博士論文

A clinical study of hypoplastic myelodysplastic syndrome

(a nationwide multicenter retrospective study)

（低形成性骨髄異形成症候群の臨床病態に関する研究

（全国多施設後方視的研究））

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Contents

Abstract

Hypoplastic myelodysplastic syndrome (hMDS) is a new entity of MDS characterized by bone marrow (BM) hypocellularity and the risk of death from BM failure (BMF). Adequate treatments for hMDS are unknown. To elucidate the characteristics of hMDS, a nationwide retrospective study was conducted. The data of 143 hMDS patients, diagnosed between April 2003 and March 2012, were collected from 21 institutions and the central review team of the Idiopathic Disorders of Hematopoietic Organs Research Committee, and compared with those of 143 non-hMDS patients. More patients of RA and fewer patients of RAEB-t and CMMoL in FAB classification, and more RCUD and MDS-U in WHO classification were found in hMDS compared with non-hMDS. The overall survival (OS) and AML progression-free survival (AML-PFS) of hMDS were higher than those of non-hMDS patients, which were attributed to hMDS of lower risk groups in IPSS and IPSS-R. Competing risks analysis exhibited that hMDS patients face lower risk of AML-progression, which were attributed to lower-risk hMDS, and higher risk of death from BMF, which were attributed to older and higher-risk hMDS. The hMDS patients at age <50 and of low risk had no risk of AML-progression and death from BMF. Cox proportional hazards models revealed that poor performance status (PS ≥2) and high karyotype risks in IPSS-R (poor and very poor) were significant risk

factors of death and progression to AML. Subset analysis of histology-proven MDS was performed to confirm that the study including patients diagnosed without biopsy still represents the characteristics of histology-proven hMDS.

1. Introduction

Myelodysplastic syndrome (MDS) is a group of hematopoietic stem cell disorders characterized by bone marrow (BM) dysplasia, which leads to ineffective production of normal blood cells, proliferation of blasts, and a risk of progression to acute myeloid leukemia (AML). [1]

The total number of MDS patients was estimated at approximately 3000 on September 1, 1991, and the incidence rates were 3.4 per 100000 men and 2.1 per 100000 women of age 15 and above. [2] As aging of the entire Japanese population progressed, this number increased to approximately 7100 in 1998. [3]

The MDS was originally mentioned and described in the early twentieth century as pseudoaplastic anemia as a combination of cytopenia and BM hypercellularity. [4, 5] This entity came to be regarded as refractory anemia, a group of disorders found with anemia which were refractory to the available therapies in those days. [5-7] When the French-American-British (FAB) classification of acute leukemia was proposed, the non-leukemic hematological disorders not requiring treatments immediately, as a whole, were described as MDS. [8] The FAB classification of MDS was also proposed in 1982, which summarized MDS into 5 categories, as follows: refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess of blasts

(RAEB), RAEB in transformation (RAEB-t), and chronic myelomonocytic leukemia (CMMoL). [9] This classification has been applied to the clinical practice by hematologists worldwide for its simplicity and clarity, but as it came to be revealed that MDS has more diverse features, the World Health Organization (WHO) classification was proposed. [10, 11] This classification was featured with the following aspects: (1) the chromosome abnormalities were taken into account as a factor of this classification, and (2) the threshold of the BM blast count was redefined as 20% instead of 30%, although whether the MDS with BM blast >20% (RAEB-t) should be regarded as acute myeloid leukemia (AML) or not is still controversial.

Based on the FAB classification, the International Prognostic Scoring System (IPSS) was proposed and widely used for evaluating the clinical outcomes and predicting the prognoses of MDS. [12] This system was refined recently with a much larger size of population, and proposed as the revised IPSS (IPSS-R), [13] which has been proved to predict the prognoses of MDS better than IPSS. [14, 15] The population for this new system includes MDS with BM blast >20% as well, so it is adequate to include RAEB-t when applying IPSS-R to the prediction of the prognoses of MDS.

The median overall survival (OS) of MDS varies from 8.8 years to 0.8 years, depending on the risk groups of MDS, [13] and some MDS patients live for more than a

decade without any treatments. Despite the fact that allogeneic hematopoietic stem cell transplantation (HSCT) is the only method that provides ultimate cure for MDS, therefore, not all of the MDS patients require immediate treatments. Asymptomatic MDS patients may need frequent examinations, laboratory studies and BM studies, but do not require intensive treatments. For MDS patients with symptomatic cytopenia, best supportive care (BSC) is indicated, such as erythrocyte and platelet transfusion for anemia and thrombocytopenia, and antibiotics for bacterial infection caused by neutropenia, respectively. The administration of recombinant granulocyte colony-stimulating factor (G-CSF) may have risk for MDS to progress to AML, [16] so it is not included in BSC as a routine therapy for neutropenia, and the indication of G-CSF needs most careful consideration even for symptomatic pancytopenia of MDS patients treated with myelo-suppressing chemotherapies. Administration of vitamin D_3 and vitamin K_2 as well as vitamin B_6 may be administered to low-risk MDS, although the evidence for the efficacy of vitamin therapy is limited. [17, 18] Anabolic steroids have also been administered despite its limited evidence of efficacy for MDS. [19-21] Immunosuppressive therapy (IST) with cyclosporin A (CsA) and/or anti-thymocyte globulin (ATG) has been studied and exhibited some treatment response for MDS, but IST may not be effective for all MDS. [22] For the anemia of low-risk MDS without the

deletion of 5q (5q-) in the chromosome, the recombinant erythropoietin (EPO) may be effective if the serum EPO level is <500 U/l, [23] but neither the administration of EPO nor the measurement of serum EPO for MDS is under the coverage of the health insurance, so it is not indicated in Japan. For low-risk MDS with 5q-, it has been shown that lenalidomide improves hematopoiesis, and it has come to be covered by health insurance. [24] These treatments, as well as BSC, have been applied to symptomatic low-risk MDS, for there has been little evidence that intensive treatments such as combination chemotherapy improve the OS of these MDS patients. Azacitidine is a novel, DNA-hypomethylating agent that is applicable to MDS in all risk groups and improves the OS of MDS in higher risk groups, but it did not exhibit the significant improvement of OS for MDS in low and intermediate-1 risk groups, so it is considered as a treatment of MDS in higher risk groups, especially the MDS of the elderly patients to whom allogeneic HSCT is not indicated. [25-27] Allogeneic HSCT is indicated for intermediate-2 and high risk groups of MDS in IPSS as soon as they are diagnosed, and it is also indicated for lower-risk MDS patients when new chromosome abnormalities appear, the cytopenia progresses to its transfusion-dependent status, or to a higher risk group. [28] Low-dose combination chemotherapy is often administered for the purpose

of blast control, although there is no acknowledged evidence that intensive or low-dose combination chemotherapy improves the survival of MDS.

The origin of the concept of hypoplastic MDS (hMDS) can be traced back to as early as late 1960s, when it was acknowledged that some of the aplastic anemia (AA) eventually developed hypoplastic leukemia. [29] As the morphological dysplasia and hypocellularity of BM were revealed in some of the patients with BM failure (BMF) at their preleukemic stages, [30] it has come to be suggested that the AA can be divided into two subgroups, namely the hypocellular MDS which has some risk to progress to AML, and the AA whose BM is not dysplastic. [31] The former subgroup was renamed as hMDS and recognized as a new disease entity of MDS characterized by BM hypocellularity and dysplasia. [32]

There have been a few studies that dealt with hMDS as a subgroup of either AA or MDS in the early literature. Fohlmeister I et al. studied the iliac crest biopsies of the hypocellular BM of 111 cases to find out that cellular atypia of megakaryocytes were found in 21 patients (19%), most of whom (19 patients) eventually developed acute non-lymphatic leukemia, and that the patients with three or more morphological features exhibited higher risk to progress to acute leukemia. [31] Although they did not divide the population clearly into hMDS and AA, they concluded that hMDS patients

have 23-82% risk to develop acute leukemia within 3 years. Therefore, the concept of hMDS arose as a subgroup of AA that has morphological atypia and some risk of progression to acute leukemia.

