Malays J Pathol 2023; 45(3) : 405 – 416

ORIGINAL ARTICLE

Clinicopathological characteristics of myelodysplastic syndromes with del(5q) in Taiwan

Ching-Fen YANG[1,2], Chih-Yi HSU[1,2,3], Liang-Tsai HSIAO[2,4,5], Shang-Wen CHEN[6], Shih-Sung CHUANG[7]*

[1] Department of Pathology and Laboratory Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [2]School of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan; [3]College of Nursing, National Taipei University of Nursing and Health Sciences, Taipei, Taiwan; [4]Division of Haematology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan; [5]Haemophilia Comprehensive Care Centre, Taipei Veterans General Hospital, Taipei,Taiwan; [6]Division of Hemato-Oncology, Department of Internal Medicine, Chi-Mei Hospital, Lioying, Tainan, Taiwan; [7]Department of Pathology, Chi-Mei Medical Center, Tainan, Taiwan

Abstract

Background: Myelodysplastic syndromes (MDS) are a group of clonal haematopoietic stem cell disorders characterised by ineffective haematopoiesis and cytopenia. Studies have reported differences in MDS between Asian and Western countries, but data from Taiwan are scarce. Materials and Methods: In this study we analysed the clinical and pathological features of 32 Taiwanese MDS patients with del(5q) (ie, del(5q) alone [Group A, n = 11], del(5q) with one additional cytogenetic abnormality other than monosomy 7 or del(7q) [Group B, del(5q)+1; n = 6], and del(5q) with ≥2 additional cytogenetic abnormalities [Group C, n = 15]). Results: Progression-free survival (PFS) and overall survival (OS) were more favourable for Group A than for Groups B ($p < 0.05$) and C ($p \leq 0.001$). Multivariate analysis showed that age >70 years, thrombocytopenia, and karyotype other than del(5q) alone were poor prognostic factors. Among the patients that had World Health Organization (WHO)-defined MDS with isolated del(5q), one patient (9%) had a typical marrow morphology of 5q minus syndrome with erythroid hypoplasia and four patients (36%) had hypolobated megakaryocytes. In addition, PFS and OS were significantly more favorable for the patients with del(5q) alone than for those with del(5q)+1 ($p < 0.05$). Conclusion: The bone marrow morphology, clinical features, and prognosis of Taiwanese MDS patients with del(5q) were different from those associated with MDS with isolated del(5q) as defined in the current WHO classification. Researchers should compare different geographic regions and racial populations to determine whether geographic and racial differences exist with respect to MDS with del(5q).

Keywords: 5q deletion syndrome; chromosome aberrations; myelodysplastic syndrome; prognosis; progression-free survival.

INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal haematopoietic stem cell disorders characterised by cytopenia, dysplasia in one or more of myeloid lineages, ineffective haematopoiesis, recurrent genetic abnormalities, and a variably increased risk of developing acute myeloid leukaemia (AML).[1] MDS can be either primary (*de novo*) or secondary to cytotoxic therapies (therapy related). *De novo* MDS occurs more frequently in older men. Although the age-standardised annual incidence rate of MDS is lower in Taiwan (0.90/100,000) than in the United States (4.3/100,000) [2,3], the incidence of MDS in Taiwan is increasing with the aging of its population. In Taiwan, the percentage of geriatric population (≥65 years old) was 1.44 times higher in 2019 (15.3%) than in 2009 (10.6%)[4], and the incidence of MDS increased 1.5 times during this period (245 vs 371 patients, 2009 vs 2019).[2,5] In addition, populations in Asia are more prone to develop high-risk MDS.[6]

**Address for correspondence*: Prof. Shih-Sung Chuang, M.D. Department of Pathology, Chi-Mei Medical Center 901 Chung-Hwa Road, Tainan, Taiwan 71004. Tel: 886-6-2812811 ext. 53686. Fax: 886-6-2511235. Email: *cmh5301@mail.chimei.org.tw*

Approximately 30% to 50% of patients with *de novo* MDS exhibit cytogenetic abnormalities. Deletion involving the long arm of chromosome 5 or del(5q), either alone or in combination with other abnormalities, is a frequently observed cytogenetic abnormality in patients with MDS.[7,8] First described by Van den Berghe *et al*. in 1974[9], 5q minus (5q–) syndrome is characterised by del(5q) with refractory macrocytic anaemia, a normal or high platelet count, erythroid hypoplasia, and an increased number of hypolobated megakaryocytes in the bone marrow (BM).[9,10] As a synonym of 5q– syndrome, MDS with isolated del(5q) was the only MDS entity defined by cytogenetic features in the third edition of the WHO classification published in 2001.[11] At that time, the disease was defined as MDS with isolated del(5q) alone and <5% blasts in the BM and peripheral blood (PB). However, the definition and diagnostic criteria of this disease changed over time (Table 1). In the fourth edition of the WHO classification

TABLE 1: Evolution of the definition of MDS with del(5q)

Year	Terminology	Cytogenetic aberrations	PB blast count	BM blast count	Auer rods	Reference
1974	Deletion of chromosome 5q	Deletion of approximately two-thirds of chromosome 5q	NA	Up to 15%.	NA	Van den Berghe *et al*.[9]
1975	5q–chromosome	Del(5q) without information on other cytogenetic abnormalities	NA	Variable (2%–10%)	NA	Sogal *et al*.[10]
1993	5q–syndrome	Del(5q) alone	NA	Up to 30% blasts.	NA	Mathew *et al*.[24]
2001	MDS with isolated del(5q)/ 5q–syndrome	Del(5q) alone	<5%	<5%	NA	WHO 3rd ed.[11]
2008	MDS with isolated del(5q)/ 5q–syndrome	Del(5q) alone, except for –Y.	<1%	<5%	Absent	WHO 4th ed.[12]
2017	MDS with isolated del(5q)/ MDS with 5q deletion/ 5q minus syndrome	Del(5q) alone, or with one cytogenetic abnormality other than –7 or del(7q)	<1%	<5%	Absent	WHO Updated 4th ed.[1]
2022	Myelodysplastic neoplasm with low blasts and 5q deletion	Del(5q) alone, or with one cytogenetic abnormality other than –7 or del(7q)	<2%	<5%	NA	WHO 5th ed.
2022	MDS with del(5q) [MDS-del(5q)]	Del(5q), with up to 1 additional cytogenetic abnormality, except –7/ del(7q)	<2%	<5%	NA	ICC[14]

