Low G0S2 gene expression levels in peripheral blood may be a genetic marker of acute myocardial infarction in patients with stable coronary atherosclerotic disease
A retrospective clinical study
Xue Wang, MD, Heyu Meng, MD, Jianjun Ruan, MD, Weiwei Chen, PhD, Fanbo Meng, PhD∗

Abstract
Background: The G0/G1 switch 2 (G0S2) gene is closely related to lipolysis, cell proliferation, apoptosis, oxidative phosphorylation, and the development of a variety of tumors. The aim of the present study was to expand the sample size to confirm the relationship between the expression of the G0S2 gene in peripheral blood and acute myocardial infarction (AMI) based on previous gene chip results.

Methods: Three hundred patients were initially selected, of which 133 were excluded in accordance with the exclusion criteria. Peripheral blood leukocytes were collected from 92 patients with AMI and 75 patients with stable coronary atherosclerotic disease (CAD). mRNA expression levels of G0S2 in peripheral blood leukocytes was measured by RT-PCR, and protein expression levels by Western blot analysis. The results of these assays in the 2 groups were compared.

Results: mRNA expression levels of G0S2 in the peripheral blood leukocytes of patients with AMI were 0.41-fold lower than those of patients with stable CAD (P < .05), and G0S2 protein expression levels were 0.45-fold lower. Multivariate logistic regression analysis indicated that low expression levels of the G0S2 gene increased the risk of AMI by 2.08-fold in stable CAD patients.

Conclusions: G0S2 gene expression in the peripheral blood leukocytes of AMI patients was lower than that of stable CAD patients. Low G0S2 gene expression in peripheral blood leukocytes is an independent risk factor for AMI in stable CAD patients.

Abbreviations: ACS = acute coronary syndrome, AMI = acute myocardial infarction, APL = acute promyelocytic leukemia, ATGL = fatty triglyceride lipase, CABG = coronary artery bypass grafting, CAD = coronary atherosclerotic disease, ECs = endothelial cells, ER+ = estrogen receptor-positive, G0S2 = G0/G1 switch 2, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, LSM = lymphocyte separation medium, PCI = percutaneous coronary intervention, RA = retinoic acid, ROS = reactive oxygen species, TC = total cholesterol, TG = triglyceride.

Keywords: acute myocardial infarction, cardio-oncology, G0S2 gene, stable coronary atherosclerotic disease

1. Introduction
Coronary artery disease, and in particular coronary atherosclerotic disease (CAD), has an incidence of epidemic proportions and has become the leading cause of death worldwide. It is estimated that the prevalence of cardiovascular disease will increase by approximately 10% over the next 20 years. Acute...
myocardial infarction (AMI) is the leading cause of hospital admissions and deaths worldwide. In the USA, more than 800,000 people suffer AMI each year, with a mortality rate of approximately 27% (due to the majority occurring prior to arrival at hospital). A number of epidemiological studies have confirmed that the occurrence and development of CAD are influenced by both environmental factors and heredity. The incidence of AMI has been significantly reduced through the primary prevention strategy for CAD, but there remain many individuals who have considerable residual risk. In this context, we can better analyze the genetic basis of CAD through early observations of differences in gene expression, so as to find genes related to the severity of coronary atherosclerosis, and provide a more accurate prediction, and so prevention, of AMI.

Analysis of gene expression in peripheral blood can predict the occurrence and development of multiple diseases. Hoffman et al demonstrated that in patients with systemic lupus erythematosus, gene expression levels of IFN in peripheral blood can be used as an independent risk factor for disease onset. Guo et al found that high expression of FUT1 and MYBPC1 genes in peripheral blood are potential biomarkers for children with pancreaticobiliary malformation. In the cardiovascular system, our team found that low expression of the CPNE3 gene in peripheral blood was associated with risk of AMI. Low PRMT5 expression in peripheral blood may be a potential independent risk factor for stable coronary artery disease and AMI. The low expression of PIK3C2A in peripheral blood may also be a potential biomarker for the occurrence of AMI and the low expression of FFAR2 in peripheral blood leukocytes may be a genetic marker for the early diagnosis of AMI. Therefore, by analyzing the difference in gene expression in the peripheral blood of patients with AMI and those with stable CAD, the risk of occurrence of AMI in patients with stable CAD may possibly complement other methods of diagnosis of AMI.

