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ORIGINAL RESEARCH

Identification of Long Non-Coding RNA *SNHG* Family as Promising Prognostic Biomarkers in Acute Myeloid Leukemia

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Background: Small nucleolar RNA host gene (*SNHG*) family members are newly recognized lncRNAs, which have been revealed to be oncogenes in several cancers. However, little studies investigated the expression and clinical implications of *SNHGs* in AML.

Methods: Herein, we systemically determined the prognostic role of the expression of *SNHG* family members in acute myeloid leukemia (AML).

Results: Among the expression of all *SNHG* family members, we identified that only *SNHG7* and *SNHG12* expression were found to have prognostic effects on overall survival (OS) and leukemia-free survival (LFS) in AML by Cox regression univariate analysis. Furthermore, Kaplan–Meier analysis showed that *SNHG7* higher-expressed cases had markedly longer OS and LFS time than *SNHG7* lower-expressed cases, whereas *SNHG12* higher-expressed cases had markedly shorter OS and LFS time than *SNHG12* lower-expressed cases. Interestingly, *SNHG7* and *SNHG12* expression were also associated with several prognosis-related clinical/molecular features such as white blood cell counts, FAB/cytogenetic classifications, *IDH1* mutation, *RUNX1* mutation, and *NPM1* mutation. Despite the associations, Cox regression multivariate analysis confirmed the independent prognostic impact of *SNHG7* and *SNHG12* expression in AML. Notably, we further validated that both *SNHG7* and *SNHG12* expression was significantly increased in newly diagnosed AML patients.

Conclusion: Our findings demonstrated that *SNHG7* and *SNHG12* expression act as independent prognostic indicators in AML.

Keywords: LncRNA, *SNHG*, expression, prognosis, AML

Introduction

Acute myeloid leukemia (AML), the most common adult leukemia, is a highly cytogenetically and molecularly heterogeneous blood cancer.[1] Cytogenetic abnormalities and molecular alterations play key roles in the processes of AML occurrence and development such as cell self-renewal, apoptosis, proliferation, and differentiation.[2] These pathological changes eventually lead to hematopoietic failure and adverse prognosis of AML patients.[3] Although numerous strategies, such as chemotherapy, hematopoietic stem cell transplantation (HSCT), and immunotherapy, have been applied to treat AML, the prognosis of this disease is still poor.[3] Consequently, it is urgent to identify new prognostic/predictive biomarkers and therapeutic targets for AML.

Over the last decade, non-coding RNAs account for 90% of human genome which do not codify for proteins but play a role in the regulation of functions have been

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shown to have multiple applications in the diagnosis, prognosis and therapeutic approach of various types of human cancers, including AML.[4,5] Non-coding RNAs can be classified into subtypes based on molecular size including microRNAs which defined as 19–25 nt in length and long non-coding RNAs (lncRNAs) which usually contain more than 200 nt in length.[6] So far, a large number of lncRNAs, such as *H19, HOTAIR, UCA1, CASC15, MEG3, PANDAR, CCDC26*, and *NEAT1*, have been explored in AML.[7,8] Small nucleolar RNA host gene (*SNHG*) family members (*SNHGs*) including *SNHG1, SNHG2/GAS5, SNHG3, SNHG4, SNHG5, SNHG6, SNHG7, SNHG8, SNHG9, SNHG10, SNHG11, SNHG12, SNHG13/DANCR, SNHG15, SNHG17, SNHG20* and *SNHG28*, are newly recognized lncRNAs, which have been revealed to be oncogenes in several cancers.[9] Also, several members of *SNHG* family including *SNHG1, SNHG3*, and *SNHG5* have been found to be dysregulated and play a crucial role in leukemogenesis, and also have prognostic value in AML.[10–14] Since little studies investigated the expression and clinical implications

Table 1 Cox Regression Univariate Analysis of Variables for Overall Survival and Leukemia-Free Survival in AML Patients

