ITDpos(group B) and those with DNMT3Awt/FLT3-ITDneg (group A) were statistically significant. The DNMT3Amut/FLT3-ITDpos (group B) had the worst OS (p=0.025) and RFS (p=0.011) compared with other groups revealed a higher relapse incidence rate (p=0.0002) (see Table 4) (Figure.3).

Multivariate analyses for OS, RFS and RI

Multivariate analyses for OS, RFS and RI was performed regarding the CR status (CR1or CR2,3..), the interval from CR1 to transplantation, FLT3-ITD mutation, DNMT3Amut/FLT3-ITDpos and DNMT3Awt/FLT3-ITDpos. The FLT3-ITD mutation (p=0.03, HR=1.84; 95% CI (1.05-3.24) and CR status (p=0.04; HR=1.78; 95% CI (1.02-3.13) were independent factors of inferior survival after Allo-HSCT. Regarding Relapse Incidence (RI), CR status to transplantation (p=0.0049, HR= 2.52;95%CI (1.32-4.8) and FLT3-ITD mutation (P=0.00015, HR= 3.49; 95CI (1.83-6.68) were significant independent prognostic factors for relapse (see Table 5).

Discussion

DNMT3A mutations were recognized as driver gene mutations in adults with AML. The biological mechanisms by which DNMT3A mutations contribute to leukemogenesis is not clear. In the past decade, however, DNMT3A mutations have been attracting much attention as a marker for risk stratification in AML patients[15].

The present study showed that DNMT3A mutations occur in 15.6% (20/128) of patients with AML, predominantly in patients with NPM1 aberration. The dominant mutation in the study population located at the hotspot region R882 is in agreement with previous studies [16,17].

The results of the present study suggest that DNMT3A R882 mutations are not associated with an inferior survival in AML patients after allogeneic HSCT. It could be argued that allogeneic HSCT ameliorates the clinical outcomes of AML patients with DNMT3A R882 mutations. In the present study, no significant difference was found in the OS, RFS and relapse incidence between patients with and without DNMT3A mutations.

Several studies with controversial results have been conducted on the prognostic impact of DNMT3A mutations in AML patients. Some studies revealed a significant difference in the OS between mutated and wild-type DNMT3A patients, with a worse OS in the mutated patients [16,18,19,20].

Metzeler etal. Showed that DNMT3A mutations are on one hand associated with inferior survival in AML patients and on the others it modulates the prognostic impact of mutated NPM1. They also observed no outcome differences between different types of DNMT3A mutations[21].Yuan etal. In a Meta-analysis study on DNMT3A R882 mutations in AML patients consist of eight competent studies with 4474 AML patients including 694 AML patients with DNMT3A R882 mutations verified significant shorter RFS (HR=1.40, 95% CI=1.24–1.59, P<0.001) and OS (HR=1.47, 95% CI=1.17–1.86, P=0.001) in AML patients with DNMT3A R882 mutations[22].

Focusing on the features and effect of DNMT3A R882 mutation in acute myeloid leukemia in the presence or absence of NPM1 and FLT3 mutations, Dushyant K etal. analyzed 174 cytogenetically normal (CN)-AML cases. They noticed DNMT3Amutations in the CN-AML patients were associated with significantly shorter overall survival and progression-free survival compared to NPM1 and FLT3 mutated patients (p = .067 and p = .065, respectively)[23].

However, few studies, as what mentioned in the following, have been conducted to determine the prognostic effect of DNMT3A mutations in AML patients treated with allogeneic HSCT.

Consistent with our results, Xu et al. compared the outcomes of 55 DNMT3A (mut) patients who underwent Allo-HSCT (twenty-three cases) or received chemotherapy (thirty-two cases) as a consolidation. They observed a significant difference in 3-year OS and a 3-year DFS between the Allo-HSCT group and the chemotherapy group. The authors concluded that DNMT3A is a poor prognostic factor for cytogenetic normal-AML (CN-AML) patients and Allo-HSCT improves survival in DNMT3A mutation-positive acute myeloid leukemia patients. The median OS in wild-type DNMT3A patients was greater compared to mutated patients; however, the difference was not statistically significant (p=0.151). No significant difference was seen in DFS between both groups of patients (p=0.304)[24].

