Original Article



# Prognostic significance of the *PANK* family expression in acute myeloid leukemia

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**Background:** Acute myeloid leukemia (AML) is a highly heterogenous hematological malignancy and its prognostication depends on the genetic mutation and expression profile of each patient. Pantothenate kinase (*PANK*) is a regulatory enzyme that controls coenzyme A (CoA) biosynthesis. It has four isoforms encoded by *PANK1-4*, respectively. Whether the expression of the *PANK* family has prognostic significance in AML remains unclear.

**Methods:** We screened The Cancer Genome Atlas database for AML patients with complete *PANK1-4* expression data. Eighty-four AML patients met the criteria and were included in this study. Clinical characteristics at diagnosis, including peripheral blood (PB) white blood cell counts (WBC), blast percentages in PB and bone marrow (BM), French-American-British (FAB) subtypes and the frequencies of common genetic mutations were described. Survival was estimated using the Kaplan-Meier method and the log-rank test. Multivariate Cox proportional hazard models were constructed for event-free survival (EFS) and overall survival (OS), using a limited backward elimination procedure.

**Results:** Patients with high *PANK2* expression had significantly longer event-free survival (EFS) and overall survival (OS) than patients with low *PANK2* expression (P=0.007, P=0.016, respectively), whereas patients with high *PANK4* expression had shorter EFS and OS than patients with low *PANK4* expression (P=0.022, P=0.015, respectively). Multivariate analysis confirmed that high *PANK4* expression was an independent risk factor for EFS and OS (both P<0.05).

**Conclusions:** Our study suggested that high *PANK2* expression might have favorable effects on AML, while high *PANK4* expression was indicative of poor prognosis.

**Keywords:** Acute myeloid leukemia (AML); heterogeneity; pantothenate kinase (*PANK*); prognosis

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## Introduction

Acute myeloid leukemia (AML) is a hematological malignancy due to unchecked clonal expansion of mutated myeloid hematopoietic cells (1). It is highly aggressive and harbors widely heterogeneous clinical and genetic features, which makes the individualized diagnosis, treatment and prognostication of each patient particularly challenging (2). The current AML risk stratification systems are not perfect, although many genetic markers have been included to assist the prognosis evaluation, such as *FLT3-ITD*, *NMP1*, *TP53* and *CEBPA*, of which *FLT3-ITD* and *TP53* mutations are adverse, and *CEBPA* double-mutations and *NPM1* mutation are favorable prognostic markers in AML (3-6). Nevertheless, with the development of next generation sequencing (NGS), the AML mutational spectrum has gained more details, more genetic and epigenetic markers are being identified for better risk stratification and therapeutic design (7,8).

Pantothenate kinase (*PANK*) is a rate-limiting enzyme in coenzyme A (CoA) synthesis (9). It has four isoforms encoded by *PANK1-4*, but only the proteins encoded by *PANK1-3* have functional pantothenate kinase activities (10). Previous studies showed that the *PANKs* are involved in tumorigenesis. *PANK2* has positive effect on the treatment of papillary and anaplastic thyroid cancer by triggering larger transcriptomic alterations (11). MiR-103, which is buried in the *PANK3* gene, is a useful prognostic biomarker for leukemia (12). *PANK1* plays an important role in the regulation of p53-dependent energy homeostasis (13). The prognostic role of the *PANK* family in AML remains unknown. Here we aim to analyze the prognostic significance of the expression of the *PANK* family in AML.

## Methods

### *Patients*

The Cancer Genome Atlas (TCGA) database (https://cancergenome.nih.gov/) was screened for AML patients with complete *PANK1-4* expression data and 84 patients who met the criteria were included in the study (14). All patients were between age 22 and 88, and only received chemotherapy, i.e., no patient had stem cell transplant. Data on the patients' clinical and molecular characteristics at diagnosis were downloaded from the database, including peripheral blood (PB) white blood cell (WBC) counts, blast percentages in PB and bone marrow (BM), the distributions of the French-American-British (FAB) subtypes and the molecular-cytogenetic risk group, and the mutation frequencies of common recurrent genetic mutations. Event-free survival (EFS) and overall survival (OS) were study endpoints. Informed consents were obtained from all patients, and the study protocol was approved by the Human Research Council of University of Washington.

