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Expression and clinical significance profile analysis of S100 family members in human acute myeloid leukemia

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Abstract. – OBJECTIVE: S100 proteins conduce to tumorigenesis and metastasis in a variety of ways, facilitating a local inflammatory environment for development and progression of tumors. However, the expression patterns and the precise roles of the S100 family members contributing to tumorigenesis and the progression of acute myeloid leukemia (AML) remain to be elucidated.

MATERIALS AND METHODS: Herein, the expression of S100 transcripts was analyzed in various tumor types in comparison to the normal controls using the ONCOMINE database, along with the corresponding expression profiles in the different subtypes of AML as retrieved from The Cancer Genome Atlas (TCGA) database. We used the Gene Expression Profiling Interactive Analysis (GEPIA) database to investigate the prognostic values of S100 mRNA expression in AML.

RESULTS: Our results indicated that high expression of S100A4 mRNA was associated with poor overall survival (OS) (p=0.026), while that of S100P was correlated with a favorable OS in AML patients (p=0.028). Other members of the S100 family did not show any correlation to the survival. Moreover, the correlation between the expression levels of *S100A4* and *S100P* and the clinical characteristics and methylation of AML patients was investigated. The results demonstrated that the promoter methylation level of *S100A4* (p=0.002) and S100P (p=0.029) was higher in 61-80-years-old group as compared to the other age groups.

CONCLUSIONS: Taken together, it can be deduced that *S100A4* and *S100P* might be novel biomarkers and crucial prognostic factors for AML.

Key Words:
Acute myeloid leukemia, S100 family, Prognostic factors.

Introduction

Acute myeloid leukemia (AML) comprises a biologically and genetically heterogeneous group of disorders characterized by the accumulation of immature myeloblasts in the bone marrow[1]. It is the most common form of acute leukemia in adults, accounting for approximately 80% of the cases[2]. Despite advances in supportive care and prognostic risk stratification with optimized established therapies, several patients with AML that respond to induction chemotherapy display pivotal concerns, such as refractory disease, poor prognosis, and high relapse, resulting in severe social and economic burden[3,4], which are yet to be addressed. Thus, the genomic background of AML needs to be under intensive focus, not only in the risk stratification of AML but also in identifying the predictive biomarkers or targets developing effective targeted therapies.

The structure and function of the S100 proteins are regulated by Ca^{2+} binding and involved in a wide range of biological processes, such as proliferation, migration, invasion, inflammation, and differentiation[5-7]. S100 proteins are shown to be biomarkers of disease progression and prognosis in various types of tumors, including breast[8], lung[9], head and neck[10], colorectal[11], melanoma[12], and hematological malignancy[13-15]. Hitherto, *S100A4*, *S100A6*, *S100A8*, *S100A9*, *S100A10*, and *S100P* are reported to play a crucial role in AML[16]. As a major transcription factor family, S100 is an ideal and attractive module for investigating the novel therapies for AML. However, the small sam-

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ple size in some studies raised doubts about the credibility and generalizability of the results. Although the dysregulated expression level of S100 factors and correlation with prognosis has been reported in AML, the comprehensive analysis of S100 protein expression has not yet been carried out. Therefore, the purpose of this study was to systematically investigate the expression and prognostic value of S100 family members with potential gene function in AML based on integrated large database. Also, we systemically described the expression profiles of each S100 family member in a large number of patients by integrating analysis through ONCOMIME, GEPIA, UALCAN, and TCGA database.

Materials and Methods

ONCOMINE Database

The mRNA levels of S100 family members in various types of cancers were determined by analysis based on the ONCOMIME database (Ann Arbon, MI, USA) (http://www.oncomine.org/). In the present study, Student's *t*-test was used to obtain a *p*-value for the comparison between cancer specimens and normal control datasets. The fold-change was defined as 2 and the *p*-value was set at 0.01.

GEPIA Dataset

GEPIA (Beijing, China) is a newly developed interactive web server for analyzing the RNA sequencing expression data of 9,736 tumors and 8,587 normal samples from TCGA and the Genotype-Tissue Expression (GTEx) projects using a standard processing pipeline (http://gepia.cancer-pku.cn/)[17]. It is involved in customizable functions, such as tumor or normal differential expression analysis, profiling according to the type of neoplasms or pathological staging, patient survival analysis, genetic testing, correlation analysis, and the analysis of dimension reduction.

UALCAN

UALCAN (Birmingham, AL, USA) is publicly available at http://ualcan.path.uab.edu. It uses TCGA level 3 RNA-seq and clinical data from 31 cancer types. It also provides an easy-to-use interactive portal for the in-depth analysis of TCGA gene expression data[18].

