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Case Report

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Cytogenetic-Phenotypic Profile of Filipinos with Myelodysplastic Syndrome in Makati Medical Center: A 10-Year Review

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Abstract

Hematologic malignancies remained to be a significant contributor in the Global Burden of Disease. Myelodysplastic syndrome is one of the hematologic malignancies and has remained to be underestimated, underreported, and underdiagnosed. It is a group of hematologic malignancies that proves a challenge in diagnosis and is characterized by clonal hematopoiesis, with one or more cytopenias. Data on Prevalence of Myelodysplastic syndrome globally is scarce, moreso, not available in the Philippines. This is the first clinical profile study in Myelodysplastic Syndrome in the Philippines. This 10-year study has shown that 240 patients were diagnosed to have Myelodysplastic syndrome but only 35 had the MDS Fluorescent-in-Situ Hybridization test done. The most common reasons for hematologic referral, chief complaint, signs, cytogenetic test are anemia, low hemoglobin, pallor and fatigue, del7q31 which belongs to the Good risk cytogenetic category respectively. The most common CBC findings were hemoglobin of 8 and above, ANC of above 800 and Platelets of 50 and higher. There was no noted significant difference in the clinical profile of patients with MDS based on FISH study results.

Keywords: Filipino, Myelodysplastic syndrome, Fluorescent-in-situ hybridization, Clinical profile

List of Abbreviations

FISH: Fluorescent-in-Situ Hybridization
MDS: Myelodysplastic Syndrome
R-ISS: Revised International Scoring System

1. Introduction

For almost three decades, Cancer disease or Neoplasm has been gaining traction as one of the causes of Global Burden of Disease based on the absolute number of Disability-adjusted life-years ranking 6th in 1990 and up to 2nd in 2017. Hematologic malignancies remained to be a significant contributor to this burden. Based on the Data of the World Health organization in 2017, Non-Hodgkin's Lymphoma remained to be the most common cause of years-of-life-lost among hematologic malignancies and remained in the top ten among other cancers. Other hematologic malignancies such as leukemias remained in the top 30 of the list [1]. Among other hematologic malignancies, Myelodysplastic syndrome has remained to be underestimated, underreported, and underdiagnosed. Based on the most recent National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) in 2011, the age-adjusted incidence of MDS is at 4.9 per 100,000 population per year from 3.28 in 2001 [2]. The myelodysplastic syndromes (MDS) are a group of hematologic malignancies that proves a challenge in diagnosis and are characterized by clonal hematopoiesis, with one or more cytopenias such as anemia, neutropenia, and/or thrombocytopenia, and abnormal cellular maturation. MDS shares clinical and pathologic features with acute myeloid leukemia (AML), but MDS is defined by having less than 20% of peripheral or marrow blasts based on World Health Organization (WHO) definition criteria. Patients with MDS are at risk for symptomatic anemia, infection, bleeding, and transformation to AML [3]. The pathophysiology of MDS centers on a mutation from an unknown precise cause. Some cases have been associated with exposure to cytotoxic chemotherapy, ionizing radiation, tobacco and benzene and to aging. Specific mutation is noted to be a spontaneous substitution through deamination of Cytosine to Thymine at the level of Nucleic acid arrangement in hematopoietic stem cell leading to a clonal hematopoiesis [4]. It is most commonly seen in elderly population with a median age of 70 years old. Annual incidence and risk of the disease is age-dependent with the highest incidence at >70 years old at 20 cases/100,000 and the risk for 80 years old and above reaching 89 cases per 100,000 population. Male is predominantly affected. Clinical manifestation varies widely from indolent, asymptomatic to aggressive transformation to Acute myeloid leukemia and death. The most common cytopenia is Anemia that is associated with fatigue that is out of proportion to the degree of anemia, weakness, exercise intolerance, dizziness, and/or angina. Other