### *Statistical analysis*

The clinical and molecular characteristics of patients were summarized using descriptive statistics. Numerical data was compared using the Mann-Whitney *U* test, and categorical data was compared using the Chi-Square test. EFS was defined as the time from diagnosis to removal from the study due to relapse, death or failure to achieve complete remission, or was censored at the last follow-up. OS was defined as the time from diagnosis to death from any cause, or was censored at the last follow-up. EFS and OS were estimated using the Kaplan-Meier method and the log-rank test. Multivariate proportional hazards models were constructed for EFS and OS, using a limited backward elimination procedure. $P<0.05$ was considered statistically significant for all analyses. All statistical tests were two sided and performed by SPSS software 20.0 and GraphPad Prism software 7.0.

## Results

### *Association of different expression levels of the PANK members with EFS and OS in AML patients*

To evaluate the association of the *PANK* family expression and survival of the AML patients who only received chemotherapy, Kaplan-Meier method and the log-rank test were performed and the results were presented in *Table 1*. High expression levels of *PANK2* and *PANK4*, i.e., the expression levels were higher than the median in the group, had associations with survival. Specifically, patients with high *PANK2* expression had longer EFS and OS than those with low *PANK2* expression (P=0.007, P=0.016, respectively, *Figure 1A,B*); patients with high *PANK4* expression had shorter EFS and OS than those with low *PANK4* expression (P=0.022, P=0.015, respectively, *Figure 1C,D*).

### *Comparison of the clinical and molecular characteristics in different expression groups of PANK2 and PANK4*

According to the median expression levels of *PANK2*

 

**Table 1** Comparison of EFS and OS between different expression levels of *PANK1-4*

| Variables | EFS | | OS | |
|---|---|---|---|---|
| | $\chi^2$ | P | $\chi^2$ | P |
| Chemotherapy-only group | | | | |
| *PANK1* (high *vs.* low) | 0.101 | 0.751 | 0.624 | 0.430 |
| *PANK2* (high *vs.* low) | 7.324 | 0.007 | 5.842 | 0.016 |
| *PANK3* (high *vs.* low) | 0.129 | 0.720 | 0.027 | 0.869 |
| *PANK4* (high *vs.* low) | 5.223 | 0.022 | 5.944 | 0.015 |
| Allo-HSCT group | | | | |
| *PANK1* (high *vs.* low) | 0.026 | 0.872 | 0.003 | 0.960 |
| *PANK2* (high *vs.* low) | 0.026 | 0.873 | 0.222 | 0.637 |
| *PANK3* (high *vs.* low) | 0.420 | 0.517 | 1.832 | 0.176 |
| *PANK4* (high *vs.* low) | 0.418 | 0.518 | 0.061 | 0.806 |

EFS, event-free survival; OS, overall survival; Allo-HSCT, allogeneic hematopoietic stem cell transplantation.

