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The prevalence, risk factors, and prognostic value of anxiety and depression in refractory or relapsed acute myeloid leukemia patients of North China

Mianmian Gu, MS[a,*], Xiaohong Hao, MM[b], Lin Cong, PhD[c], Jie Sun, MM[d]

Abstract

This study aimed at investigating the prevalence of anxiety and depression, and their risk factors as well as their correlation with prognosis in refractory or relapsed (R/R) acute myeloid leukemia (AML) patients.

A total of 180 R/R AML patients were enrolled and their anxiety and depression were assessed by Hospital Anxiety and Depression Scale (HADS) before treatment. Besides, HADS was also evaluated in 180 de novo AML patients prior treatment and 180 healthy controls (HCs), respectively.

Both the HADS-Anxiety and HADS-Depression scores were increased in R/R AML patients compared with de novo AML patients and HCs (all $P < .001$). Meanwhile, the prevalence of anxiety and depression was 53.9% and 45.6% in R/R AML patients, which were also greatly higher compared with de novo AML patients and HCs (all $P < .01$). Regarding risk factors, higher Eastern Cooperative Oncology Group score and lines of salvage therapy were correlated with anxiety and depression in R/R AML patients (all $P < .05$). Furthermore, anxiety and depression were associated with shorter overall survival (OS) in R/R AML patients (all $P < .05$), while no association of different degrees of anxiety and depression with OS was observed (all $P > .05$).

Anxiety and depression are highly prevalent and implicated in the management and prognosis of R/R AML.

Abbreviations: AML = acute myeloid leukemia, ANOVA = one-way analysis of variance, BM = bone marrow, CR = complete remission, ECOG = Eastern Cooperative Oncology Group, HADS = Hospital Anxiety and Depression Scale, HADS-A = HADS-Anxiety, HADS-D = HADS-Depression, HCs = healthy controls, HL = Hodgkin lymphoma, NCCN = National Comprehensive Cancer Network, OS = overall survival, R/R AML = refractory or relapse AML, SD = standard deviation, WHO = World Health Organization.

Keywords: acute myeloid leukemia, anxiety, depression, prognosis, refractory or relapsed

1. Introduction

Acute myeloid leukemia (AML), a rapidly progressing hematological malignancy, is characterized by the abnormal proliferation of myeloid progenitor cells that interferes with normal hematopoiesis.[1–4] Approximately 50% of AML patients present disease recurrence after transient remission, and nearly 25% of AML patients fail to achieve remission after AML treatment, these patients were identified as refractory or relapse (R/R) AML.[1,5]

Despite of the development of new potential therapies over the past years, the prognosis of R/R AML patients remains poor with a 3-year overall survival (OS) at no more than 10%.[6–8] Besides, R/R AML treatments, such as intensive chemotherapy and bone marrow transplantation, are aggressive and correlated with severe adverse events, long hospitalization and high costs, which leads to a marked deterioration of quality of life and psychological problems such as fear of death, social isolation, increased anxiety and depression in R/R AML patients.[9,10] Therefore, it is essential to closely monitor the psychological disorders especially anxiety and depression in R/R AML patients.

Existing studies illuminate that patient-related factors, disease- and treatment-related variables, and factors related to the patient's environment are associated with risk of anxiety and depression in patients with hematological malignancies.[11,12] However, information on risk factors for anxiety and depression is lacking in R/R AML patients. Besides, it is reported that anxiety and depression are associated with poor prognosis in patients with hematological malignancies.[13–15] For example, 1 study displays that anxiety and depression are predictive for poor survival in patients with hematological malignancies [including Hodgkin lymphoma (HL), AML and others].[14] Another study elucidates that the depressed mood prior to bone marrow transplantation in patients with acute leukemia is associated with decreased survival after transplantation.[15] Little attention has been directed towards the role of anxiety and depression in the prognosis of R/R AML patients currently. Considering the poor

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disease outcome, short survival in R/R AML patients and the effect of anxiety/depression on prognosis in hematological malignancies, it would be of value to investigate the risk factors for anxiety and depression as well as the role of anxiety and depression in the prognosis of R/R AML, which may offer insights into improving their quality of life and survival.

Therefore, this study aimed at investigating the prevalence and risk factors of anxiety and depression as well as their correlation with prognosis in R/R AML patients.

2. Methods

2.1. Subjects

From March 2015 to February 2019, 180 R/R AML patients admitted to our hospital were consecutively enrolled in this study. The inclusion criteria were:

1. had a diagnosis of AML according to the 2008 World Health Organization (WHO) classification criteria;[16]
2. confirmed relapsed or refractory disease, and the relapsed AML following a complete remission (CR) was defined as reappearance of blasts in the blood or the finding of more than 5% blasts in the bone marrow or development of extramedullary disease;[17] the refractory AML was defined as failing to respond to 1 or 2 cycles of induction treatment;[18]
3. age more than 18 years old;
4. able to understand the study contents and fulfill the Hospital Anxiety and Depression Scale (HADS) independently.