presents with a manifestation related to the cell lines affected such as recurrent infection with leukopenia or Neutropenia or bleeding and bruising to those with thrombocytopenia. Presence of concomitant comorbidities may complicate the disease process such as those with autoimmune disease, Thalassemia, Renal or Cardiovascular disease. Clinical evaluation of patient suspected to have myelodysplastic syndrome involves a thorough acquisition of history of constitutional symptoms (fatigue, bruising, infections), nutrition, substance abuse, drug intake, exposure to toxic chemicals, occupation, previous treatment with chemotherapy, HIV infection; Complete Blood count, peripheral blood smear and Bone marrow examination, flow cytometry, cytogenetic testing such as Fluorescence In-Situ Hybridization (FISH), and immunohistochemistry. All Diagnosed case should be categorized according to the World Health organization classification system and must be pursued to any person with unexplained cytopenia and/or with corresponding clinical manifestation [3]. In general, diagnosis is made based on the three parameters: First, the presence of one or more cytopenia; Second, presence of 10% or higher dysplastic cells in one lineage, and no blasts cells of about 20% or higher in the blood and bone marrow. Also, the presence of a characteristic cytogenetic or molecular findings without any alternate cause strengthens the diagnosis. Cytogenetic abnormality identification or Karyotyping is one of the main constituents of the international Prognostic Scoring System (IPSS) and its revised format and remains to be the cornerstone for prognostication of patients with MDS. The most extensively studied abnormalities are Del (5q), -7/del (7q), +8 and -Y. The molecular sequences of different cytogenetic abnormalities allow for modification of treatment regimens based on available drugs that act on specific sequences and promote individualized approach to treatment. Deletion of the long arm of Chromosome 5 (5q) are the most frequently found chromosomal abnormalities in MDS and the isolated form is associated with better prognosis. It has an incidence of about 15% of diagnosed cases. On the other hand, chromosome 7 deletion is associated with poor prognosis and overall survival. Patients with multiple cytogenetic abnormalities follow an aggressive disease course with substantially lower treatment response [5].

Association of race and MDS remains to be elucidated. As stated, registries in the western countries proves that MDS is an underdiagnosed and underreported disease and awareness of its clinical and laboratory picture among physicians needs to be strengthened to improve work-up and thus documentation of the disease. In Asia, there is no available registry to date. There is an ongoing study which started on May 30, 2017, entitled "Clinical and Genomic Registry of MDS in Asia" that targets to enroll 2,600 MDS cases among Asians. This study is expected to conclude on June 30, 2022 [6]. There is tons of information that needs to be elucidated mostly about the true prevalence of MDS in the world including cases in Asia. This can be addressed by increasing awareness of this disease entity, improving diagnostic capability, providing an efficient reporting system and enhancing research support in this area of medicine.

The provision of a clear association of cytogenetic profile of patients who are presenting with signs and symptoms of Myelodysplasia in a proper clinical context, most importantly, those who are already diagnosed, would allow proper prognostication and treatment planning [7]. Further studies are needed to strengthen the information on how to integrate this test into a treatment plan. The development of MDS involves a series of genetic changes at the level of hematopoietic stem cells. These changes lead to the accumulation of abnormally developed cell lines affecting its maturity and functionality. The challenge to associate these genetic changes to its phenotypic presentation comes as these occur in normal individuals without any cellular changes. Specific cytogenetic predispositions to develop MDS have been identified. Almost 50% of those with primary MDS have clonal chromosomal abnormalities detected in the bone marrow. Rates differ based on population and technique used for identification. The most common cytogenetic abnormalities in MDS are del (5q),-7 or del (7q), trisomy 8, del (20q) and loss of the Y chromosome [8].

Data regarding the prevalence of Myelodysplastic syndrome globally and most especially, in Asia is scarce. In fact, in a span of 16 years there are only 25 studies which reported its incidence and 2 studies reported on its prevalence. There are only 3 studies in Asia. In its analysis, the incidence rates are reported by region for those studies reporting overall rates across clinical factors, age and gender (27 articles), the Incidence for MDS were noted to be from 0.06-0.26 per 100,000. In general, incidence rates increased with increasing age in studies that reported results by age group. Prevalence of MDS ranged from 0.22-13.2 per 100,000 for all age categories, genders and ethnicities. This is the first study to report on the global incidence of MDS and whether or not the disease occurs as a result of treatment for another oncologic condition or occurs de novo. Variation in study designs and heterogeneous population characteristics make interpretation of results challenging. In this study, prevalence and incidence of AML were also analyzed.

In the Philippines, the disease entity variability and information scarcity among internists, less so among hematologists, resonates in the lack of data on the prevalence and incidence of Myelodysplastic syndrome. This may be rooted in a lack of standardized reporting system, from underdiagnosis of patients who may be presenting with subtle signs of the disease and underutilization of hematology as a specialty. Consistent with the literature review done in 2016, the Philippines has yet to consolidate data and prevalence rate of Myelodysplastic syndrome. Together with the prevalence of other hematologic malignancies, a study is ongoing to document a one year prevalence of hematologic malignancies in the country in the year 2020. The study is called the Bloom Study which is already in the data analysis stage. Moreover, being a third world country makes testing for chromosomal abnormality inaccessible both in availability and cost. To date, there are only two centers who can perform Cytogenetic testing by FISH namely the National kidney Transplant Institute (NKTI) which is a government funded institution, and St. Luke's Medical center (SLMC), a private hospital. Despite government funding, NKTI still has a steep price for the test at around Php 13,675($273.5) but far less compared to

SLMC's price of 33,622.22($672). The prices are net of hospital sent-out processing fee making the test more difficult to be done.

