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Research paper

Prognostic significance of MYC oncoprotein expression on survival outcome in patients with acute myeloid leukemia with myelodysplasia related changes (AML-MRC)

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ABSTRACT

MYC is an oncoprotein that coordinates the expression of genes involved in metabolism, cell differentiation and survival in various types of malignancies. However, the underlying oncogenic mechanisms and the clinical significance of MYC expression in the acute myeloid leukemia with myelodysplasia related changes (AML-MRC) remain to be answered. A total of 135 patients were retrospectively identified using Total Cancer Care (TCC) Moffitt Cancer Center (MCC) databases. Diagnosis of AML-MRC was based on the 2016 WHO classification utilizing bone marrow (BM) evaluation. MYC protein expression level was assessed by immunohistochemistry (IHC) staining using paraffin-embedded BM trephine biopsy samples obtained at the time of diagnosis or relapse. Concurrent somatic mutations were assessed using targeted next generation sequencing that include 54 genes. A total of 38% (n = 51) and 62% (n = 84) patients had high and low MYC expression, respectively. The most common somatic mutation in our cohort was *TP53* followed by *DNMT3A,* and *ASXL1*. The median OS was significantly longer in low MYC patients (median OS 42.3 *vs.* 17.05 months, $p = 0.0109$). Multivariate analysis including MYC expression level, transplantation status, gender and age demonstrated high MYC expression (HR 1.77, 95% CI 1.004–3.104, $p = 0.045$) to be an independent poor prognostic factor. Further studies are needed to identify the underlying mechanism of MYC driven oncogenesis in AML-MRC. Additionally, the prognostic impact of MYC on the AML survival in a larger cohort that include diverse somatic mutations and chromosomal abnormalities requires further investigation.

1. Introduction

Acute myeloid leukemia with myelodysplasia related changes (AML-MRC) is a hematopoietic clonal disorder that is characterized by dysplasia, increased myeloblasts and impaired hematopoiesis [1]. AML-MRC patients were shown to have aggressive clinical courses with 5 year overall survival (OS) less than 30% [2,3]. Recent studies demonstrated a complex composition of somatic mutations and cytogenetics that are associated with heterogeneous disease course in the *de novo* and secondary AML patients [4–7]. These somatic mutations and chromosomal abnormalities involve genes that regulate RNA splicing, metabolism, signaling cascades, and epigenetics [4–6]. Among these, acquired *MYC* somatic mutations and gene amplifications are frequently identified in both pediatric and adult AML patients [8–11].

MYC is a well-known oncoprotein that coordinates the expression of genes involved in the metabolism, nutrient transport, and cell proliferation and growth [12,13]. Clinical significance of *MYC* translocation and amplification has been extensively studied in a variety of malignancies including lymphomas [14–16], however, relatively less in AML. Recent preclinical studies have shown that MYC regulates downstream genes that are important for the cell death and differentiation in the AML cells. Further, MYC was shown to be overexpressed and/or required for the myeloid leukemia triggered by FLT3-ITD and PML-RARα, RUNX1-RUNX1T1 and BCR-ABL fusion oncoproteins [17–19].

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Although the underlying oncogenic mechanism of MYC is unclear, a recent study showed that high levels of MYC expression is associated with inferior survival outcomes in *de novo* AML patients [20,21]. Compared to other subtypes of AML, AML-MRC patients were shown to have dynamic range of MYC protein expression [20], yet the clinical significance of MYC expression in these unique patient population is unknown. Our study attempts to explore the prognostic impact of MYC protein levels on the survival outcomes in AML-MRC patients and assess somatic mutational landscapes in low *vs*. high MYC AML-MRC patients.