Patients were excluded if they had history of psychiatric disorders before establishing diagnosis of AML or were unable to be regularly followed up (which was evaluated by the investigators) or were pregnant or breast-feeding women. Besides, the current study also recruited 180 de novo AML patients and 180 healthy controls (HCs) from our hospital during the same period, which were served as controls in the analysis of anxiety and depression prevalence. All *de novo* AML patients had a diagnosis of AML in accordance with WHO classification criteria,[16] with age above 18 years old, without other malignancies. All HCs had healthy status confirmed by physical examination. Both de novo AML patients and HCs were required to have ability to independently complete the HADS assessment.

2.2. Ethics approval

The approval for performing the study was obtained from the Institutional Review Board of Yantai YEDA Hospital and Yan Taishan Hospital, and the written informed consents were collected from all enrolled subjects before enrollment.

2.3. Baseline data collection

After the completion of enrollment, baseline characteristics of R/R AML patients were documented, such as age, gender, disease status (relapsed, refractory or secondary disease), risk stratification [assessed according to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology of AML (Version 2.2014)], Eastern Cooperative Oncology Group (ECOG) score, proportion of bone marrow (BM) blast at diagnosis, remission status at first induction, previous Allo-HSCT status, and lines of salvage therapy.

2.4. Anxiety and depression assessment

After enrollment, researchers provided all enrolled subjects with guidance on how to fill out the HADS; then subjects were required to independently fulfill the HADS for assessment of anxiety and depression. HADS was originally developed as a psychometric instrument to identify depression and generalized anxiety in medical patients, which comprised of 2 subscales: HADS-Anxiety (HADS-A) subscale and HADS-Depression (HADS-D) subscale. Both the HADS-A subscale and the HADS-D subscale consisted of 7 items which were scored from 0 to 3 points individually, resulting in 0 to 21 points totally, and the severity of anxiety and depression were categorized as follows: 0 to 7, no anxiety/depression; 8 to 10, mild anxiety/depression; 11 to 14, moderate anxiety/depression; 15 to 21, severe anxiety/depression.[19]

2.5. Treatment and follow-up

According to the clinical status, all R/R AML patients received appropriate salvage treatments, including

1. FLAG regimen [fludarabine 30 mg/m^2/d (days 1–5), cytarabine 1–2 g/m^2/d (days 1–5), and G-CSF 300 μg/m^2/d (days 0–5), with or without idarubicin 10 mg/m^2/d for 3 days],
2. CAG/DAG regimen [CAG: aclarubicin 20 mg/d (days 1–4), cytarabine 15–20 mg/m^2/12 hours (days 1–14), and G-CSF 150 μg/m^2/12 hours (days 1–14); DAG: daunorubicin 40 mg/m^2/d (days 1–3), cytarabine 15–20 mg/m^2/12 hours (days 1–7 or days 1–10), G-CSF 300 μg/d (days 1–7 or days 1–10), with or without decitabine 20 mg/m^2/d for 3 days],
3. CLAG regimen [cladribine 5 mg/m^2/d (days 1–5), cytarabine 1–2 g/m^2/d (days 1–5) and G-CSF 300 μg/m^2/d (days 0–5), with or without mitoxantrone 10 mg/m^2/d (days 1–3)],
4. MEA regimen [mitoxantrone 10 mg/m^2/day (days 1–5), etoposide 100 mg/m^2/day (days 1–5), cytarabine 100–150 mg/m^2/d (days 1–7)],
5. IA/DA/MA regimen [IA: idarubicin 8–18 mg/m^2/d (days 1–3), cytarabine 100 mg/m^2/d (days 1–7); DA: daunorubicin 45–60 mg/m^2/d (days 1–3), cytarabine 100 mg/m^2/d (days 1–7); MA: mitoxantrone 8 mg/m^2/d (days 1–3), cytarabine 100 mg/m^2/d (days 1–7)],
6. HAA/HAD regimen [HAA: homoharringtonine 2 mg/m^2/d (days 1–7), cytarabine 100–200 mg/m^2 (days 1–7) and aclarubicin 20 mg/m^2/d (days 1–7); HAD: homoharringtonine 2 mg/m^2/d (days 1–7), cytarabine 100–200 mg/m^2 (days 1–7) and daunorubicin 40 mg/m^2/d (days 1–7)].

In addition, all R/R AML patients were followed up regularly by clinic visit, hospitalization or telephone, and the last follow-up date was 2019/2/28. OS was defined as the time from the date of entry into the study to the date of death; patients not known to have died at last follow-up were censored on the date they were last known to be alive.

2.6. Statistical analysis

All statistical analyses were performed using SPSS 24.0 statistical software (IBM, Chicago, IL, USA), and all figures were plotted using GraphPad Prism 7.00 software (GraphPad Software Inc, San Diego, California, USA). Continuous variables were presented as mean ± standard deviation (SD), and categorical variables were presented as count (percentage). Comparisons of

HADS-A score or HADS-D score among groups were determined by one-way analysis of variance (ANOVA) followed by the Bonferroni *t* test. Comparisons of anxiety or depression prevalence between groups were determined by Chi-Squared test. Comparisons of anxiety or depression severity between groups were determined by Wilcoxon rank sum test. Correlation of anxiety or depression with clinical characteristics was determined by Chi-Squared test or Wilcoxon rank sum test. OS was displayed with Kaplan–Meier curve. The difference of OS in subgroups was determined by log-rank test. *P* value < .05 was considered significant.