The completion of the Human Genome project paved the way for an immense research opportunity for scholars to perform to maximize the available genetic information to know more about its clinical significance in view of disease risks. The role of genetic information in the practice of medicine is increasing at a rapid pace. The regulation of gene expression is much more complex. The mode of inheritance describes the manner by which a trait is expressed in the members of the family. The human genome is rich in variation and it is categorized into three broad groups from single nucleotide changes to change of the entire chromosome. It is also described based on germline or somatic mutation. The implication of genetic information is on the associated diseases as well as on the therapeutic effect of these changes. Technologies are available to detect multiple genetic variations. All types of genetic variation have the potential to cause disease or contribute to disease susceptibility risk. The role of a variant disease pathogenesis is determined by its functional impact on gene expression or protein function [9].

A variety of classification conventions have been applied by clinical laboratories when reporting back results of genetic testing. In an attempt to standardize this, the American College of Medical Genetics and Genomics (ACMG), together with the Association for Molecular Pathology and the College of American Pathologists, developed a set of guidelines for variant reporting and have recommended use of a five-tier classification system consisting of the following designations [10].

Pathogenic: A pathogenic variant is a disease-causing variant, as determined by very strong genetic and experimental evidence, including consistent familial co-segregation with disease and definitive functional studies.

Likely pathogenic: A likely pathogenic variant is a variant with strong, but not definitive, evidence of pathogenicity based on its similarity to known pathogenic variants, co-segregation with disease in families or populations, and functional evidence.

Uncertain significance: A variant of uncertain significance (VUS) is a variant for which the specific criteria for the other four categories are not met, or when contradictory lines of evidence in support of both benign and pathogenic classifications are present.

Likely benign: A likely benign variant is a variant with multiple supporting (but not conclusive) lines of evidence suggesting it is not disease causing.

Benign: A benign variant is a variant with conclusive evidence that it is not disease causing, as determined typically (but not exclusively) by a high prevalence of the variant in the general (healthy) population, at a prevalence that exceeds that of the suspected disease.

The recommendations were accompanied by a detailed description of the process for variant classification [10]. This process combines multiple lines of evidence, including allele frequency data from the general population, evidence for co-segregation of variant with disease in families, results from prediction algorithms that considered the functional potential and cross-species conservation, and experimental studies demonstrating altered gene or protein function. Individual testing laboratories may classify a particular genetic variant differently depending on their assessments of the evidence [9].

The concept of Cytogenetics has greatly impacted the approach to patients with Hematological malignancies. The detection of clonal cytogenetic abnormalities can be useful in several ways; First is to establish the specific diagnosis, example is the Philadelphia chromosome in chronic myeloid leukemia. Second, to distinguish between benign reactive processes such as lymphoid or myeloid hyperplasia and a monoclonal malignant proliferation. Third, to enhance our understanding of the pathogenesis of the disease and to identify genes that are critical for the control of cell growth and leukemogenesis. Fourth, to help in the planning of treatment, since some chromosomal changes predict response (or nonresponse) to specific therapies, or to inform the selection of a targeted therapy. Lastly, to estimate prognosis, based on the presence of a recurring abnormality, appearance of new karyotypic abnormalities, or the existence of clonal heterogeneity/evolution, which often signal a change in the pace of the disease, usually to a more aggressive course [11].

More so, the general principle in the application of Cytogenetics in the diagnosis and treatment of hematological malignancies considers the following: Quantitative changes in the transcript level which are used clinically to detect minimal residual disease and assess treatment response; Qualitative changes in the cells can be detected which may signify transformation to a more advanced stage or a more aggressive form of disease; Timing of disease process and the optimal timing of initiation of treatment [11].

Cytogenetic analyses are based upon the direct evaluation of the tumor cells. Tumor cells can be seen using tissue samples obtained from involved lymph nodes, tumor mass specimens, or malignant effusions, bone marrow aspiration, bone marrow biopsy or a sample of peripheral blood. The specimen is typically cultured for 24 to 48 hours. Conventional cytogenetic studies can be performed only on specimens that contain viable dividing cells; samples immersed in preservatives or fixatives cannot be used. Blood or bone marrow (5 mL) should be aspirated into a syringe coated with preservative-free heparin, and transferred to a tube containing an appropriate culture medium. It is critical that the specimen be transported at room temperature to the cytogenetics laboratory without delay [11].