2. Methods

2.1. Patients and sample acquisition

Using Total Cancer Care (TCC) Moffitt Cancer Center (MCC) databases, we retrospectively identified histologically confirmed AML-MRC patients from 2011 to 2018 (**Figure S1**). The research proposal was approved by institutional research board (IRB). Patient had provided written informed consent to be included in the database. Diagnosis of AML-MRC were based on bone marrow (BM) evaluation and classified based on the 2016 WHO classification of tumors of hematopoietic and lymphoid tissues [22]. We included both *de novo* AML-MRC cases and AML-MRC with preceding MDS or MDS/MPN. Therapy related AML (tAML) cases were not included in the study (**Figure S1**). The BM biopsy samples harvested at the time of AML-MRC diagnosis or at the time of relapse were collected to confirm morphologic and molecular diagnosis as well as for the retrospective immunohistochemistry study to assess expression of MYC protein. Detailed information regarding patient selection process is described in the **Figure S1**. The patients' demographic data, diagnosis, laboratory results including complete blood counts (CBC), cytogenetics, NGS myeloid mutation profile, clinical treatment and overall survival were retrieved and summarized in Table 1.

2.2. Assessment of MYC protein expression

MYC protein expression was assessed by immunohistochemistry (IHC) staining using paraffin-embedded BM trephine biopsy samples. Blocks were sectioned 4.0 μm in thickness and unstained slides were deparaffinized using EZ Prep solution (Ventana Medical System, Tucson). Slides were stained with anti-MYC antibody (Ventana, Cat No. 790-4628; prediluted) using Ventana Discovery XT automated system (Fig. 1). We used 5% as cut-off (calculated as MYC positive cells out of total counted blasts in the selected area with sheets of blasts) as previously reported [20].

2.3. Assessment of targeted next generation sequencing and cytogenetics

Somatic mutations were assessed by 54 myeloid targeted gene sequencing as described previously [23]. Genomic DNA was isolated from BM or peripheral blood (PB) mononuclear cells. DNA samples were subjected to targeted genome sequencing using Illumina HiSeq2000. For our pathogenic *vs*. non-pathogenic call algorithm, we used a modification of the ACMG classification scheme that was developed for germline variants for the classification of somatic sequence variants [24]. We established filters to determine clinically actionable pathogenic alterations and to filter out benign variants or polymorphism, which were clinically validated as described previously [23]. Conventional karyotyping or/and fluorescence in-situ hybridization (FISH) were performed on the patients' BM specimens to assess any cytogenetic aberrations.

2.4. Statistical analysis

Clinical variables and disease-related prognostic factors including age, gender, cytogenetics and somatic mutations were characterized at the time of AML-MRC diagnosis and were annotated using descriptive statistics. The overall survival (OS) outcomes were estimated with the Kaplan-Meier method and compared using the log-rank test. All statistical analyses were performed using SPSS v24.0 and GraphPad Prism 7.

Table 1
Baseline characteristics of the study cohort.

Characteristic	Low MYC patients (n = 84)	High MYC patients (n = 51)	All patients (n = 135)
Age at AML-MRC diagnosis (years)	65.1 (22.3-85.6)	68.5 (44.4-85.93)	67.3 (22.3-85.9)
Gender (%)	Male 51 (61) Female 33 (39)	Male 33 (65) Female 18 (35)	Male 84 (62) Female 51 (38)
CBC (range)			
Hemoglobin (g/dL)	9 (7.1-12.5)	8.4 (6.5-10.7)	8.7 (6.5-12.7)
Platelet counts ($x10^9$/L)	43 (3-697)	40 (2-945)	42 (2-945)
White blood counts ($x10^9$/L)	2.53 (0.12-78.07)	2.95 (0.1-216.8)	2.8 (0.1-216.8)
ANC ($x10^9$/L)	0.77 (0-42.94)	0.33 (0-17.62)	0.67 (0-42.94)
Blasts, % (range)			
Peripheral blood	25 (1-87)	40 (5-93)	28 (10-93)
Bone marrow	25 (1-90)	35 (10-95)	29 (10-95)
Cytogenetics(%)			
5q deletion	23 (27)	24 (47)	47 (35)
Trisomy 8	11 (13)	15 (29)	26 (19)
7 deletion	19 (23)	13 (25)	32 (24)
12 deletion	5 (6)	5 (10)	10 (7)
20 deletion	10 (12)	2 (4)	12 (9)
17p deletion	18 (21)	17 (33)	35 (26)
Complex karyotype	27 (32)	20 (39)	47 (35)
NGS assessments (%)			
TP53	23 (35)	23 (51)	46 (41)
DNMT3A	8 (12)	15 (33)	23 (21)
ASXL1	15 (23)	7 (16)	22 (20)
SRSF2	9 (14)	7 (16)	16 (14)
IDH1	5 (8)	8 (18)	13 (12)
RUNX1	9 (14)	4 (9)	13 (12)
NRAS	9 (14)	3 (7)	12 (11)
TET2	7 (11)	5 (11)	12 (11)
NPM1	5 (8)	4 (9)	9 (8)
BCOR	5 (8)	2 (4)	7 (6)
KRAS	3 (5)	4 (9)	7 (6)
SF3B1	6 (9)	1 (2)	7 (6)
Treatment (%)			
Hypomethylating agents	16 (19)	8 (16)	24 (18)
Intensive chemotherapy	47 (56)	27 (53)	74 (55)
Low dose cytarabine	0 (0)	0 (0)	0 (0)
Allo-SCT	21 (25)	10 (20)	31 (23)
Median OS, months	42.3	17.0	20.0