3. Results

3.1. Characteristics of R/R AML patients

In R/R AML patients, the mean age was 51.5 ± 17.4 years, and there were 79 (43.9%) females as well as 101 (56.1%) males. Besides, there were 112 (62.2%) relapsed AML patients, 68 (37.8%) refractory AML patients. And there were 45 (25.0%) secondary AML patients. In respect of risk stratification, 18 (10.0%), 89 (49.5%), 67 (37.2%), and 6 (3.3%) R/R AML patients were with better risk, intermediate risk, poor risk, and undefined risk, respectively. Regarding performance status, 52 (28.9%), 110 (61.1%), and 18 (10.0%) of R/R AML patients were with ECOG score 0, 1, and 2, respectively. As for lines of salvage therapy, 135 (75.0%) R/R AML patients received first salvage therapy and 45 (25.0%) R/R AML patients received second or higher salvage therapy. Other detailed characteristics were shown in Table 1.

Table 1

Characteristics of R/R AML patients.

Items	R/R AML patients (N = 180)
Age (years), mean ± SD	51.5 ± 17.4
Gender, No. (%)	
Female	79 (43.9)
Male	101 (56.1)
Relapsed AML, No. (%)	112 (62.2)
Refractory AML, No. (%)	68 (37.8)
Secondary AML, No. (%)	45 (25.0)
Risk stratification, No. (%)	
Better	18 (10.0)
Intermediate	89 (49.5)
Poor	67 (37.2)
Undefined	6 (3.3)
ECOG score, No. (%)	
0	52 (28.9)
1	110 (61.1)
2	18 (10.0)
BM blast at diagnosis (%), mean ± SD	44.9 ± 21.7
CR at first induction, No. (%)	81 (45.0)
Previous allo-HSCT, No. (%)	34 (18.9)
Lines of salvage therapy, No. (%)	
First salvage therapy	135 (75.0)
Second or higher salvage therapy	45 (25.0)
Salvage chemotherapy regimens, No. (%)	
FLAG	58 (32.2)
CAG/DAG	39 (21.7)
CLAG	36 (20.0)
MEA	20 (11.1)
IA/DA/MA	17 (9.4)
HAA/HAD	10 (5.6)

allo-HSCT = allo-hematopoietic stem cell transplantation, BM = bone marrow, CAG/DAG = aclarubicin, cytarabine and granulocyte colony-stimulating factor or daunorubicin, cytarabine and granulocyte colony-stimulating factor, CLAG = cladribine, cytarabine, and granulocyte colony-stimulating factor, CR = complete response, ECOG = Eastern Cooperative Oncology Group, FLAG = fludarabine, cytarabine and granulocyte colony-stimulating factor, HAA/HAD = homoharringtonine, cytarabine and aclarubicin or homoharringtonine, cytarabine and daunorubicin., IA/DA/MA = idarubicin and cytarabine or daunorubicin and cytarabine or mitoxantrone and cytarabine, MEA = mitoxantrone, etoposide and cytarabine, R/R AML = relapsed or refractory acute myeloid leukemia, SD = standard deviation.

3.2. Prevalence and severity of anxiety in R/R, de novo AML patients and HCs

R/R AML patients (9.1 ± 4.0) (N = 180) were with higher HADS-A score than that in de novo AML patients (7.5 ± 3.4) (N = 180) (*P* < .001), and HCs (4.6 ± 2.5) (N = 180) (*P* < .001) (Fig. 1A). And the prevalence of anxiety was increased in R/R AML patients (53.9%) compared with de novo AML patients (40.0%) (*P* = .008) and HCs (11.7%) (*P* < .001) as well (Fig. 1B). Regarding anxiety severity, it was elevated in R/R AML patients compared with HCs (*P* < .001), while no difference was observed between R/R AML patients and de novo AML patients (*P* = .081) (Fig. 1C). These data implied that R/R AML patients had higher prevalence of anxiety than that in de novo AML patients and HCs.