Ahn J-S et al. described DNMT3A R882mut and FLT3-ITDpos as both unfavorable prognostic markers for OS and significant risk factors for EFS and relapse. They declared that patients with coexistence of DNMT3A R882 /FLT3-ITDpos had the worse OS, EFS and higher relapse rates compared with other mutations. Indeed, the DNMT3A R882mut/FLT3-ITDpos status was a significant prognostic marker for poor clinical outcome by increasing relapse incidence rates even after HSCT[25].

Tang S et al. verified that DNMT3A R882 mutations confer an inferior survival in AML patients. Their results also indicated that FLT3-ITD and DNMT3A R882 double mutation were independent factors for poor prognosis after Allo-HSCT[26].

Contrary to our results, the Ahn J-S and Tang S findings considered DNMT3A R882 as an unfavorable prognostic marker in AML patients treated with Allo-HSCT. The discrepancy between the results is not clear, but unknown cooperating genetic aberrations may be involved. Several studies have shown that Allo-HSCT cannot abrogate the unfavorable effect of FLT3-ITD in AML patients[27,28]. Therefore in the next step, we analyzed the surveillance factors OS, RFS and RI in FLT3-ITDpos/DNMT3A R882mut AML patients and encountered with the worst condition compared with other groups. These results are in line with the findings of the above-mentioned studies [25, 26].

Our data also highlited that CR status prior to transplantation was more obvious than other risk factors in delineating risk of relapse. The More advanced disease stage (CR 2,3), the more relapse incidence (RI) occurs. From this point of view, our data in accordance with the previous studies [29,30].

The limitations of this research include the followings: firstly, a relatively small sample size was used; secondly, the analysis was limited to exon 23 of the DNMT3A gene and thirdly, there is absence of cytogenetic findings. Hence, the results of this study should be interpreted with caution.

The initial goal of Allo-HSCT is to improve the hematological disorders with minimizing residual disability as much as possible. To achieve this goal the patient should be supported through a conditioning regimen and its associated complications such as GVHD while avoiding relapse. Anti-thymocyte globulin (ATG) can reduce the risk of GVHD, although ATG formulation (dose and type), donor type and other medications that used for GVHD prophylaxis affect the outcome of Allo-HSCT[31]. In the present study in order to prevent a decrease in the number of AML patients the role of ATG and donor source were ignored.

Allo-HSCT is the only pragmatic treatment option for relapsed and/ or refractory AML patients; however, it seems Allo-HSCT cannot override the inferior outcomes conferred by the coexistence of DNMT3Amut/FLT3-ITDpos. Increasing our knowledge of genetic and epigenetic alterations in AML resulted in the emergence of new drugs such as FLT3 inhibitors, CPX-351 and epigenetic modifiers. Indeed, it is necessary to accompany molecularly targeted therapy with Allo-HSCT for poor prognosis of AML patients.

Conclusion

Taken together, according to the results of the present study, DNMT3A R882 mutations seem not to affect the clinical outcomes of AML patients treated with Allo-HSCT. On the other hand, Allo-HSCT probably improves the clinical outcomes of AML patients with DNMT3A R882 mutations. When DNMT3A R882 mutations were accompanied by FLT3-ITD mutations (DNMT3A R882mut/FLT3-ITDpos), the overall survival significantly

reduced even after Allo-HSCT. Indeed, FLT3-ITD is a significant negative prognostic marker compared with the DNMT3A R882 mutation. Further studies are needed to better clarify a rationale for the integration of DNMT3A R882mut/FLT3-ITDpos status in the treatment decision of patients with AML.

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Ethics

Ethics committee approval: This study was approved by the local ethics committee of Iran university of medical sciences (approval number: 1394.26066). Written informed consent was obtained from all patients in agreement with the Declaration of Helsinki.

Authorships contributions

concept: M.T. Ardestani, Sh.Rostami.; Design: M.T. Ardestani, Sh.Rostami, B.Chahardouli, A.Kazemi.; Data collection: M.T. Ardestani, S. Mohammadi, M.Nikbakht, Analysis or interpretation: Sh. Rostami, M. Jalili, M.Vaezi.; Literature Search: M.T. Ardestani, A. Ghavamzadeh, K. Alimoghaddam; Editing and Revising: F. Zaker, B. Toosi.