Abbreviation: complete blood count (CBC), next generation sequencing (NGS), allogeneic stem cell transplant (Allo-SCT), overall survival (OS).

3. Results

3.1. Patient characteristics

A total of 135 AML-MRC patients were included in this study. The median age at AML-MRC diagnosis was 67.3 (22.3–85.9) years and 62% of patients were male (n = 84) (Table 1). A total of 55% (n = 74) of patients were treated with intensive chemotherapy including 7 + 3 (cytarabine 100 mg/m^2 /day continuous IV infusion for 7 days and daunorubicin 45–90 mg/m^2/day or idarubicin 12 mg/m^2 /day for 3 days), CLAG (cladribine 5 mg/m^2 /day and cytarabine 2 g/m^2 /day for 5 days, G-CSF 300mcg for 6 days), CLAG-M (CLAG and mitoxantrone 10 mg/m^2 /day for 3 days), or MEC (mitoxantrone 8 mg/m^2 /day, etoposide 100 mg/m^2 /day, and cytarabine 1 g/m^2 /day for 5 days) and 18% (n = 24) were treated with hypomethylating agents (decitabine or azacitidine). Allogeneic stem cell transplant (allo-SCT) was performed in 23% (n = 31) patients (Table 1).

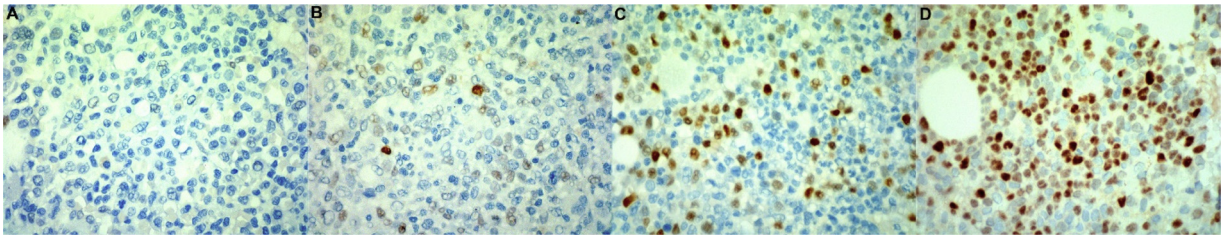

Fig. 1. MYC Immunohistochemistry Staining in AML-MRC Patients. Examples of IHC staining results in low (A and B) and high (C and D) MYC protein expressing AM-MRC patients.