3.3. Prevalence and severity of depression in R/R, de novo AML patients, and HCs

HADS-D score was raised in R/R AML patients (8.0 ± 3.7) (N = 180) compared with de novo AML patients (6.7 ± 3.0) (N = 180) (*P* < .001) and HCs (4.2 ± 2.5) (N = 180) (*P* < .001) (Fig. 2A). And the prevalence of depression was also higher in R/R AML

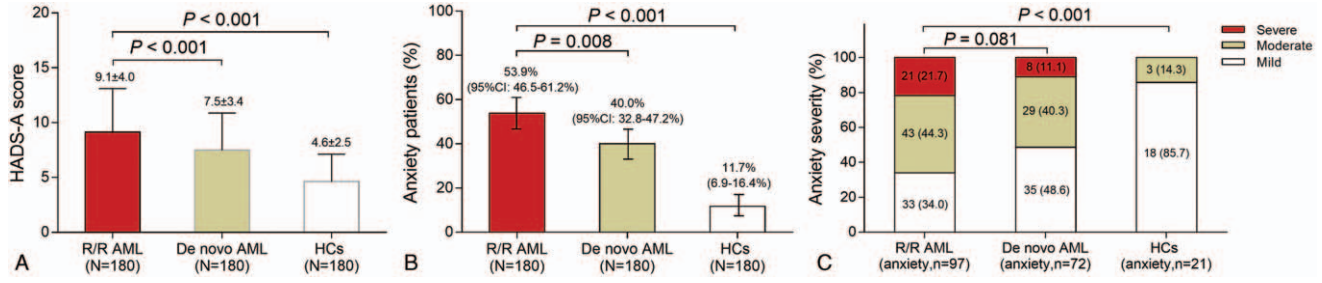

Figure 1. Comparison of anxiety prevalence and severity. Comparisons of HADS-A score (A), anxiety prevalence (B), and anxiety severity (C) among R/R, de novo AML patients and HCs. Comparison of HADS-A score among these 3 groups was determined by ANOVA followed by the Bonferroni *t* test and data were presented as the means ± SD; comparison of anxiety prevalence was assessed by Chi-Squared test and data were presented as the percentage and 95%CI; comparison of severity was conducted by Wilcoxon rank sum test. *P* < .05 was considered significant. AML = acute myeloid leukemia, ANOVA = analysis of variance, CI = confidence interval, HADS-A = Hospital Anxiety and Depression Scale-Anxiety, HCs = healthy controls, R/R = relapsed or refractory, SD = standard deviation.

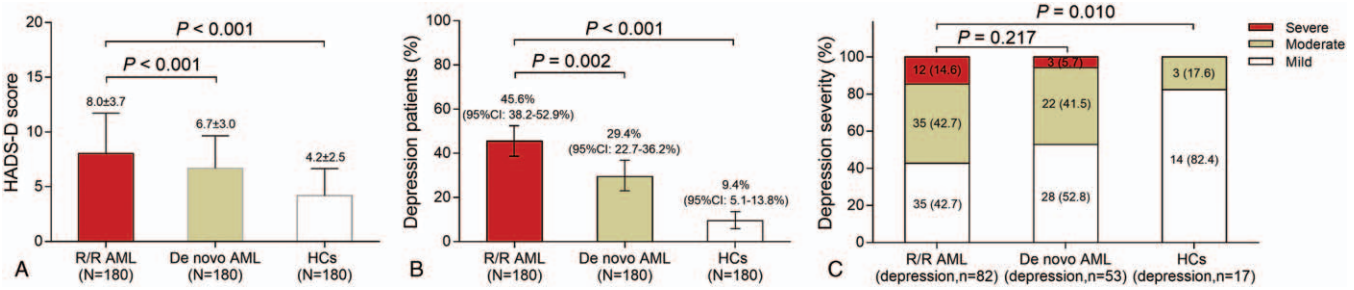

Figure 2. Comparisons of depression prevalence and severity. Comparisons of HADS-D score (A), depression prevalence (B), and depression severity (C) among R/R AML, de novo AML patients and HCs. Comparison of HADS-D score among these 3 groups was assessed by ANOVA followed by the Bonferroni *t* test and data were presented as the means ± SD; comparison of depression prevalence was evaluated by Chi-Squared test and data were presented as the percentage and 95%CI; comparison of severity was performed by Wilcoxon rank sum test. $P < .05$ was considered significant. AML = acute myeloid leukemia, ANOVA = analysis of variance, CI = confidence interval, HADS-D = Hospital Anxiety and Depression Scale-Depression, HCs = healthy controls, R/R = relapsed or refractory, SD = standard deviation.

patients (45.6%) than that in de novo AML patients (29.4%) ($P = .002$) and HCs (9.4%) ($P < .001$) (Fig. 2B). In respect of depression severity, it was increased in R/R AML patients compared with HCs ($P = .010$), while it was of no difference between R/R and de novo AML patients ($P = .217$) (Fig. 2C). These data implied that R/R AML patients had higher prevalence of depression than that in de novo AML patients and HCs.

3.4. Association of anxiety with clinical characteristics in R/R AML patients

Higher ECOG score ($P = .003$) and lines of salvage therapy ($P = .020$) were associated with anxiety in R/R AML patients (Table 2). While there was no association of age ($P = .263$), gender ($P = .053$), disease status ($P = .913$), secondary AML ($P = .262$), risk stratification ($P = .524$), BM blast at diagnosis ($P = .067$), CR at first induction ($P = .845$), previous allo-HSCT ($P = .902$) or salvage chemotherapy regimens (all $P > .05$) with anxiety in R/R AML patients. These data suggested that higher ECOG score and lines of salvage therapy were associated with the anxiety in R/R AML patients.