Nand S and Godwin JE, who called this entity hMDS for the first time, reported that 11 of 64 MDS patients (17%) were found with the BM cellularity ≤25%, who exhibited no abnormal karyotype and higher rates of OS than non-hMDS. [32] They concluded that hMDS appears to be a distinct entity of MDS with severer pancytopenia, lower frequency to progress to acute leukemia, and no abnormalities of the karyotype.

Yoshida Y et al. dealt with 33 cases of refractory myelodysplastic anemia (RMDA) with hypocellular BM (7.7%), which consisted of RA, RARS, and RAEB in FAB classification but not RAEB-t, and concluded that hypocellular RMDA and non-hypocellular RMDA exhibit similar prognoses. [33] Likewise, Maschek H et al. studied 352 primary MDS patients to find out that 42 of them (12%) were hMDS, but they also exhibited similar OS to those of non-hMDS, as well as lower frequencies of morphological atypia and more karyotype abnormalities involving chromosome 7 than non-hMDS, and a high incidence of hMDS to develop acute leukemia (33%). [34]

Thus, they all acknowledge hMDS as a new, distinct entity of MDS, but its prognosis is still controversial, and a study of hMDS with a larger size of population is desirable.

Hematologists perform BM aspiration as an essential procedure to diagnose the hematological disorders, and the BM cellularity is roughly estimated as hypocellular, normocellular or hypercellular by microscopic views of the smeared samples of the BM aspirates at low power. [35-39] There exists some evidence that BM cellularity estimated by BM aspirate and its clot sample correlate with the cellularity measured by BM biopsy, [40, 41] but this estimate may deviate from the cellularity of BM biopsy due to the contamination of sinusoidal blood. [41] Therefore, the rigorous definition of BM cellularity has been given only for the biopsy sample. [42, 43]

The criterion for the hypocellularity of BM varied from ≤25% to <30% in the previously published literature, [32, 34] while some other studies were without any threshold criterion for BM hypocellularity. [31] However, based on the evidence that BM cellularity decreases with aging, [44] a stratified criterion of BM cellularity <30% for patients younger than age 60 and <20% for patients older than age 60 has been proposed for the definition of hMDS, [33, 45] while others propose a stratification for BM cellularity of hMDS at age 70. [46, 47]

It is often difficult but desirable to distinguish hMDS from AA, because both the treatments and prognosis of hMDS may differ from AA. [48] Although there have been several reports to propose the criteria for distinction, such as CD34-positive BM cell analysis and measurement of tumor necrosis factor receptors, [49, 50] the morphological study of the BM still remains to be the standard way of diagnosing hMDS and distinguishing it from AA.

The concept of BMF was first mentioned and described in detail in early 1960s by Harris JW, who stated that "Bone marrow failure can be said to exist when, in absolute terms, a normal number of erythrocytes is not delivered to the peripheral blood. In addition bone marrow failure exists when the marrow does not increase its production as much as would a normal marrow in response to the same stimulus." [51] The BMF was first dealt with as anemia from all kinds of etiologies, including AA, hypoplastic anemia, sideroachrestic anemia, and anemia associated with malignancy, rheumatoid arthritis, renal disease, liver disease, chronic infection, endocrine abnormalities, ionizing radiation, myelophthisis, myelofibrosis, and osteoporosis, while the concept of MDS had not been established in those days. [52]

The BMF syndrome is discussed nowadays as the heterogeneous group of disorders with hematopoiesis that result in anemia, leucopenia and/or thrombocytopenia,

which includes AA, MDS, and paroxysmal nocturnal hemoglobinuria (PNH) as the representative entities. [47] The concept of BMF has been discussed either morphologically or pathologically, but hardly quantitatively. Gordon-Smith EC studied 16 patients with pancytopenia of peripheral blood (PB) at the following criteria: hemoglobin <12.5 g/dl for men, <11.5 g/dl for women; neutrophils <2500 /μl; platelets <150000 /μl; and no blasts/promyelocytes. [52] In this study, patients were categorized into two groups: AA, and RA with proliferative dysplasia; the former was the group of patients found with hypocellular BM, and the latter was the group with normocellular or hypercellular BM. The group of AA exhibited fairly good response to oxymetholone and did not require blood transfusion after the discontinuation of oxymetholone, whereas the group of RA with proliferative dysplasia exhibited relapses of pancytopenia slowly after the discontinuation of oxymetholone. This study was an attempt to explain pancytopenia with BM hypercellularity, and in terms of AA and MDS today, the latter group may represent a group of normo-/hypercellular MDS but not hMDS. Furthermore, the majority of the MDS patients may satisfy the PB criteria of pancytopenia mentioned above, and the risk of death from BMF should be discussed with much severer criteria when dealing with hMDS.

On the other hand, Mizoguchi H et al. dealt with the effect of EPO on the BM cells of patients with BMF in vitro, for which the samples were aspirated from the BM of patients who had presented with pancytopenia, refractoriness to hematopoietic agents (iron, vitamin B_6/B_{12}, or folic acid), hypocellular BM, and decreased erythropoiesis measured by ^{59}Fe. [53] The samples for this study in vitro may represent the population of the BMF syndrome, including both AA and hMDS, but they were not separable with responsiveness to EPO alone, and the information on the morphological dysplasia of these BM cells were not given in this study.

Bennett JM and Orazi A proposed diagnostic procedures to distinguish hMDS from AA, but morphological studies of blood cells in BM and PB may not be sufficient, and other techniques such as immunohistochemistry may be required as well. [54]

A study by Huang TC et al. is the only study in the latest literature that dealt with hMDS specifically in comparison with non-hMDS according to the risk groups of IPSS. [55] In this study, they showed that hMDS has more favorable prognosis than non-hMDS, especially in lower risk groups (low and intermediate-1 in IPSS), and that hMDS also has lower risk to progress to acute leukemia. The prognosis according to IPSS-R and the risk of death from BMF were not dealt with in this study, and since IPSS-R was made available and proved to predict the clinical outcomes of MDS better

than IPSS, [14, 15] it is desirable to investigate the outcomes of hMDS according to IPSS-R as well. Another prognostic scoring system was proposed as the WHO classification-based Prognostic Scoring System (WPSS), which includes the WHO classification and transfusion dependence as the prognostic variables. [56, 57] This scoring system is well known, but has not been applied to the clinical practice of hematologists as much as the IPSS.

The standard therapy for hMDS remains unknown, but there have been a few reports on the treatments specifically for hMDS. A report from Czech included 9 hMDS patients in the total of 17 MDS patients to whom CsA was administered, and 8 hMDS patients (89%) responded well to CsA alone or in combination with other agents such as EPO, but such responsiveness was observed in non-hMDS patients as well. [58] In contrast, a report from the United Kingdom included 2 hMDS patients in the total of 6 patients, who all responded poorly to CsA and remained transfusion-dependent. [59] A larger study of IST with ATG and CsA by Sloand EM et al. included 43 hMDS patients (33%), some of whom responded well to IST, but their responses were not discussed separately from non-hMDS patients. [22, 60] The patients in these studies did not progress to acute leukemia after IST, but there is a report on a patient with hMDS who

transformed to AML after the administration CsA for only a few months, [61] so it remains to be studied to what extent IST is indicated for hMDS.

A study on successful allogeneic HSCT including one patient with hMDS has been reported, [62] but the age of this patient was 19; another study on the randomized study to compare the outcomes of two preconditioning regimens for allogeneic HSCT for AA and hMDS, but only 4 of them were hMDS patients, and the median age of this study was 34, much younger than the median of the hMDS patients. [63] The accumulation of data on the outcomes of HSCT for hMDS including the elderly patients is desired.