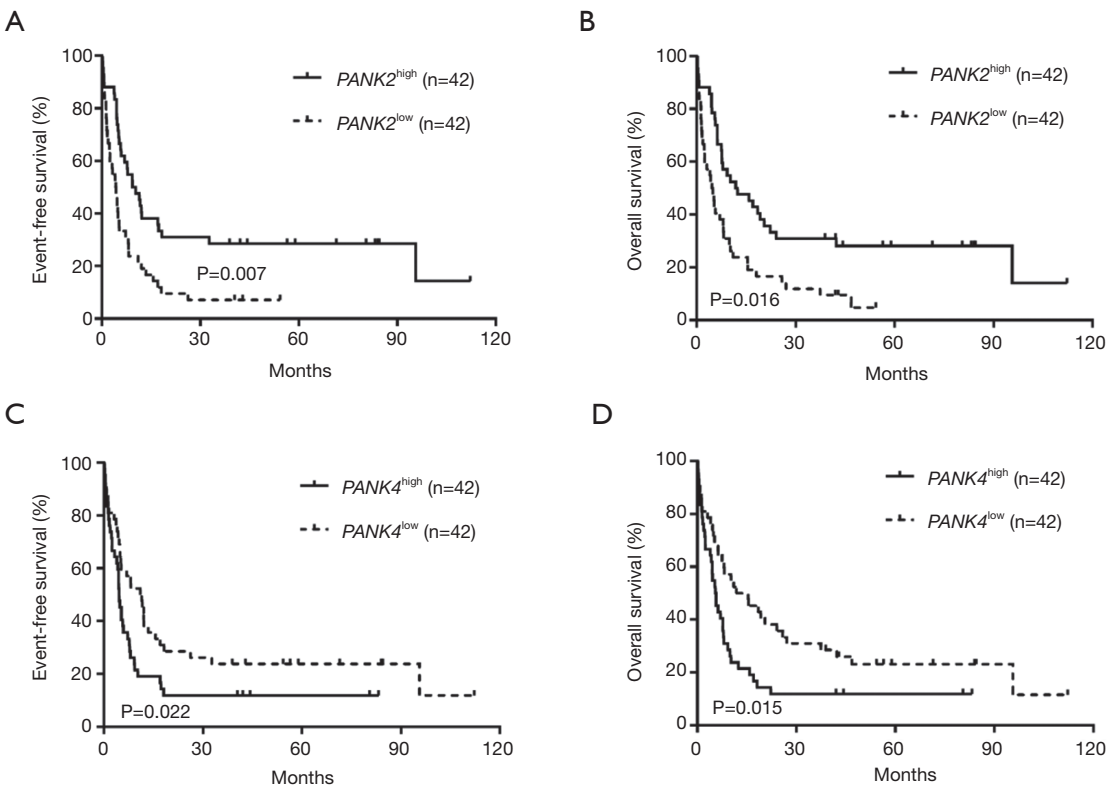


**Figure 1** Kaplan-Meier curves of EFS and OS based on expression levels of *PANK2* and *PANK4*. (A,B) Patients with high *PANK2* expression had longer EFS and OS than the patients with low expression of *PANK2*. (C,D) Patients with high *PANK4* expression had shorter EFS and OS than the patients with low expression of *PANK4*. EFS, event-free survival; OS, overall survival.

 

or *PANK4*, all patients were divided into high and low expression groups respectively. Comparison of the clinical and molecular characteristics between different groups were summarized in *Table 2*. The *PANK2*$^{high}$ group had more patients with age <60 years (P=0.018), lower PB blasts percentage (P=0.014), more FAB-M5 patients (P=0.004), and fewer patients with complex karyotype than the *PANK2*$^{low}$ group. No significant differences were found in gender distribution, race, peripheral WBC count, BM blasts, risk-group distribution and frequencies of common genetic mutations (*FLT3-ITD*, *NPM1*, *DNMT3A*, *RUNX1*, *TET2*, *TP53*, *TTN*, *MT-CO2*, *CEBPA*, *IDH1/IDH2*, *NRAS/KRAS*) between the two groups. The *PANK4*$^{high}$ group had more male patients (P=0.049), lower PB blasts percentage (P=0.003), more patients with complex karyotype (P=0.004), more patients with poor-risk cytogenetics (P=0.004), lower mutation frequency of *IDH1/IDH2* (P=0.046) and higher frequency of *TP53* (P=0.002). No significant differences were found in age, race, peripheral WBC count, BM blasts, FAB subtypes and frequencies of other common genetic mutations (*FLT3-ITD*, *NPM1*, *DNMT3A*, *RUNX1*, *TET2*, *TTN*, *MT.CO2*, *CEBPA*, *NRAS/KRAS*) between the two groups.

### *Prognostic value of PANK2 and PANK4 expression in AML patients*

To further evaluate prognostic value of *PANK2* and *PANK4*, multivariate Cox proportional hazard models were constructed, involving factors that had significant association (P<0.05) with EFS and/or OS in the Univariate analysis (*Table S1*), such as the expression levels of *PANK2* and *PANK4* (high *vs.* low), age (≥60 *vs.* <60 years), BM blast percentage (≥70% *vs.* <70%), PB blast percentage (≥70% *vs.* <70%) and recurrent genetic mutations (*DNMT3A* and *TP53*, mutated *vs.* wild type). We also involved factors that had established survival impact on AML, including peripheral WBC count (≥15×10$^9$/L *vs.* <15×10$^9$/L), *FLT3-ITD* (positive *vs.* negative), and genetic mutations (*NPM1* mutated *vs.* wild type). Results of the multivariate analysis were shown in *Table 3*. High *PANK4* expression and age ≥60 years were independent risk factors for EFS and OS (all P<0.05). In addition, PB blasts ≥70% and *TP53* mutation were independent risk factors for EFS (all P=0.031).