Results

Differentiation of mRNA Expression Levels of the S100 Family Transcript in Pan-Cancer

In order to elucidate the mRNA expression of S100 family between cancer and normal tissues in multiple cancers, S100 family members, such as *S100A1*, *S100A2*, *S100A3*, *S100A4*, *S100A5*, *S100A6*, *S100A7*, *S100A8*, *S100A9*, *S100A10*, *S100A11*, *S100A12*, *S100A13*, *S100A14*, *S100B* and *S100P* were explored in human cancers using the ONCOMIME online database. As shown in Figure 1, the ONCOMIME database consists of a total of 443, 429, 436, 403, 394, 337, 414, 438, 420, 446, 408, 438, 437, 342, 456, and 438 unique analyses including *S100A1*-*S100P* genes, respectively. Interestingly, *S100A5*, *S100A7*, and all S100 family members were significantly downregulated or upregulated in a majority of human cancers. The expression of seven S100 family members were upregulated in most of the cancers: upregulated *vs.* downregulated members (*S100A2* 33:10; *S100A6* 18:13; *S100A7* 9:0; *S100A10* 29:21; *S100A11* 54:15; *S100A13* 17:7; *S100P* 38:25) (Figure 1). In addition, nine of the S100 family members were downregulated in the majority of cancers: unregulated *vs.* downregulated members (*S100A1* 4:19; *S100A3* 6:9; *S100A4* 17:22; *S100A5* 0:1; *S100A8* 10:29; *S100A9* 12:21; *S100A12* 4:20; *S100A14* 13:22; *S100B* 2:18) (Figure 1). Intriguingly, the expression of *S100A2*, *S100A11*, and *S100P* mRNA increased in 16 *vs.* 0 cases, 54 *vs.* 15 cases, and 38 *vs.* 25 cases in colorectal cancer. In lymphoma cancer, the expression of *S100A4*, *S100A6*, *S100A11*, and *S100A13* genes was unregulated. In lung carcinoma, the expression of *S100A3*, *S100A4*, *S100A8*, and *S100A4* was significantly downregulated in 8, 12, 8, and 6 studies, respectively (Figure 1). In leukemia, three studies showed that *S100A4* was upregulated, and three studies showed it was downregulated. *S100A6*, *S100A8*, *S100A9*, *S100A11*, *S100A12* and *S100P* were downregulated, while *S100A13* was upregulated. However, the other members did not differ significantly in leukemia, as assessed in the validated studies.

Expression Levels of S100 Family Members in Human AML

We utilized the GEPIA dataset to compare the mRNA expression of S100 family between AML and normal blood samples. The gene expression profile analysis demonstrated that the level of *S100A4*, *S100A6*, *S100A8*, *S100A9*, *S100A10*, *S100A12*, and *S100B* was higher in AML than in normal blood samples (Figure 2A).

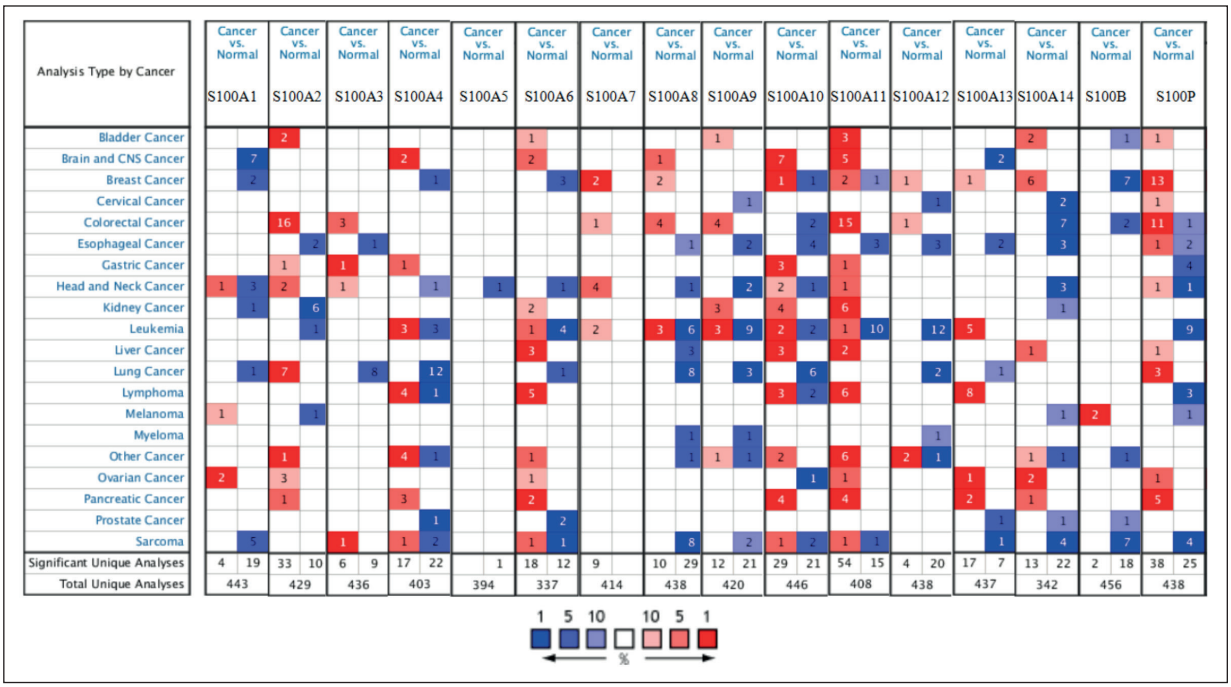

Figure 1. mRNA expression levels of S100 calcium-binding protein family members in human cancers. The mRNA expression of the GATA family members (cancer vs. normal tissue) in pan-cancers analyzed using the ONCOMINE database. The number in the colored cell represents the number of analyses meeting thresholds. The cell color was defined as the gene rank percentile in the study. The intense red (overexpression) or blue (underexpression) indicates a significantly overexpressed or underexpressed gene, respectively.