Little has been discussed on the patient backgrounds of hMDS. The median age of hMDS in the previously published literature varied from 46 to 69, [32-34, 46, 55, 64] whereas some other cases of much younger patients with hMDS have also been reported. [62] The majority of hMDS patients were male, [33, 46, 55, 64] although there were some studies with more female hMDS patients than male. [32, 34] More than 50% of hMDS patients were RA in FAB classification. [32, 24, 55] Other background information, such as past medical histories, family histories and smoking habits, has hardly been discussed. Furthermore, there has been no clinical study on hMDS that dealt with IPSS-R.

The purpose of this study is to compare the patient backgrounds, clinical characteristics, treatment responses, and prognosis of hMDS patients with those of non-hMDS patients by nationwide multicenter survey, retrospectively analyze the survival and risk factors for death and AML-progression of these patients, and elucidate the characteristics of hMDS. In particular, this study is focused on the prognosis of subpopulations according to the age and risk groups of hMDS.

2. Materials and methods

2.1. Participations of institutions and approvals of their ethics committees

The medical institutions participating in the National Research Group on Idiopathic Bone Marrow Failure Syndromes and its central review team were contacted by e-mail on September 10, 2012. The protocol of this study was approved by the Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo (No. 3949), and by the ethics committee of each participating institution.

The nationwide survey data were collected from the institutions willing to participate in this study and from the database of the central review team by October 7, 2013. The actual contents of the survey, as well as the documents submitted to the Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo, are attached in the appendix.

2.2. Eligibility of patients and the period for the patient data of this study

The MDS patients according to French-American-British (FAB) classification, who had been diagnosed as hMDS between April 2003 and March 2012, were enrolled in this study, and their medical records and data were studied throughout the same period. The patients diagnosed as MDS in FAB classification before April 2003 were

included in this study and observed from April 2003 if they were diagnosed by BM analysis between April 2003 and March 2012 and had been untreated until April 2003; those who had not been diagnosed by BM analysis between April 2003 and March 2012 were excluded from the study.

The data collected for this study included the patient's clinical characteristics such as age at diagnosis, sex, past medical history and family history of malignancies and/or hematological diseases, performance status (PS), complete blood counts (CBC), blasts in PB and BM, cellularity of BM, chromosome abnormalities, FAB and WHO classifications, risk groups of international IPSS and IPSS-R, treatments, the dates of initial diagnosis, progression to AML, and death or the last follow-up. The data of the hMDS patients were compared with those of non-hMDS patients of The University of Tokyo Hospital in terms of clinical characteristics, survival, risk factors, causes of death, and responses to treatments.

2.3. Criteria for the hypocellularity of hMDS

The criteria for the hypocellularity of hMDS for this study are the BM cellularity <30% for patients at age <60, and <20% for age ≥60; [33, 44, 45] for patients diagnosed without BM biopsy, the same criterion was applied to the clot samples of the BM aspirates. [40, 41, 53] The MDS with the BM cellularity above these criteria were

regarded as non-hMDS. Therefore, the patients who had been diagnosed as hMDS at the participating institutions but did not meet these criteria of BM cellularity were excluded from the study. Also, the patients whose data did not contain the evidence for the BM hypocellularity of hMDS were excluded from the study.

2.4. BM aspiration and trephine biopsy

The techniques of BM aspiration and biopsy are described in the literature by pathologists. [65-70] The aspirated sample of the BM is transferred to a Wintrobe hematocrit tube and centrifuged to calculate the percentage of BM cellularity as (1–"fat fraction")×100 (%). [70, 71] Likewise, the BM cellularity of the trephine biopsy sample is calculated in the same way by the point-counting method as shown in Hartsock RJ et al. [44, 72]

2.5. FAB classification for MDS

The classification system for MDS proposed by the FAB cooperative group categorizes MDS into 5 groups, primarily by the BM blast percentage, as follows: [9]

Refractory anemia (RA); BM blasts <5%, PB blasts <1%, no Auer rods, monocytes ≤1000 /μl, ringed sideroblasts ≤15% of nucleated erythroids in BM. Neutropenia or thrombocytopenia instead of anemia can also be included in this category.

RA with ringed sideroblasts (RARS); the same as RA, except for ringed sideroblasts >15% of nucleated erythroids in BM.

RA with excess blasts (RAEB); BM blasts between 5% and 20%, PB blasts <5%, no Auer rods, and monocytes ≤1000 /μl.

RAEB in transformation (RAEB-t); BM blasts between 21% and 30%, or PB blasts ≥5%.

Chronic myelomonocytic leukemia (CMMoL); BM blasts ≤20%, PB blasts <5%, and monocytes >1000 /μl.

All of the patients enrolled in this study were patients with MDS in FAB classification. At least one lineage should be found with some morphological dysplasia, although the FAB cooperative group did not specify the threshold percentage of dysplastic cells. The patients with cytopenia in at least one lineage but with neither morphological dysplasia nor chromosomal abnormalities were regarded as AA and excluded from the study. The WHO classification suggested the threshold percentage of dysplastic cells in at least one lineage for the diagnosis of MDS, which will be described below.

2.6. WHO classification for MDS

The classification system for MDS proposed by WHO takes both the explicit threshold percentage of dysplasia and cytogenetic abnormalities into account, and categorizes MDS into 7 groups, as follows: [10, 11]

Refractory cytopenia with unilineage dysplasia (RCUD); RA, refractory neutropenia (RN), or refractory thrombocytopenia (RT); mono-/bicytopenia, unilineage dysplasia (defined as ≥10% of dysplastic cells in only one lineage), BM blasts <5%, ringed sideroblasts <15% of nucleated erythroids in BM, and PB blasts <1%.

RARS; anemia, only the erythroid dysplasia in BM, ringed sideroblasts ≥15% of nucleated erythroids in BM, BM blasts <5%, and no PB blasts.

Refractory cytopenia with multilineage dysplasia (RCMD); cytopenia(s), multilineage dysplasia (defined as dysplasia in ≥2 lineages), BM blasts <5%, PB blasts <1%, monocytes <1000 /μl, and no Auer rods in both BM and PB.

RAEB-1; cytopenia(s), uniliniage or multiliniage dysplasia, 5-9% blasts in BM, PB blasts <5%, monocytes <1000 /μl, and no Auer rods in both BM and PB.

RAEB-2; cytopenia(s), uniliniage or multiliniage dysplasia, 10-19% blasts in BM, 5-19% blasts in PB, monocytes <1000 /μl.

MDS-unclassified (MDS-U); cytopenias, dysplasia of <10% cells in at least one lineage and cytogenetic abnormalities, BM blasts <5%, PB blasts <1%.

MDS associated with isolated del(5q) (5q- syndrome); anemia, normal/increased megakaryocytes (MgK) with hypolobulated nuclei, del(5q) but no other cytogenetic abnormalities, no Auer rods in BM and PB, BM blasts <5%, PB blasts <1%, and usually normal/increased platelets.

The RAEB-t in FAB classification was excluded from MDS and included in AML, and CMMoL was also excluded from MDS and included in the new category of myelodysplastic/myeloproliferative neoplasms (MPN).

As given above, WHO classification gives the recommended threshold percentage of dysplasia in any of the three lineages, and if the dysplastic cells do not exceed 10%, it is considered as MDS-U when cytogenetic abnormalities were detected but excluded from MDS when no cytogenetic abnormalities were detected.

2.7. Morphological manifestations of dysplasia

Various kinds of dysplasia, while without the threshold percentage of nuclear cells in BM, were listed as a part of the FAB classification. [9] As the threshold percentage was given at 10% for significant dysplasia in the WHO classification, a much simpler list of dysplasia was given as follows: [10, 11]

Dyserythropoiesis; nuclear budding, internuclear bridging, karyorrhexis, multinuclearity, nuclear hyperlobulation, megaloblastic changes, ring sideroblasts, vacuolization, and periodic acid-Schiff positivity.