Variables	Whole-Cohort AML		CN-AML	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Overall Survival				
SNHG1 expression	0.862 (0.596–1.245)	0.427	0.738 (0.431–1.263)	0.267
SNHG2/GAS5 expression	1.008 (0.698–1.455)	0.968	0.901 (0.528–1.540)	0.704
SNHG3 expression	1.336 (0.923–1.934)	0.124	1.290 (0.752–2.213)	0.356
SNHG4 expression	1.007 (0.697–1.455)	0.970	0.568 (0.330–0.977)	0.041
SNHG5 expression	0.905 (0.626–1.307)	0.594	1.631 (0.949–2.802)	0.076
SNHG6 expression	1.165 (0.807–1.683)	0.415	1.155 (0.676–1.975)	0.598
SNHG7 expression	0.635 (0.438–0.921)	0.017	0.463 (0.260–0.823)	0.009
SNHG8 expression	0.931 (0.644–1.344)	0.701	1.236 (0.723–2.111)	0.438
SNHG9 expression	1.201 (0.831–1.735)	0.330	1.073 (0.629–1.832)	0.795
SNHG10 expression	0.952 (0.659–1.376)	0.795	0.657 (0.381–1.133)	0.131
SNHG11 expression	0.820 (0.567–1.186)	0.292	0.654 (0.382–1.121)	0.123
SNHG12 expression	1.470 (1.015–2.129)	0.041	1.683 (0.979–2.894)	0.060
SNHG13/DANCR expression	1.005 (0.696–1.451)	0.979	0.787 (0.452–1.371)	0.398
SNHG15 expression	0.779 (0.538–1.127)	0.186	0.839 (0.489–1.437)	0.522
SNHG17 expression	0.827 (0.572–1.194)	0.310	0.794 (0.465–1.358)	0.400
SNHG20 expression	0.955 (0.660–1.382)	0.808	0.708 (0.413–1.214)	0.210
SNHG28 expression	1.070 (0.741–1.545)	0.719	1.160 (0.678–1.984)	0.588
Leukemia-Free Survival				
SNHG1 expression	0.897 (0.621–1.296)	0.563	0.773 (0.451–1.322)	0.347
SNHG2/GAS5 expression	1.029 (0.713–1.487)	0.877	1.042 (0.610–1.781)	0.881
SNHG3 expression	1.409 (0.973–2.041)	0.069	1.370 (0.798–2.352)	0.254
SNHG4 expression	1.025 (0.710–1.480)	0.896	0.602 (0.350–1.035)	0.067
SNHG5 expression	0.844 (0.584–1.220)	0.367	1.555 (0.906–2.669)	0.109
SNHG6 expression	1.077 (0.746–1.556)	0.693	1.116 (0.653–1.908)	0.687
SNHG7 expression	0.599 (0.412–0.870)	0.007	0.493 (0.279–0.873)	0.015
SNHG8 expression	0.920 (0.637–1.328)	0.656	1.346 (0.788–2.301)	0.277
SNHG9 expression	1.179 (0.817–1.703)	0.379	0.998 (0.585–1.703)	0.995
SNHG10 expression	0.908 (0.628–1.312)	0.606	0.675 (0.391–1.165)	0.158
SNHG11 expression	0.792 (0.547–1.146)	0.216	0.634 (0.370–1.088)	0.098
SNHG12 expression	1.516 (1.047–2.194)	0.027	1.729 (1.008–2.966)	0.047
SNHG13/DANCR expression	1.025 (0.710–1.481)	0.894	0.819 (0.470–1.425)	0.480
SNHG15 expression	0.770 (0.532–1.114)	0.165	0.907 (0.530–1.553)	0.723
SNHG17 expression	0.839 (0.580–1.212)	0.348	0.841 (0.493–1.435)	0.525
SNHG20 expression	0.979 (0.678–1.415)	0.912	0.808 (0.472–1.382)	0.436
SNHG28 expression	1.108 (0.767–1.599)	0.586	1.128 (0.660–1.927)	0.660

Abbreviations: AML, acute myeloid leukemia; CN-AML, cytogenetically normal AML; HR, hazard ratio; CI, confidence interval.

of *SNHGs* in AML, we systemically determined the prognostic role of *SNHGs* expression in patients with AML.

Materials and Methods

Patients

A total of 173 AML patients were obtained for *SNHGs* expression data from The Cancer Genome Atlas (TCGA) databases.[15] Clinical and molecular characteristics of these patients including age, gender, white blood cell (WBC) counts, peripheral blood (PB) blasts, bone marrow (BM) blasts, French-American-British (FAB) subtypes, karyotypes, and the frequencies of AML-associated genetic mutations were obtained. Treatments of these patients were induction chemotherapy together with chemotherapy and HSCT as consolidation treatment as reported.[15]

Another cohort of 50 AML patients and 25 healthy volunteers from the Affiliated Hospital of Nantong University was also enrolled in the study. The study was