Conflict of interest disclosures

The authors declare that they have no conflict of interest.

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percent	Number of patients	TYPE	mutation
%8.6	11	missense	R882H
%4.7	6	missense	R882P
%1.5	2	missense	R882C
%0.8	1	missense	Q905R
%2.3	3	synonymous	G884C

Table 1: Frequency of DNMT3A exon 23 mutations in AML patients

Table 2. Clinical characteristic of AML patients according to DNMT3A status.

Clinical characteristic	DNMT3A Mutation	DNMT3A Wild Type	P value
Age,years(median±SD)	39±11	32±12	
Range	21-57	16-67	0.1
Gender			
Male	12	72	0. 4
Female	8	36	
FAB subtypes			
M0/M1/M2/M3/M4/M5/M6/M7	0/3/6/0/5/4/2/0	3/16/38/1/36/12/2/0	0.75
WBC at diagnosis			
Median	6200	13000	0.65
Range	700-151000	240-257000	
PLT at diagnosis			
Median	30500	61000	0.12
Range	6000-712000	6000-340000	
Molecular abnormalities			
NPM1 wild type	11	93	
NPM1 mutation	7	17	0.014*
FLT3-ITD^{neg}	13	79	
FLT3-ITD^{pos}	5	31	0.28
Interval from CR1 to transplantation months			
Median	3.1	4.6	
Range	1-13.4	0.3-35.4	0.2

Donor type			
Matched sibling donor	15	85	
Others	3	25	0.4
A GVHD			
Yes	12	95	
No	6	15	0.07
C GVHD			
Yes	13	93	
No	5	17	0.19

SD: standard deviation, CR: complete remission, WBC:white blood cell, PLT:platelet, GVHD:graft versus host diseases

*p<0.05 is considered significant

Table 3. Clinical characteristic of AML patients according to DNMT3AR882/FLT3-ITD groups

Risk factors	DNMT3A$^+$/FLT3-ITD$^+$(n=8)	DNMT3A$^-$/FLT3-ITD$^+$(n=29)	DNMT3A$^+$/FLT3-ITD$^-$(n=12)	DNMT3A$^-$/FLT3-ITD$^-$(n=79)	P.Value
WBC	11200(3100-152000)	26000(2600-226000)	5400(700-100000)	6700(240-257000)	0.003
CR					
First CR	5	15	11	61	
≥Second CR	3	14	1	18	0.022
Interval from CR1 to HSCT Median(month)					
> median	7	12	7	40	0.13
< median	1	17	5	39	
NPM1 mutation					
Mutated	3	19	9	73	
Wild- type	5	10	3	6	0.008
aGVHD					
No	5	25	8	68	
Yes	3	4	4	11	0.14
cGVHD					
No	6	17	8	65	
Yes	2	12	4	14	0.3

Table 4.Univariate and Multivariate analysis of surveillance factor according to DNMT3AR882/FLT3-ITD groups

Risk factor Status	OS					RFS			
	Univariate		Multivariate			Univariate	Multivariate		
	N(%)	rate at 5 years(%)	P Value	P Value	HR (95%CI)	rate at 5 years(%)	P Value	P Value	HR (95%CI)
DNMT3A$^+$/FLT3-ITD$^+$	8(6.25)	0	0.025*	0.29	2.68(1.10-6.94)	0	0.011*	0.18	2.91(1.20-7.06)
DNMT3A$^+$/FLT3-ITD$^-$	12(9.4)	57±0.15	0.72	0.71	1.2(0.46-3.08)	55±0.15	0.76	0.76	1.16(0.44-2.9)

DNMT3A$^-$/FLT3-ITD$^+$	29(22.6)	38±0.11	0.038*	0.36	1.94(1.03-3.65)	41±0.12	0.037*	0.35	1.97(1.05-3.7)
DNMT3A$^-$/FLT3-ITD$^-$	79(61.75)	62±0.6				63±0.6			