ICC, International Consensus Classification; MDS, myelodysplastic syndrome; NA, not available.

published in 2008, MDS with isolated del(5q) was refined to myeloblasts of <5% in the BM, myeloblasts of <1% in PB, and absence of Auer rods.[12] In the updated fourth edition published in 2017, MDS with isolated del(5q) is defined as MDS with anemia and del(5q) alone or with one other cytogenetic abnormality other than monosomy 7 or del(7q) [(del(5q)+1].[1] The rationale of the aforementioned definition is that cases with these cytogenetic abnormalities lead to similar outcomes.[1] The diagnostic criteria remain essentially unchanged in the upcoming 5th edition of the WHO Classification of Haematolymphoid Tumours and the 2022 ICC (International Consensus Classification), except that up to 2% of blasts are allowed in the PB.[13,14] However, the findings regarding the effect of one additional cytogenetic abnormality are inconsistent in various studies.[15-18]

To the best of our knowledge, no study has explored the prognostic effect of del(5q) on MDS from Taiwan. This study aimed to characterize the clinicopathological features of MDS patients with del(5q) in Taiwan and to compare the prognostic significance of cases with del(5q) alone and those with additional cytogenetic abnormalities.

METHODS

Study cohort and diagnostic criteria

We searched the cytogenetics database of the Department of Pathology and Laboratory Medicine of Taipei Veterans General Hospital (VGH-Taipei, Taipei, Taiwan) for the period from January 2000 to December 2020 for MDS cases with del(5q). Diagnoses of MDS were made in accordance with the 2017 WHO classification.[1] The inclusion criteria were as follows: presence of cytopenia in at least one haematopoietic lineage without any identifiable cause for at least 2 months, presence of del(5q) alone or with additional abnormalities as revealed through BM cytogenetic studies, and marrow and PB blast counts of <20%. We collected the included patients' marrow blast counts, cytogenetic results, haemoglobin levels, absolute neutrophil counts (ANC) and platelet counts at diagnosis; and their follow-up data. The Institutional Review Board of VHG-Taipei approved this study. Fig. 1 presents the flowchart of this study.

Cytogenetic investigation

The marrow aspiration specimens were directly cultured for 24 h and subjected to conventional cytogenetic investigation. Karyotype analyses were performed using the G-banding technique, and clonal cytogenetic abnormalities were identified in accordance with up-to-date International System for Human Cytogenetic Nomenclature definitions.

Data analysis

We performed Fisher's exact test and the Mann-Whitney test for comparisons of categorical and continuous variables, respectively. Overall survival (OS) was defined as the time between

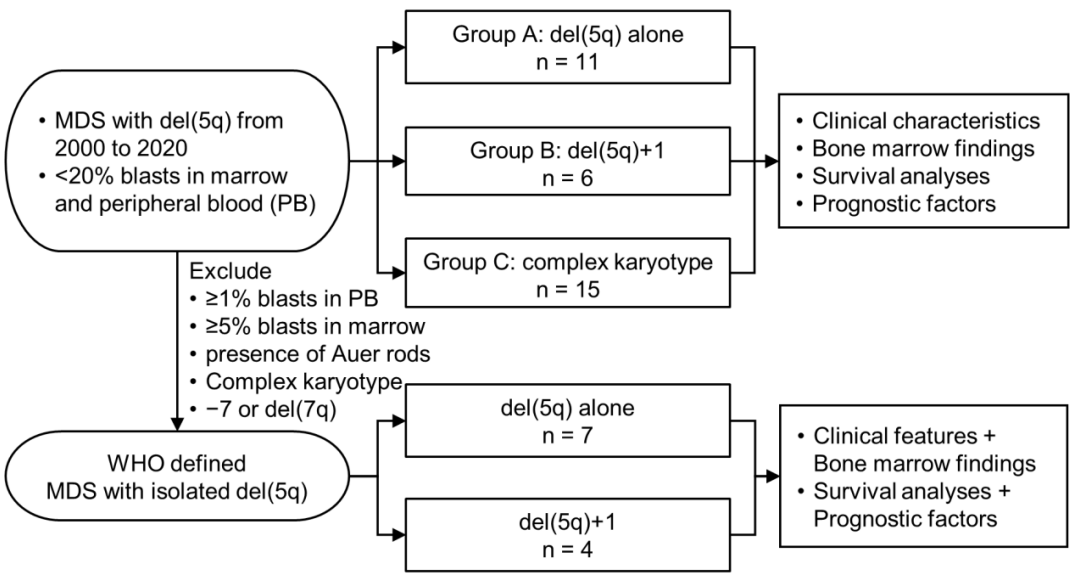

FIG. 1. Diagnostic flowchart for MDS patients with del(5q) in present study.

the date of diagnosis through biopsy and the date of death or final follow-up. Progression-free survival (PFS) was defined as the time from the date of diagnosis to the date of progression to leukaemia or death from any cause. Patients who underwent stem-cell transplantation or received AML-directed chemotherapy were censored at the time of management. The survival function was determined using the Kaplan-Meier method, and survival difference was calculated using the log-rank test. Statistical analyses were performed using Stata 12.1 software (StataCorp, College Station, TX, USA). All variables that were revealed to have a *p*-value of <0.1 through univariate analysis were candidates for multivariate Cox models. The final model was obtained using backwards elimination and included only significant variables. *P*-values were obtained through 2-tailed tests, and a *p*-value of <0.05 was regarded as significant.