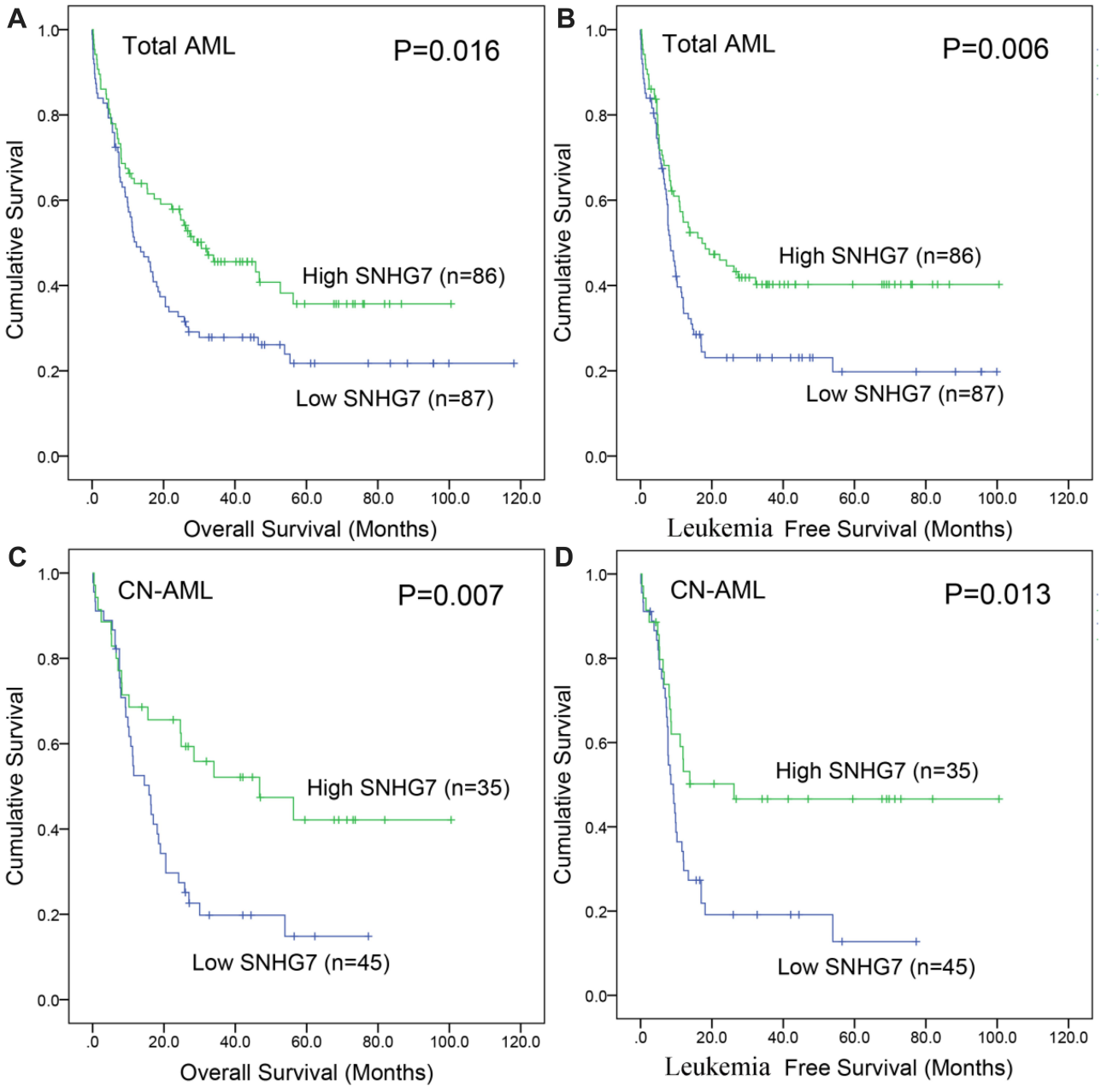

Figure 1 The impact of *SNHG7* expression on survival of AML patients. Kaplan–Meier survival curves of overall survival and disease-free survival in AML patients. (**A**) Overall survival in total AML; (**B**) leukemia-free survival in total AML; (**C**) overall survival in cytogenetically normal AML; (**D**) leukemia-free survival in cytogenetically normal AML.

approved by the Institutional Review Board of the Affiliated Hospital of Nantong University, and all participants provided informed consents.

Samples Preparation, RNA Isolation, and Reverse Transcription

Peripheral blood (PB) specimens were collected from 25 controls and 50 AML patients at diagnosis time. PB nucleated cells were obtained after using red blood cell lysis buffer (Solarbio, Beijing, China). Total RNA was extracted from PB nucleated cells using Trizol reagent (Invitrogen, Carlsbad, CA, USA). Reverse transcription was performed to synthesize cDNA using PrimeScript™ RT reagent Kit (TaKaRa, Tokyo, Japan). The program of reverse transcription was performed according to the manufacturer's instructions.