Risk factor Status	**RI**				**NRM**			
	Univariate				**Univariate**			
	N(%)	**rate at 5years(%)**	**P Value**		**rate at 5 years(%)**	**P Value**		
DNMT3A$^+$/FLT3-ITD$^+$	8(6.25)	81.2(9.1-98.2)	0.0002*		-	0.18		
DNMT3A$^+$/FLT3-ITD$^-$	12(9.4)	8.3(0.4-32.6)	0.33		36.1(9.4-64.5)	-		
DNMT3A$^-$/FLT3-ITD$^+$	29(22.6)	52.3(25.5-73.5)	0.003*		6.9(1.2-20.1)	-		
DNMT3A$^-$/FLT3-ITD$^-$	79(61.75)	21.3(12.7-31.3)	-		22.9(9.6-39.7)	-		

, OS: overall surviva, RFS:relapse- free survival , RI: relapse incidence, NRM: non relapse mortality, HR: hazard ratio, CI: confident interval, *p<0.05 is considered significant

Table 5. Univariate and Multivariate analysis of surveillance factor according to risk factor status

Risk factor Status	**OS**					**RFS**			
	Univariate		**Multivariate**			**Univariate**		**Multivariate**	
	N(%)	**rate at 5years(%)**	**P value**	**P Value**	**HR (95%CI)**	**rate at 5years(%)**	**P Value**	**P Value**	**HR (95%CI)**
Age			0.54				0.59		
>34	66(51.6)	53.2±6.9				53.6±6.8			
≤34	62(48.4)	55±6.6				56±6.6			
WBC Count			0.52				0.49		
CR			0.011*	0.04*	1.78(1.02-3.13)		0.007*	0.027*	1.87(1.07-3.27)
First CR	92(71.8)	60.3±5.6				60.9±5.5			
≥Second CR	36(28.2)	38.6±8.5				39.7±8.5			
Interval from CR1 to HSCT Median(months)			0.094*	0.24			0.09		
> median	66(51.6)	61±6.6				62±6.5			
< median	62(48.4)	45.9±6.9				46.7±6.8			
Donor type			0.45				0.5		
HLA identical sibling	100(78.1)	55±5.4				55.9±5.4			
others	28(21.9)	48±10.4				49.8±10.2			
DNMT3Aexon 23			0.29				0.287		
Mutated	20(15.6)	40±12.2				40±11.9			
Wild-type	108(84.4)	56.7±5				57±5			
FLT3-ITD									

mutation			0.015*	0.03*	1.84(1.05-3.24)		0.012*	0.022*	1.97(1.094-3.36)
Positive	37(28.9)	31.6±10.8				34±10.9			
Negative	91(71.1)	60.4±5.4				61.1±5.3			
NPM1 mutation	24(18.75)	58±10	0.83			58.3±10	0.71		
Mutated	104(81.25)	53±5.4				53.9±5.3			
Wild-type									
A GVHD			0.4				0.37		
No	22(17.2)	51.5±5.3				52.1±5.3			
Yes	106(82.8)	68±9.9				68.2±5.4			
C GVHD			0.5				0.484		
No	21(16.4)	55.7±12.7				57.1±12.5			
Yes	92(83.6)	62.5±5.5				63.2±5.4			