Cytogenetic abnormalities may be detected using conventional metaphase cytogenetic analysis, fluorescence in situ hybridization (FISH) analysis, reverse transcription-polymerase chain reaction (RT-PCR), microarray-based genomic copy number analysis, or DNA or RNA sequencing. Conventional metaphase cytogenetic analysis is technically difficult, but allows for the examination of

the entire tumor genome. This is of particular importance in the evaluation of hematologic malignancies that have many potential genetic abnormalities (eg, acute myeloid leukemia). Florence In-Situ Hybridization (FISH) is a rapid and sensitive method of detecting recurring numerical and structural abnormalities. FISH is most useful when the analysis is targeted toward those abnormalities that are known to be associated with a particular tumor or disease. However, additional abnormalities or multiple clones will not be detected by this method alone. Therefore, the FISH technique serves in most clinical cases as a complement to conventional cytogenetic analysis. RT-PCR has high sensitivity and is ideally suited to detect fusion genes. The identity of the amplified product can be confirmed by DNA sequencing. The high sensitivity of RT-PCR means that patients in clinical remission can be tested to detect measurable residual disease (MRD; previously referred to as minimal residual disease). Genomic microarray technology using single nucleotide polymorphisms (SNPs) allows genome-wide association studies for the identification of disease susceptibility loci, and the identification of acquired abnormalities, such as genomic imbalances (eg, cryptic deletions and duplications), and loss of heterozygosity (LOH) that occurs without concurrent changes in the gene copy number as copy-neutral LOH, or uniparental disomy. Numerous studies have validated the diagnostic utility of this technology in hematologic malignancies; however, this technology is generally suboptimal for the detection of the balanced chromosome translocations or inversions. Alterations in the expression of the genes that are located at the breakpoints of the chromosomal translocations or in the properties of the encoded proteins play an important role in the process of malignant transformation. Of these, genes that encode proteins that regulate transcription are the most commonly involved. There are several mechanisms by which chromosomal translocations result in altered gene function, such as impaired regulation of gene expression and expression of a novel fusion protein.

Specific cytogenetic abnormalities identified by karyotype analysis or fluorescence in situ hybridization (FISH) analysis have prognostic significance for patients with primary MDS and affect treatment planning. Certain gene mutations also confer prognostic significance in adult patients with MDS, but it is not yet clear how to incorporate these changes into treatment planning. Even those patients without obvious abnormalities detected by karyotypic analysis, FISH, or gene mutation analyses likely have abnormalities in gene expression profiles or have acquired copy number alterations that may help to identify genes important for the pathogenesis of MDS [7].

Fluorescence In-Situ Hybridization is an advanced technological technique that identifies specific DNA sequences for the purpose of diagnosing human diseases associated with certain sets of genetic aberration. This technique is commonly employed in cancer diagnosis. It uses a fluorescent reporter molecule that targets a specific DNA sequence which lights up and can be identified using fluorescence microscopy [13].

This study aims to identify the Clinical and Cytogenetic profile (by FISH) of Filipinos with Myelodysplastic Syndrome in Makati Medical Center in the past 10 years (2011-2021). Specifically, to know the prevalence of Myelodysplastic Syndrome (MDS) in Filipino patients in Makati Medical Center who have Positive Fluorescence In Situ Hybridization (FISH) test and negative Fluorescence In Situ Hybridization (FISH) test seen as outpatient and inpatient. To know the **clinical profiles** of Myelodysplastic Syndrome (MDS) in Filipino patients in Makati Medical Center who have **Positive** Fluorescence In Situ Hybridization (FISH) test and **negative** Fluorescence In Situ Hybridization (FISH) test seen as outpatient and inpatient based on the demographics, clinical history, chief complaint, history of Present Illness, past medical history, family medical history, personal and social history and physical examination on initial consult.

Lastly, to know the most common **Complete blood count findings, Peripheral Blood smear findings, Bone marrow aspiration and biopsy findings, Whole abdominal Ultrasound findings, prognostic score (R-IPSS) computed** of Myelodysplastic Syndrome (MDS) in Filipino patients in Makati Medical Center on initial consult with the hematologist who have Positive Fluorescence In Situ Hybridization (FISH) test and negative Fluorescence In Situ Hybridization(FISH) test seen as outpatient and inpatient.

2. Methodology

A review of the 10-year chart record from 2011 to 2021 of the medical records department, lab-coordinator, external partners (NKTI, SLMC), and outpatient clinic charts were reviewed and included if they are 18 years old and above, MDS FISH test is done, initial consult done as outpatient or inpatient for reason attributable to MDS as diagnosed by hematologist, at any point of care with MDS as a consideration, formally referred to a Hematologist, clinical Diagnosis of MDS as diagnosed by a Hematologist in the year 2011 to 2021. A patient is excluded if the diagnosis is changed from MDS to other diagnoses in the middle of data collection not attributable to disease evolution or if the patient has been previously diagnosed with hematologic or oncologic malignancy. If a patient's diagnosis is MDS and a FISH test was requested and done with results available for review, it is included in the study sample and entered in the sample database. The included patients in-patient and outpatient charts were thoroughly reviewed and data on initial consultation about patient's clinical history and laboratories namely complete blood count, peripheral blood smear, whole abdominal ultrasound, bone marrow aspiration and biopsy histology. The patient will be enrolled in the study to document work-up done including and most importantly FISH test, the patient name, age, gender will be listed in the MMC MDS FISH Study database. Once inclusion and exclusion criteria have been met, an identification code was assigned for each enrolled patient (Eg. MDS MMC 001). The code INPT indicates that the patient was referred while still admitted while the code OPT will indicate that the patient was initially seen as outpatient. Encoding of patient's demographics, clinical history, Physical examination findings, functional status, baseline