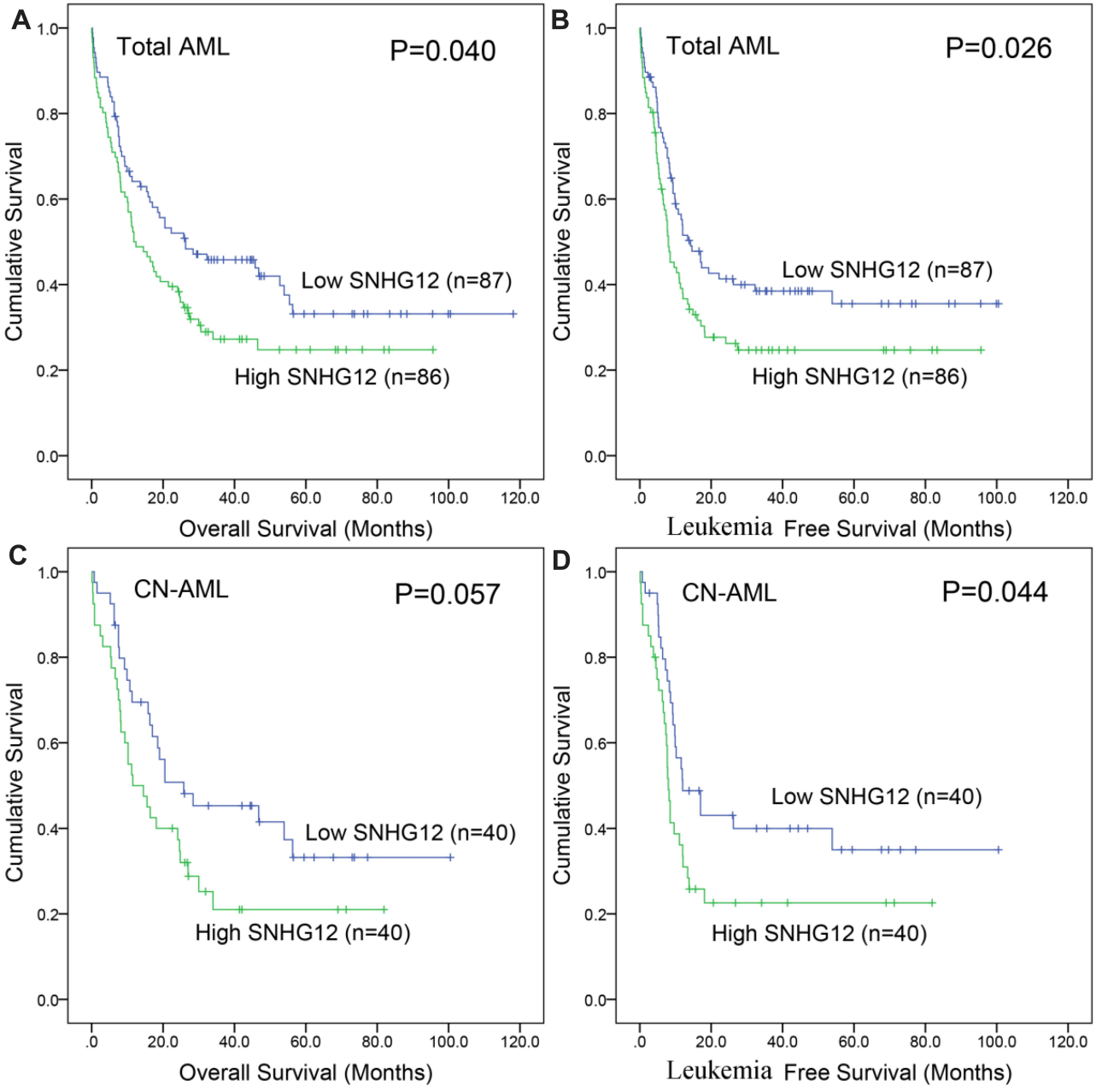

Figure 2 The impact of *SNHG12* expression on survival of AML patients. Kaplan–Meier survival curves of overall survival and disease-free survival in AML patients. (**A**) Overall survival in total AML; (**B**) leukemia-free survival in total AML; (**C**) overall survival in cytogenetically normal AML; (**D**) leukemia-free survival in cytogenetically normal AML.

RT-qPCR

Real-time quantitative PCR (RT-qPCR) was conducted to detect *SNHG7, SNHG12* and *GAPDH* transcript using TB Green Premix Ex Taq™ II (TaKaRa, Tokyo, Japan). The primers used for *SNHG7* were 5′-GTGACTTCGCCT GTGATGGA-3′ (forward) and 5′-TGCTGCCTGGCTTTG GTT-3′ (reverse). The primers used for *SNHG12* were 5′-A GATGGTGGTGAATGTGGC-3′ (forward), and 5′-AGT CTTGATGGGACCGTTTT-3′ (reverse). The primers used for *GAPDH* were 5′- AATCCCATCACCATCTT CCAG-3′ (forward) and 5′-GAGCCCCAGCCTTCTCC AT-3′ (reverse). Housekeeping gene *GAPDH* was detected as the reference gene. Relative *SNHG7* and *SNHG12* transcript level was calculated based on 2-ΔΔCT method.

Statistical Analysis

Mann–Whitney's *U*-test and Pearson Chi-square/Fisher exact test were used for the comparison of continuous variables and categorical variables, respectively. The effect of *SNHG7* and *SNHG12* expression on leukemia-free survival (LFS) and overall survival (OS) analyzed through Cox regression analysis and Kaplan-Meier analysis. The two-tailed *P* value <0.05 in all statistical analyses was defined as statistically significant.

Results

Identification of Prognosis-Related SNHGs Expression in AML

In order to evaluate the prognostic significance of *SNHGs* expression in AML, we extracted the expression data of *SNHGs* (*SNHG1, SNHG2/GAS5, SNHG3, SNHG4, SNHG5, SNHG6, SNHG7, SNHG8, SNHG9, SNHG10, SNHG11, SNHG12, SNHG13/DANCR, SNHG15, SNHG17, SNHG20*, and *SNHG28*) in AML from the TCGA databases. Prognostic significance of *SNHGs* expression was analyzed between two groups (lower and higher) divided by the median level of each *SNHG* member mRNA, respectively. By Cox regression univariate analysis, only *SNHG7* and *SNHG12* expression were found to have prognostic effects on OS and LFS among both total AML and cytogenetically normal AML (CN-AML) patients (Table 1). Furthermore, among both total AML and CN-AML, Kaplan-Meier analysis also showed that *SNHG7* higher-expressed cases had markedly longer OS and LFS time than *SNHG7* lower-expressed cases (Figure 1), whereas *SNHG12* higher-expressed cases had markedly shorter OS and LFS time than *SNHG12* lower-expressed cases (Figure 2).

Validation of SNHG7/12 Overexpression in Newly Diagnosed AML

In order to explore the expression pattern of *SNHG7* and *SNHG12* in AML, we further examined *SNHG7* and *SNHG12* mRNA in newly diagnosed AML patients. By RT-qPCR results, both *SNHG7* and *SNHG12* expression were significantly increased in newly diagnosed AML as compared with normal controls (Figure 3).

Clinical Implications of SNHG7/12 Expression in AML

Due to the prognostic effect of *SNHG7* and *SNHG12* expression in AML, we further analyzed the associations of *SNHG7/12* expression with clinical/biological features of AML patients. As presented in Table 2, patients with higher expression of *SNHG7* presented lower WBCs and higher percentage of PB blasts than those with lower expression of *SNHG7* patients. Moreover, significant difference was observed between two groups among the distributions of FAB classifications (Table 2). Higher expression of *SNHG7* was frequently occurred in FAB-M1/M2 and less frequently happened in FAB-M4/5 (Table 2). Although no significant difference was observed between two groups among the distributions of cytogenetic classifications, higher expression of *SNHG7* was closely associated −7/del(7) subtype (Table 2).