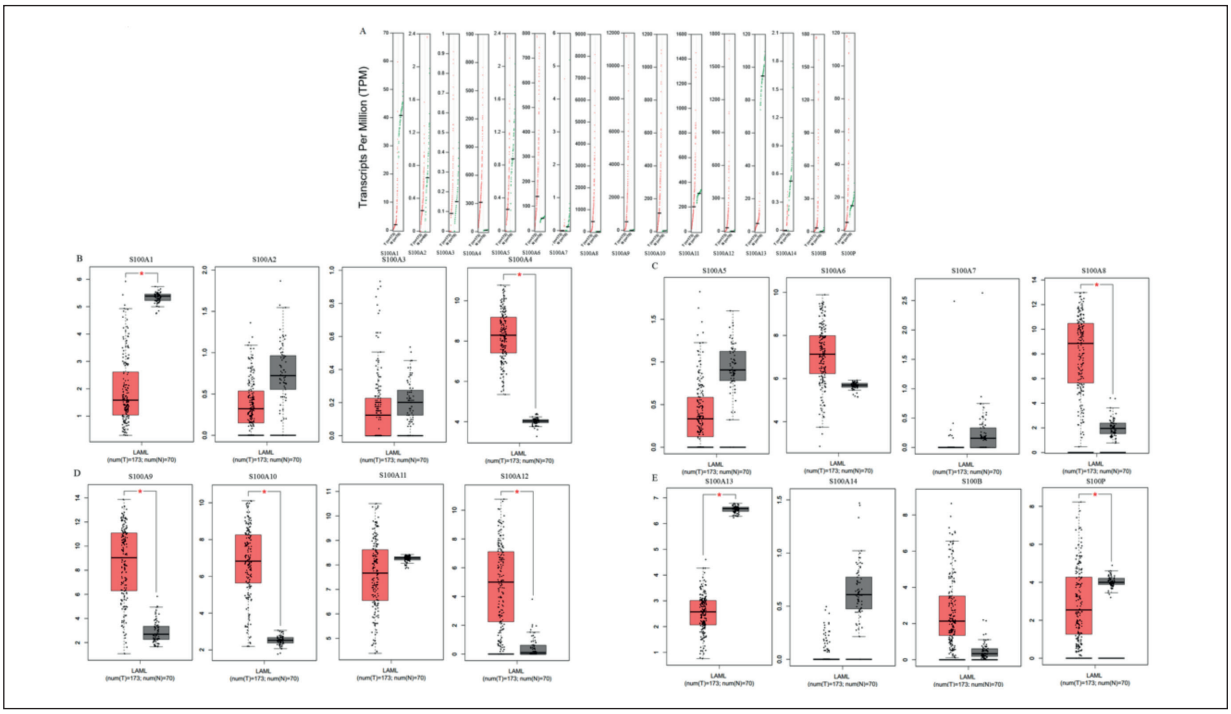

Figure 2. RNA-seq profile of S100 family members in human AML and normal samples. **A**, The expression after normalization by log2 (TPM + 1) for log-scale as compared to the tumor and normal samples in AML. **B-E**, Box plot of the expression profile of the S100 family members in AML and normal blood samples. A t-test was used to compare the difference in expression between tumor and normal tissues.

In addition, the box plots of the RNA-seq expression in 173 AML blood samples *vs.* 70 normal blood samples demonstrated that *S100A4*, *S100A8*, *S100A9*, *S100A10*, and *S100A12* was significantly increased (p=0.01, Figure 2B, 2C, and 2D). Moreover, the transcription level of *S100A1*, *S100A13*, and *S100P* was decreased significantly in AML *vs.* normal samples (p=0.01, Figure 2B and 2E). However, other S100 family members did not reveal any statistical significance in AML blood samples as compared to normal blood samples, including *S100A2*, *S100A3*, *S100A5*, *S100A6*, *S100A7*, *S100A11*, *S100A14*, and *S100B* (Figure 2B, 2C, 2D, and 2E).