3.5. Association of depression with clinical characteristics in R/R AML patients

Higher ECOG score ($P = .002$) and lines of salvage therapy ($P = .025$) were associated with depression in R/R AML patients (Table 3). While no association of age ($P = .263$), gender ($P = .131$), disease status ($P = .351$), secondary AML ($P = .863$), risk stratification ($P = .379$), BM blast at diagnosis ($P = .191$), CR at first induction ($P = .383$), previous allo-HSCT ($P = .569$), or salvage chemotherapy regimens (all $P > .05$) with depression was observed in R/R AML patients. These data indicated that higher ECOG score and lines of salvage therapy were associated with the depression in R/R AML patients.

3.6. Correlation of anxiety with treatment response in R/R AML patients

No difference of CR ($P = .434$) or ORR ($P = .810$) was observed between anxiety R/R AML patients and non-anxiety R/R AML patients (Fig. 3). These indicated that anxiety was not correlated with CR and ORR in R/R AML patients.

Table 2

Correlation of anxiety with clinical characteristics.

Items	Anxiety	Non-anxiety	*P* value
Age, No. (%)			.263
<60 years	48 (50.0)	48 (50.0)	
≥60 years	49 (58.3)	35 (41.7)	
Gender, No. (%)			.053
Female	49 (62.0)	30 (38.0)	
Male	48 (47.5)	53 (52.5)	
Disease status, No. (%)			.913
Relapsed AML	60 (53.6)	52 (46.4)	
Refractory AML	37 (54.4)	31 (45.6)	
Secondary AML, No. (%)			.262
No	76 (56.3)	59 (43.7)	
Yes	21 (46.7)	24 (53.3)	
Risk stratification, No. (%)			.524
Better	7 (38.9)	11 (61.1)	
Intermediate	48 (53.9)	41 (46.1)	
Poor	38 (56.7)	29 (43.3)	
Undefined	4 (66.7)	2 (33.3)	
ECOG score, No. (%)			.003
0	21 (40.4)	31 (59.6)	
1	61 (55.5)	49 (44.5)	
2	15 (83.3)	3 (16.7)	
BM blast at diagnosis, No. (%)			.067
<42.0%	53 (60.9)	34 (39.1)	
≥42.0%	44 (47.3)	49 (52.7)	
CR at first induction, No. (%)			.845
No	54 (54.5)	45 (45.5)	
Yes	43 (53.1)	38 (46.9)	
Previous allo-HSCT, No. (%)			.902
No	79 (54.1)	67 (45.9)	
Yes	18 (52.9)	16 (47.1)	
Lines of salvage therapy, No. (%)			.020
First salvage therapy	66 (48.9)	69 (51.1)	
Second or higher salvage therapy	31 (68.9)	14 (31.1)	
Salvage chemotherapy regimens, No. (%)			
FLAG	29 (50.0)	29 (50.0)	.470
CAG/DAG	22 (56.4)	17 (43.6)	.721
CLAG	18 (50.0)	18 (50.0)	.601
MEA	11 (55.0)	9 (45.0)	.916
IA/DA/MA	10 (58.8)	7 (41.2)	.668
HAA/HAD	7 (70.0)	3 (30.0)	.293

Correlation was determined by Chi-Squared test or Wilcoxon rank sum test. allo-HSCT = allo-hematopoietic stem cell transplantation, AML = acute myeloid leukemia, BM = bone marrow, CAG/DAG = aclarubicin, cytarabine and granulocyte colony-stimulating factor or daunorubicin, cytarabine and granulocyte colony-stimulating factor, CLAG = cladribine, cytarabine, and granulocyte colony-stimulating factor, CR = complete response, ECOG = Eastern Cooperative Oncology Group, FLAG = fludarabine, cytarabine and granulocyte colony-stimulating factor, HAA/HAD = homoharringtonine, cytarabine and aclarubicin or homoharringtonine, cytarabine and daunorubicin., IA/DA/MA = idarubicin and cytarabine or daunorubicin and cytarabine or mitoxantrone and cytarabine, MEA = mitoxantrone, etoposide and cytarabine.

Table 3

Correlation of depression with clinical characteristics.