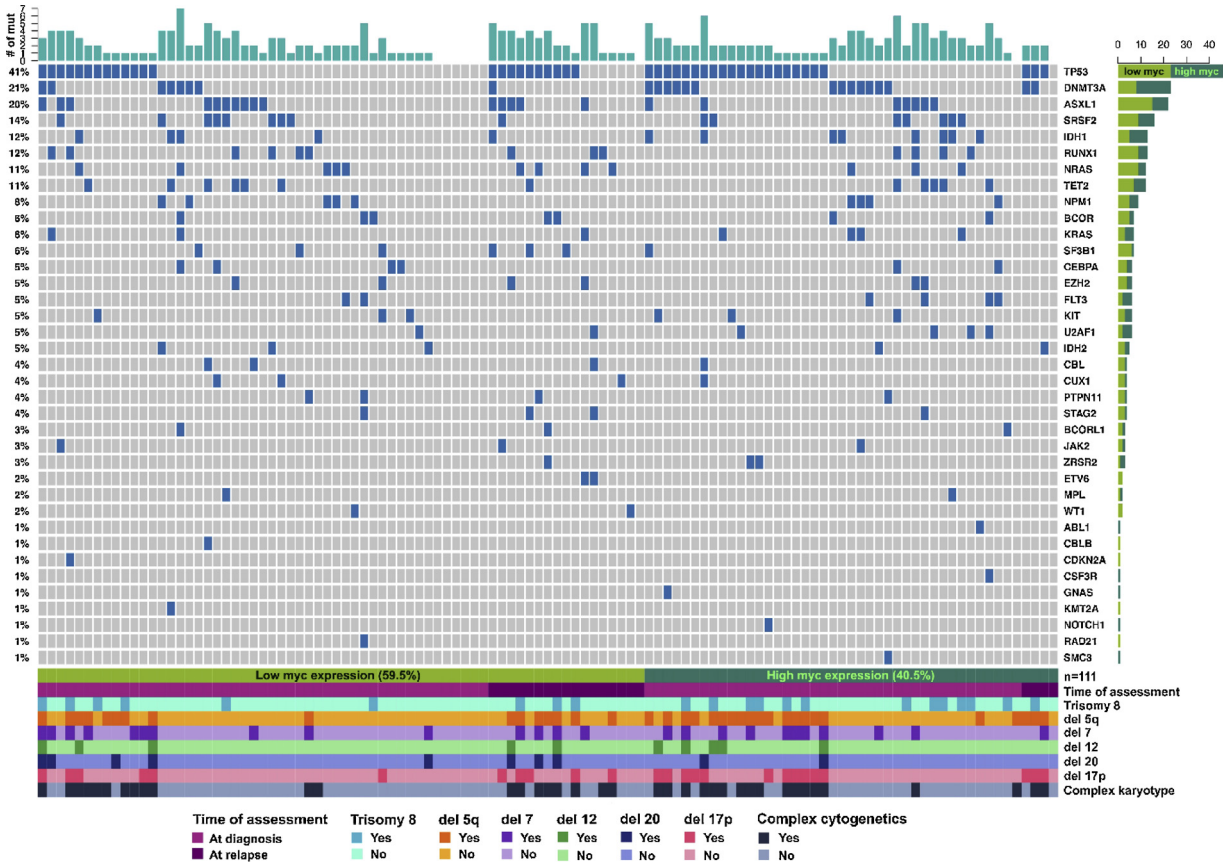

Fig. 2. Landscape of Concurrent Somatic Mutations and Cytogenetic Abnormalities in High *vs*. Low MYC Patients. Individual column is somatic mutation data from individual patient. Each row is showing the presence of individual mutation in the patient cohort (name of mutation is described on the right side and rate of mutations are described on the left side). The presence of concurrent abnormal cytogenetics including trisomy 8, deletion 5q, monosomy 7, monosomy 12, deletion 20, and deletion 17p, and complex karyotypes are shown at the bottom of the plot.