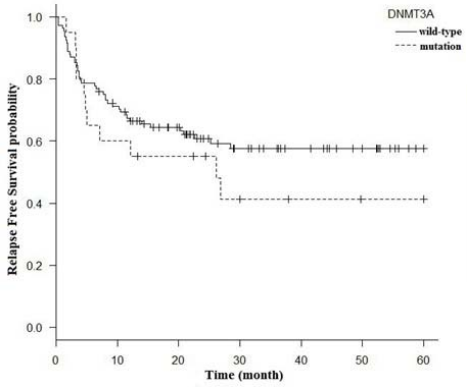
Table5.Continued

Risk Factor Status	**RI**					**NRM**			
Univariate	**Univariate**			**Multivariate**		**Univariate**		**Multivariate**	
	N(%)	**rate at 5years (%)**	**P Value**	**P Value**	**HR (95%CI)**	**rate at 5years (%)**	**P Value**	**P Value**	**HR (95%CI)**
Age									
≥34	66(51.6)	33.8(21.2-46.8)	0.45			13(6-22)	0.59		
<34	62(48.4)	28.1(17.2-40.1)				26(9-46.7)			
CR		23.4(14.6-33.4)	0.001*	0.0049	2.52(1.32-4.8)	21.7(10.3-35.7)	0.48		
First CR	92(71.8)					11.8(3.6-25.5)			
≥Second CR	36(28.2)	29.6(31.5-65.4)							
Interval from CR1 to HSCT Median…month		28.8(17.4-41.2)	0.53			9.5(3.8-18.3) 27.4(12.9-44.2)	0.76		
> median		33.2(21.1-45.8)							
< median	66(51.6) 62(48.4)								
Donor type		31.7(22.1-41.7)	0.7			17.6(8.1-30) 23.2(8.8-41.6)	0.2		
HLA identical sibling	100(78.1)	28.6(12-47.7)							
others	28(21.9)								
DNMT3A exon 23		29.6(20.6-39)	0.5			19.3(8.5-33.4) 21.9(6-43.7)	0.6		
Mutated	20(15.6)	36.9(15.3-58.8)							
Wild-type	108(84.4)								
FLT3-ITD		20.2(12.3-29.5)	0.00003	0.00015*	3.49(1.83-	23.8(12.4-	0.11		

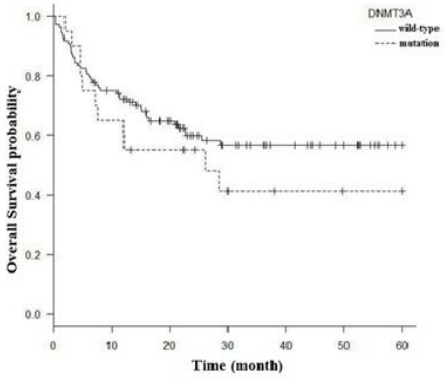
mutation		61.6(37.2-78.8)		6.68)	37.2)			
Positive	37(28.9)				5.4(0.9-			
Negative	91(71.1)				16.1)			
NPM1 mutation		28.4(19.2-38.1)	0.04		24.4(12.2-	0.02		
Mutated	24(18.75)	42(21.8-60.9)			38.8)			
Wild-type	104(81.25)				0			
A GVHD		34.2(24.6-44)	0.12		21.7(8.5-	0.7		
No	22(17.2)	13.6(3.2-31.4)			38.8)			
Yes	106(82.8)				18.2(5.5-			
					36.8)			
C GVHD		30.7(20.9-41)	0.12		12.4(3-28.8)	0.00	0.00	5.23(1.66-
No	21(16.4)	10(1.6-27.8)			30(8.9-55)	9	7*	16.5)
Yes	92(83.6)							

CR: complete remission, WBC:white blood cell, GVHD:graft versus host diseases, OS: overall surviva, RFS:relapse- free survival, RI: relapse incidence, NRM: non relapse mortality, HR: hazard ratio, CI: confident interval, *p<0.05 is considered significant

a)



b)



c)

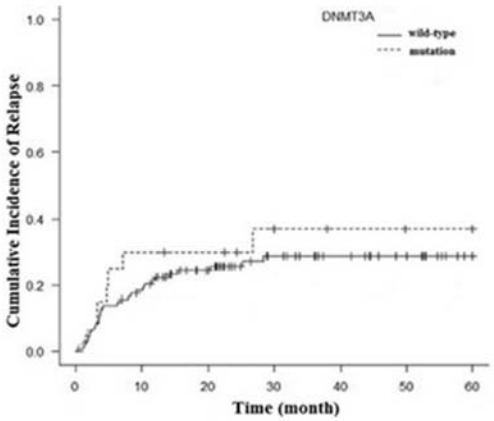
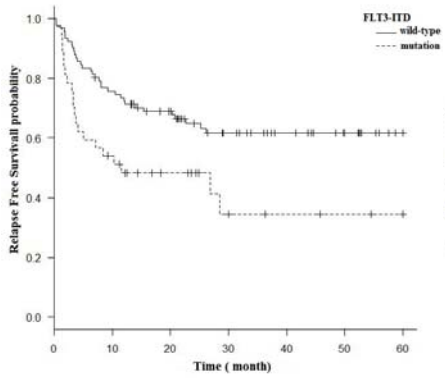
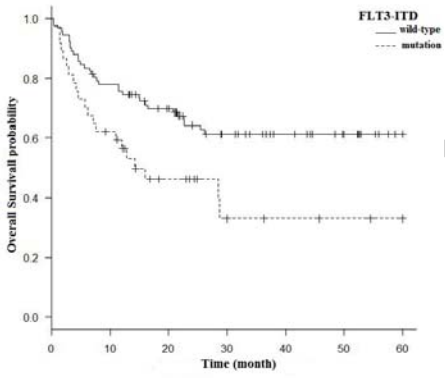