RESULTS

Clinical characteristics of MDS patients with del(5q)

For the study period, we identified 1296 specimens from 978 patients for whom BM cytogenetic studies for cytopenia were performed. Among these patients, 30 (3.07%) had MDS with del(5q). In addition, there were 2 consultation cases involving MDS with del(5q) (to C.-F. Y.; Case no. 10 and 11) during this period. Thirty-two cases with del(5q) were classified by karyotype into 3 groups, namely a group comprising patients with del(5q) alone (n = 11; Group A), a group comprising patients with del(5q) and one additional cytogenetic abnormality other than monosomy 7 or del(7q) (n = 6; Group B), and a group comprising patients with del(5q) and ≥2 additional cytogenetic abnormalities (n = 15; Group C). For 15 (47%) patients, the BM blast was ≥5%. In addition, 5 (33%) Group C patients had therapy-related MDS. Table 2 lists the clinical characteristics of the MDS patients with del(5q). No significant differences were detected between Groups A and B, except for a significantly lower IPSS risk score in Group A than in Group B ($p = 0.035$). Compared with the patients from Group C, who exhibited complex cytogenetic abnormalities, those from Groups A (del(5q) alone) and B (del(5q)+1) were mostly female ($p = 0.002$) and had higher platelet counts ($p = 0.005$). Macrocytic anaemia was present in 45% and 50% of the patients in Groups A and B, respectively. In addition, thrombocytopenia, higher International Prognostic Scoring System (IPSS) risk, Revised International Prognostic Scoring System (IPSS-R) risk, and WHO classification-based Prognostic Scoring System (WPSS) risk scores were more frequently exhibited by patients in Group C than patients in Groups A and B (all $p \leq 0.005$).

BM findings pertaining to MDS patients with MDS with del(5q)

Table 3 lists the BM findings of this study cohort. Seventeen (53%) patients had a marrow blast <5%, and 15 (47%) had a blast ≥5%. Twenty-eight (88%) patients had normocellular or hypercellular BM. A low myeloid/erythroid ratio was identified in 15 (47%) patients, and none of the patients had Auer rods. Hypolobated megakaryocytes were present in 45%, 83%, and 73% of the patients from Groups A, B, and C, respectively. However, no significant differences between these 3 groups were identified with respect to blast count, cellularity, myeloid/erythroid ratio, frequency of granulocyte dysplasia, and dyserythropoiesis, or hypolobated megakaryocytes.

Survival of MDS patients with del(5q)

Fig. 2 presents the survival curves of the patients. The PFS (median 76.8 months) and OS (median not reached) of Group A patients were more favourable than those of Groups B (medians of 7.9 and 12.3 months for PFS and OS, respectively; PFS, $p = 0.035$; OS, $p = 0.048$) and C (median of 7.3 months for both PFS and OS; PFS, $p < 0.001$; OS, $p = 0.001$). The survival differences between the patients from Groups B and C were nonsignificant.

Prognostic factors for MDS patients with del(5q)

Table 4 lists the risk factors for disease progression. Univariate analysis revealed that age >70 years ($p = 0.014$), male sex ($p < 0.001$), thrombocytopenia ($p < 0.001$), pancytopenia ($p = 0.002$), Group A karyotype ($p = 0.001$), an IPSS risk score of >1.0 ($p = 0.043$), and an IPSS-R risk score of ≥5.0 ($p = 0.009$) were significant factors; by contrast, a BM blast count of ≥5% and the other examined variables had nonsignificant effects. When all the variables with $p < 0.1$ were included in the multivariate Cox regression model analysis, an age of >70 years, the presence of thrombocytopenia and a Group A karyotype were still significant factors for PFS and OS after the backward elimination of nonsignificant variables.

TABLE 2: Comparison of clinical characteristics of 3 groups of MDS patients with del(5q)

Characteristics	Group A del(5q) alone (*n* = 11)	Group B del(5q)+1 (*n* = 6)	Group C Complex (*n* = 15)	*p*†	*p*‡
Age, median years (range)	76 (47–87)	74 (66–82)	76 (58–88)	0.823	0.802
>70 years, n (%)	6 (55%)	5 (83%)	10 (67%)	0.492	0.333
Female, n (%)	11 (100%)	5 (83%)	6 (40%)	**0.002**	0.353
ANC ($\times 10^9$/L), median (range)	1.3 (0.5–15.4)	1.7 (0.6–3.3)	1.4 (0.4–5.1)	0.803	0.841
ANC < 1.8 $\times 10^9$/L, n (%)	6 (55%)	3 (50%)	11 (73%)	0.449	1.000
ANC < 0.8 $\times 10^9$/L, n (%)	2 (18%)	1 (17%)	2 (13%)	1.000	1.000
Hb (g/dL), median (range)	7.6 (2.6–10.7)	6.6 (5.4–11.2)	8.4 (2.8–11.9)	0.288	0.580
Hb < 10 g/dL, n (%)	8 (73%)	5 (83%)	13 (87%)	0.834	1.000
Hb < 8 g/dL, n (%)	7 (64%)	5 (83%)	6 (40%)	0.208	0.600
Platelet ($\times 10^9$/L), median (range)	265 (72–1,088)	210 (16–448)	66 (31–585)	**0.005**	0.315
Platelet > 400 $\times 10^9$/L, n (%)	3 (27%)	1 (17%)	1 (7%)	0.308	1.000
Platelet < 100 $\times 10^9$/L, n (%)	2 (18%)	3 (50%)	12 (80%)	**0.007**	0.280
Platelet < 50 $\times 10^9$/L, n (%)	0 (0%)	1 (17%)	6 (40%)	**0.038**	0.353
Macrocytic anaemia§, n (%)	5 (45%)	3 (50%)	3 (20%)	0.294	1.000
Cytopenia¶	9 (82%)	5 (83%)	14 (93%)	0.508	1.000
Anaemia alone, n (%)	3 (27%)	1 (17%)	0 (0%)	0.075	1.000
Bicytopenia††, n (%)	5 (45%)	2 (33%)	6 (40%)	1.000	1.000
Pancytopenia‡‡, n (%)	1 (9%)	2 (33%)	8 (53%)	0.073	0.515
IPSS risk score, median (range)	0.5 (0–2.0)	1.0 (0.5–1.5)	2 (1.5–3.0)	**<0.001**	**0.035**
IPSS risk group				**<0.001**	0.568
Low (score = 0)	3 (27%)	0 (0%)	0 (0%)		
Intermediate-1 (score = 0.5–1)	7 (64%)	5 (83%)	0 (0%)		
Intermediate-2 (score = 1.5–2)	1 (9%)	1 (17%)	11 (73%)		
High (score = 5–6)	0 (0%)	0 (0%)	4 (27%)		
IPSS-R risk score, median (range)	2.5 (1.0–6.5)	3.5 (1.0–4.5)	7.5 (6.0–9.0)	**<0.001**	0.514
IPSS-R risk group				**<0.001**	0.564
Very low (score ≤ 1.5)	3 (27%)	1 (17%)	0 (0%)		
Low (score = 2–3)	4 (36%)	1 (17%)	0 (0%)		
Intermediate (score = 3.5–4.5)	3 (27%)	4 (67%)	0 (0%)		
High (score = 5–6)	0 (0%)	0 (0%)	5 (33%)		
Very high (score ≥ 6.5)	1 (9%)	0 (0%)	10 (67%)		
WPSS risk score, median (range)	1 (0–4)	3 (1–4)	5 (3–6)	**<0.001**	0.088
WPSS risk group				**0.001**	0.336
Very low (score = 0)	3 (27%)	0 (0%)	0 (0%)		
Low (score = 1)	4 (36%)	1 (17%)	0 (0%)		
Intermediate (score = 2)	1 (9%)	2 (33%)	1 (7%)		
High (score = 3–4)	3 (27%)	3 (50%)	6 (40%)		
Very high (score = 5–6)	0 (0%)	0 (0%)	8 (53%)		