Our previous gene chip study found that G0S2 gene expression in the peripheral blood leukocytes of AMI patients was 0.20-fold lower than that of stable CAD patients. It has previously been established that greater mRNA expression of the G0/G1 switch 2 (G0S2) gene is associated with cells re-entering the G1 phase from G0. Later studies have shown that expression is closely related to lipolysis, cell proliferation, apoptosis, and oxidative phosphorylation mediated by fatty triglyceride lipase (ATGL). As a result, we aimed to increase the sample size of patients compared to those studies to verify whether the expression of the G0S2 gene is down-regulated in AMI patients from a larger population through clinically available peripheral blood samples.

2. Methods

2.1. Research subjects

A total of 300 patients who had been hospitalized in the Department of Cardiology in The Third Hospital of Jilin University from March 2018 to May 2018 were selected for the present study. In accordance with the exclusion criteria, 92 patients with acute myocardial infarction were finally allocated to the experimental group, and 75 with stable coronary atherosclerotic disease to the control group. The medical history, levels of serum triglyceride (TG), serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and other blood biochemical indicators, history of hypertension and smoking, and other relevant clinical data were recorded. The inclusion criteria for AMI were based on the latest guidelines for AMI issued by the European Society of Cardiology in 2017, namely patients with a deterministic vascular disease confirmed by coronary angiography, severe coronary stenosis, or occlusion of the main coronary artery (left main coronary artery) or right coronary artery, etc., and the main branches (circular and anterior descending branches, etc.). AMI exclusion criteria:

1. Myocardial infarction secondary to ischemic imbalance (47 patients excluded);
2. Myocardial infarction resulting in death where biomarker values (troponin or myoglobin) were not available (38 patients excluded);
3. Myocardial infarction associated with percutaneous coronary intervention or stent thrombosis (44 patients excluded);
4. Myocardial infarction associated with coronary artery bypass grafting (CABG) (4 patients excluded).

The inclusion criteria for the stable CAD group were any of the following mutually exclusive presentations: a history of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (excluding AMI factors), or stenosis of more than 50% in at least one coronary artery confirmed by angiography.

2.2. Study methods

2.2.1. Peripheral blood lymphocyte acquisition. In the morning, 6 ml of fasting peripheral blood were collected from each research subject and stored in an EDTA anticoagulant tube at 4°C. Lymphocytes were extracted from peripheral blood within 4 hours of sample collection. The detailed steps were as follows:

1. fresh anticoagulated blood was mixed with an equal volume 0.9% sodium chloride injection;
2. the mixture was carefully added to an equal volume of 0.9% sodium chloride injection and peripheral blood lymphocyte separation medium (LSM), centrifuged at 3000g for 20 minutes;
3. through centrifugation, the blood divided into 4 layers, namely, from top to bottom, the plasma layer, the milky lymphocyte layer, the transparent density gradient layer, and the red blood cell layer.

The lymphocyte layer was removed and used in subsequent experiments.

2.2.2. Synthesis of cDNA from peripheral blood lymphocytes. ① Blood Total RNA kits (Xinjing Biological Reagent Development Co., Ltd., Hangzhou) were used to extract total RNA from the isolated lymphocytes. Extraction was conducted in strict accordance with the manufacturers instructions to avoid RNA degradation or contamination. The quality of the RNA was determined by polyacrylamide gel electrophoresis. The 28S and 18S rRNA bands could be clearly identified, the brightness of the 28S rRNA bands being approximately twice that of the 18S rRNA. The concentration and absorbance of the samples were required to conform to the standards of the enzyme marker. It was ensured that the A260/A280 ratio was within the range 1.7–2.1 and the A260/A230 ratio >2.0. Reverse transcription was performed after fulfilling the requirements of the reverse transcription kit. ② Reverse transcription of the total RNA was performed in one-step and removal of genomic cDNA using
first-strand synthetic premix in accordance with the kit instructions (FastKing gDNA Dispelling RT SuperMix, Tiangen Biochemical Technology Co., Ltd., Beijing). The concentration of RNA was consistent in each sample. The cDNA obtained was stored at −80°C for subsequent fluorescent quantitative PCR measurements.