CBC on referral, PBS on referral, Bone Marrow Aspiration and Biopsy findings. Whole Abdominal Ultrasound findings in the MDS MMC Enrollment Database was done. Patients with MDS FISH test positive results were assigned to the MDS-FISH Positive Arm for clinical observation. An identification number was assigned under the test positive arm. (Eg. MDS MMC FISH+ 001). Patient's data is transferred to MDS-FISH Positive excel data collection file and succeeding observational notes and data were encoded here as well. Patients with MDS FISH Test negative were assigned to MDS-FISH Negative Arm for clinical observation. An identification number was assigned under the test negative arm. (Eg. MDS MMC FISH - 001). Patient's data were transferred to MDS-FISH Negative excel data collection file and succeeding observational notes and data were encoded. Diagnosed patients regardless of the MDS FISH test status, will be scored based on the IPSS-R scoring system. Prevalence of MDS FISH positive and negative patients was determined and Quantitative and Qualitative findings were recorded. Results between two arms will be identified and compared using SPSS and with the assistance of the resident statistician of the institution. Pearson Coefficient correlation will be used to establish association between clinical profile and MDS FISH result and T-test. A 95% confidence interval has been used.

All statistical analysis was done using STATA version 15. Categorical data were presented as frequency and percentage. Differences in the characteristics between MDS FISH+ and MDS FISH- were compared using Chi-Square test or Fischer's Exact Test, whichever is applicable. P values <0.05 were considered statistically significant.

3. Results

A total of 240 patients have been registered from the outpatient and inpatient chart search from 2011 to 2021 with Myelodysplastic Syndrome as diagnosis in the chart. A total of 35 patients were noted to have MDS FISH test done based on orders in the chart and available test retrieved directly from the third-party center (National Kidney and Transplant Institute) where the FISH test is done. A total of 85% were considered drop out since they don't have an available MDS FISH test result. There were four patients who were removed from the list even if they had a FISH test done since they were diagnosed with Non-MDS Disease namely chronic lymphocytic leukemia, Anemia of chronic disease (2), and Aplastic Anemia. Among the 35 patients with MDS FISH test done, 60% (N=21) were noted to be negative in the mutation while 40% (N=14) were noted to have positive test results. The most common mutation seen is 7q31 deletion (N=10) with 23% of among with results followed by 5q31 deletion (N=9) with 21% of those tested and at 5% (N=2) are those with monosomy 7 and trisomy. There were no documented mutations for monosomy 5 and 20q12 deletion. In view of the prognostication group, majority (N=28, 80%) of those tested are categorized under Good cytogenetic group followed by intermediate cytogenetic group at 17%, N=6 and lastly by 1 patient(3%) under poor cytogenetic group. The most cytogenetic mutation was determined to be three (3) found in only one patient. Majority did not show any mutation (N=21,49%) followed by 1 cytogenetic mutation(N=10, 23%), and 2 cytogenetic mutations(N=3,7%). The youngest in the series is 36 years old while the oldest in the record is 87 years old with a mean age of 70 years □13 years. Majority of those with FISH positive test belong to the age group 60-69 years (N=5,36%), 70-79 years (N=4,29%) while those with FISH negative test majority belong to the age group 60-89 years (N=12, 57%). There is an almost equal distribution of FISH positive and negative in both sexes. Majority (N=25, 71%) of patients were initially seen and worked-up as in-patients. In both FISH positive and negative patients, the most common chief complaint and reason for referral is Anemia, followed by pancytopenia and bicytopenia (Anemia, Thrombocytopenia). Majority of the patients have Hypertension, Diabetes Mellitus, Heart Disease and Hypothyroidism. Family history reveals Hypertension, Diabetes Mellitus Type 2, and heart disease are prevalent in the family of the patients. There is no difference in the distribution of those with positive FISH test among smokers, non-smokers and alcoholic beverage drinkers and non-alcoholic beverage drinkers. In the negative FISH test, a significant majority are non-smoker and nonalcoholic beverage drinkers. Majority of both with positive and negative FISH tests were noted to have pallor and generally normal physical examination on initial assessment. Complete Blood Count of patients with MDS FISH positive test result shows a majority of Hemoglobin of 8 and above (N=10, 71%) while those with negative test majority of Hemoglobin is below 8 (N=10, 71%). Majority of ANC was noted to be 800 and above. Platelet counts were noted to be 50,000 and above for about 17% of those with FISH positive test while those with 13% of those with negative test. A significant majority of patients have no morphologic diagnosis since Bone marrow aspiration biopsy was not done. Thirteen out of fourteen FISH positive tests had no BMA and biopsy done; the same with the 19 out of 21 FISH negative test patients; more than 90% of the patients have no documented Peripheral blood smear, more than 70% have no whole abdominal ultrasound results. The overall R-ISS shows 93% has incomplete data for the FISH positive test group while 90% in the FISH negative test group. Considering the available data, for the FISH positive group, 43% were classified as intermediate risk, 36% as low risk and 21% as very low risk. For the FISH negative group, 52% were classified as Low risk, 24% for both Very Low risk and Intermediate risk. No patient in both groups has reached the High risk score group and beyond. The performance scores on initial consult were not recorded in any of the consultation records. There was no noted significant difference in the clinical profile between the two groups. Please see below for tables and Appendix A for other tables.