Dysgranulopoiesis; small or unusually large size, nuclear hypolobulation (pseudo Pelger-Huët), irregular hypersegmentation, hypogranularity, agranularity, pseudo Chédiak-Higashi granules, and Auer rods.

Dysmegakaryocytopoiesis; micromegakaryocytes, nuclear hypolobation, and multinucleation.

This list of dysplasia was used for the diagnosis of patients enrolled in this study, and the detection of >10% dysplastic cells in each lineage was regarded as significant dysplasia.

2.8. Chromosome abnormalities of MDS

When the new classification for MDS was proposed by WHO, the chromosome abnormalities frequently observed among MDS patients were given as follows: [11]

+8, -7/del(7q), -5/del(5q), del(20q), -Y, i(17q)/t(17p), -13/del(13q), del(11q), del(12p)/t(12p), del(9q), idic(X)(q13), t(11;16)(q23;p13.3), t(3;21)(q26.2;q22.1), t(1;3)(p36.3;q21.2), t(2;11)(p21;q23), inv(3)(q21q26.2), t(6;9)(p23;q34).

This list was given in the survey for this study to categorize the hMDS patients into 4 groups of IPSS. [12] According to the risk groups of IPSS-R, however, some of the chromosome abnormalities, such as –Y and del(11q), exhibit better prognoses than the normal karyotype, and even the prognoses of patients with -7 and those with del(7q) differ from one another. [13] Therefore, the results of chromosome abnormalities were obtained in full detail from the participating institutions and the hMDS patients who had been enrolled in this study were categorized according to the IPSS-R as well.

2.9. Risk groups of IPSS

The International MDS Risk Analysis Workshop collected the data of 816 patients and analyzed them to propose a new prognostic scoring system. [12] The score values for three prognostic variables are as follows:

BM blasts; 0 for <5%, 0.5 for 5-10%, 1.5 for 11-20%, and 2.0 for 21-30%.

Karyotype; 0 for good (normal, -Y, del(5q) only, del(20q) only, -Y), 1.0 for poor (complex (≥3 abnormalities) or chromosome 7 anomalies), and 0.5 for intermediate (other abnormalities).

Cytopenias; 0 for cytopenia in 0/1 lineage, and 0.5 for cytopenia in 2/3 lineages.

The score values of these three prognostic variables were summed up to evaluate the risk of death and AML-progression as follows:

Low, 0; Intermediate-1 (Int-1), 0.5-1.0; Intermediate-2 (Int-2), 1.5-2.0; and High, ≥2.5.

2.10. Risk groups of IPSS-R

A new system to predict the prognoses of MDS patients by studying a much larger population of 7012 MDS patients was proposed recently as the IPSS-R. [13] This system has the following prognostic variables:

Cytogenetics; 0 for the very good karyotype risk group (-Y, del(11q)), 1 for the good karyotype risk group (normal, del(5q), del(12p), del(20q), and double including del(5q)), 2 for the intermediate karyotype risk group (del(7q), +8, +19, i(17q), and any other single or double independent clones), 3 for the poor karyotype risk groups (-7, inv(3)/t(3q)/del(3q), double including -7/del(q), and 3 complex abnormalities), and 4 for the very poor karyotype risk groups (>3 complex abnormalities).

BM blasts (%); 0 for ≤2, 1 for >2 and <5, 2 for 5-10, and 3 for >10.

Hemoglobin (g/dl); 0 for ≥10, 1 for ≥8 and <10, and 1.5 for <8.

Platelets ($\times 10^4$ /μl); 0 for ≥10, 0.5 for ≥5 and <10, and 1 for <5.

Absolute neutrophil count (/μl); 0 for ≥800, and 0.5 for <800.

The scores of these 5 prognostic variables were summed up to evaluate the risk of death and AML-progression as follows:

Very low, ≤1.5; low, >1.5 and ≤3; intermediate, >3 and ≤4.5; high, >4.5 and ≤6; and very high, >6.

2.11. Statistical methods

2.11.1. Two-sample t-test and Fisher's exact test

After the normality of the continuous background variables for both hMDS and non-hMDS, such as age, complete blood counts (CBC) and blast percentage of the PB, and BM blast percentage, was tested by Shapiro-Wilk test, [73] the two-sample version of Student's *t*-test was applied to test whether the means of the background values of hMDS differ from those of non-hMDS. [74-76] For continuous background variables whose equality of variance was rejected by the variance test, [77, 78] Welch's *t*-test was applied. [79] The median, range, and *P*-value were given for each variable. The criterion for the significance is $P<0.05$ throughout this study. [80, 81]

For discrete categorical variables, such as sex, past illness, family history, smoking habits, FAB classification, WHO classification, IPSS and IPSS-R, Fisher's exact test was applied to calculate the *P*-values. [82] The number of patients for each category and its percentage were given.

2.11.2. Kaplan-Meier method and log-rank test for OS and AML-PFS

The OS was defined as the time from the initial diagnosis to death; patients who had been alive at the last follow-up were censored. AML progression-free survival (AML-PFS) was defined as the time from the initial diagnosis to the date on which the patient is found with leukemia either by CBC or bone marrow analysis or to the date of death. The Kaplan-Meier method was used to compute the estimates of the OS and AML progression-free survival (AML-PFS), [83] and the plots of the Kaplan-Meier estimates were depicted as the survival curves, with the percentage of survival on the vertical axis and the survival years on the horizontal axis.

To compare the survival distributions of hMDS and non-hMDS, or of the subgroups within the hMDS population, log-rank test was applied to estimate the *P*-values. [84-87]

The OS and the AML-PFS of hMDS patients as a whole were estimated first, and the hMDS patients were divided further into subgroups according to their ages and risk groups of IPSS and IPSS-R to investigate their rates of survival for each category. Based on the distributions of the survival curves of hMDS, the population was divided into two subpopulations according to their ages and risk groups, so that the OS and the AML-PFS of hMDS and non-hMDS would be analyzed for those subpopulations as

well to find out which subpopulations the differences in the rates of survival between hMDS and non-hMDS were attributed to. Furthermore, the subset analysis was performed for the patients whose rates of survival exhibited the most significant differences between hMDS and non-hMDS.

As mentioned earlier, the BM cellularity was originally defined for BM biopsy, [42, 43] although the BM cellularity estimated by the clot of the BM aspirate correlate well with that of the BM biopsy. [40, 41] Therefore, the subset analysis of histology-proven MDS patients (i.e., the MDS patients diagnosed by BM biopsy) were performed, and the OS and the AML-PFS of histology-proven hMDS patients were compared with those of histology-proven non-hMDS patients.

Also, the MDS patients were divided by their initial treatments, and the OS for each initial treatment was analyzed and compared between hMDS and non-hMDS. For the subgroups of MDS patients who were with no treatment and those with BSC, the survival time was measured from the day of diagnosis (or from April 1, 2003 for those who had been diagnosed as MDS before and diagnosed again sometime between April 2003 and March 2012) to March 31, 2012 (or to the day on which the patient was censored); and for the subgroups of MDS patients treated with other treatments, the survival time was measured from the first day of the initial treatment. As mentioned in

the Introduction, G-CSF is not administered routinely to patients with neutropenia, and the indication of G-CSF needs most careful consideration because of its risk to increase AML-progression. [16] Therefore, G-CSF was not included in BSC for this study.

2.11.3. Competing risks analysis and the definition of death from BMF

The competing risks analysis model was applied to analyze the risk of AML-progression, with the possibility of death from other causes into account. [88] The 5-year cumulative incidence of AML-progression was given for hMDS and non-hMDS. Furthermore, the subset analysis was performed according to the ages and risk groups of IPSS and IPSS-R.