2.2.3. RT-PCR analysis. After dilution of the cDNA 20-fold, PCR amplification was performed using a SYBR green quantitative fluorescence kit (Taq qPCR synthesis premix). The reaction conditions consisted of pre-denaturation at 95°C for 5 minutes, denaturation at 95°C for 30 seconds, annealing at 60°C for 30 seconds, and 72°C for 20 seconds for a total of 40 cycles. Dissolution and amplification curves were performed at 95°C for 15 seconds, 60°C for 1 minute, and 95°C for 15 seconds. With GAPDH as the internal reference gene and G0S2 as the target gene, the specificity of amplification conditions was determined according to the dissociation curve calculated by the ABI-FAST7500 instrument software. PCR primer sequences are shown in Table 1.

2.2.4. Western blot analysis. Peripheral white blood cells were collected by radio-immunoprecipitation then centrifuged. The supernatant was collected and incubated in a 98°C water bath for 10 minutes, then 5 (x) buffer and 15 μg sample protein were added. The proteins were separated by electrophoresis, initially at 60 V then adjusted to 110 V until the process had terminated. Proteins were transferred to polyvinylidene fluoride film, incubated overnight with primary antibody at 4°C, then with secondary antibody at room temperature for 1 hour. Protein bands were then analyzed using a chemiluminescence imaging system.

2.3. Statistical analysis

SPSS v25.0 software was used for statistical analysis. A normality test was used for measurement data. Normally distributed data (P > .1) are presented as means ± SD, and a comparison of differences of 2 groups was accomplished using an independent samples t-test. Non-normally distributed data (P < .1) were described using medians and interquartile ranges, differences between groups analyzed using non-parametric ranks, and a t-test of 2 independent samples. Categorical data were collected in terms of frequency for statistical analysis, and group differences analyzed using a χ² test. Risk factors associated with AMI were analyzed using multivariate logistic regression. Results were considered statistically significant where bilateral P ≤ .05.

Table 1

| RT-PCR primer sequences. | Genes | Primer sequence (5’-3’). |
|--------------------------|-------|--------------------------|
| GAPDH                   | Fa: Upstream primer. | Rb: Downstream primers. |
| G0S2                    | Fa: AGGAGATGATGGCCCAGAAG | Rb: AGGGCTTGCTTCTGGAGAG |

3. Results

3.1. Basic data analysis of research subjects

Analysis of the clinical data of the research subjects indicated that in terms of gender, age, history of hypertension and smoking, type 2 diabetes, and levels of TG, TC, LDL-C, and HDL-C, there was no significant difference between the 2 groups. The detailed results are displayed in Table 2.

3.2. Identification of G0S2 gene amplification products in peripheral blood leukocytes by RT-PCR

All amplification curves of the reference and target genes were a smooth “s-type,” and the dissociation curves had a single, rather than multiple peaks. This indicates that the amplification primers had strong specificity, the reaction conditions were appropriate, and that no nonspecific amplification was observed (Fig. 1a and b).

3.2.1. mRNA expression levels of G0S2 in peripheral blood leukocytes. Gene expression was repeated in triplicate using RT-PCR, at an appropriate level of standard deviation. Relative G0S2 gene expression, calculated by 2^{ΔCt}, was 2.04 (0.85–15.08) in AMI patients and 4.94 (1.14–27.98) in the control group, a difference that was statistically significant (P < .05), that is the relative expression level of G0S2 mRNA in the peripheral leukocytes.
blood leukocytes of AMI patients was significantly lower than that of stable CAD patients, a relative expression level of 0.41-fold that of the stable CAD group (Fig. 2).

3.2.2. Protein expression levels of G0S2 in peripheral blood leukocytes. In the present study, levels of G0S2 protein in peripheral blood leukocytes were measured in triplicate in each group using β-actin as the internal reference protein. Western blot analysis indicated that the mean relative expression of the G0S2 gene in the AMI group was 0.35, and 0.77 in the control group. Thus, the expression of the G0S2 gene at the protein level was 2.20-fold higher in the control group than in the AMI group (Fig. 3a and b).

3.3. Correlation analysis of relative expression levels of the GOS gene in peripheral blood leukocytes with blood triglycerides

The mRNA expression of the G0S2 gene in peripheral blood leukocyte was correlated with triglyceride levels in peripheral blood.

All subjects were divided into either a hypertriglyceridemia group (≥1.7 mmol/L) or a non-hypertriglyceridemia group (<1.7 mmol/L). The relative mRNA expression levels of the G0S2 gene in peripheral blood leukocytes of each study subject, expressed as 2^ΔCt, was correlated with blood triglyceride levels.