ANC, Absolute neutrophil count; del(5q), 5q deletion alone; del(5q)+1, del(5q) plus one other abnormality other than –7 or del(7q); Hb, haemoglobin; IPSS, International Prognostic Scoring System; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndrome; WPSS, WHO Classification–based Prognostic Scoring System.

† Differences among del(5q) alone, del(5q)+1 and complex.

‡ Differences between del(5q) alone and del(5q)+1.

§ Mean corpuscular volume ≥ 100 fL and haemoglobin < 12 g/dL for female, < 13 g/dL for male.

¶ Absolute neutrophil count < 1.8×10^9/L, Hb < 10 g/dL, or platelet < 100×10^9/L.

†† Cytopenia of any two lineages.

‡‡ Cytopenia of all three lineages.

TABLE 3: Bone marrow findings pertaining to MDS patients with del(5q)

Bone marrow findings	Group A del(5q) alone (n = 11)	Group B del(5q)+1 (n = 6)	Group C Complex (n = 15)	*p*†	*p*‡
Blast, median (range)	1 (1–15)	1 (1–5)	6 (1–15)	0.195	0.763
≤2%, n (%)	7 (64%)	4 (67%)	6 (40%)	0.274	1.000
>2% – <5%, n (%)	0 (0%)	0 (0%)	0 (0%)		
5% – 10%, n (%)	3 (27%)	2 (33%)	3 (20%)		
>10%, n (%)	1 (9%)	0 (0%)	6 (40%)		
Cellularity, median (range)	45 (20–95)	25 (10–60)	40 (25–95)	0.098	0.070
Decreased, n (%)	0 (0%)	3 (50%)	1 (7%)	0.079	0.081
Normal, n (%)	6 (55%)	1 (17%)	5 (33%)		
Increased, n (%)	5 (45%)	2 (33%)	9 (60%)		
Myeloid/erythroid ratio, median (range)	2.0 (0.3–6.0)	2.0 (0.5–5.0)	1.0 (0.2–6.0)	0.752	1.000
Decreased, n (%)	5 (45%)	2 (33%)	8 (53%)	0.832	1.000
Normal, n (%)	5 (45%)	3 (50%)	4 (27%)		
Increased, n (%)	1 (9%)	1 (17%)	3 (20%)		
Granulocyte dysplasia, n (%)	3 (27%)	1 (17%)	8 (53%)	0.220	1.000
Dyserythropoiesis, n (%)	8 (73%)	2 (33%)	12 (80%)	0.172	0.162
Hypolobated megakaryocytes, n (%)	5 (45%)	5 (83%)	11 (73%)	0.262	0.304
Increased megakaryocytes, n (%)	7 (64%)	3 (50%)	8 (53%)	0.807	0.644
Decreased megakaryocytes, n (%)	1 (9%)	1 (17%)	1 (7%)	0.767	1.000

del(5q), deletion of 5q only; del(5q)+1, deletion of 5q and one other abnormality other than –7 or del(7q); IQR, interquartile range; MDS, myelodysplastic syndrome.

† Differences among del(5q) alone, del(5q)+1 and complex.

‡ Differences between del(5q) alone and del(5q)+1.

Clinical characteristics and BM findings pertaining to MDS patients with WHO-defined isolated del(5q)

After cases with excess blasts were excluded, 11 patients fitted the WHO criteria for MDS with isolated del(5q)[1], including 7 from Group A and 4 from Group B. Seven (64%) patients exhibited considerable anaemia (Hb < 10 g/dL), including a Group A patient who had microcytic anaemia alone without leukopenia or thrombocytopenia. Furthermore, 5 (45%) and 2 (18%) patients had bicytopenia and pancytopenia, respectively. Thrombocytosis was noted in only 1 (9%) patient, and 4 (36%) had thrombocytopenia accompanied by either anemia and/or leukopenia (bicytopenia or pancytopenia). One (9%) patient had erythroid hypoplasia (increased myeloid/erythroid ratio), and 4 (36%) had hypolobated megakaryocytes in the BM. The clinical characteristics and BM findings revealed no significant difference between the del(5q) alone and del(5q)+1 groups, except for the association of an additional cytogenetic abnormality with increases of 0.5 and 1.0 point in IPSS and WPSS risk scores, respectively.