## Discussion

In this study, we found that high *PANK2* expression could have a favorable prognostic impact on AML, although the effect was not independent, but high *PANK4* expression definitely played an independently negative role in the survival of AML patients who only received chemotherapy.

Several studies demonstrated a significant role of the *PANK* family in cancer. A study found that *PANK2* can be a therapeutic target for thyroid cancer (11). MiR-103, which is encoded by the *PANK3* gene, and is expressed as a biproduct of *PANK3*, plays an important role in prognosis of leukemia (12). *PANK1*, a direct transcriptional target of p53, is associated with the regulation of energy homeostasis in human colon cancer cells (13). Taken together, these results, although limited, indicated that *PANK* members may exert important effects on tumorigenesis.

In this study, we found that the *PANK2*$^{high}$ group had more young patients, lower PB blast percentage and fewer patients with FAB-M5 subtype, suggesting that these factors may have some combined favorable effect in AML. In addition, we found that high *PANK4* expression was more common in patients with poor-risk and complex karyotype. This concurred with previous studies that the prognosis of AML patients with complex karyotype and poor-risk is generally poor (15,16). High *PANK4* expression was more likely to co-exist with *TP53* mutation and FAB-M5 subtype. It is known that FAB-M5 patients usually are more refractory to treatment and have poor prognosis (17), and *TP53* mutation are related to adverse prognosis in complex karyotype AML (18). Moreover, high *PANK4*, but not high *PANK2* expression, was an independent risk factor for EFS and OS, demonstrated by multivariate analysis. Hence, high expressions of *PANK2* and *PANK4* all can affect the prognosis of AML patients, but high *PANK4* expression has a stronger effect.

The mechanisms of the tumorigenic role of *PANK2* and *PANK4* are under investigation. Zhou *et al.* reported that abnormal expression of *PANK2* leads to aggregation of cysteine and synthesis of oxygen free radicals, further regulating oxidative stress inside cells (19). AML cells are susceptible to oxidative stress due to low spare reserve capacity in their respiratory chain (20), therefore *PANK2* may affect the survival of patients by enhancing the oxidative stress in leukemic cells and promote cell death. Previous research also reported that overexpression of *PANK4* could inhibit cell apoptosis in the pancreas by decreasing the transcriptional level of pro-caspase-9 (21). Combined with our results, we speculated that high *PANK4* expression might also suppress AML cell apoptosis by inhibiting pro-caspase-9 expression, leading to shorter

 