3.2. Spectrum of MYC oncoprotein expression and associated mutational landscape and cytogenetic abnormalities

A total of 38% (n = 51) patients had high MYC expression and 62% (n = 84) patients had low MYC expression (Table 1). Somatic mutations were assessed in 82% (n = 111) (Fig. 2). In these patients, most common somatic mutation in all patients was *TP53* (41%) followed by *DNMT3A* (21%), *ASXL1* (20%), *SRSF2* (14%), *IDH1* (12%), *RUNX1* (12%), *NRAS* (11%), and *TET2* (8%) (Fig. 2 and Table 1). Among 51 patients with high MYC protein expression, the most common comutation was *TP53* (51%) followed by *DNMT3A* (33%), *IDH1* (18%), *ASXL1* (16%), *SRSF2* (16%), and *TET2* (11%) (Fig. 2 and Table 1). In patients with low MYC protein expression, the most common comutation was *TP53* (35%) followed by *ASXL1* (23%), *RUNX1* (14%), *NRAS* (14%), and *DNMT3A* (12%) (Fig. 2 and Table 1). Fisher's Exact test revealed that the rates of *TP53* ($p = 0.0255$) and *DNMT3A* ($p = 0.0043$) mutations were significant higher in high MYC patients (Table 1). AML-MRC patients with *TP53* mutation had numerically higher expression of MYC oncoprotein (9.1% *vs*. 6.1%, $p = 0.2058$), but this was not statistically significant (Fig. 3). We also assessed the cytogenetics in our study cohort. A total of 26% (n = 35) patients had chromosome 17p deletion [del(17p)] and 22% (n = 30) had both del(17p) and *TP53* mutation (Table 1). Additional chromosomal abnormalities including deletion 5q, trisomy 8, deletion 7q, deletion 20q, and complex karyotypes were observed in 35% (n = 47), 19% (n = 26), 24% (n = 32), 9% (n = 12), and 35% (n = 47) of patients, respectively (Table 1). The most common chromosomal abnormality in low MYC patients was complex karyotype (32%, n = 27) followed by 5q deletion (27%, n = 23), deletion 7 (23%, n = 19), and del(17p) (21%, n = 18) (Table 1). In high MYC patients, the most common cytogenetics was 5q deletion (47%, n = 24) that was followed by complex karyotypes (39%, n = 20), del(17p) (33%, n = 17), trisomy 8 (29%, n = 15), and deletion 7 (25%, n = 13) (Table 1).