Regarding *SNHG12*, patients with higher expression of *SNHG12* presented higher percentage of PB blasts than those with lower expression of *SNHG12* patients (Table 2).

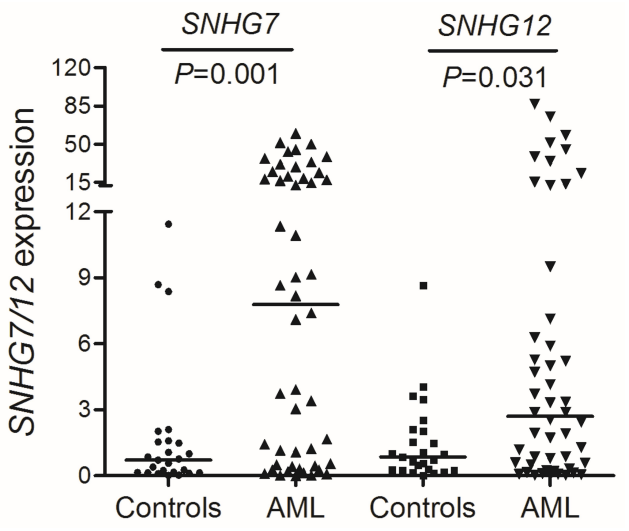

Figure 3 *SNHG7/12* expression in AML. *SNHG7/12* transcript level in controls and AML patients, which was detected by RT-qPCR.

Table 2 Correlation of *SNHG7*/*SNHG12* Expression with Clinic-Pathologic Characteristics in AML

Patient's Parameters	*SNHG7* Expression			*SNHG12* Expression		
	Low (n=87)	High (n=86)	*P*	Low (n=87)	High (n=86)	*P*
Sex, male/female	52/35	40/46	0.095	50/37	42/44	0.288
Median age, years (range)	59 (18–81)	57.5 (21–88)	0.873	59 (18–82)	57 (21–88)	0.783
Median WBC, $\times 10^9$/L (range)	30.5 (0.4–223.8)	10.55 (0.6–297.4)	0.008	15.1 (0.4–223.8)	22.4 (0.7–297.4)	0.474
Median PB blasts, % (range)	18 (0–97)	48 (0–98)	0.027	23.5 (0–97)	49 (0–98)	0.017
Median BM blasts, % (range)	74 (30–97)	70 (33–100)	0.627	72 (32–99)	72.5 (30–100)	0.733
FAB classifications			0.000			0.055
M0	5	11	NS	8	8	NS
M1	16	28	0.037	16	28	0.037
M2	13	25	0.028	17	21	NS
M3	7	9	NS	7	9	NS
M4	24	10	0.012	24	10	0.012
M5	16	2	0.001	12	6	NS
M6	2	0	NS	1	1	NS
M7	3	0	NS	2	1	NS
No data	1	1	NS	0	2	NS
Cytogenetics			0.062			0.004
Normal	45	35	NS	40	40	NS
t(15;17)	7	8	NS	7	8	NS
t(8;21)	1	6	NS	2	5	NS
inv(16)	5	5	NS	9	1	0.018
+8	3	5	NS	3	5	NS
del(5)	0	1	NS	1	0	NS
−7/del(7)	0	7	0.007	3	4	NS
11q23	2	1	NS	2	1	NS
Others	7	7	NS	12	2	0.010
Complex	16	9	NS	8	17	0.054
No data	1	2	NS	0	3	NS
Gene mutation						
FLT3 (±)	31/56	18/68	0.043	22/65	27/59	0.402
NPM1 (±)	31/56	17/69	0.027	19/68	29/57	0.091
DNMT3A (±)	27/60	15/71	0.051	20/67	22/64	0.725
IDH2 (±)	7/80	10/76	0.456	9/78	8/78	1.000
IDH1 (±)	2/85	14/72	0.001	6/81	10/76	0.307
TET2 (±)	4/83	11/75	0.063	9/78	6/80	0.590
RUNX1 (±)	5/82	10/76	0.188	12/75	3/83	0.028
TP53 (±)	10/77	4/82	0.162	4/83	10/76	0.103
NRAS (±)	8/79	4/82	0.370	8/79	4/82	0.370
CEBPA (±)	9/78	4/82	0.248	9/78	4/82	0.248
WT1 (±)	5/82	5/81	1.000	5/82	5/81	1.000
PTPN11 (±)	4/83	4/82	1.000	6/81	2/84	0.278
KIT (±)	4/83	3/83	1.000	5/82	2/84	0.443
U2AF1 (±)	2/85	5/81	0.278	4/83	3/83	1.000
KRAS (±)	2/85	5/81	0.278	3/84	4/82	0.720

Abbreviations: AML, acute myeloid leukemia; WBC, white blood cells; PB, peripheral blood; BM, bone marrow; FAB, French-American-British; NS, no significance.

Moreover, significant difference was observed between two groups among the distributions of cytogenetic classifications (Table 2). Higher expression of *SNHG12* was less frequently occurred in inv(16) and other subtypes (Table 2). Although no significant difference was observed between two groups among the distributions of FAB classifications, higher

expression of *SNHG12* was frequently occurred in FAB-M1 and less frequently happened in FAB-M4 (Table 2).