The results suggest that no significant correlation existed between mRNA levels of the G0S2 gene in peripheral leukocyte and triglyceride levels (P=.14), as displayed in Table 3.

3.4. Multivariate logistic regression analysis of mRNA expression levels of the G0S2 gene in peripheral blood leukocyte and AMI

The mRNA expression levels of the G0S2 gene in peripheral blood leukocytes was expressed as 2^ΔCt. Both AMI and CAD patients where expression was ≥4.30 were allocated to the increased mRNA expression group and those where the expression was <4.30 to the reduced mRNA expression group. In accordance with Chinese age grading standards, all included subjects were divided into an advanced age group (≥65) and a younger age group (<65). Increased or decreased mRNA expression of the G0S2 gene in peripheral blood leukocytes was correlated with AMI, as shown in Table 4.
The results revealed that GOS2 gene expression in peripheral blood leukocytes in the AMI group was lower than that in the stable CAD group, a difference that was statistically significant ($P < .05$). Advanced age ($P = .34$) and being male ($P = .87$) were not significantly correlated with the occurrence of acute myocardial infarction. The risk of AMI in the group with low GOS2 gene expression in peripheral blood leukocytes was 2.08-fold higher than that in the high GOS2 gene expression group.

### 4. Discussion

In the present study, the results demonstrated that mRNA and protein expression levels of the GOS2 gene in peripheral blood leukocytes were lower in patients with AMI than in the control group.

The G0/G1 switch gene 2 (G0S2) translates to a small 12kDa protein located in lipid droplets in mitochondria, the endoplasmic reticulum, and fat cells. It has been shown to play a variety of important roles in cellular function in both humans and mice, such as cell proliferation, apoptosis, and oxidative phosphorylation. Over expression of GOS2 in the liver results
in the increased accumulation of triglycerides and promotes the formation of fatty liver.\textsuperscript{24,25} In fat cells, the G0S2 gene expression product can directly bind to ATGL and reduce ATGL-mediated lipolysis by inhibiting the activity of its triacylglycerol hydrolase.\textsuperscript{177}

G0S2 gene-related pathway data in the KEGG (Kyoto Encyclopedia of Genes and Genomes; https://www.kegg.jp/ or https://www.genome.jp/kegg/) database indicates that the G0S2 gene is closely related to the metabolism of triglycerides. In the present study, all subjects were divided into a hypertriglyceridemia group (≥1.7 mmol/L) and a non-hypertriglyceridemia group (<1.7 mmol/L). Correlation analysis of the relative mRNA expression levels of the G0S2 gene in peripheral blood leukocytes demonstrated that there was a trend in decreased G0S2 expression in the hypertriglyceridemia group, although the difference was not significant (\(P = .14\)). Epidemiological studies have found that AMI is associated with higher triglyceride levels. Therefore, it would be reasonable to expect that AMI may be caused by the low expression of the G0S2 gene which may be related to triglyceride metabolism. However, the analysis did not find a statistical difference between the 2 groups. This may be because the emergence of acute coronary syndrome (ACS) may cause a change in blood lipids that depends on the time of onset of AMI. The mean reduction in triglycerides from day 1 to day 2 to 4 was 0.10 mmol/L.\textsuperscript{26} The collection of blood from AMI patients was mostly during emergency PCI or in the morning of the second day after admission, within the time range when TG was reduced due to the onset of AMI.

Many recent studies have found that the physiological enhancement of G0S2 gene expression prevents cellular ATP consumption and induces cell tolerance to hypoxic stress. The transience of hypoxia-induced endogenous G0S2 expression may play a protective role in the early stages of an energy crisis.\textsuperscript{27} In the cardiovascular system, atherosclerosis leads to increased levels of reactive oxygen species (ROS), excessive production of which induces a stress response leading to the apoptosis of vascular endothelial cells (ECs),\textsuperscript{28} which is exacerbated by the development of plaques.\textsuperscript{29} The over expression of the G0S2 gene prevents ECs from consuming ATP and the accumulation of ROS induced by serum-free hunger stress, leading to reduced EC apoptosis.\textsuperscript{30} That mechanism may be a factor contributing to the occurrence of AMI due to the low expression of the G0S2 gene in patients with stable CAD. In other words, G0S2 expression in patients with AMI is lower than in patients with stable CAD. Additionally, vascular endothelial cells in AMI patients have reduced tolerance to hypoxia and are relatively vulnerable to the stress response induced by ROS and apoptosis of ECs, leading to severe atherosclerosis in stable CAD patients. As a result, it is more likely that AMI would be triggered, although the mechanism requires additional study.