Items	Depression	Non-depression	*P* value
Age, No. (%)			.263
<60 years	40 (41.7)	56 (58.3)	
≥60 years	42 (50.0)	42 (50.0)	
Gender, No. (%)			.131
Female	41 (51.9)	38 (48.1)	
Male	41 (40.6)	60 (59.4)	
Disease status, No. (%)			.351
Relapsed AML	48 (42.9)	64 (57.1)	
Refractory AML	34 (50.0)	34 (50.0)	
Secondary AML, No. (%)			.863
No	61 (45.2)	74 (54.8)	
Yes	21 (46.7)	24 (53.3)	
Risk stratification, No. (%)			.379
Better	6 (33.3)	12 (66.7)	
Intermediate	44 (49.4)	45 (50.6)	
Poor	28 (41.8)	39 (58.2)	
Undefined	4 (66.7)	2 (33.3)	
ECOG score, No. (%)			.002
0	15 (28.8)	37 (71.2)	
1	55 (50.0)	55 (50.0)	
2	12 (66.7)	6 (33.3)	
BM blast at diagnosis, No. (%)			.191
<42.0%	44 (50.6)	43 (49.4)	
≥42.0%	38 (40.9)	55 (59.1)	
CR at first induction, No. (%)			.383
No	48 (48.5)	51 (51.5)	
Yes	34 (42.0)	47 (58.0)	
Previous allo-HSCT, No. (%)			.569
No	68 (46.6)	78 (53.4)	
Yes	14 (41.2)	20 (58.8)	
Lines of salvage therapy, No. (%)			.025
First salvage therapy	55 (40.7)	80 (59.3)	
Second or higher salvage therapy	27 (60.0)	18 (40.0)	
Salvage chemotherapy regimens, No. (%)			
FLAG	26 (44.8)	32 (55.2)	.892
CAG/DAG	21 (53.8)	18 (46.2)	.240
CLAG	12 (33.3)	24 (66.7)	.100
MEA	8 (40.0)	12 (60.0)	.597
IA/DA/MA	9 (52.9)	8 (47.1)	.521
HAA/HAD	6 (60.0)	4 (40.0)	.345

Correlation was determined by Chi-Squared test or Wilcoxon rank sum test. allo-HSCT = allo-hematopoietic stem cell transplantation, AML = acute myeloid leukemia, BMvbone marrow, CAG/DAG = aclarubicin, cytarabine and granulocyte colony-stimulating factor or daunorubicin, cytarabine and granulocyte colony-stimulating factor, CLAG = cladribine, cytarabine, and granulocyte colony-stimulating factor, CR = complete response, ECOG = Eastern Cooperative Oncology Group, FLAG = fludarabine, cytarabine and granulocyte colony-stimulating factor, HAA/HAD = homoharringtonine, cytarabine and aclarubicin or homoharringtonine, cytarabine and daunorubicin., IA/DA/MAvidarubicin and cytarabine or daunorubicin and cytarabine or mitoxantrone and cytarabine, MEA = mitoxantrone, etoposide and cytarabine.

3.7. Correlation of depression with treatment response in R/R AML patients

CR ($P = .578$) or ORR ($P = .484$) was of no difference between depression R/R AML patients and non-depression R/R AML patients (Fig. 4). These implied that depression was not correlated with CR and ORR in R/R AML patients.

3.8. Correlation of anxiety with OS in R/R AML patients

Accumulating OS was decreased in anxiety R/R AML patients compared with non-anxiety R/R AML patients ($P = .019$) (Fig. 5A). While accumulation OS was of no difference among mild, moderate, and severe anxiety R/R AML patients ($P = .230$) (Fig. 5B). These data implied that anxiety was correlated with shorter accumulating OS in R/R AML patients.

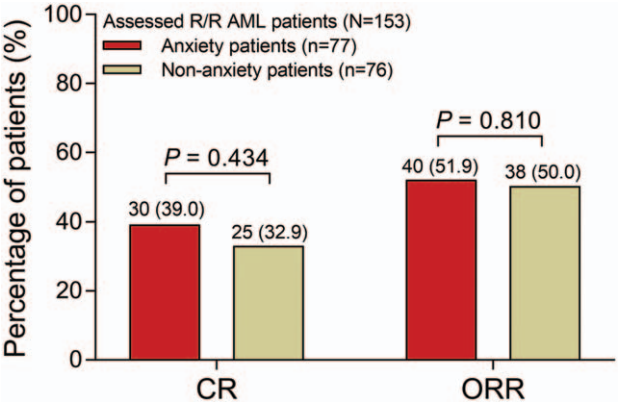

Figure 3. CR and ORR in anxiety R/R AML patients and non-anxiety R/R AML patients. Comparison of CR and ORR between anxiety R/R AML patients and non-anxiety R/R AML patients were assessed by Chi-Squared test. $P < .05$ was considered significant. AML = acute myeloid leukemia, CR = complete response, ORR = objective response rate, R/R = relapsed or refractory.

3.9. Correlation of depression with OS in R/R AML patients

Accumulating OS was lower in depression R/R AML patients than that of non-depression R/R AML patients ($P < .001$) (Fig. 6A). There was no difference of accumulating OS among mild, moderate and severe depression R/R AML patients ($P = .092$) (Fig. 6B). These data indicated that the depression was associated with worse accumulating OS in R/R AML patients.