Table 1. 2011-2021	f	%
Total MDS Cases	240	100
MDS Cases with FISH Test	35	15
No FISH Test	205	85

Table 1: 2011-2021.

Table 2. MDS Cases with FISH Test	MDS FISH+	MDS FISH-
N of Test Results	14	21
% Share	40	60

Table 2: MDS Cases with FISH Test.

Table 3. Cytogenetic group	f	%
Very good: del(11q) or -Y	0	0
Good: normal karyotype, del(20q), del(5q), del(12p), or double including del(5q)	28	80
Intermediate: +8, del(7q), i(17q), +19, or any other single or double independent clone	6	17
Poor: -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), or complex (3 abnormalities)	1	3
Very poor: complex >3 abnormalities	0	0

Table 3: Cytogenetic group.

Table 4. Cytogenetics	f	%
5q31 deletion	9	21
Monosomy 5	0	0
7q31 deletion	10	23
Monosomy 7	2	5
20q12 deletion	0	0
Trisomy	2	5
Normal	22	51

Table 4: Cytogenetics.

Table 5. No of Cytogenetics Mutation	f	%
0	21	49
1	10	23
2	3	7
3	1	2
4	0	0
5	0	0

Table 5: No of Cytogenetics Mutation.

Table 6. Age Distribution	MDS FISH+ (n=14)	MDS FISH-(n=21)	p-value
30-39	1 (7.1)	0 (0.0)	0.623
40-49	0	2 (9.5)	
50-59	2 (14.3)	1 (4.8)	
60-69	5 (35.7)	6 (28.6)	
70-79	4 (28.6)	5 (23.8)	
80-89	2 (14.3)	6 (28.6)	
90-100	0	1 (4.8)	

Table 6: Age Distribution

Table 7. Sex Distribution	MDS FISH+ (n = 14)	MDS FISH-(n=21)	p-value
Male	7 (50.0)	10 (47.6)	0.890
Female	7 (50.0)	11 (52.4)	

Table 7: Sex Distribution.

Table 8. Area of Initial Consult	MDS FISH+ (n=14)	MDS FISH- (n=21)	p-value
In-Patient	10 (71.4)	15 (71.4)	1.000
Out-Patient	2(14.3)	3(14.3)	
NoResponse	2(14.3)	3(14.3)	

Chief Complaint	MDS FISH+ (n = 14)	MDS FISH- (n=21)	p-value
Low hgb	5 (35.7)	5 (23.8)	1.000
Pancytopenia	2 (14.3)	1 (4.8)	
Low hgb, low plts	1 (7.1)	2 (9.5)	
Easy fatigability	1 (7.1)	1 (4.8)	
Blurring of vision	1 (7.1)	0	
Gum bleeding	1 (7.1)	0	
Incidental findings	0	1 (4.8)	
Low wbc	0	1 (4.8)	
Fever	0	1 (4.8)	
Body weakness	0	1 (4.8)	
Dizziness	0	1 (4.8)	
Palpitation	0	1 (4.8)	
No response	3 (21.4)	4 (19.0)	
Generalized body weakness	0	1 (4.8)	
Multiple erythematous papules on both lower legs	0	0	
Shortness of breath	0	1 (4.8)	