**Table 2** Comparison of clinical and molecular characteristics in different groups

| Characteristics | *PANK2* | | | *PANK4* | | |
|---|---|---|---|---|---|---|
| | High (n=42) | Low (n=42) | P | High (n=42) | Low (n=42) | P |
| Age/years, median [range] | 63.33 [25–88] | 68.25 [22–88] | 0.237* | 66.83 [33–88] | 65.6 [22–82] | 0.479* |
| Age group/n (%) | | | 0.018§ | | | 0.637§ |
| <60 years | 18 (42.9) | 8 (19.0) | | 12 (28.6) | 14 (33.3) | |
| ≥60 years | 24 (57.1) | 34 (81.0) | | 30 (71.4) | 28 (66.7) | |
| Gender/n (%) | | | 0.274§ | | | 0.049§ |
| Male | 25 (59.5) | 20 (47.6) | | 27 (64.3) | 18 (42.9) | |
| Female | 17 (40.5) | 22 (52.4) | | 15 (35.7) | 24 (57.1) | |
| Race/n (%) | | | 0.078§ | | | 0.801§ |
| White | 35 (83.3) | 28 (66.7) | | 31 (73.8) | 32 (76.2) | |
| Others | 7 (16.7) | 14 (33.3) | | 11 (26.2) | 10 (23.8) | |
| WBC/$\times10^9$/L, median (range) | 24.05 (1.9–134.4) | 8.35 (0.7–297.4) | 0.145* | 14.8 (0.7–134.4) | 14.6 (1–297.4) | 0.925* |
| BM blasts/%, median [range] | 72 [32–95] | 71.33 [30–90] | 0.996* | 70.5 [30–97] | 73.5 [35–99] | 0.101* |
| PB blasts/%, median [range] | 15.5 [0–97] | 39 [0–98] | 0.014* | 11.67 [0–90] | 49 [0–98] | 0.003* |
| FAB subtypes/n (%) | | | | | | |
| M0 | 1 (2.4) | 6 (14.3) | 0.059§ | 4 (9.5) | 3 (7.1) | 0.705§ |
| M1 | 6 (14.3) | 14 (33.3) | 0.074§ | 9 (21.4) | 11 (26.2) | 0.655§ |
| M2 | 8 (19.0) | 13 (31.0) | 0.275§ | 6 (14.3) | 15 (35.7) | 0.050§ |
| M4 | 13 (31.0) | 7 (16.7) | 0.180§ | 10 (23.8) | 10 (23.8) | 1.000§ |
| M5 | 11 (26.2) | 1 (2.4) | 0.004§ | 10 (23.8) | 2 (4.8) | 0.021§ |
| M6 | 1 (2.4) | 0 (0.0) | 1.000§ | 0 (0.0) | 1 (2.4) | 0.314§ |
| M7 | 2 (4.8) | 1 (2.4) | 0.564§ | 3 (7.1) | 0 (0.0) | 0.317§ |
| Cytogenetics/n (%) | | | | | | |
| Normal | 21 (50.0) | 17 (40.5) | 0.381§ | 18 (42.9) | 22 (52.4) | 0.527§ |
| Complex | 3 (7.1) | 8 (19.0) | 0.106§ | 11 (26.2) | 0 (0.0) | 0.004§ |
| inv(16)/CBFβ-MYH11 | 4 (9.5) | 2 (4.8) | 0.397§ | 3 (7.1) | 3 (7.1) | 1.000§ |
| t(8;21)/RUNX1-RUNX1T1 | 4 (9.5) | 2 (4.8) | 0.397§ | 1 (2.4) | 5 (11.9) | 0.102§ |
| 11q23/MLL | 2 (4.8) | 1 (2.4) | 0.557§ | 3 (7.1) | 0 (0.0) | 0.317§ |
| -7/7q- | 0 (0.0) | 3 (7.1) | 0.078§ | 1 (2.4) | 2 (4.8) | 0.564§ |
| t(9;22)/BCR-ABL1 | 1 (2.4) | 0 (0.0) | 0.314§ | 1 (2.4) | 0 (0.0) | 0.314§ |
| Others | 6 (14.3) | 6 (14.3) | 1.000§ | 3 (7.1) | 9 (21.4) | 0.083§ |
| Risk/n (%) | | | | | | |
| Good | 8 (19.5) | 4 (9.8) | 0.212§ | 4 (9.8) | 8 (19.5) | 0.248§ |
| Intermediate | 22 (53.7) | 24 (58.5) | 0.656§ | 18 (43.9) | 28 (68.3) | 0.140§ |
| Poor | 11 (26.8) | 13 (31.7) | 0.627§ | 19 (46.3) | 5 (12.2) | 0.004§ |