4. Discussion

In this study, we discovered that:

1. Anxiety and depression prevalence were observed in 53.9% and 45.6% of R/R AML patients, respectively, which were

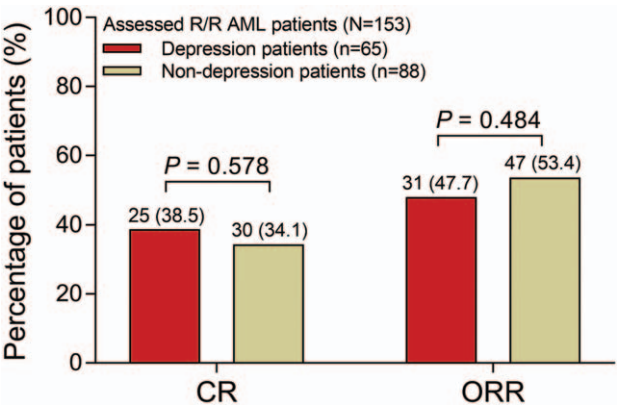

Figure 4. CR and ORR in depression R/R AML patients and non-depression R/R AML patients. Comparison of CR and ORR between depression R/R AML patients and non-depression R/R AML patients was analyzed by Chi-Squared test. $P < .05$ was considered significant. AML = acute myeloid leukemia, CR = complete response, ORR = objective response rate, R/R = relapsed or refractory.

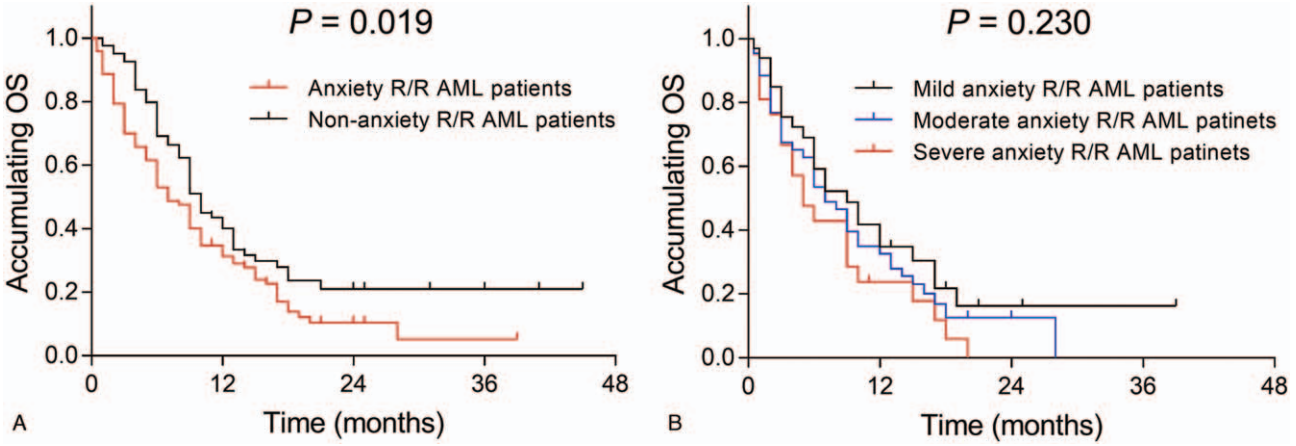

Figure 5. Accumulating OS in anxiety R/R AML patients and non-anxiety R/R AML patients. The accumulating OS in anxiety and non-anxiety R/R AML patients (A). And the accumulating OS in mild anxiety, moderate anxiety, and severe anxiety R/R AML patients (B). OS was displayed with Kaplan–Meier curve, and the difference of OS in subgroups was determined by log-rank test. $P < .05$ was considered significant. OS = overall survival, R/R AML = relapsed or refractory acute myeloid leukemia.

significantly higher than those in de novo AML patients and HCs.
2. Higher ECOG score and lines of salvage therapies correlated with anxiety and depression in R/R AML patients.
3. Anxiety and depression correlated with shorter OS in R/R AML patients.

Considering the symptom burden and financial hardship, patients with hematological malignancies tend to experience psychological stress, phobia, isolation, and anger, which impaired their quality of life.[9,20,21] One study reports that 22.3% and 46.5% of patients with hematological malignancies (including non-Hodgkin lymphoma, AML, and others) presents anxiety and depression, respectively.[22] Another study characterizes that 33.3% and 30.0% of older patients newly diagnosed with AML reports anxiety and depression symptoms, respectively.[23] However, there is no study that investigates the anxiety and depression prevalence in R/R AML patients. Our study displayed that 53.9% and 45.6% of R/R AML patients were with anxiety and depression, respectively, which were significantly higher than those in de novo AML patients and HCs (all $P < .01$). The possible reasons were as follows:

1. The life- threatening nature of R/R AML and the aggressive treatments might evoke the shock, fear, and social isolation; thus, led to an increased risk of anxiety and depression.
2. The key symptoms of R/R AML (including dizziness, fatigue, fever, and weakness) might disrupt patients' daily activities and diminish their ability to maintain social and family roles; thus, resulted in greater risk and severity of anxiety as well as depression in R/R AML patients.