SNHG7/12 Expression Associated with Gene Mutations in AML

We also observed the associations of *SNHG7/12* expression with AML-associated gene mutations. Higher *SNHG7* expression was associated with *FLT3* and *NPM1* wild type as well as *IDH1* mutation (Table 2). In addition, higher *SNHG12* expression was associated with *RUNX1* wild type (Table 2). In order to confirm the significant correlations of *SNHG7/12* expression with these gene mutations, we also compared the *SNHG7/12* expression with and without these gene mutations. As presented in Figure 4, patients with *IDH1* and *RUNX1* mutations showed significantly higher *SNHG7* expression (P=0.001 and 0.037, respectively), whereas cases with *NPM1* mutation showed markedly higher *SNHG12* expression (P=0.014).

The Independent Prognostic Value of SNHG7/12 Expression in AML

Since *SNHG7/12* expression was associated with well-known prognostic factors such as WBC and gene mutations in AML, we further performed Cox regression multivariate analysis adjusting for prognosis-related factors. As shown in Table 3, both *SNHG7* and *SNHG12* could act as independent prognostic factors for OS and LFS in both total AML and CN-AML.

Discussion

The oncogenic role of *SNHGs* in diverse human cancers is supported by solid scientific data, which show that they are related to stimulation of the following malignant processes: epithelial to mesenchymal transition, invasion, proliferation, cell cycle, and apoptosis evasion.[9] We intended to test the *SNHGs* expression and determined their clinical implication in AML. In this study, we for

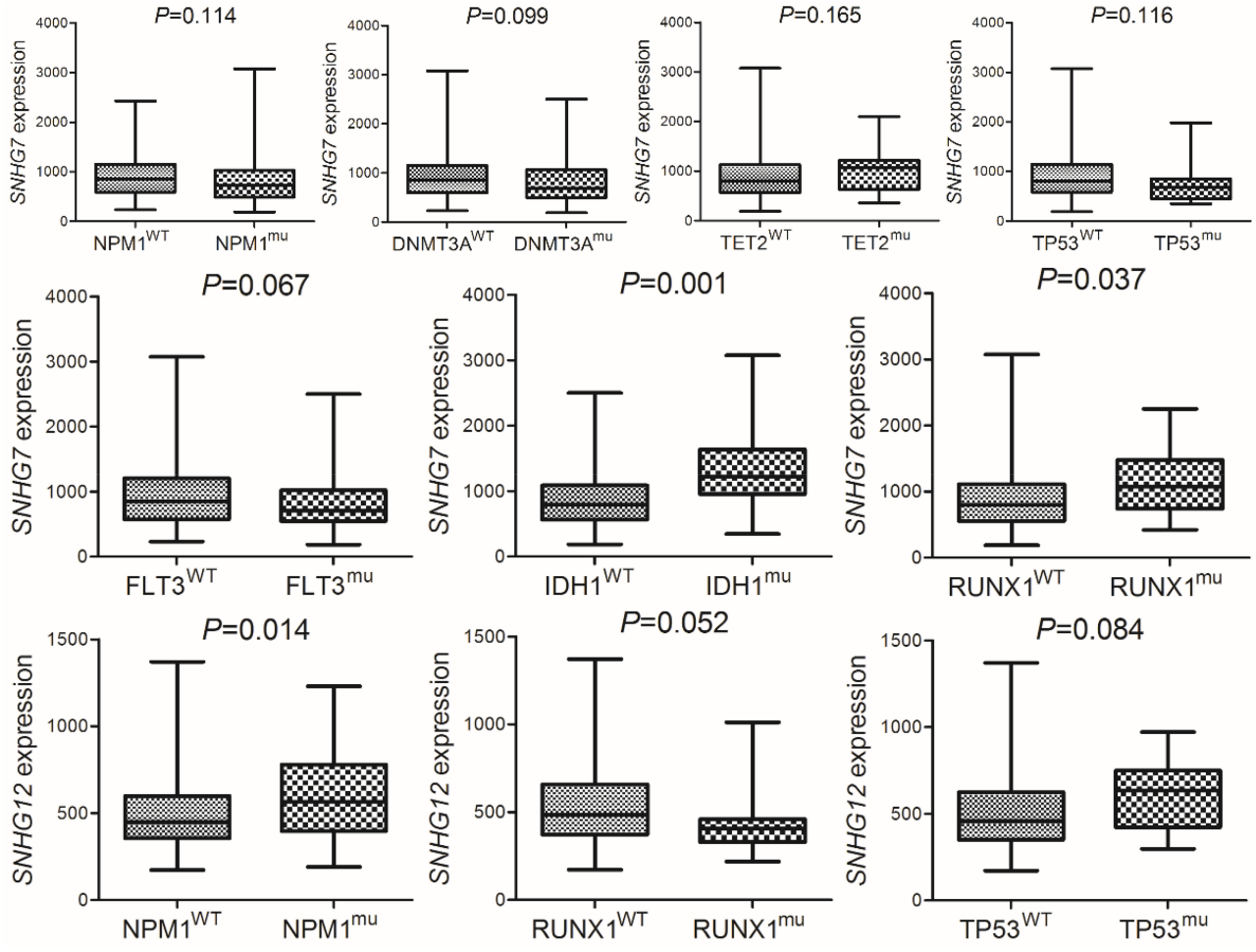

Figure 4 The associations of *SNHG7/12* expression with gene mutations in AML. *SNHG7/12* expression in AML patients with and without gene mutations.