**Table 2** (*continued*)

**Table 2** (*continued*)

| Characteristics | *PANK2* | | | *PANK4* | | |
|---|---|---|---|---|---|---|
| | High (n=42) | Low (n=42) | P | High (n=42) | Low (n=42) | P |
| *FLT3*/n (%) | | | | | | |
| *FLT3-ITD* | 5 (11.9) | 10 (23.8) | 0.154§ | 6 (14.3) | 9 (21.4) | 0.439§ |
| *FLT3-TKD* | 5 (11.9) | 2 (4.8) | 0.236§ | 2 (4.8) | 5 (11.9) | 0.257§ |
| Wild type | 31 (73.8) | 31 (73.8) | 1.000§ | 34 (81) | 28 (66.7) | 0.446§ |
| *NPM1*/n (%) | | | 0.483§ | | | 0.483§ |
| Mutation | 15 (35.7) | 12 (28.6) | | 12 (28.6) | 15 (35.7) | |
| Wild type | 27 (64.3) | 30 (71.4) | | 30 (71.4) | 27 (64.3) | |
| *DNMT3A*/n (%) | | | 0.463§ | | | 0.807§ |
| Mutation | 11 (23.8) | 12 (31.0) | | 11 (26.2) | 12 (28.6) | |
| Wild type | 31 (76.2) | 30 (69.0) | | 31 (73.8) | 30 (71.4) | |
| *IDH1*/*IDH2*/n (%) | | | 0.154§ | | | 0.046§ |
| Mutation | 5 (11.9) | 10 (23.8) | | 4 (9.5) | 11 (26.2) | |
| Wild type | 37 (88.1) | 32 (76.2) | | 38 (90.5) | 31 (73.8) | |
| *RUNX1*/n (%) | | | 0.457§ | | | 0.457§ |
| Mutation | 3 (7.1) | 5 (11.9) | | 3 (7.1) | 5 (11.9) | |
| Wild type | 39 (92.9) | 37 (88.1) | | 39 (92.9) | 37 (88.1) | |
| *NRAS*/*KRAS*/n (%) | | | 0.061§ | | | 0.061§ |
| Mutation | 9 (21.4) | 3 (7.1) | | 9 (21.4) | 3 (7.1) | |
| Wild type | 33 (78.6) | 39 (92.9) | | 33 (78.6) | 39 (92.9) | |
| *TET2*/n (%) | | | 0.106§ | | | 0.106§ |
| Mutation | 3 (7.1) | 8 (19.0) | | 3 (7.1) | 8 (19.0) | |
| Wild type | 39 (92.9) | 34 (81.0) | | 39 (92.9) | 34 (81.0) | |
| *TP53*/n (%) | | | 0.061§ | | | 0.002§ |
| Mutation | 3 (7.1) | 9 (21.4) | | 11 (26.2) | 1 (2.4) | |
| Wild type | 39 (92.9) | 33 (78.6) | | 31 (73.8) | 41 (97.6) | |
| *TTN*/n (%) | | | 1.000§ | | | 0.306§ |
| Mutation | 2 (4.8) | 2 (4.8) | | 3 (7.1) | 1 (2.4) | |
| Wild type | 40 (95.2) | 40 (95.2) | | 39 (92.9) | 41 (97.6) | |
| *MT.CO2*/n (%) | | | 0.167§ | | | 0.645§ |
| Mutation | 1 (2.4) | 4 (9.5) | | 3 (7.1) | 2 (4.8) | |
| Wild type | 41 (97.6) | 38 (90.5) | | 39 (92.9) | 40 (95.2) | |
| *CEBPA*/n (%) | | | 0.557§ | | | 0.557§ |
| Mutation | 1 (2.4) | 2 (4.8) | | 1 (2.4) | 2 (4.8) | |
| Wild type | 41 (97.6) | 40 (95.2) | | 41 (97.6) | 40 (95.2) | |

WBC, white blood cell; BM, bone marrow; PB, peripheral blood; FAB, French American British. *, denotes Mann-Whitney U test; §, denotes Chi-square test.

 

**Table 3** Multivariate analysis of EFS and OS

| Variables | EFS | | OS | |
|---|---|---|---|---|
| | HR (95% CI) | P | HR (95% CI) | P |
| *PANK2* (high *vs.* low) | 0.729 (0.421–1.262) | 0.259 | 0.756 (0.430–1.328) | 0.331 |
| *PANK4* (high *vs.* low) | 1.727 (1.005–2.965) | 0.048 | 1.824 (1.034–3.215) | 0.038 |
| Age (≥60 *vs.* <60 years) | 4.169 (2.060–8.437) | 0.000 | 3.420 (1.718–6.805) | 0.000 |
| WBC (≥15 *vs.* <15×$10^9$/L) | 1.141 (0.654–1.989) | 0.642 | 1.146 (0.645–2.034) | 0.643 |
| BM blasts (≥70% *vs.* <70%) | 1.745 (0.986–3.087) | 0.056 | 1.708 (0.967–3.017) | 0.065 |
| PB blasts (≥70% *vs.* <70%) | 2.268 (1.076–4.781) | 0.031 | 1.602 (0.744–3.452) | 0.229 |
| *FLT3-ITD* (positive *vs.* negative) | 1.128 (0.589–2.160) | 0.717 | 0.955 (0.481–1.899) | 0.897 |
| *NPM1* (mutated *vs.* wild) | 0.936 (0.491–1.786) | 0.841 | 0.848 (0.442–1.628) | 0.621 |
| *DNMT3A* (mutated *vs.* wild) | 1.555 (0.878–2.753) | 0.130 | 1.627 (0.941–2.811) | 0.081 |
| *TP53* (mutated *vs.* wild) | 2.392 (1.082–5.288) | 0.031 | 2.020 (0.914–4.464) | 0.082 |