A few studies have illuminated that anxiety and depression were associated with sociodemographic and clinical characteristics in patients of hematological malignancies.[13,22,24] For example, 1 study reveals that tense home atmosphere and the presence of comorbidities is correlated with high prevalence of anxiety and depression in patients with hematological malignancies including

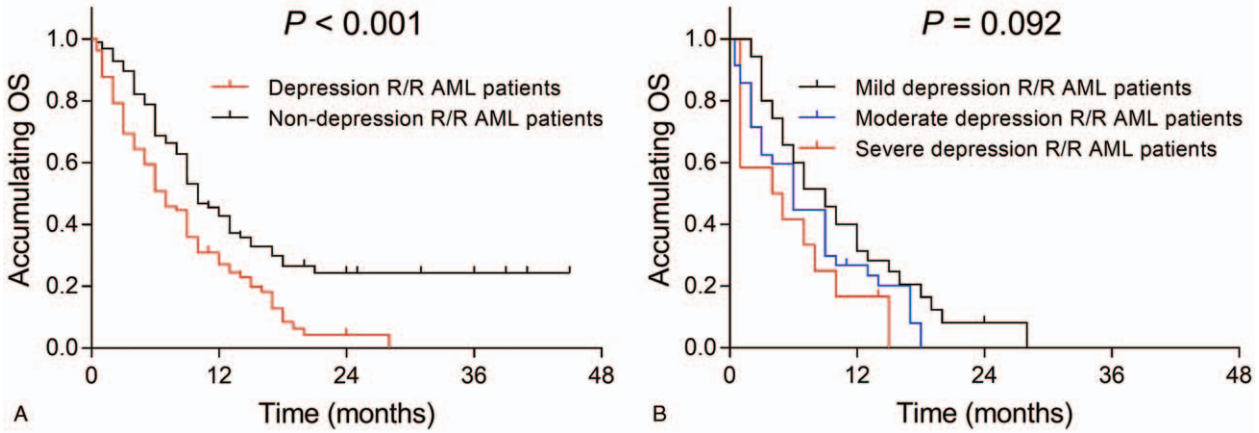

Figure 6. Accumulating OS in R/R AML patients in depression and non-depression R/R AML patients. The accumulating OS in depression and non-depression R/R AML patients (A), and the accumulating OS in mild depression, moderate depression, and severe depression R/R AML patients (B). OS was displayed with Kaplan–Meier curve, and the difference of OS in subgroups was determined by log-rank test. $P < .05$ was considered significant. OS = overall survival, R/R AML = relapsed or refractory acute myeloid leukemia.

HL, AML, multiple myeloma, and so on.[22] Another study exhibits that patients with hematological malignancies (including lymphoma, leukemia, myeloma, and other blood cancers) who relocate for treatment present greater risk of anxiety and/or depression, and former smokers have higher risk of anxiety and/or depression compared with those patients who never smoke.[24] However, little is known regarding the risk factors of anxiety and depression in R/R AML patients. Our study illustrated that higher ECOG score and lines of salvage therapy were associated with anxiety and depression in R/R AML patients. The possible reasons might be:

1. ECOG score reflected the patients' functional status and the ability of patients to tolerant chemotherapy. Thus, R/R AML patients with higher ECOG score exhibited chemotherapy intolerance and poor functional status, resulted in increased disease burden and higher susceptibility to anxiety and depression.
2. Higher lines of salvage therapy were associated with more severe treatment-related adverse events, longer recovery time, and increased disease severity, which put R/R AML patients at greater risk of anxiety and depression.

Evidences reveal that emotional burdens such as anxiety and depression influence the disease progression and prognosis in patients with leukemia.[12,15,25] For example, 1 study identifies that anxiety is correlated with poor post-bone marrow transplant survival in either acute or chronic leukemia patients who received allogeneic bone marrow transplant.[25] Another study characterizes that acute leukemia patients with depression at pretransplant evaluation had poorer survival rates following transplantation compared to patients without depression.[12] However, no study explores the correlation of anxiety and depression with survival in R/R AML patients. Our study reported that anxiety and depression were associated with worse OS in R/R AML patients. These might be explained as follows:

1. R/R AML patients with anxiety and depression were less likely to adhere to preventive screening procedures, prescribed medication regimens or routine clinical visits and thus, resulted in elevated disease severity and unfavorable disease outcome.
2. Anxiety and depression might provoke the production of pro-inflammatory cytokines and activate the hypothalamic-pituitary-adrenocortical axis, which led to the dysregulation of cellular immune response that impaired cellular basis of tumor surveillance and containment[26,27] and thus, resulting in accelerated tumor progression and decreased OS in R/R AML patients.

Limitations to our study must be acknowledged.

1. The recruited R/R AML patients mainly came from North China, which might limit the generalizability of our findings.
2. Only 1 scale (HADS score) was performed to evaluate anxiety and depression, and more anxiety as well as depression assessments needed for validation in the future.
3. The underlying mechanism of anxiety and depression in affecting the survival of R/R AML patients was not identified, thus, further experiments should be carried out in the future.

5. Conclusion

In conclusion, the anxiety and depression are highly prevalent, and correlates with higher ECOG score and lines of salvage therapies, as well as predict unsatisfied OS in R/R AML patients. These findings stress the importance of the early identification of anxiety and depression as well as the implementation of flexible physiological interventions for R/R AML patients in the future clinical practice.

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