As mentioned in the introduction, there have been no adequate threshold criteria to diagnose and deal with BMF, although it has been defined and discussed pathologically as a group of hematological disorders characterized by the failure of BM to produce the normal levels of blood cells in PB. [47, 51, 52] For the purpose of this study to analyze the risk of death from pancytopenia, the criterion for the death from BMF was defined as the death caused by the cytopenia of at least two lineages; the death from cytopenia as a result of suppression by the extreme infiltration of blasts in BM/PB was excluded. The results of the analysis were given in the same way as the subset analysis for AML-progression.

2.11.4. Cox proportional hazards regression models

The risk factors of death and AML-progression were analyzed for hMDS patients, non-hMDS patients, and all patients (both hMDS and non-hMDS), using the univariate and multivariate Cox proportional hazards models. [86, 89] The categorical variables for Cox proportional hazards models were:

Sex; male =1, and female=0.

Performance status (PS); 1 for score ≥2, and 0 for score <2.

Karyotype risks of IPSS-R; 1 for poor and very poor, and 0 for very low, low and intermediate.

Past illness and family history (of malignancies and/or hematological diseases) and smoking; 1 for with, and 0 for without.

The data of continuous background variables were used in the analysis as they were. The univariate Cox proportional hazards analysis was performed for each background variable, whose hazard ratio, 95% confidence interval (C. I.), and *P*-value were given as well.

For the multivariate Cox proportional hazards analysis, the statistically significant risk factors were selected from the results of the univariate analysis, and the variables were selected to minimize the Akaike information criterion. [90]

2.11.5. Two-sample Kolmogorov-Smirnov test

In order to confirm further whether it was adequate to include the MDS patients diagnosed with BM aspiration but without BM biopsy, the two-sample Kolmogorov-Smirnov test was applied to compare the distributions of the continuous background variables of histology-proven MDS patients with those of MDS patients diagnosed with BM aspiration alone. [91-93] This test was used to test the null hypothesis that the distributions of a continuous variable from two samples differed from one another. The two-sample Kolmogorov-Smirnov statistics is defined as

$$D_{n,m} = \sup_x \left| F_{1,n}(x) - F_{2,m}(x) \right|$$

where $F_{1,n}(x)$ and $F_{2,m}(x)$ are the cumulative distribution function of the first sample with the sample size of n and that of the second sample with the sample size of m, respectively. The null hypothesis is rejected if

$$D_{n,m} > c(\alpha)\sqrt{\frac{n+m}{nm}}$$

where $c(\alpha)$ is the coefficient that varies depending on the confidence level. In this study, the confidence level was set at $\alpha = 0.05$, and in this case this value is $c(\alpha) = 1.36$.

Likewise, in order to confirm the randomness of the non-hMDS patients, the distributions of the continuous background variables of the non-hMDS patients from

The University of Tokyo Hospital were compared with those of the non-hMDS patients from the database of the central review team by the two-sample Kolmogorov-Smirnov test, so that the data of the non-hMDS patients from The University of Tokyo Hospital could be regarded as the randomly sampled data and proved be comparable with the data of the hMDS patients collected from all over this nation.

The advantage of the Kolmogorov-Smirnov test is that it does not require any specific probability distribution, and the only requirement for this test is the existence of the moment generating function, which gives the representative statistical values of the population such as the mean and the variance. Therefore, it is applicable to the clinical data of any populations, which may not always follow the normal distribution.

2.11.6. R: the statistical program package for this study

R is a programming package for statistical analysis and graphics, originally created by Ross Ihaka and Robert Gentleman at the University of Auckland, New Zealand (http://cran.r-project.org). [94] An increasing number of articles published in the medical journals have been using R for their statistical analyses (http://www.okada.jp.org/RWiki/).

Throughout this study, all of the statistical analyses were performed using R version 3.0.0. [94, 95]

3. Results

3.1. Patients enrolled in this study

Thirty-four of the 54 institutions responded to the preliminary survey (63.0%); 28 institutions agreed to participating in the study, 4 institutions had no hMDS cases, and 2 institutions withdrew from the study. The data of 143 patients with hMDS were collected from 21 institutions and from the central review team of the National Research Group on Idiopathic Bone Marrow Failure Syndromes by September 7, 2013. These data were compared with 143 non-hMDS cases of The University of Tokyo Hospital. Excluding 2 institutions whose total numbers of MDS patients were unknown, the percentage of hMDS patients was 6.3% (139/2200) (Appendix).

3.2. Patient backgrounds

Table 1 provides the demographic and clinical characteristics of patients at their initial diagnoses, and some of them are depicted in Figure 1 as well. The number of hMDS patients with family histories of malignancies and/or hematological diseases was significantly fewer than that of non-hMDS patients (Table 1A, Figure 1B). Patients with hMDS exhibited significantly lower platelet, neutrophil and blast counts in PB than non-hMDS patients (Table 1A, Figure 1F – 1H). Also, statistically significant differences between hMDS and non-hMDS patients were found in FAB classification

Table 1. Patient characteristics at initial diagnosis

Table 1A. Patient backgrounds, PB counts and BM blast counts

Variables	hMDS (*N*=143)	non-hMDS (*N*=143)	*P*-value
Age, years			0.58
Median (range)	65 (16-90)	65 (15-88)	
Sex			0.22
Male (%)	85 (59)	96 (67)	
Female (%)	57 (40)	47 (33)	
Unknown (%)	1 (0.70)	0 (0)	
Past illness† (%)	48 (34)	40 (28)	0.45
Family history† (%)	22 (15)	49 (34)	<0.001*
Smoking (%)	37 (26)	69 (48)	<0.001*
Hemoglobin, g/dl			0.66
Median (range)	9.2 (4.9-14.3)	8.9 (4.4-15.7)	
Platelet, $\times 10^4/\mu l$			0.0011*
Median (range)	7.1 (0.60-44.2)	9.2 (0.50-86.8)	
Neutrophil, $\times 10^3/\mu l$			0.0011*
Median (range)	1.2 (0.042-9.9)	1.3 (0.11-36)	
PB blast, %			0.018*
Median (range)	0 (0-19)	0 (0-16)	
BM blast, %			0.31
Median (range)	2.0 (0-29)	2.7 (0-25)	