Expression Analysis Of S100 Family Members in Different Molecular Subtypes of Human AML

Morphologically, AML was divided into eight groups in the French-American-British classification (FAB) system (FAB M0-M7), wherein the cells are classified as no/minimal minimum differentiation signs (FAB M0/M1) or a mature phenotype (FAB M5-7)[19,20]. To further understand the expression of S100 family members between different subtypes of AML, we analyzed the AML subtypes from the TCGA database. The results showed that *S100A1* was highly expressed in M3, M5, and M7, especially M7, but lowly expressed in M0, M1, M2, M4, and M6, especially M6 (Figure 3A, ***Supplementary Table I***). The expression of *S100A2* was highly expressed in M1, M5, M6 and M7 and lowly expressed in M0, M2, M3 and M4. However, statistically significant differences were not detected in the expression between each subtype group (Figure 3A, ***Supplementary Table II***). *S100A3* was significantly overexpressed in M6 as compared to other molecular subtypes, especially M0, M1, and M2 (Figure 3B, ***Supplementary Table III***).

S100A4 was highly expressed in M4 and M5, and lowly expressed in M0, M1, M2, M3, M6, and M7 (Figure 3A, ***Supplementary Table IV***). Similar results were observed for *S100A6* and *S100A8* (Figure 3C and D, ***Supplementary Tables VI*** and ***VII***). *S100A5* was highly expressed in M4, M5, M6, and M7, especially M7, while low expression was detected in M0, M1, M2, and M3, especially M2 (Figure 3C, ***Supplementary Table V***). *S100A7* was expressed in M7 and not in other

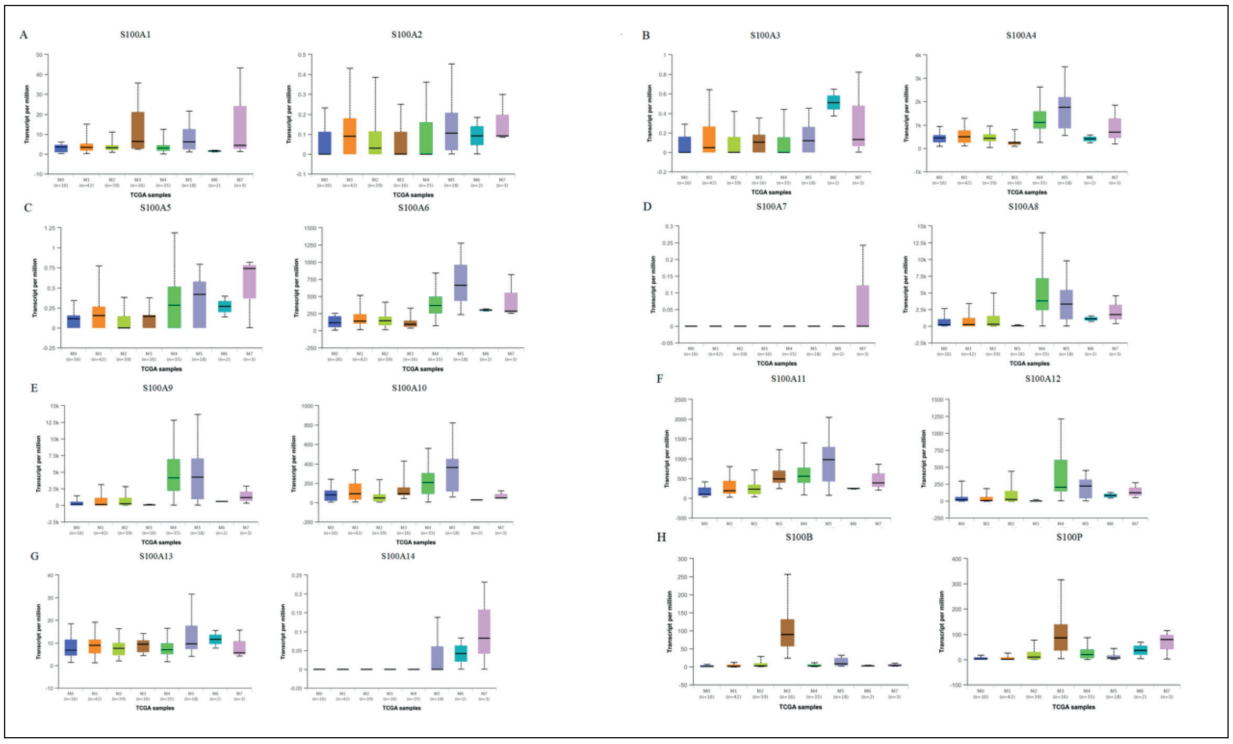

Figure 3. Box plots representing the mRNA expression levels of the S100 family members in various classes of AML in the TCGA database.

subtypes (Figure 3D). *S100A9* and *S100A10* were highly expressed in M4 and M5, while showed a low expression in M0, M1, M2, M3, M7, and were not expressed in M6 (Figure 3E, ***Supplementary Table VIII*** and ***IX***). *S100A11* was highly expressed in M3, M4, and M5 and lowly in M0, M1, M2, M6, and M7 (Figure 3F, ***Supplementary Table X***).