Past Medical History	MDS FISH+ (n=14)	MDS FISH- (n=21)	p-value
Hypertension	5 (35.7)	12 (57.1)	0.214
DM2	5 (35.7)	7 (33.3)	0.884
Post-surgical	2 (14.3)	5 (23.8)	0.490
Post-chemotherapy	1 (7.1)	1 (4.8)	1.000
PTB	1 (25.0)	3 (14.3)	0.635
Colon CA	2 (14.3)	0	0.153
Aneurysm	1 (7.1)	0	0.400
CVD	1 (7.1)	0	0.400
Hyperthyroidism	1 (7.1)	0	0.400
Hypothyroidism	3 (21.4)	0	0.056
Dyslipidemia	2 (14.3)	1 (4.8)	0.551
Heart Disease	1 (7.1)	5 (23.8)	0.366
CKD	2 (14.3)	4 (19.0)	1.000
Raynauds Disease	1 (7.1)	0	0.400
Breast CA	1 (7.1)	1 (4.8)	1.000
Potts Disease	0	1 (4.8)	1.000
UTI	0	1 (4.8)	1.000
Atherosclerotic Vascular Disease	0	1 (4.8)	1.000
Fatty Liver	0	1 (4.8)	1.000
Colonic Diverticulosis	0	1 (4.8)	1.000
Aplastic Anemia	0	2 (9.5)	0.506
Lymphoma	0	1 (4.8)	1.000
Bronchial Asthma	0	1 (4.8)	1.000
Gastritis	0	1 (4.8)	1.000
BPPV	0	1 (4.8)	1.000
Gouty Arthritis	0	1 (4.8)	1.000
BPH	0	1 (4.8)	1.000
Depression	0	1 (4.8)	1.000

Family Medical History	MDS FISH+ (n = 14)	MDS FISH- (n=21)	p-value
Hypertension	3 (21.4)	8 (38.1)	0.298
Bronchial Asthma	1 (7.1)	2 (9.5)	1.000
Ovarian CA	0	0	
Prostate CA	1 (7.1)	0	0.400
Breast CA	1 (7.1)	1 (4.8)	1.000
Bone CA	1 (7.1)	0	0.400
DM2	3 (21.4)	8 (38.1)	0.298
Lung CA	0	2 (9.5)	0.506
MDS	0	1 (4.8)	1.000
CVD	0	1 (4.8)	1.000
Liver CA	0	1 (4.8)	1.000
CA	0	2 (9.5)	0.506

Heart Disease	0	3 (14.3)	0.259
MPN	0	1 (4.8)	1.000

Personal and Social Medical History	**MDS FISH+ (n=14)**	**MDS FISH- (n=21)**	**p-value**
Smoker	5 (35.7)	1 (4.8)	0.045
Non-Smoker	4 (28.6)	12 (57.1)	
No data	5 (35.7)	8 (38.1)	
Alcoholic Drinker	4 (28.6)	4 (19.0)	0.820
Non-Alcoholic Drinker	4 (28.6)	7 (33.3)	
No data	6 (42.9)	10 (47.6)	

Physical Examination	**MDS FISH+ (n = 14)**	**MDS FISH- (n=21)**	**p-value**
Pallor	4 (28.6)	6 (28.6)	0.680
Generally normal	4 (28.6)	6 (28.6)	
No data	3 (21.4)	5 (23.8)	
Inflamed gingiva with caries	1 (7.1)	0	
Fever	0	1 (4.8)	
Edema	0	2 (9.5)	
Pallor, edema	1 (7.1)	0	
Purpura, edema	1 (7.1)	0	
Pallor, weak-looking, tachycardia	0	1 (9.5)	

CBC	MDS FISH+ (n = 14)	MDS FISH- (n=21)	p-value
Hgb 10 and above	5 (35.7)	3 (15.0)	0.307
8 to 10	5 (35.7)	5 (25.0)	
<8	3 (21.4)	10 (50.0)	
No data	1 (7.1)	2 (10.0)	
ANC 800 and above	10 (71.4)	13 (61.9)	0.877
<800	2 (14.3)	3 (14.3)	
No data	2 (14.3)	5 (23.8)	
Platelets 100 and above	4 (28.6)	9 (42.9)	0.575
50-100	3 (21.4)	5 (23.8)	
<50	5 (35.7)	3 (14.3)	
No data	2 (14.3)	4 (19.0)	

Medullary Blast	**MDS FISH+ (n=14)**	**MDS FISH- (n=21)**	**p-value**
≤2	1 (7.1)	2 (9.5)	
>2 to <5	0	0	
5 to 10	0	1 (4.8)	
>10	0	0	
No Data	7	12	
No BMA	6	6	
Total	14	21	

R-ISS	MDS FISH+ (n=14)	MDS FISH- (n=21)	p-value
Very Low (1.5 and below)	3 (21.4)	5 (23.8)	0.472
Low (>1.5 to 3)	5 (35.7)	11 (52.4)	
Intermediate (>3 to 4.5)	6 (42.9)	5 (23.8)	
High (>4.5 to 6)	0	0	
Very High (>6)	0	0	

Table 8: Area of Initial Consult.