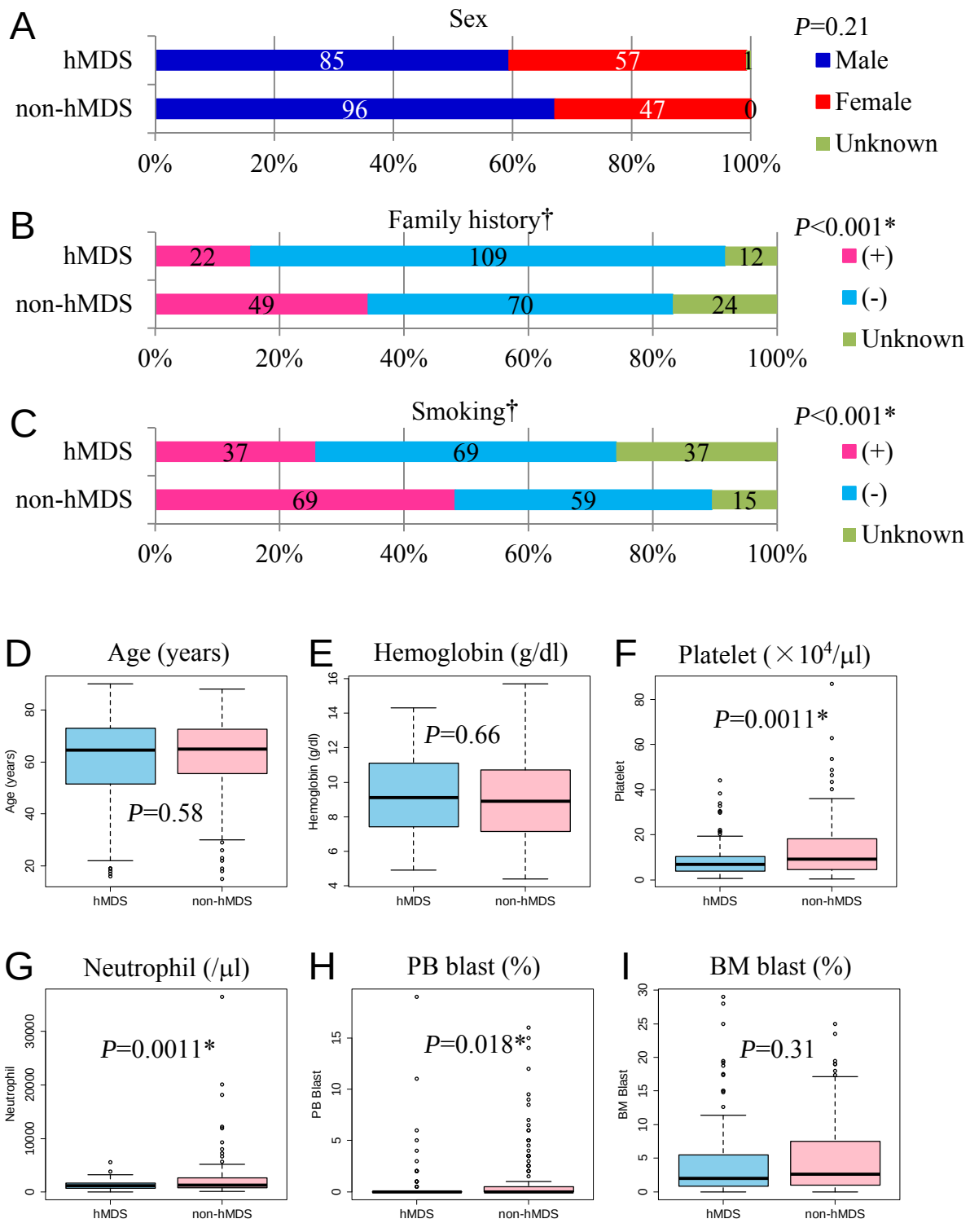
The *P*-values of the continuous variables (age, hemoglobin, platelet, neutrophil, PB blast, and BM blast) were given by two-sample *t*-test, and those of the categorical variables (sex, past illness, family history, and smoking) were given by Fisher's exact test. The sample size is *N*=143 for both hMDS and non-hMDS. hMDS: hypoplastic myelodysplastic syndrome. *: statistically significant. †: of malignancies and/or hematological diseases. PB: peripheral blood. BM: bone marrow.

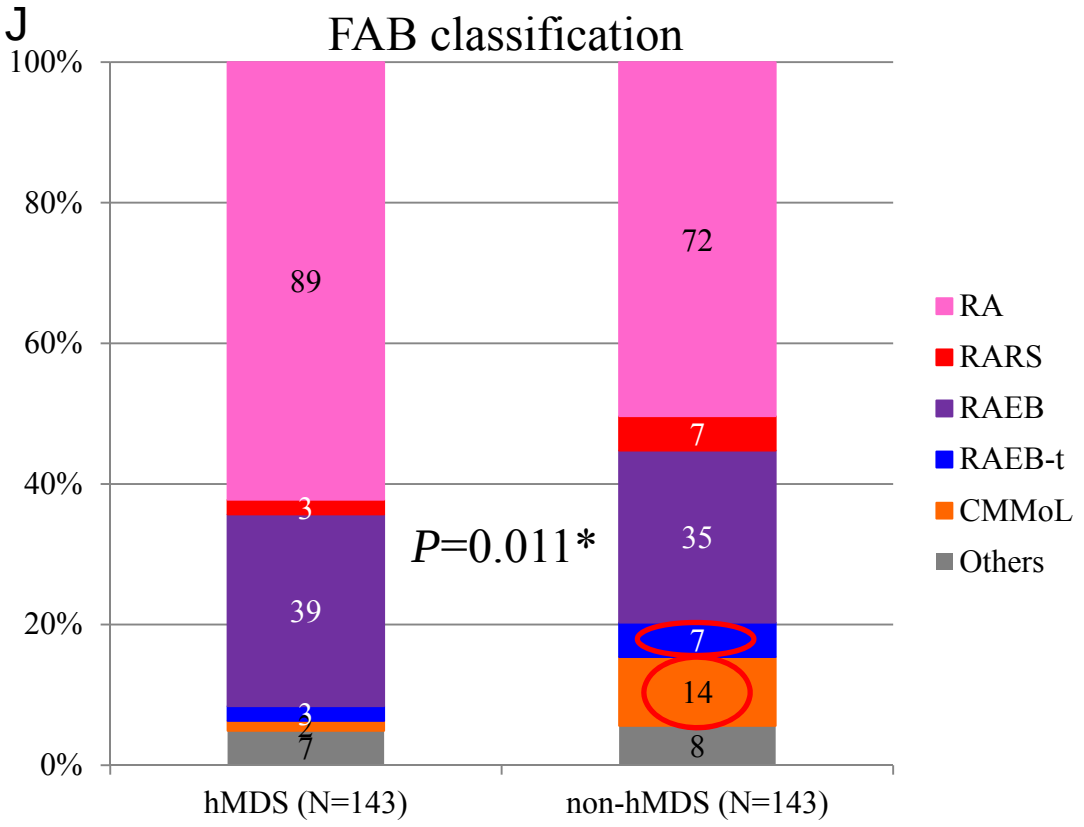
Table 1B. Patient backgrounds, FAB and WHO classifications

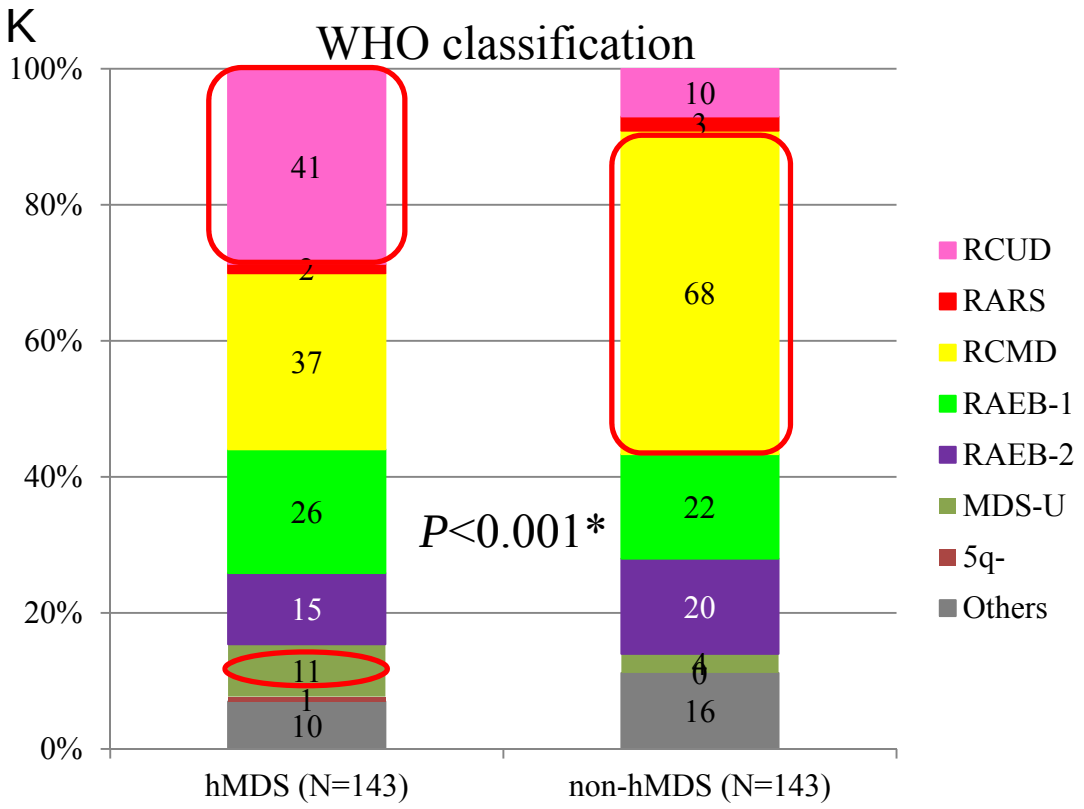
Variables	hMDS (*N*=143)	non-hMDS (*N*=143)	*P*-value
FAB classification (%)			<0.001*
RA	89 (62)	72 (50)	
RARS	3 (2.1)	7 (4.9)	
RAEB	39 (27)	35 (24)	
RAEB-t	3 (2.1)	7 (4.9)	
CMMoL	2 (1.4)	14 (9.8)	
Unknown/others	7 (4.9)	8 (5.6)	
WHO classification (%)			<0.001*
RCUD	41 (29)	10 (7.0)	
RARS	2 (1.4)	3 (2.1)	
RCMD	37 (26)	68 (48)	
RAEB-1	26 (18)	22 (15)	
RAEB-2	15 (10)	20 (14)	
MDS-U	11 (7.7)	4 (2.8)	
5q-	1 (0.70)	0 (0)	
Unknown/others	10 (7.0)	16 (11)	
IPSS (%)			0.56
Low	20 (14)	22 (15)	
Intermediate-1	69 (48)	71 (50)	
Intermediate-2	37 (26)	32 (22)	
High	10 (7.0)	15 (10)	
Unknown	7 (4.9)	3 (2.1)	
IPSS-R (%)			0.47
Very low	10 (7.0)	8 (5.6)	
Low	40 (28)	43 (30)	
Intermediate	35 (24)	37 (26)	
High	26 (18)	25 (17)	
Very high	22 (15)	27 (19)	
Unknown	10 (7.0)	3 (2.1)	

