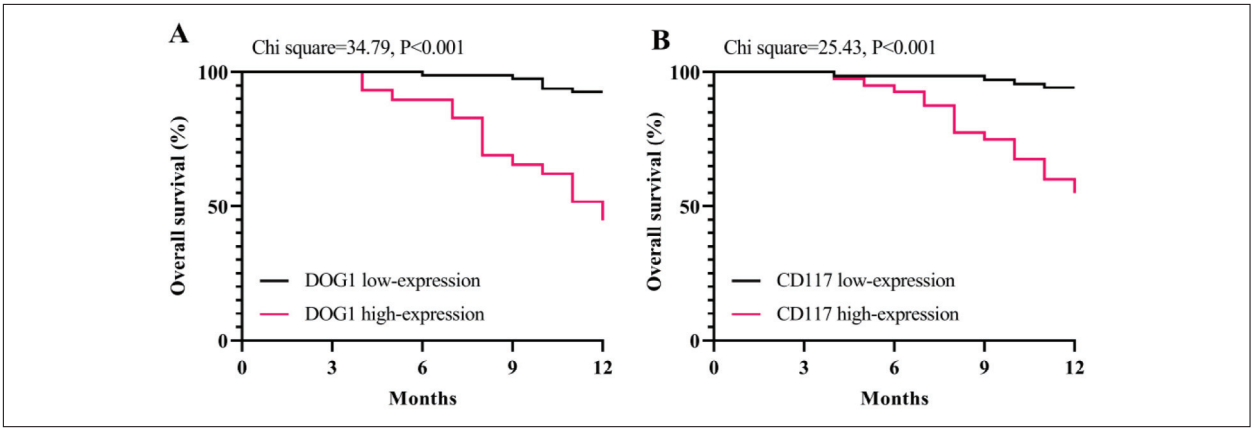

Figure 4 Kaplan-Meier survival analysis according to DOG1 and CD117 mRNA expression levels.

(A) One-year overall survival stratified by DOG1 mRNA expression. (B) One-year overall survival stratified by CD117 mRNA expression.

Predictive performance of DOG1 and CD117 mRNA expression for 1-year all-cause mortality

Follow-up showed that 22 patients died, corresponding to an overall mortality rate of 20.00%. Compared with survivors, patients who died within 1 year had higher DOG1 and CD117 mRNA expression levels ($P<0.05$). ROC curve analysis indicated that the mRNA expression levels of both DOG1 and CD117 had good predictive value for 1-year all-cause mortality after surgery in patients with GIST. DOG1 showed better performance, with an area under the curve (AUC) of 0.7991 (95% CI: 0.6882–0.9099). When the optimal cutoff value was set at 3.160, the sensitivity was 72.73% and the specificity was 82.95%. The AUC of CD117 was 0.7546 (95% CI: 0.6529–0.8563, *Figure 3*).

Association of DOG1 and CD117 mRNA expression stratification with 1-year survival outcomes

Kaplan-Meier survival analysis based on the above cutoff values further confirmed that DOG1 and CD117 expression levels were directly associated with short-term postoperative survival outcomes. The 1-year overall survival rate was lower in the DOG1 high-expression group than in the low-expression group ($\chi^2=34.79$, $P<0.001$). The same trend was observed for CD117, with the high-expression group also showing a lower survival rate ($\chi^2=25.43$, $P<0.001$, *Figure 4*).

Discussion

The present study showed that DOG1 and CD117 mRNA were characteristically overexpressed in GIST tissues and were significantly higher than in

matched adjacent normal tissues, which is consistent with their known biological roles as GIST-specific laboratory diagnostic markers. We also found that transcriptional upregulation of these two genes was stably and moderately positively correlated with elevated preoperative serum inflammatory biomarkers. In addition, quantitative detection of DOG1 and CD117 provided moderate predictive value for 1-year all-cause mortality after surgery in patients with GIST, suggesting that these markers may serve as useful quantitative references in laboratory-based risk assessment for this disease.

We first observed increased DOG1 and CD117 mRNA expression in GIST tissues. This finding not only supports the molecular basis for considering these two genes as core laboratory diagnostic markers of GIST, but also addresses a limitation of conventional qualitative immunohistochemistry by adding a quantitative transcriptional readout. Most earlier studies defined marker expression simply by positive or negative immunohistochemical staining and paid little attention to continuous quantitative variation at the transcriptional level (16, 17). In the present study, standardized qRT-PCR allowed more precise measurement of marker expression and therefore provided more reliable laboratory data for the subsequent correlation analyses. A meta-analysis reported that the transcriptional levels of CD117 and DOG1 in GIST tissues were, on average, more than twofold higher than those in normal gastrointestinal tissues (18). This is in line with our findings and further supports the stability of the laboratory testing system used in the present study.