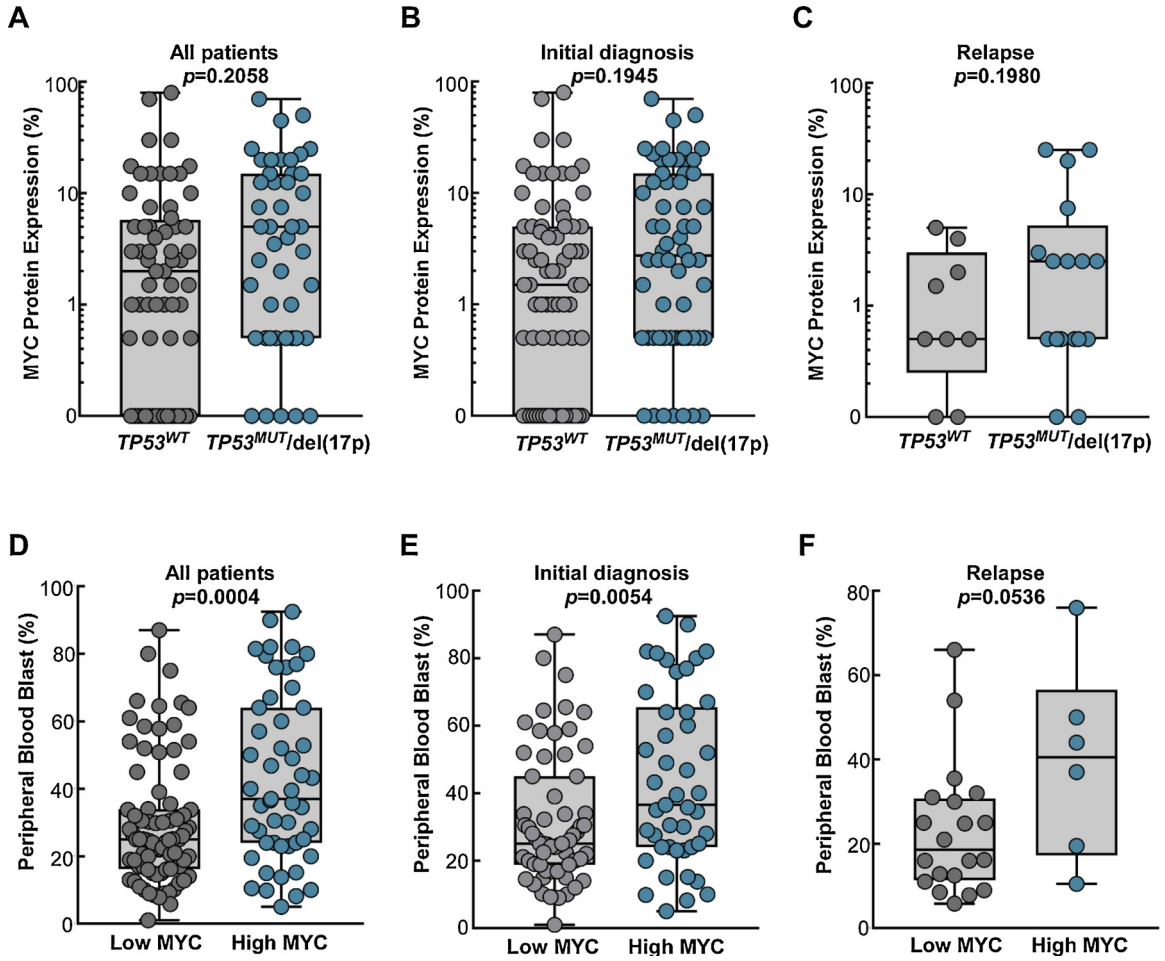

Fig. 3. MYC Protein Expression Levels in *TP53* Wild Type *vs*. Mutant Patients and Peripheral Blast Counts in Low *vs*. High MYC Patients. MYC protein expression levels were assessed at the time of AML-MRC in the majority of the patients (n = 109) and some patients had MYC protein expression assessed at the time of relapse (n = 26). MYC levels are plotted as the separate groups; all patients (A), patients with MYC assessment at the diagnosis (B), and patients with assessment at the time of relapse (C). Blast counts (%) in the peripheral blood are shown in three different patient groups: all patient (D), patients with MYC assessment at the time of diagnosis (E), and patients with assessment at the time of relapse (F).

3.3. Impact of MYC expression on blast counts and overall survival

The PB blast counts were significantly higher in high MYC patients compared to low MYC patients (40% *vs*. 25%, $p = 0.0004$) (Fig. 3). Notably, the median OS was significantly longer in low MYC patients compared to high MYC patients (median OS 42.3 *vs*. 17.05 months, $p = 0.0109$) (Fig. 4A). Further, when considering only *TP53* wild type patients without del(17p), low MYC patients had even longer median OS (median OS 58.6 *vs*. 17.0 months, $p = 0.0338$) (Fig. 4B). In AML-MRC patients with either *TP53* mutation and/or del(17p), there was no statistical OS difference between low and high MYC groups (median OS 33.1 *vs*. 15.2 months, $p = 0.17$) (Fig. 4C). In an additional analysis including high MYC patient only, there was no OS difference between *TP53* wild type patients *vs*. mutant patients ($p = 0.7995$) (**Figure S2**).