Table 3 Cox Regression Multivariate Analysis of Variables for Overall Survival and Leukemia-Free Survival in AML Patients

Variables	Whole-Cohort AML		CN-AML	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Overall Survival				
Age	1.043 (1.027–1.058)	0.000	1.026 (1.006–1.046)	0.010
WBC	1.005 (1.000–1.009)	0.046	1.003 (0.998–1.008)	0.279
Karyotype risks	2.051 (1.498–2.809)	0.000	–	–
SNHG7 expression	0.663 (0.449–0.979)	0.039	0.404 (0.223–0.732)	0.003
SNHG12 expression	1.405 (0.953–2.072)	0.086	2.437 (1.374–4.324)	0.002
FLT3 mutation	1.502 (0.972–2.322)	0.067	1.353 (0.724–2.529)	0.344
NPM1 mutation	0.741 (0.434–1.265)	0.272	0.732 (0.417–1.283)	0.276
CEBPA mutation	1.647 (0.775–3.504)	0.195	1.243 (0.387–3.998)	0.715
RUNX1 mutation	1.637 (1.104–2.427)	0.014	1.511 (0.552–4.135)	0.421
IDH1 mutation	0.888 (0.434–1.816)	0.745	0.792 (0.253–2.482)	0.689
Leukemia-Free Survival				
Age	1.038 (1.023–1.053)	0.000	1.020 (1.000–1.039)	0.045
WBC	1.005 (1.001–1.009)	0.024	1.003 (0.998–1.009)	0.230
Karyotype risks	1.905 (1.411–2.572)	0.000	–	–
SNHG7 expression	0.614 (0.414–0.912)	0.016	0.443 (0.244–0.804)	0.007
SNHG12 expression	1.549 (1.048–2.288)	0.028	2.349 (1.339–4.119)	0.003
FLT3 mutation	1.590 (1.031–2.453)	0.036	1.309 (0.751–2.280)	0.342
NPM1 mutation	0.769 (0.459–1.287)	0.317	0.677 (0.367–1.247)	0.210
CEBPA mutation	1.638 (0.773–3.473)	0.198	1.360 (0.436–4.239)	0.596
RUNX1 mutation	1.475 (0.999–2.179)	0.051	1.725 (0.619–4.811)	0.297
IDH1 mutation	0.952 (0.462–1.961)	0.894	0.865 (0.266–2.808)	0.809

Notes: Variables including age (continuous variables), WBC (continuous variables), and ELN risks (good, intermediate, poor, and unknown).
Abbreviations: AML, acute myeloid leukemia; CN-AML, cytogenetically normal AML; WBC, white blood cells.

the first time revealed clinical implications of *SNHGs* expression in AML. Among all members of *SNHG* family, we only observed that *SNHG7* and *SNHG12* expression have prognostic value in AML. Moreover, we also validated that both *SNHG7* and *SNHG12* were significantly overexpressed in newly diagnosed AML. Notably, by our study, higher *SNHG7* expression was associated with favorable prognosis, whereas higher *SNHG12* expression was correlated with poor prognosis in AML. These results indicated that *SNHG7* and *SNHG12* may play different roles in AML during occurrence and development. However, until now, no clinical or functional studies were observed regarding *SNHG7* and *SNHG12* in AML. In solid tumors, a variety of studies have investigated the potential role of *SNHG7* in the development and progression of multiple human cancers such as bladder, breast, colorectal, esophageal, gastric, and prostate cancer, as well as osteosarcoma.[16] *SNHG7* was reported to promote proliferation and metastasis, while inhibiting apoptosis in these types of cancer cells.[16] Moreover, high expression of *SNHG7* predicts poor prognosis and poor survival for such patients.[16] Also, the underlying role of *SNHG12* was also determined in a number of cancers, such as breast, gastric, osteosarcoma, and glioma.[17] The increased expression of *SNHG12* in these cancers has been correlated with the viability, proliferation, metastasis, and invasion of tumor cells, impacting the prognosis and survival of cancer patients.[17] Further functional studies are needed to investigate the underlying role of *SNHG7* and *SNHG12* in AML occurrence and development.

Interestingly, previous studies have shown that *SNHG1* expression was up-regulated and associated with poor prognosis in AML.[10] Moreover, *SNHG1* promoted cell proliferation and inhibited the cell apoptosis by inhibiting *miR-101* or *miR-488*/*NUP205* axis in AML.[10,11] Peng et al reported that *SNHG3* elicited a growth-promoting role via sponging *miR-758-3p* to regulate *SRGN* expression in AML.[12] In addition, Li et al showed that *SNHG5* was increased and served as a potential prognostic biomarker in AML.[13] Mechanically, *SHNG5* played a crucial role in AML chemotherapy resistance by targeting the *miR-32*/*DNAJB9* axis.[14] However, we did not observe the prognostic value of *SNHG1/3/5* expression in AML. The conflicting results may be attributed to the differences in

ethnics and in AML subtype distribution with different phenotypes and genotypes. Due to the limitation of our clinical samples, we could not perform a validation study regarding the prognostic value of *SNHG7* and *SNHG12* to further confirm our results identified by TCGA data. Obviously, further studies are required to validate the results in different ethnics before *SNHGs* expression could be used routinely as a promising biomarker for risk stratification in AML.