On that basis, we found that the transcriptional levels of DOG1 and CD117 were significantly positively correlated with serum inflammatory markers measured under standardized conditions with strict quality control. From the perspective of medical biochemistry, this relationship is unlikely to be merely a secondary reflection of clinical phenotype; it may also involve direct biochemical pathway regulation. Sustained activation of the tyrosine kinase receptor encoded by CD117 can directly promote the transcription and translation of inflammatory factors through the NF-κB signaling pathway, thereby increasing circulating inflammatory protein levels (19). The calcium-activated chloride channel encoded by DOG1 may, in turn, influence the activation and chemotaxis of inflammatory cells by regulating intracellular calcium homeostasis, indirectly amplifying the systemic inflammatory response (20). Throughout the study, all serum marker measurements were performed under strict internal quality-control and external quality-assessment standards, and the results were traceable to international reference materials. This helped minimize laboratory system error and enhanced the reliability of the correlation analysis.

The ROC and survival analyses further showed that the quantitative transcriptional levels of DOG1 and CD117 had moderate predictive value for 1-year all-cause mortality after surgery in patients with GIST. This finding underscores the practical value of precise biochemical quantification in laboratory risk stratification. Immunohistochemistry is essentially qualitative and cannot capture subtle expression differences that may be associated with prognosis (21). By contrast, qRT-PCR can detect such variation more sensitively and may therefore provide a more precise quantitative basis for laboratory risk evaluation.

Still, as an observational study centered on medical biochemistry and laboratory testing, this work has several limitations related to detection methods, standardization, and clinical translation. First, although the relative qRT-PCR protocol used here followed relevant technical standards, it remained a laboratory-developed method. Absolute quantification traceable to reference standards was not achieved with digital PCR, which limits inter-laboratory comparability and does not fully satisfy the requirement for whole-process standardization in clinical biochemical testing. Second, only surgically resected tissue specimens were analyzed. No noninvasive strategy based on circulating tumor RNA in peripheral blood was explored, so the findings cannot yet be applied to preoperative noninvasive laboratory assessment. In addition, only a single preoperative serum sample was tested. Postoperative dynamic changes in inflammatory markers were not monitored, which limits the evaluation of their correlation with long-term prognosis, and means the value of these biochemical indicators in postoperative surveillance of GIST remains uncertain. Fourth, this was a single-center study, which may lead to inherent selection bias due to the homogeneity of the enrolled population, and the results may not be fully generalizable to populations in other regions. Finally, important pre-analytical factors in biochemical testing, such as specimen holding time, centrifugation conditions, and the number of freeze-thaw cycles, were not systematically evaluated and may therefore have introduced potential confounding. At the same time, only single-marker association analyses were performed, and no standardized combined detection scoring model was established, which limits its direct translation into routine clinical laboratory practice. Based on the above limitations, future research should be carried out in the following directions: first, expand multicenter, large-sample cohorts to verify the results of this study and reduce selection bias; second, establish a combined detection scoring model of DOG1/CD117 and inflammatory biomarkers to improve the predictive efficiency for GIST prognosis; third, explore noninvasive detection methods based on peripheral blood circulating tumor RNA to expand the clinical application scenarios of the markers.

Conclusion

DOG1 and CD117 were consistently upregulated at the transcriptional level in primary GIST tissues. Their expression levels were significantly positively correlated with preoperative serum inflammatory biomarkers, and both markers had moderate predictive value for 1-year all-cause mortality after surgery in patients with GIST. These findings provide precisely quantifiable biochemical indicators for laboratory diagnosis and risk stratification of GIST, and they also supply reliable clinical laboratory data for research on the biochemical links between GIST driver genes and the inflammatory microenvironment. Further studies are needed to optimize detection methods, improve the standardization system, and expand multicenter validation cohorts, so that the clinical applicability of these assays can be strengthened further.

Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Funding

No funds, grants, or other support was received.

Acknowledgements

Not applicable.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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Recieved: March 12, 2026
Accepted: April 06, 2026