We performed additional survival analysis including newly diagnosed AML-MRC patients only (n = 109) and the results were similar (**Figure S3**). In the univariate analysis with newly diagnosed AML-MRC patients (n = 109), high MYC protein expression was associated with inferior OS (HR 1.817, 95% CI 1.042–3.169, $p = 0.034$). Multivariate analysis including MYC expression level, transplantation status, gender

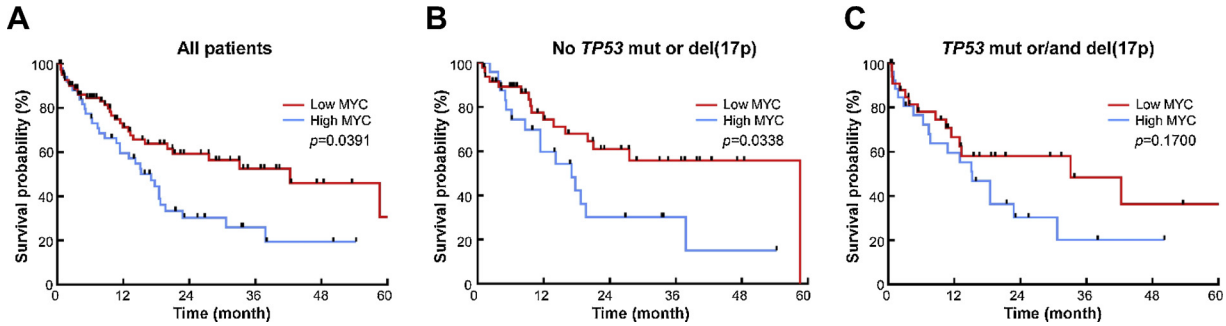

Fig. 4. Overall Survival Based on MYC Expression in AML-MRC Patients. (A) Overall survival in all patients, (B) in patients with no *TP53* mutation or del(17p), and (C) in patients with *TP53* mutations or/and del(17p).

Table 2
Prognostic Impact of MYC oncoprotein expression in the univariate (log-rank) and multivariate (cox-regression) analyses*.

	Overall Survival					
	Univariate			Multivariable*		
Variable	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
High MYC	1.817	1.042 to 3.169	0.034	1.765	1.004 to 3.104	0.048
Age	1.019	0.992 to 1.047	0.992	1.000	0.972 to 1.028	0.989
Gender (female)	1.557	0.860 to 2.819	0.144	1.444	0.785 to 2.656	0.238
No allogeneic transplant	3.445	1.526 to 7.779	0.003	3.232	1.396 to 7.486	0.006

Abbreviation: HR (hazard ratio), CI (confidence interval). *The univariate and multivariate analyses included newly diagnosed AML-MRC patients whose MYC proteins expression levels were assessed at the time of diagnosis.

and age demonstrated high MYC expression (HR 1.77, 95% CI 1.004–3.104, p = 0.045) and no allogeneic transplant (HR 3.23, 95% CI 1.396–7.486, $p = 0.006$) are poor prognostic factors for the OS outcome (Table 2).

4. Discussion

Among many of the common somatic mutations and abnormal cytogenetics associated with AML, *MYC* gene rearrangement, copy number gain, and somatic mutations have been frequently reported in the pediatric and adult AML patients [8–11]. Previous studies using *in vivo* mice models have demonstrated that MYC is sufficient to induce AML and MYC was shown to be overexpressed or/and required for AML provoked by various fusion oncogenes such as *PML-RARα, RUNX1-RUNX1T1* and *BCR-ABL1* [17–19]. Although MYC was shown to play a pivotal role in regulating myeloid differentiation and cell death, the exact mechanisms underlying MYC-driven oncogenesis remains to be unanswered in AML. As the first step to understand the oncogenic role of MYC in AML patients, we attempted to analyze the prognostic impact of MYC oncoprotein expression in AML-MRC patients with and without preceding MDS and MDS/MPN and the landscapes of co-mutations in high *vs*. low MYC patients.