Survival and prognostic factors pertaining to MDS patients with WHO-defined isolated del(5q)

Among the 11 patients with WHO-defined MDS with isolated del(5q), the PFS and OS of the patients with del(5q) alone (median of 76.8 months for both PFS and OS) were more favourable than those of the patients with del(5q)+1 (PFS, median = 3.7 months, p = 0.022; OS, median = 7.1 months, p = 0.049; Fig. 3). Univariate analyses revealed that an age of >70 years and the presence of anemia, pancytopenia, hypolobated megakaryocytes, Group A karyotype, IPSS-R and WPSS risk group were significant factors for PFS. However, a multivariate Cox model analysis was not conducted because of the small number of cases.

DISCUSSION

MDS with del(5q) is rare in Asia.[19-22] The

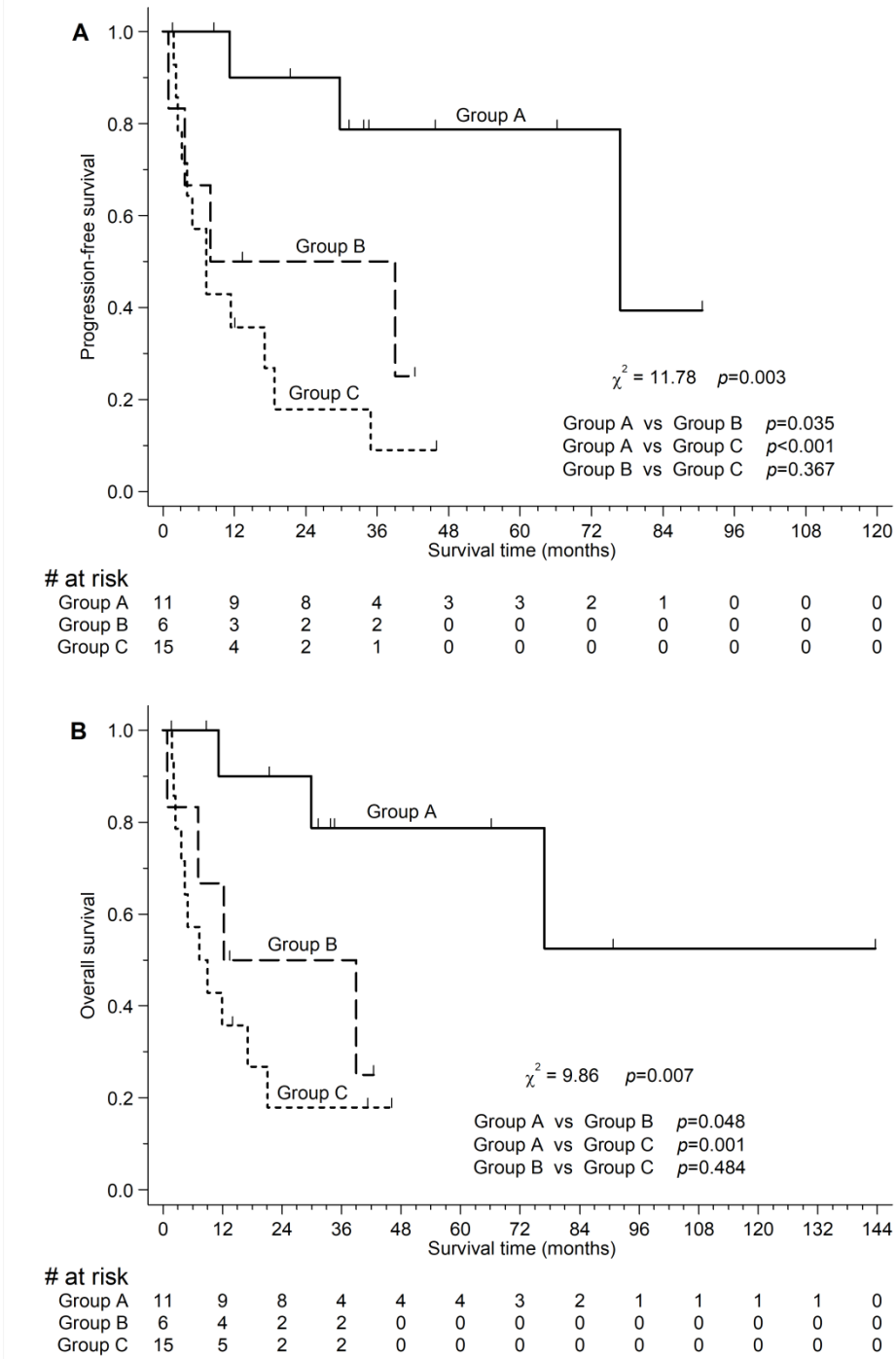

FIG. 2: Progression-free (A) and overall (B) survival curves of MDS patients with del(5q) as stratified by cytogenetic findings (Groups A–C).

incidence and presentation of MDS with isolated del(5q) have not yet been reported in Taiwan.[23] We collected the data of 32 Taiwanese MDS patients with del(5q) and analysed their clinical and pathological features. Only 11 patients had WHO-defined MDS with isolated del(5q). Compared with reported presentations of 5q– syndrome in the literature[24,25], those of the patients we analyzed exhibited a lower frequency of macrocytic anaemia (literature vs present study, 66% vs 45%), a higher frequency of bicytopenia (rare vs 45%), and a lower frequency

TABLE 4: Risk factors for disease progression in MDS patients with del(5q)