Genetic alterations and epigenetic modifications are common molecular events involved in the process of leukemogenesis and interacted with each other. Evidences have shown that somatic gene mutations such as *RUNX1* mutation affected transcription activation in AML.[18] In our study, we further identified the association between *SNHG7/12* and common gene mutations such as *IDH1/2, RUNX1* and *NPM1* mutations in patients with AML. However, the potential connections between *SNHG7/12* expression and these gene mutations remain poorly defined. Further studies are required to determine the potential role of *SNHG7* and *SNHG12* overexpression during the leukemogenesis caused by *IDH1/2, RUNX1* and *NPM1* mutations.

Collectively, our findings demonstrated that *SNHG7* and *SNHG12* expression act as independent prognostic indicators in AML.

Abbreviations

AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplantation; LncRNAs, long non-coding RNAs; *SNHG*, small nucleolar RNA host gene; TCGA, The Cancer Genome Atlas; WBC, white blood cell; PB, peripheral blood; BM, bone marrow; FAB, French-American-British; CN-AML, cytogenetically normal AML; LFS, leukemia-free survival; OS, overall survival.

Ethics Statements

All procedures performed in studies involving human participants were approved by the Ethics Committee of Affiliated Hospital of Nantong University with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all patients included in this study.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Döhner H, Weisdorf DJ, Bloomfield CD. Acute myeloid leukemia. *N Engl J Med*. 2015;373(12):1136–1152. doi:10.1056/NEJMra1406184
2. Chen J, Odenike O, Rowley JD. Leukaemogenesis: more than mutant genes. *Nat Rev Cancer*. 2010;10(1):23–36. doi:10.1038/nrc2765
3. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. 2017;129(4):424–447.
4. Prensner JR, Chinnaiyan AM. The emergence of lncRNAs in cancer biology. *Cancer Discov*. 2011;1(5):391–407. doi:10.1158/2159-8290.CD-11-0209
5. Garitano-Trojaola A, Agirre X, Prósper F, Fortes P. Long non-coding RNAs in haematological malignancies. *Int J Mol Sci*. 2013;14(8):15386–15422. doi:10.3390/ijms140815386
6. Beermann J, Piccoli MT, Viereck J, Thum T. Non-coding RNAs in development and disease: background, mechanisms, and therapeutic approaches. *Physiol Rev*. 2016;96(4):1297–1325. doi:10.1152/physrev.00041.2015
7. Zhang TJ, Zhou JD, Zhang W, et al. H19 overexpression promotes leukemogenesis and predicts unfavorable prognosis in acute myeloid leukemia. *Clin Epigenetics*. 2018;10:47. doi:10.1186/s13148-018-0486-z
8. Gourvest M, Brousset P, Bousquet M. Long noncoding RNAs in acute myeloid leukemia: functional characterization and clinical relevance. *Cancers*. 2019;11(11):1638. doi:10.3390/cancers11111638
9. Zimta -A-A, Tigu AB, Braicu C, Stefan C, Ionescu C, Berindan-Neagoe I. An emerging class of long non-coding RNA with oncogenic role arises from the snoRNA host genes. *Front Oncol*. 2020;10:389. doi:10.3389/fonc.2020.00389
10. Tian M, Gong W, Guo J. Long non-coding RNA SNHG1 indicates poor prognosis and facilitates disease progression in acute myeloid leukemia. *Biol Open*. 2019;8(10):bio046417. doi:10.1242/bio.046417
11. Bao XL, Zhang L, Song WP. LncRNA SNHG1 overexpression regulates the proliferation of acute myeloid leukemia cells through miR-488-5p/NUP205 axis. *Eur Rev Med Pharmacol Sci*. 2019;23(13):5896–5903. doi:10.26355/eurrev_201907_18334
12. Peng L, Zhang Y, Xin H. lncRNA SNHG3 facilitates acute myeloid leukemia cell growth via the regulation of miR-758-3p/SRGN axis. *J Cell Biochem*. 2020;121(2):1023–1031. doi:10.1002/jcb.29336
13. Li J, Sun CK. Long noncoding RNA SNHG5 is up-regulated and serves as a potential prognostic biomarker in acute myeloid leukemia. *Eur Rev Med Pharmacol Sci*. 2018;22(11):3342–3347. doi:10.26355/eurrev_201806_15154
14. Wang D, Zeng T, Lin Z, et al. Long non-coding RNA SNHG5 regulates chemotherapy resistance through the miR-32/DNAJB9 axis in acute myeloid leukemia. *Biomed Pharmacother*. 2019;123:109802. doi:10.1016/j.biopha.2019.109802
15. Cancer Genome Atlas Research Network. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. *N Engl J Med*. 2013;368(22):2059–2074. doi:10.1056/NEJMoa1301689
16. Zhou Y, Tian B, Tang J, et al. SNHG7: a novel vital oncogenic lncRNA in human cancers. *Biomed Pharmacother*. 2020;124:109921. doi:10.1016/j.biopha.2020.109921
17. Tamang S, Acharya V, Roy D, et al. SNHG12: an LncRNA as a potential therapeutic target and biomarker for human cancer. *Front Oncol*. 2019;9:901. doi:10.3389/fonc.2019.00901
18. Mujahed H, Miliara S, Neddermeyer A, et al. AML displays increased CTCF occupancy associated with aberrant gene expression and transcription factor binding. *Blood*. 2020;136(3):339–352. doi:10.1182/blood.2019002326