The results indicate that G0S2 gene expression in peripheral blood leukocytes in AMI patients is lower than that of stable CAD patients. The risk of AMI in patients with low G0S2 gene expression was 2.08-fold higher than those with high G0S2 gene expression. Low expression of the G0S2 gene in peripheral blood leukocytes did not correlate with triglyceride levels, an independent risk factor for AMI in stable CAD patients. The experimental specimens in the present study were peripheral blood samples of patients which are easily available clinically, which were analyzed by PCR technology which can predict the possibility of acute myocardial infarction in patients with stable coronary atherosclerotic disease. This is a novel detection method which could assist in the early diagnosis of acute myocardial infarction. It is anticipated that early diagnosis and treatment would improve patient prognosis.

Interestingly, the G0S2 gene was found to be associated with a variety of tumors. For example, low expression of the G0S2 gene inhibits the occurrence of glioma in vivo.\textsuperscript{18} However, in breast cancer, especially in patients that are estrogen receptor-positive (ER+), low G0S2 gene expression is associated with an increased rate of recurrence.\textsuperscript{13} In addition, DNA methylation of the G0S2 gene may be an important biomarker for squamous cell lung cancer.\textsuperscript{32} In patients with acute promyelocytic leukemia (APL), the G0S2 gene may be used as a target of all-trans retinoic acid (RA), with patients expressing t (15; 17) product PML/RARA able to be successfully treated by RA.\textsuperscript{33}

In a previous study, our team found that tumor-related genes are associated with the development of coronary artery disease. For example, the CPNE3 gene is associated with small-cell lung cancer and prostate cancer,\textsuperscript{11} the PIK3C2A gene is associated with gastrointestinal stromal tumor, liver cancer and other cancers,\textsuperscript{13,34,35} and the PRMT5 gene is considered a potential oncogene.\textsuperscript{12,36} Additionally, the FFAR2 gene is associated with gastrointestinal tumors,\textsuperscript{14,37} and the G0S2 gene is associated with a variety of cancers, and in the present study, it was shown to be associated with a lower incidence of AMI. The correlation between tumor genes and AMI found by our team may assist in the study of tumor cardiology.

There are various limitations associated with this study. G0S2 expression was measured in peripheral blood, which does not reflect levels in cardiomyocytes. The subsequent use of cytological methods may better elucidate the related mechanisms. The present study was a retrospective analysis. It would be more meaningful if differential gene expression of genetic markers that promote the occurrence of AMI were studied in a prospective study. However, in the present study, we found that low G0S2 gene expression in peripheral blood is related to the occurrence of AMI.

### 5. Conclusions

G0S2 gene expression in the peripheral blood leukocytes of AMI patients was lower than that of stable CAD patients. Low expression of the G0S2 gene in peripheral blood leukocytes is an independent risk factor for AMI in stable CAD patients.

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**Table 4**

|                | B   | Standard error | Vard | DOF | P    | OR   | 95%CI          |
|----------------|-----|----------------|------|-----|------|------|----------------|
| Low expression of G0S2 gene | 0.73 | 0.32           | 5.17 | 1   | .02  | 2.08 | 1.11–3.89     |
| Age increase   | 0.32 | 0.33           | 0.92 | 1   | .34  | 1.37 | 0.72–2.62     |
| Male           | −0.06 | 0.37          | 0.03 | 1   | .87  | 0.94 | 0.45–1.95     |

AMI = acute myocardial infarction.
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Author contributions
Conceptualization: Xue Wang, Fanbo Meng.
Data curation: Xue Wang, Weimei Chen.
Formal analysis: Xue Wang, Heyu Meng, Jianjun Ruan, Fanbo Meng.
Funding acquisition: Fanbo Meng.
Investigation: Xue Wang, Heyu Meng.
Methodology: Weimei Chen, Fanbo Meng.
Project administration: Fanbo Meng.
Resources: Fanbo Meng.
Software: Fanbo Meng.
Writing – original draft: Xue Wang.
Writing – review & editing: Xue Wang, Fanbo Meng.

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