Factors	n (%)	Median PFS (months)	*p*
Age >70 years	21 (66%)	11.2	0.014
Male	10 (31%)	4.1	<0.001
Neutropenia (ANC < 1.8 $\times 10^9$/L)	20 (63%)	11.4	0.511
Anaemia (Hb < 10 g/dL)	26 (81%)	18.8	0.198
Macrocytic anaemia[†]	11 (34%)	34.9	0.631
Thrombocytopenia (platelet < 100 $\times 10^9$/L)	17 (53%)	7.3	<0.001
Cytopenia[‡] more than one lineage	24 (75%)	11.2	0.062
Pancytopenia[§]	11 (34%)	4.9	0.002
BM blast ≥ 5%	15 (47%)	34.9	0.422
BM hypocellularity	4 (13%)	18.8	0.848
Decreased myeloid/erythroid ratio	15 (47%)	17.1	0.502
Granulocyte dysplasia	12 (38%)	17.1	0.608
Dyserythropoiesis	22 (69%)	11.4	0.256
Hypolobated megakaryocytes	21 (66%)	18.8	0.661
Increased megakaryocytes	18 (56%)	39.0	0.184
Decreased of megakaryocytes	3 (9%)	17.1	0.344
Group A karyotype[¶]	11 (34%)	76.8	0.001
IPSS risk group			0.211
Low (score = 0)	3 (9%)	76.8	
Intermediate-1 (score = 0.5–1.0)	12 (38%)	39.0	
Intermediate-2 (score = 1.5–2.0)	13 (41%)	7.3	
High (score ≥ 2.5)	4 (13%)	4.1	
IPSS risk score > 1.0	17 (53%)	7.3	0.039
IPSS-R risk group			0.041
Very low (score ≤ 1.5)	4 (13%)	76.8	
Low (score = 2.0–3.0)	5 (16%)	29.7	
Intermediate (score = 3.5–4.5)	7 (22%)	NR	
High (score = 5.0–6.0)	5 (16%)	7.3	
Very high (score ≥ 6.5)	11 (34%)	4.9	
IPSS-R risk score ≥ 5.0	16 (50%)	7.3	0.008
WPSS risk group			0.169
Very low (score = 0)	3 (9%)	76.8	
Low (score = 1)	5 (16%)	29.7	
Intermediate (score = 2)	5 (16%)	7.9	
High (score = 3 – 4)	11 (34%)	39.0	
Very high (score = 3–4)	8 (25%)	4.1	
WPSS risk score ≥ 3	19 (59%)	17.1	0.334

ANC, Absolute neutrophil count; BM, bone marrow; del(5q)+1, deletion of 5q and one other abnormality other than –7 or del(7q); Hb, hemoglobin; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; NR, not reached; PFS, progression-free survival; WPSS, WHO Classification–based Prognostic Scoring System.

[†] Mean corpuscular volume ≥ 100 fL and hemoglobin < 12 g/dL for female, < 13 g/dL for male.

[‡] Absolute neutrophil count < 1.8×10^9/L, Hb < 10 g/dL, or platelet < 100×10^9/L.

[§] Absolute neutrophil count < 1.8×10^9/L Hb < 10 g/dL, and platelet < 100×10^9/L.

[¶] Deletion of 5q alone.

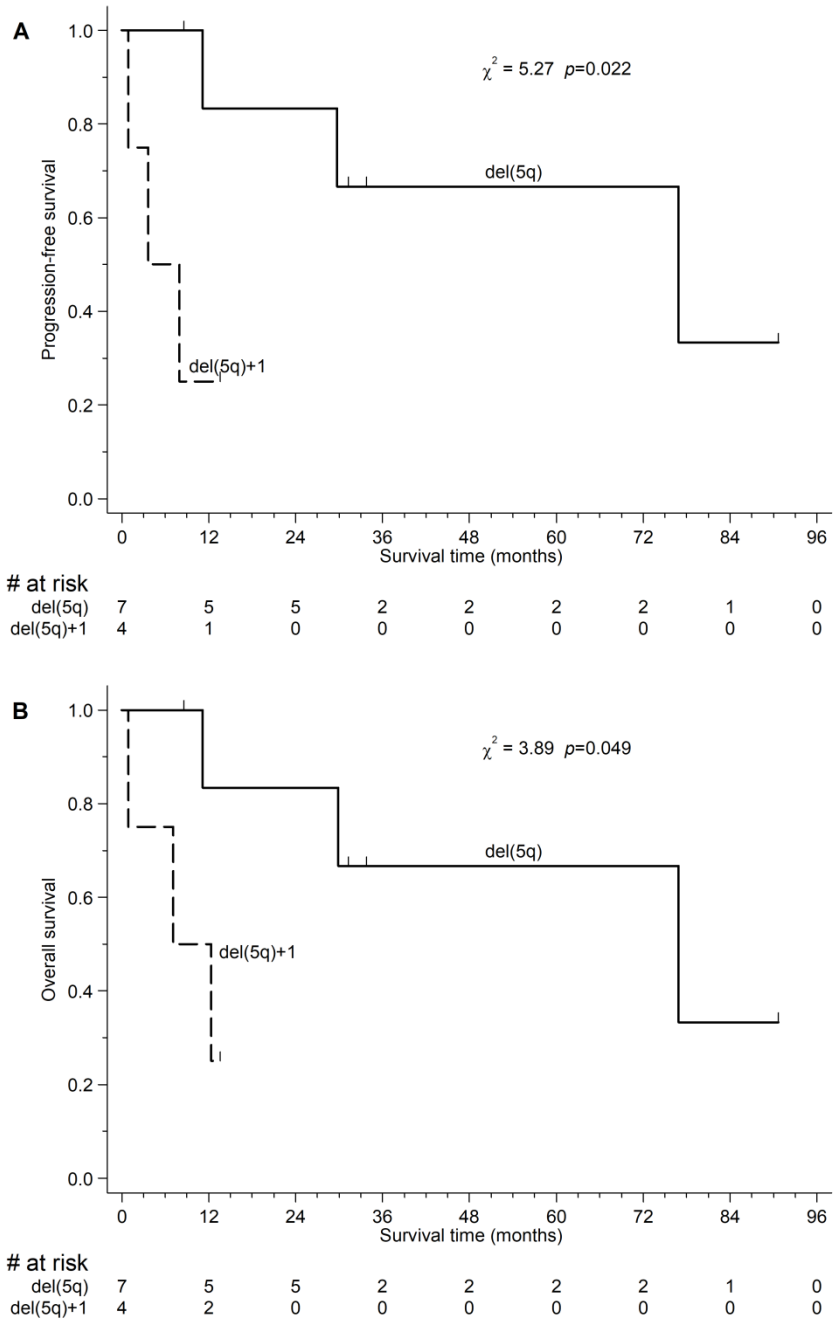

FIG. 3: Progression-free (A) and overall (B) survival curves of patients with WHO-defined MDS with isolated del(5q).