4. Discussion

Myelodysplastic syndrome is an underdiagnosed disease entity mostly among developing countries, especially the Philippines. Access to tests and specialists has been a great challenge to overcome adding up to the burden of difficult diagnosis. The result seen in this study spanning for 10 years has highlighted the need to standardize the diagnostic process for Myelodysplastic syndrome in practice as well as the need to subsidize the test utilized to confirm the diagnosis to allow more Filipino patients to be diagnosed appropriately. The results in this study in view of age are consistent with the mean age of patients with MDS in the literature [14]. A clinical profile study done in Kozhikode, India [15] shows the same mean age result. This is contrary to the clinical profile study done by Ankita Sen in West Bengal India [16] where mean age was 55 years old. Sex distribution was noted to be consistently predominantly male in published literature but in our study male and female had a 1:1 ratio. Fatigue was consistently the most common symptom together with pallor as the most common sign. Anemia is the most common reason for referral. Low hemoglobin or Anemia was found as the most common reason for consultation to a hematologist as opposed to fatigue which is seen in the literature reaching 90% of the afflicted patients. Anemia was also noted to be the most common cytopenia in this study but few needed transfusion as compared to those seen in literature where most anemic requires red cell transfusion due to mean Hgb of 5.5 g/dl. Platelet levels and White cell count in this study is not severely affected since 71% of patient had ANC above 800 cells (mean 4,167.9□5761), while 50% has been noted to have platelets above 50,000 with mean Platelet of 133,000□137,000. In the Indian study the mean few patients had platelet count above 50,000 (18%) and mean ANC above 4095/dl. Very few patients had results of their peripheral blood smear, bone marrow aspiration biopsy and whole abdominal ultrasound. The literature shows that the majority of the patients with MDS show multilineage dysplasia and uncommonly with ringed sideroblast. Peripheral blood smear may be an insignificant test for MDS since it was not included in the test to be reviewed in both Indian studies. Past medical history, family history, personal and social history were not included in the MDS clinical profile study in the literature. The most common cytogenetic findings in this study is normal MDS FISH which is about 51% of those tested. This is the same in the two Indian studies which is about 48.3% and 65.4% of the sample tested. But the most common mutation in these studies were monosomy 7 with deletion 5q and 5q deletion respectively. The same were noted in this study where 7q31 deletion (23%) and 5q deletion (21%) were the most prevalent mutations. 5q deletion is considered as a good prognostic marker with a 5-year treatment survival of 54% [18]. Lenalidomide is an immunomodulatory agent that has a particular suppressing effect in 5q deletion clones [17]. Using the R-ISS to analyze the sets of data, more than 90% of the sample was noted to have incomplete data. Only 1 patient has complete data in MDS FISH + patients while 2 patients in MDS FISH negative. In the same Indian studies, the most common R-ISS category of patients is Intermediate Risk (36.5%) and Low Risk (48.3%). The Revised International prognostic Scoring system has determined the prognostic risk categories where cytogenetics, Bone marrow blast percentage, level of cytopenias (Hemoglobin, platelets, Absolute Neutrophil count) are assigned to specific risk scores. Risk Categories have been assigned to 5 classes namely Very Low risk, Low risk, Intermediate, High, Very High with median overall survival in years of 8.8, 5.3, 3, 1.6 and 0.8 respectively. The risk to 25% AML evolution median time is 10.8 years in Low risk, 3.2 years in Intermediate years, 1.4 years in High risk and 0.73 years in Very High risk. Overall, the result of this study has shown that there is no significant difference in the clinical profile of those patients diagnosed with Myelodysplastic syndrome in view of the FISH test results. In the presence of karyotyping as part of work for prognostication, FISH tests rarely add additional value [19]. A prospective type of study is recommended to be done to improve the quality of results obtained.

5. Conclusion

This study has highlighted the clinical profile of Filipino patients with Myelodysplastic Syndrome which has shown no difference in view of cytogenetic mutation by Fluorescence-in-situ-hybridization. Using R-ISS as a prognostication tool is a well validated tool and has proven beneficial in predicting the clinical outcome of patients with untreated myelodysplastic syndrome. Thus, full work-up with the goal of establishing a patient's prognosis is imperative to deliver a holistic treatment decision. In view of this, utilizing the private-public partnership through the effort of the society of hematologists to subsidize the cost of work-up is needed to provide better hematology care for the Filipino community.

Consent

This study underwent the Makati Medical Center's Internal Research Board approval.

Competing Interests

There is no competing interest in making this study.

Author's Information

The author is a registered nurse, trained in Oncology and intensive care; A graduate of Medical Doctor degree in University of the East Ramon Magsaysay Memorial Medical Center Inc.,; Had his Internal Medicine training in Victor R Potenciano Medical Center; currently doing his Hematology fellowship, Year 3, in Makati Medical Center. Has presented and published research papers in Hong Kong, Dubai, UAE and Valencia, Spain.

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