S100A12 was highly expressed in M4 and M5, while lowly in M0, M1, M2, M3, M6, and M7, especially M3 (Figure 3F, ***Supplementary Table XI***). *S100A13* was upregulated in M1, M3, M5, and M6 and downregulated in M0, M2, M4, and M7 (Figure 3G, ***Supplementary Table XII***). *S100A14* was lowly expressed in M5, while no expression was detected in M0, M1, M2, M3, and M4 and high expression was observed in M6 and M7 (Figure 3G). *S100B* was highly expressed in M3, while the other subtypes were lowly expressed (Figure 3H, ***Supplementary Table XIII***). *S100P* was highly expressed in M3 and M7, and lowly in the other subtypes (Figure 3H, ***Supplementary Table XIV***). The results showed that the members of the S100 family differentially expressed in each subtype of AML, which might be due to the heterogeneity of the subtypes. Taken together, these findings provided the basis for studying the expression patterns and functions of S100 family members in various subtypes of AML.

Prognostic Values of S100 Family Members in Human AML

Next, we proceeded to determine whether S100 family members were associated with the prognosis of human AML patients using GEPIA databases. Interestingly, the increased level of *S100A4* was associated with poor OS in AML (Hazard ratio (HR)=1.9; p=0.026, Figure 4), while decreased *S100P* was associated with poor OS (HR=0.53; p=0.028, Figure 4). However, statistical significance was not detected for *S100A1* (HR=1.1; p=0.83), *S100A2* (HR=1.2; p=0.52), *S100A3* (HR=0.68; p=0.17), *S100A5* (HR=1.1; p=0.7), *S100A6* (HR=1.5; p=0.15), *S100A8* (HR=1.3; p=0.3), *S100A9* (HR=1.5; p=0.18), *S100A10* (HR=1.4; p=0.21), *S100A11* (HR=1.2; p=0.48), *S100A12* (HR=1.4; p=0.26), *S100A13* (HR=1.1; p=0.78), and *S100B* (HR=0.98; p=0.94) (Figure 4). The GEPIA databases did not provide survival analysis results of *S100A7* and *S100A14* as their expression was not detected in the majority of the molecular subtypes of AML. Hence, highly expressed *S100A4* and lowly expressed *S100P* is correlated with the prognosis of AML.

Correlation between S100A4 and S100P expression and clinical characteristics of AML patients

The above analysis demonstrated that *S100A4* and *S100P* is a valuable molecular marker for predicting the prognosis in AML. In addition, the correlation between *S100A4* and *S100P* expression levels and clinical characteristics of AML patients was analyzed. Clinical features, including age, FLT3 mutation, PML/RAR-fusion, gender, RAS activation, and patients' race, were analyzed. The results showed that the expression of *S100A4* did not differ significantly with respect to these clinical characteristics (Figure 5A). However, *S100P* was highly expressed in AML patients without FLT3 mutation as compared to those with FLT3 mutation (p=0.019, Figure 5B). Furthermore, *FLT3* and *S100P* were negatively correlated (R=-0.26, p=0.00061, Figure 5C). Next, the correlation analysis between *S100A4* and *S100P* expression levels and the methylation of AML patients demonstrated that the promoter methylation level of *S100A4* and *S100P* was higher in the 61-80-year-old group (Figure 6A-B). Consequently, the expression of *S100P* in AML was found to be negatively correlated with that of FLT3. In addition, the high expression of *S100A4* and *S100P* in AML patients of the 60-81-year-old group was related to methylation, which provided new clinical prognostic indicators for the specific age group.

Discussion

S100 has been widely recognized as an important family of transcription factors that play a pivotal role in a variety of human tumors[21,22]. This study is the first to investigate the mRNA expression and prognostic values of different S100 family members in AML. The current findings would contribute to the existing knowledge, enhance therapeutic strategies, and improve the accuracy of prognosis in AML patients.

We also found that the level of *S100A1*, *S100A13*, and *S100P* was downregulated in AML patients as compared to normal blood samples. However, the level of *S100A4*, *S100A8*, *S100A9*, *S100A10*, and *S100A12* was upregulated in AML. The expression of other S100 proteins, including *S100A2*, *S100A3*, *S100A5*, *S100A6*, *S100A7*, *S100A11*, *S100A14*, and *S100B* mRNA showed no significant difference between the patients with AML and normal blood samples. The results revealed that some S100 family members showed a remarkable difference in the mRNA expression between AML patients and normal blood samples.