The *P*-values of the categorical variables (FAB classification, WHO classification, IPSS, and IPSS-R) were given by Fisher's exact test. The sample size is *N*=143 for both hMDS and non-hMDS. hMDS: hypoplastic myelodysplastic syndrome. FAB: French-American-British. WHO: World Health Organization. IPSS: International Prognostic Scoring System. IPSS-R: revised IPSS. *: statistically significant. †: malignancies and/or hematological diseases.

Figure 1: Graphs of the patient backgrounds




J
FAB classification
100%
80%
60%
40%
20%
0%
89
3
39
3
2
7
72
7
35
7
14
8
P=0.011*
hMDS (N=143)
non-hMDS (N=143)
RA
RARS
RAEB
RAEB-t
CMMoL
Others


K
WHO classification
100%
80%
60%
40%
20%
0%
41
2
37
26
15
11
1
10
10
3
68
22
20
4
0
16
P<0.001*
hMDS (N=143)
non-hMDS (N=143)
RCUD
RARS
RCMD
RAEB-1
RAEB-2
MDS-U
5q-
Others

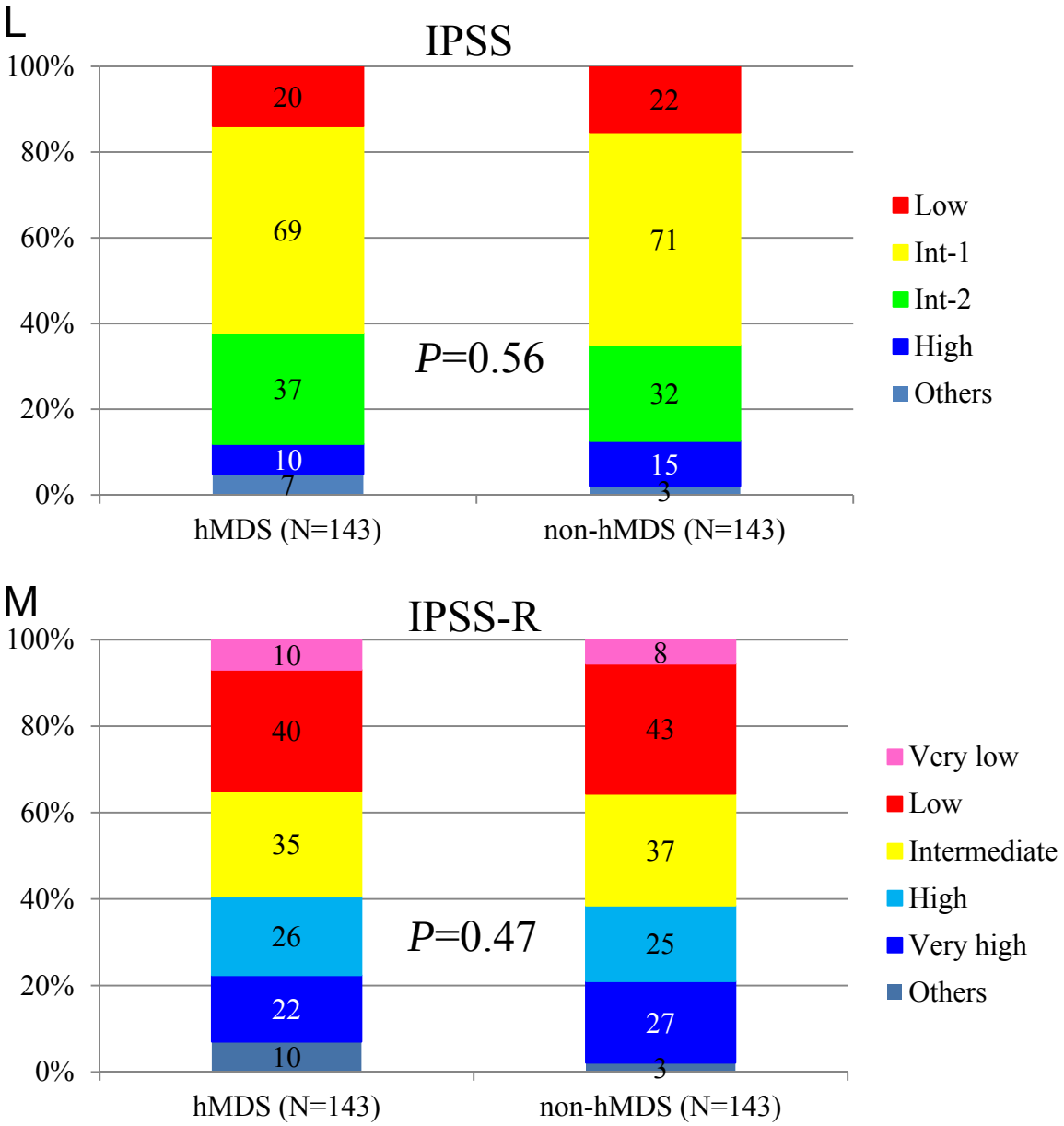


Figure 1: The graphs of some of the background variables given in Table 1. The sample size is *N*=143 for both hMDS and non-hMDS. The *P*-values of the categorical variables (sex, family history, smoking, FAB classification, WHO classification, IPSS, and IPSS-R) were given by Fisher's exact test, and the continuous variables (age, hemoglobin, platelet, neutrophil, PB blast, and BM blast) were given by two-sample *t*-test. hMDS: hypoplastic myelodysplastic syndrome. *: statistically significant. †: of malignancies and/or hematological diseases. PB: peripheral blood. BM: bone marrow. FAB: French-American-British. WHO: World Health Organization. IPSS: International Prognostic Scoring System. IPSS-R: revised IPSS.

and WHO classification; in particular, more patients with RAEB-t and CMMoL were found in non-hMDS than in hMDS (Table 1B, Figure 1J), and the percentage of RCUD was higher in hMDS patients whereas that of RCMD was higher in non-hMDS patients, and more MDS-U patients were found in hMDS patients than in non-hMDS patients (Table 1B, Figure 1K), whereas the differences between hMDS and non-hMDS in other characteristics such as past medical histories were not statistically significant.