Figure 1. Survival curves of AML patients according to mutational status of DNMT3A (a)Relapse- Free Survival, (b) Overall Survival, (c) Cumulative Incidence of Relapse

a)



b)



c)

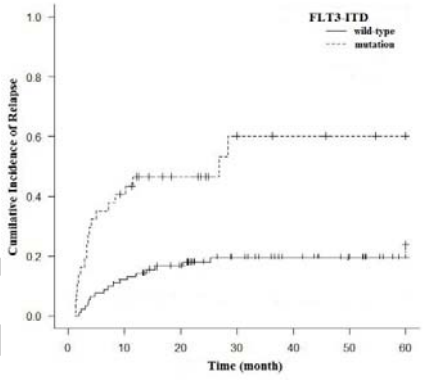
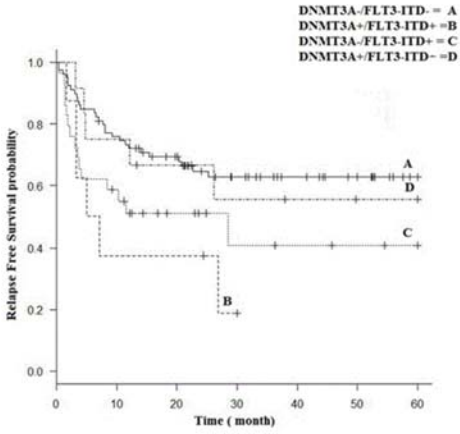
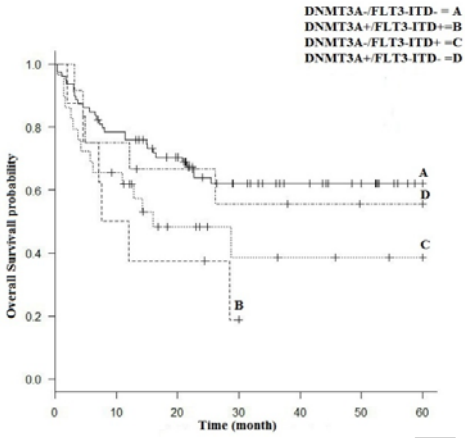


Figure 2. Survival curves of AML patients, according to mutational status of FLT3-ITD (a) Relapse- Free Survival, (b) Overall Survival, (c) Cumulative Incidence of Relapse.

a)



b)



c)

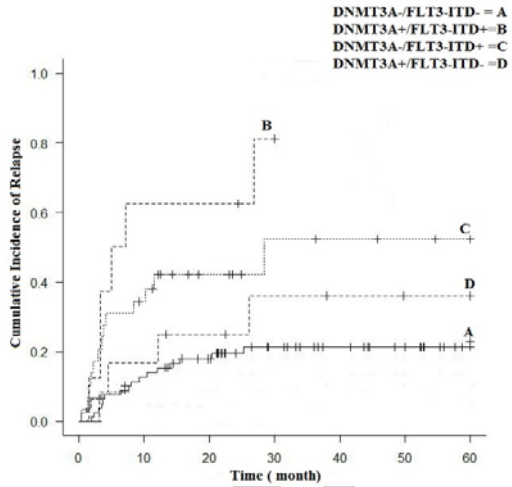


Figure.3: Survival curves of AML patients, according to mutational status of DNMT3A/FLT3-ITD (a) Relapse-Free Survival, (b) Overall Survival, (c) Cumulative Incidence of Relapse