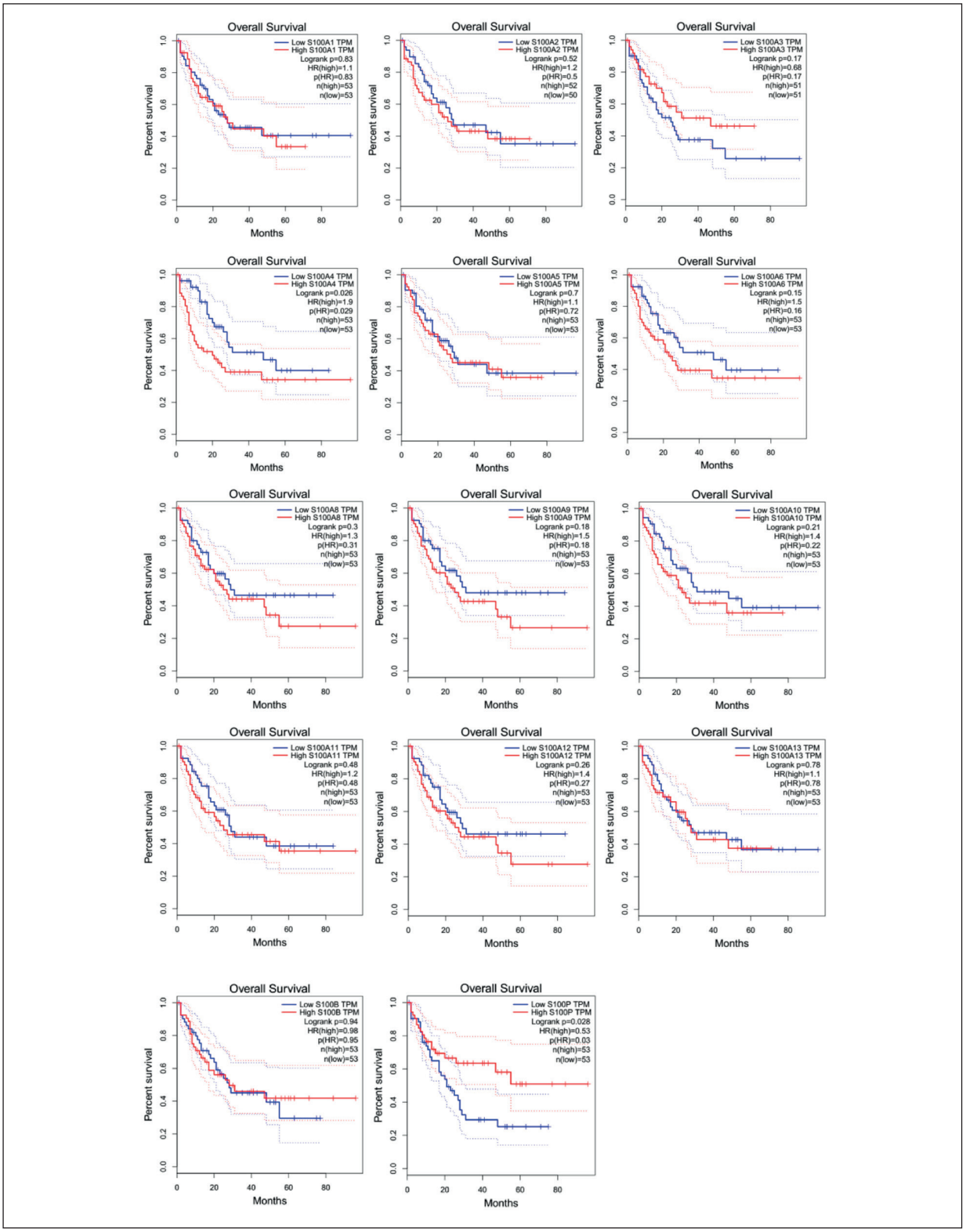

Figure 4. Prognostic values of the S100 family members in AML. OS is selected as a terminal event for the pooled Kaplan–Meier survival analysis. The median expression is set as a separate line for each S100 family member. A p-value < 0.05 was considered statistically significant.