of erythroid hypoplasia in the BM (84% vs 9%). The PFS and OS of patients in del(5q) alone were significantly more favourable than those of the patients with del(5q)+1 ($p = 0.022$ [PFS] and 0.049 [OS]). These results challenge the current WHO definition of MDS with isolated del(5q), including del(5q) with one additional cytogenetic abnormality.

Del(5q) has been reported in 10% to 15% of patients with de novo MDS, and it is the most frequently documented recurrent cytogenetic abnormality in MDS.[18] In Asia, the frequency of del(5q) among patients with MDS (0% to 15.3%) is considerably lower than that in

Western countries (8.7% to 23.4%).[21-23,26] In our department at VGH-Taipei, del(5q) was only identified in 1.48% (249/16,808) of conventional cytogenetic specimens. This abnormality was usually accompanied by complex chromosome abnormalities and was frequently associated with AML. MDS with del(5q) is rare, accounting for only 3.0% of MDS cases. With cases with excess blasts excluded, the incidence of WHO-defined MDS with isolated del(5q) was only 1.0% (10/978).

Although studies have not reported a significant difference in OS between MDS with del(5q) alone and del(5q)+1, their findings differ with respect to leukaemia-free survival.[15-18] The largest retrospective study to date, which involved 541 MDS patients with del(5q) and was conducted by Mallo *et al*.,[18] reported that 55.3% of them had del(5q) as the sole chromosomal abnormality (equivalent to Group A in the present study), 17.2% had one additional abnormality (Group B), and 27.5% had a complex karyotype with ≥2 associated abnormalities (Group C). Most of the patients they analysed received supportive care and that additional chromosomal abnormalities associated with del(5q) were linked to significantly lower leukaemia-free survival and shorter (nonsignificant) overall survival.[18] Although the size of our case sample was small, our findings corresponded to those of Mallo *et al*.; that is, the PFS and OS of Group A were more favorable than those of Groups B ($p = 0.030$ [PFS] and 0.040 [OS]) and C (PFS, $p < 0.001$; OS, $p = 0.002$). Liu *et al*. analysed 77 patients from China with MDS with isolated del(5q) as defined by the 2017 WHO classification.[27] They compared patients with del(5q) alone versus del(5q)+1 and reported a similar complete response rate to lenalidomide and a similar median OS between both groups of patients.[27] This result could be attributed to the treatment effect of lenalidomide having a positive effect in prolonging OS, and their findings could not be easily compared with ours because most of the patients we analysed only received supportive care. More studies (preferably prospective studies) should be conducted to identify prognostic differences between MDS with del(5q) alone and MDS with del(5q)+1.

The prognostic factors for MDS include MDS subtype, number and severity of cytopenias, the percentage of blasts in the BM, and cytogenetic abnormalities.[1,28-30] Differences between Asian and Western populations in terms of the recurrent cytogenetic abnormalities and clinical features of MDS have been consistently reported; specifically, relative to Western patients, Asian patients were more likely to be classified under the high- and very-high risk groups, which was supported by the identification of a higher proportion of high-risk cytogenetic aberrations.[6,20,31] The IPSS and WPSS prognostic scores for MDS with del(5q) alone (Group A in our study) are lower than that for MDS with del(5q) with one additional chromosome abnormality other than monosomy 7 or del(7q) (del(5q)+1, Group B).[28,30] However, the IPSS-R prognostic score for del(5q) is the same as that for del(5q)+1.[32] Yang *et al*. reported that IPSS-R predicted the clinical outcomes of patients with primary MDS in Taiwan but had limitations pertaining to low-risk categories[23]; however, their study did not include any case of 5q− syndrome. For our MDS patient with WHO-defined isolated del(5q), IPSS-R and WPSS could predict the outcome of patients in very-low-, low- and intermediate-risk categories.

The major weakness of our observational study was its retrospective nature and the small number of cases examined. Furthermore, the analyzed patients were managed heterogeneously, with most of them receiving only supportive care. Nonetheless, this is the first study of MDS with del(5q) conducted in Taiwan, which is an Asian country where the frequency of del(5q) among patients with MDS is low. We characterised the clinical and pathological features of this heterogeneous category of diseases and discovered that patients with del(5q) alone exhibited more favorable PFS and OS relative to those with del(5q)+1; these findings differ from those based on the 2017 WHO classification.

In conclusion, the BM morphology, clinical features, and prognosis of MDS with isolated del(5q) in Taiwan differ from those of MDS with isolated del(5q) typically found in the West. In Taiwan, MDS patients with del(5q) alone (Group A) had long-term survival, but those with del(5q)+1 (Group B) had poor prognoses.

Acknowledgement: None

Authors' contribution: CFY and SSC designed the study, CFY, CYH, LTH, SWC and SSC analyzed the data, CYH performed statistical analysis, CFY and CYH wrote the manuscript, SSC reviewed and revised the manuscript, all authors approved the manuscript.