Two previous studies have assessed the prognostic significance of MYC oncoprotein in AML patients [20,21]. In the first study performed by Mughal et al. that included a total of 199 AML patients, high MYC level (IHC staining at or above median score and more than 1 + staining intensity) was associated with poor OS in patients with favorable and intermediate cytogenetic groups although it did not reach the statistical significance in the multivariate analysis adjusted by age and cytogenetic risk group [21]. In an independent study performed by Ohanian et al. that included a total of 265 untreated AML patients, high MYC protein expression (> 6%) was associated with inferior complete remission duration when compared to the low expression (12 *vs.* 23 months, $p = 0.028$) [20]. Importantly, among 241 patients with higher risk for relapse (age ≥55 years, intermediate and high risk groups), high MYC expression was associated with inferior median OS (24 *vs.* 13 months, $p = 0.042$), event free survival (14 *vs.* 6 months, $p = 0.048$), and relapse free survival (25 *vs.* 12 months, $p = 0.024$) [20]. In consistent with these reports [20,21], we observed a dynamic range of MYC oncoprotein expression in AML-MRC patients (0–100%) and inferior OS in the high MYC patients. In patients without *TP53* somatic mutations, high MYC level remains to be an independent poor prognostic factor although there was no OS difference between high and low MYC groups in patients with *TP53* mutations or/and del(17p). Supporting these observations, concurrent *TP53* mutation rate was significantly higher in high MYC patients and MYC levels were maintained higher in patients with *TP53* mutation or/and del(17p) although the difference was not significant. In an additional analysis in high MYC patients only, there was no OS difference between patients with *TP53* mutation or/and del (17p) *vs*. patients with no *TP53*/del(17p). Collectively, these observations suggest that *TP53* mutation/del(17p) associated poor prognosis may result from high MYC accumulation driven by *TP53* mutation/del (17p). In previous studies, wild type p53 was shown to transcriptionally repress *MYC* expression and induce miR-145 suppressing *MYC* expression [25,26]. Further studies are warranted to investigate the detail mechanisms of mutant p53 dependent MYC upregulation in AML patients.

The most common somatic mutation in *de novo* AML patients from TCGA database was *FLT3* (28%) which is followed by *NPM1* (27%), *DNMT3A* (24.5%), *RUNX1* (13%), *IDH2* (10%), *IDH1* (9.5%), and *TET2* (8.5%) [27]. In contrast, *ASXL1* (32%) was the most common somatic mutation in the secondary AML patients and this was followed by *RUNX1* (31%), *NRAS* (23%), *TET2* (20%), *SRSF2* (20%), *DNMT3A* (19%), *FLT3* (19%), *U2AF1* (16%), and *TP53* (15%) [7]. Similar to this study, *TP53* (41%), *DNMT3A* (21%), *ASXL1* (20%), *SRSF2* (14%), *IDH1* (12%), *RUNX1* (12%), *NRAS* (11%), and *TET2* (8%) mutations were frequently identified in our AML-MRC patient cohort. Of note, we observed more frequent *DNMT3A* mutations and higher blasts counts at the time of diagnosis in high MYC patients. These observations suggest that MYC oncoprotein may provide proliferative potential to MDS cells harboring *DNMT3A* mutations, leading to MDS to AML progression. The initial BM biopsy specimens at the time of MDS diagnosis were not available in many of the referred patients in our study. Therefore, we were unable to compare the MYC levels between MDS *vs*. AML-MRC in the individual patient and to determine whether increase of MYC expression contributes to MDS to AML progression. However, it is worthy of exploration in the future study. Additionally, on-going study to investigate the underlying molecular contribution of MYC oncoprotein in AML cell differentiation and survival will answer this question (data not published).

In conclusion, AML-MRC patients with high MYC expression have inferior OS outcome compared to low MYC patients. Further, multivariate analysis established that high MYC level is a poor prognostic factor in AML-MRC patients. These findings warrant further study of the prognostic impact of MYC expression in addition to *MYC* gene amplification or/and somatic mutations in AML patients, with larger numbers of patients having other somatic mutations or chromosomal abnormalities that have adverse outcomes.

Authorship

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Manuscript writing: S.Y., R.S., O.C., N.D.V., I.A., J.L.C., L.Z.

Declaration of competing interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.leukres.2019.106194.

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