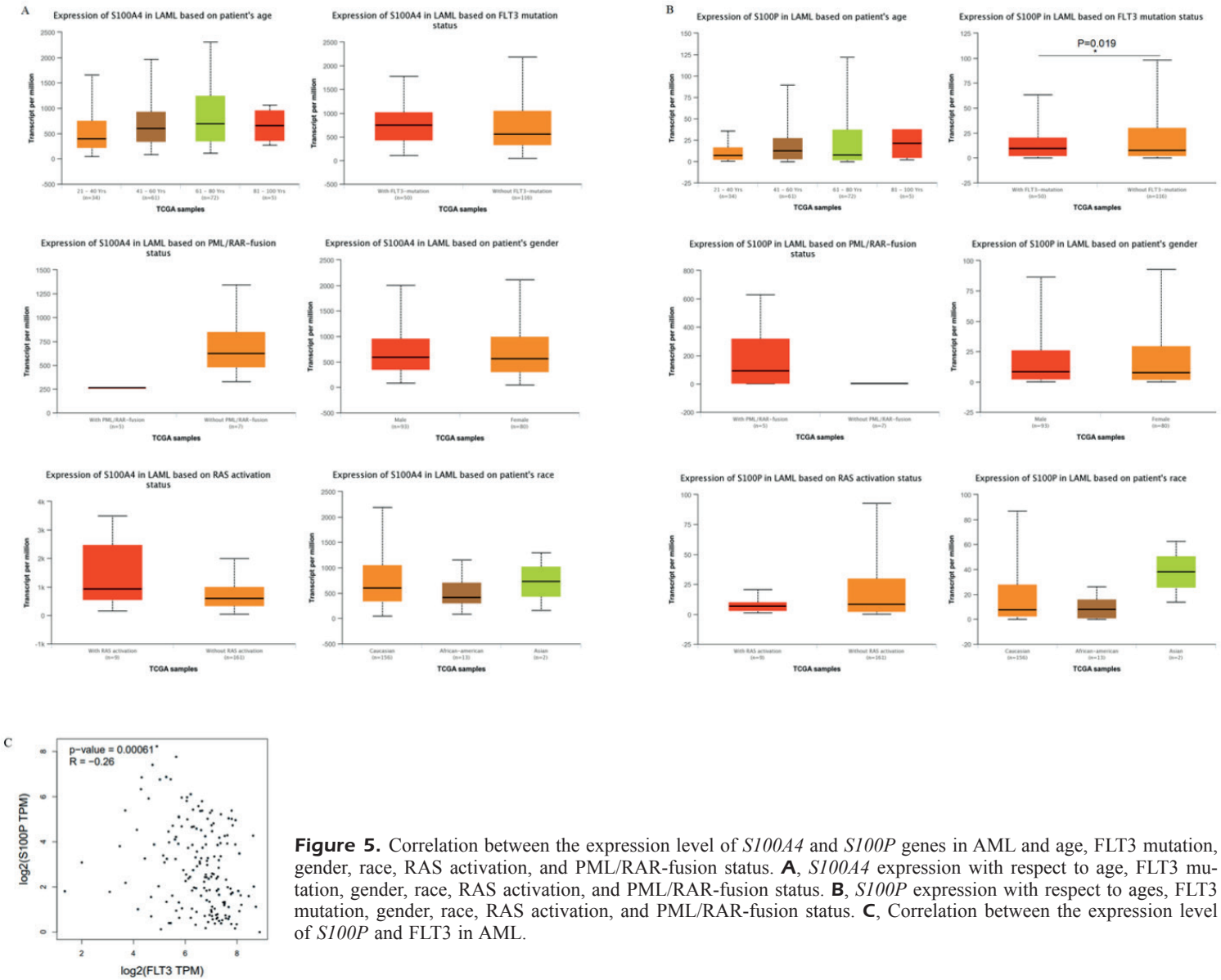

Figure 5. Correlation between the expression level of *S100A4* and *S100P* genes in AML and age, FLT3 mutation, gender, race, RAS activation, and PML/RAR-fusion status. **A**, *S100A4* expression with respect to age, FLT3 mutation, gender, race, RAS activation, and PML/RAR-fusion status. **B**, *S100P* expression with respect to ages, FLT3 mutation, gender, race, RAS activation, and PML/RAR-fusion status. **C**, Correlation between the expression level of *S100P* and FLT3 in AML.

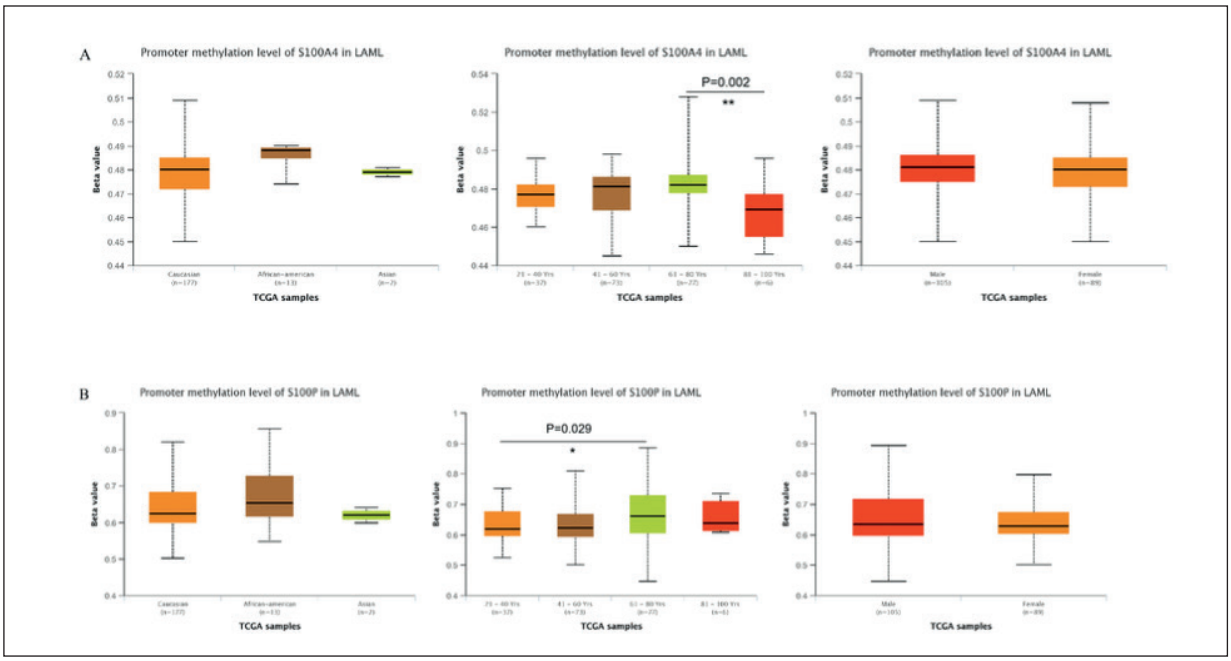

Figure 6. Promoter methylation level of *S100A4* and *S100P* in AML. **A**, *S100A4* expression with respect to race, age, and gender. **B**, *S100P* expression with respect to race, age, and gender.