EFS, event-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; WBC, white blood cell; BM, bone marrow; PB, peripheral blood.

survival of patients.

In addition to the above findings, in multivariate analysis, we also found that age ≥60 years, PB blasts ≥70% and *TP53* mutation had adverse effects on EFS and OS, consistent with the facts that elderly AML patients usually had adverse prognosis due to higher mutation frequency, poorer baseline performance status and more comorbidities (22), and the well-established knowledge that *TP53* mutation conferred adverse prognosis in complex karyotype AML (16). In studies of childhood acute lymphoblastic leukemia, PB blast percentage is an adverse prognostic factor, yet this role has not been well-recognized in AML (23).

## Conclusions

In summary, our study revealed that high expressions of *PANK2* was associated with better survival, but *PANK4* was an independent poor prognostic factor, in AML patients who only received chemotherapy. Due to the limitation of sample size, our study would require further verification by large prospective cohorts.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* Informed consents were obtained from all patients, and the study protocol was approved by the Human Research Council of University of Washington.

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## Supplementary

**Table S1** Univariate analysis of EFS and OS

| Variables | EFS | | OS | |
|---|---|---|---|---|
| | HR (95% CI) | P | HR (95% CI) | P |
| *PANK2* (high *vs.* low) | 0.526 (0.317–0.846) | 0.008 | 0.560 (0.348–0.904) | 0.018 |
| *PANK4* (high *vs.* low) | 1.726 (1.071–2.779) | 0.025 | 1.804 (1.114–2.922) | 0.017 |
| Age (≥60 *vs.* <60 years) | 3.146 (1.748–5.663) | 0.000 | 3.151 (1.731–5.738) | 0.000 |
| WBC (≥15 *vs.* <15×$10^9$/L) | 1.123 (0.704–1.792) | 0.625 | 1.102 (0.689–1.762) | 0.685 |
| BM blasts (≥70% *vs.* <70%) | 1.525 (0.859–2.706) | 0.150 | 1.742 (1.071–2.835) | 0.025 |
| PB blasts (≥70% *vs.* <70%) | 1.880 (1.158–3.052) | 0.011 | 1.237 (0.687–2.227) | 0.479 |
| *FLT3-ITD* (positive *vs.* negative) | 1.136 (0.621–2.077) | 0.679 | 1.095 (0.599–2.003) | 0.768 |
| *NPM1* (mutated *vs.* wild) | 1.311 (0.799–2.149) | 0.284 | 1.163 (0.704–1.920) | 0.556 |
| *DNMT3A* (mutated *vs.* wild) | 1.747 (1.049–2.911) | 0.032 | 1.676 (1.001–2.806) | 0.050 |
| *NRAS*/*KRAS* (mutated *vs.* wild) | 1.042 (0.533–2.038) | 0.904 | 1.087 (0.555–2.127) | 0.808 |
| IDH1/*IDH2* (mutated *vs.* wild) | 0.994 (0.552–1.787) | 0.983 | 0.951 (0.519–1.741) | 0.870 |
| *TET2* (mutated *vs.* wild) | 0.835 (0.414–1.682) | 0.613 | 0.742 (0.368–1.499) | 0.406 |
| *TP53* (mutated *vs.* wild) | 3.203 (1.658–6.184) | 0.001 | 3.166 (1.644–6.099) | 0.001 |
| *RUNX1* (mutated *vs.* wild) | 1.478 (0.704–3.102) | 0.302 | 1.619 (0.770–3.405) | 0.204 |

EFS, event-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; WBC, white blood cell; BM, bone marrow; PB, peripheral blood.