REFERENCES

1. Swerdlow S, Campo E, Harris N, *et al*. WHO classification of tumours of haematopoietic and lymphoid tissues. Revised 4th ed. Lyon, France: IARC press; 2017.
2. Health Promotion Administration, Ministry of Health and Welfare, Taiwan. Cancer registry annual report, 2019. Available at https://www.hpa.gov.tw/Pages/Detail.aspx?nodeid=269&pid=14913.
3. Howlader N, Noone A, Krapcho M, *et al*. SEER Cancer Statistics Review, 1975-2017. Bethesda, MD: National Cancer Institute, 2020. Available at https://seer.cancer.gov/archive/csr/1975_2017/results_merged/sect_30_mds.pdf.
4. Department of Household Registration, Ministry of the Interior, Taiwan. Population by age, sex and marital status. Available at https://www.ris.gov.tw/documents/data/en/3/Table-3-y2021.xls.
5. Bureau of Health Promotion Administration, Department of Health, Taiwan. Cancer registry annual report, 2009. Available at https://www.hpa.gov.tw/File/Attach/6518/File_6182.pdf.
6. Jiang Y, Eveillard JR, Couturier MA, *et al*. Asian population is more prone to develop high-risk myelodysplastic syndrome, concordantly with their propensity to exhibit high-risk cytogenetic aberrations. Cancers (Basel). 2021;13(3):481.
7. Kawankar N, Vundinti BR. Cytogenetic abnormalities in myelodysplastic syndrome: an overview. Hematology. 2011;16(3):131–8.
8. List A, Ebert BL, Fenaux P. A decade of progress in myelodysplastic syndrome with chromosome 5q deletion. Leukemia. 2018;32(7):1493–9.
9. Van den Berghe H, Cassiman JJ, David G, Fryns JP, Michaux JL, Sokal G. Distinct haematological disorder with deletion of long arm of no. 5 chromosome. Nature. 1974;251(5474):437–8.
10. Sokal G, Michaux JL, Van Den Berghe H, *et al*. A new hematologic syndrome with a distinct karyotype: the 5 q - chromosome. Blood. 1975;46(4):519–33.
11. Jaffe E, Harris N, Stein H, Vardiman J. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC press; 2001.
12. Swerdlow S, Campo E, Harris N, *et al*. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: IARC press; 2008.
13. Khoury JD, Solary E, Abla O, *et al*. The 5th edition of the World Health Organization classification of haematolymphoid tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703–19.
14. Arber DA, Orazi A, Hasserjian RP, *et al*. International Consensus Classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200–28.
15. Germing U, Lauseker M, Hildebrandt B, *et al*. Survival, prognostic factors and rates of leukemic transformation in 381 untreated patients with MDS and del(5q): a multicenter study. Leukemia. 2012;26(6):1286–92.
16. Gurney M, Patnaik MM, Hanson CA, *et al*. The 2016 revised World Health Organization definition of 'myelodysplastic syndrome with isolated del(5q)'; prognostic implications of single versus double cytogenetic abnormalities. Br J Haematol. 2017;178(1):57–60.
17. Schanz J, Tüchler H, Solé F, *et al*. New comprehensive cytogenetic scoring system for primary myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia after MDS derived from an international database merge. J Clin Oncol. 2012;30(8):820–9.
18. Mallo M, Cervera J, Schanz J, *et al*. Impact of adjunct cytogenetic abnormalities for prognostic stratification in patients with myelodysplastic syndrome and deletion 5q. Leukemia. 2011;25(1):110–20.
19. Vu MP, Ha HQ, Nguyen CN. Cytogenetic characteristics in Vietnamese patients diagnosed with primary myelodysplastic syndromes. Leuk Res Rep. 2022;18:100343.
20. Miyazaki Y, Tuechler H, Sanz G, *et al*. Differing clinical features between Japanese and Caucasian patients with myelodysplastic syndromes: Analysis from the International Working Group for Prognosis of MDS. Leuk Res. 2018;73:51–7.
21. Lee HR, Oh B, Hong DS, *et al*. Cytogenetic features of 5q deletion and 5q- syndrome in myelodysplastic syndrome in Korea; marker chromosomes proved to be chromosome 5 with interstitial deletion by fluorescence in situ hybridization. Cancer Genet Cytogenet. 2010;203(2):193–202.
22. Li L, Liu XP, Nie L, *et al*. Unique cytogenetic features of primary myelodysplastic syndromes in Chinese patients. Leuk Res. 2009;33(9):1194–8.
23. Yang YT, Hou HA, Liu CY, *et al*. IPSS-R in 555 Taiwanese patients with primary MDS: Integration of monosomal karyotype can better risk-stratify the patients. Am J Hematol. 2014;89(9):E142–9.
24. Mathew P, Tefferi A, Dewald GW, *et al*. The 5q- syndrome: a single-institution study of 43 consecutive patients. Blood. 1993;81(4):1040–5.
25. Washington LT, Doherty D, Glassman A, Martins J, Ibrahim S, Lai R. Myeloid disorders with deletion of 5q as the sole karyotypic abnormality: the clinical and pathologic spectrum. Leuk Lymphoma. 2002;43(4):761–5.
26. Tasaka T, Tohyama K, Kishimoto M, *et al*. Myelodysplastic syndrome with chromosome 5 abnormalities: a nationwide survey in Japan. Leukemia. 2008;22(10):1874–81.
27. Liu D, Xu ZF, Qin TJ, *et al*. Analysis of clinical characteristics, treatment response rate and survival of 77 myelodysplastic syndrome patients with del (5q) syndrome. Zhonghua Xue Ye Xue Za Zhi. 2019;40(11):895–900.
28. Greenberg P, Cox C, LeBeau MM, *et al*. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89(6):2079–88.
29. Garcia-Manero G, Chien KS, Montalban-Bravo G. Myelodysplastic syndromes: 2021 update on diagnosis, risk stratification and management. Am J Hematol. 2020;95(11):1399–420.
30. Malcovati L, Germing U, Kuendgen A, *et al*. Time-dependent prognostic scoring system for predicting

survival and leukemic evolution in myelodysplastic syndromes. J Clin Oncol. 2007;25(23):3503–10.
31. Yan X, Wang L, Jiang L, *et al*. Clinical significance of cytogenetic and molecular genetic abnormalities in 634 Chinese patients with myelodysplastic syndromes. Cancer Med. 2021;10(5):1759–71.
32. Greenberg PL, Tuechler H, Schanz J, *et al*. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120(12):2454–65.