Hitherto, in clinical samples of patients with AML, *S100A4* has been researched in both patients with AML and chronic myeloid leukemia (CML). The expression level of *S100A4* mRNA in 52 children patients with AML was 3-fold higher than that in the control groups[23,24]. The current result for *S100A4* was consistent with that previously reported. Furthermore, the GEPIA datasets showed that *S100A4* expression was higher in AML than in normal blood samples. UALCAN datasets also showed that *S100A4* was maximally expressed in M5. Based on the GEPIA datasets, we identified the prognostic value of *S100A4* in AML patients and found that a high *S100A4* expression was significantly associated with poor OS in AML.

In hematological malignancies, the expression level of S100A6 was elevated in AML[25]. The current result for *S100A6* was consistent with that previously reported. Compared to poorly differentiated AML (FAB M0 and M1), *S100A8* and *S100A9* were highly expressed in myelomonocytic and monocytic AMLs (FAB M4 and M5)[15]. In AML patients, elevated *S100A8* and *S100A9* expression levels were also found in plasma as compared to healthy individuals. In addition, the high level of expression of *S100A8* was related to poor prognosis in AML[26-28]. The expression analysis in the current study showed that the mRNA levels of *S100A8* and *S100A9* were increased in AML as compared to those in normal blood samples. The levels were also high in the leukemia subtypes M4 and M5, which was associated with a poor prognosis in AML, albeit without statistical significance. In AML, *S100A10* is relevant to coagulopathy in patients with FAB M3[29,30]. It is known that the molecule protects primary AML and acute lymphocytic leulemia (ALL) blasts from chemotherapy[31]. Therefore, high expression of *S100A10* mRNA was found in pediatric B-cell ALL, and these elevated levels were also in connection with early recurrence[32]. In the current study, the high expression of *S100A10* was observed in AML, especially in M3, M4 and M5. However, high *S100A10* expression was not associated with poor OS in AML. High expression *S100P* was associated with cell proliferation, metastasis, and carcinogenesis[33-35]. However, increased expression levels of *S100P* appear to be beneficial in patients with AML. Ishii et al[36] reported that *S100P* was upregulated maximally when treated with cytokines in AML cell lines (HL-60, THP-1, NB4). Therefore, the induction of *S100P* expression might be a feasible method to offset the differentiation block in AML. Moreover, the high expression of *S100P* contributes positively to a favorable prognosis[16]. The survival analysis indicated

that the elevated level of *S100P* mRNA in AML was significantly associated with improved OS in AML, thereby suggesting the tumor-suppressive role of *S100P* in AML.

The 5-year OS of AML patients aged ≥60-years-old was still <10%[37]. Reportedly, the median survival of 65-year-old patients receiving anti-leukemia treatment was 6 months, and the 5-year survival rate was <5%[38]. The refractory/early relapsed (Ref/eRel) AML in patients ≥ 60-years-old is a medical requisite in the salvage setting, wherein outcomes are poor[39]. Consequently, treating elderly AML patients is challenging. Aberrant promoter DNA methylation is the main mechanism of the development of leukemia, including AML[40]. In addition, decitabine (DAC) and azacytidine (AZA), nucleoside analogues that inhibit DNA methylation, have shown clinical efficacy in the treatment of AML, emphasizing the epigenetic regulation in AML[41]. The current results demonstrated that the promoter methylation level of *S100A4* and *S100P* was higher in 61-80-years-old group as compared to the other age groups. These findings indicated that *S100A4* and *S100P* expression was relevant to the promoter methylation, which is a valuable biomarker for predicting poor prognosis and demethylation therapy in 61-80-years-old AML patients.

Conclusions

Understand comprehensively the S100 family members on the diagnosis and prognosis of AML, patients may have a guiding significance. Our study indicated that the upregulated expression of S100A4 and downregulated expression of S100P plays a major role in AML tumorigenesis according to the integrative databases and bioinformatics analysis. Furthermore, *S100A4* and *S100P*, rather than other S100 family members, might serve as potential prognostic biomarkers and targets for new therapies of AML. Although additional clinical investigations are essential, this study has provided an insight into the prognostic role of *S100A4* and *S100P* in AML.

Acknowledgments

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Authors' Contributions

Xiaoyan Yang contributed to the data acquisition, analysis, and manuscript draft; Xiaoyan Yang, Jin Jiao, Huang Jing, Xue Jianwei, Xijun Wu, and Peng Li prepared the figures; Zhixu He contributed to the study design. The final manuscript was reviewed by Zhixu He and approved by all the listed authors.

Conflict of Interests

The authors declare that they have no conflict of interests.

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