3.3. The distributions of the background variables of non-hMDS patients

Only the data of hMDS patients were collected from the participating institutions, and in order to reveal the characteristics of hMDS in comparison with non-hMDS, the data of non-hMDS patients from The University of Tokyo Hospital were used. In order to confirm the adequacy of this sample, the two-sample Kolmogorov-Smirnov test was applied to the data of continuous background variables of non-hMDS patients from The University of Tokyo Hospital and those of non-hMDS patients from the database of the central review team of the National Research Group on Idiopathic Bone Marrow Failure Syndromes (Table 2). The database of the central review team consisted of the data of patients sent from all over this nation for the confirmations of the diagnoses. In this central review database, 74 patients were diagnosed as non-hMDS between April 2003 and March 2012 ($m = 74$ in the formulae

of $D_{n,m}$ in 2.11.5.) and the sample size of the non-hMDS patients from The University of Tokyo Hospital is 143 ($n = 143$ in the formulae of $D_{n,m}$ in 2.11.5.). For these sample sizes, the null hypothesis that these two distributions differ is rejected if $D_{143,74} > 0.19$. The *D*-values for the continuous background variables did not satisfy this inequality, and it was confirmed that the non-hMDS patients of The University of Tokyo Hospital and those of the central review database can be interpreted to follow the same probability distribution, which can also be interpreted as a randomly sampled population.

Table 2. Two-sample Kolmogorov-Smirnov test for the non-hMDS of UT and CR.

Variables	Kolmogorov-Smirnov	
	D-value	*P*-value
Age, years	0.15	0.25
Hemoglobin, g/dl	0.098	0.74
Platelet count, $\times 10^4/\mu l$	0.11	0.56
Neutrophil count, /μl	0.12	0.54
PB Blast, %	0.12	0.54
BM blast, %	0.15	0.24

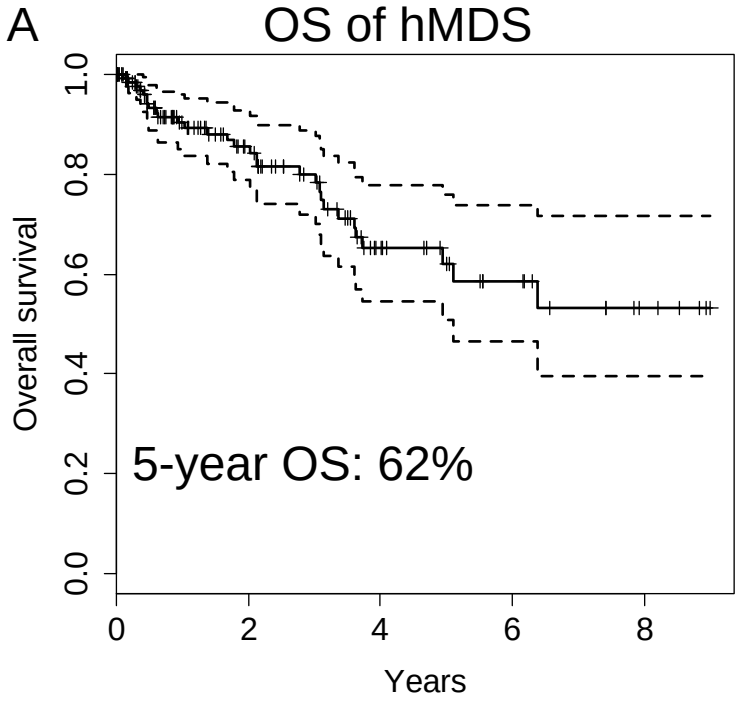
Testing the equality of the distributions of the non-hMDS patients from The University of Tokyo Hospital and those from the central review database of the National Research Group on Idiopathic Bone Marrow Failure Syndromes. The numbers of the non-hMDS patients of UT and CR are 143 and 74, respectively ($n = 143$ and $m = 74$ for the formulae in 2.11.5.), and the null hypothesis that the two one-dimensional probability distributions are the same is rejected if *D*-value exceeds 0.19. In all of these continuous background variables, two populations proved to be from the same distribution by Kolmogorov-Smirnov test. UT: The University of Tokyo Hospital. CR: The central review team of the National Research Group on Idiopathic Bone Marrow Failure Syndromes. PB: peripheral blood. BM: bone marrow.

3.4. The OS and the AML-PFS of hMDS

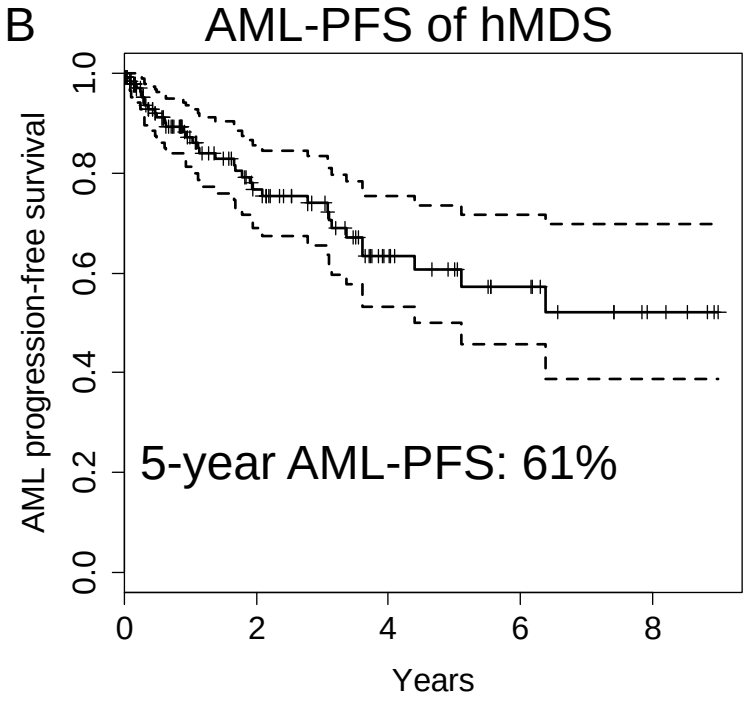
The OS and the AML-PFS of hMDS patients were evaluated by Kaplan-Meier method, and analyzed further by dividing the hMDS patients into two groups according to the age, IPSS, and IPSS-R (Figure 2). The 5-year OS of hMDS patients was 62% (95 % confidence interval (C. I.) = 51 to 76%) (Figure 2A), whereas their 5-year AML-PFS was 61% (95% C. I. = 50 to 74%) (Figure 2B). Patients at age <50 showed significantly higher 5-year OS and AML-PFS than patients at age ≥50 (94% versus 55% (P=0.014), and 94% versus 53% (P=0.0058), respectively) (Figure 1C, 1D). According to the IPSS, 5-year OS and AML-PFS were significantly higher in low and intermediate-1 risk groups than in intermediate-2 and high risk groups (77% versus 31% (P<0.001), and 80% versus 24% (P<0.001), respectively) (Figure 2E, 2F), whereas the 5-year OS and AML-PFS in very low, low and intermediate risk groups in IPSS-R were significantly higher than in high and very high risk groups (88% versus 8.1% (P<0.001), and 88% versus 7.3% (P<0.001), respectively) (Figure 2G, 2H).

The dichotomies of the hMDS population by age, IPSS, and IPSS-R were based on the survival analyses according to the original age groups and risk groups (Figure 2I – 2N), in which the rates of OS and AML-PFS could by divided into age <50 and age ≥50, low – int-1 and int-2 – high, and very low – intermediate and high – very

Figure 2. OS and AML-PFS of hMDS



hMDS (*N*=143)	143	70	32	18	11



hMDS (*N*=142)	142	62	34	18	11

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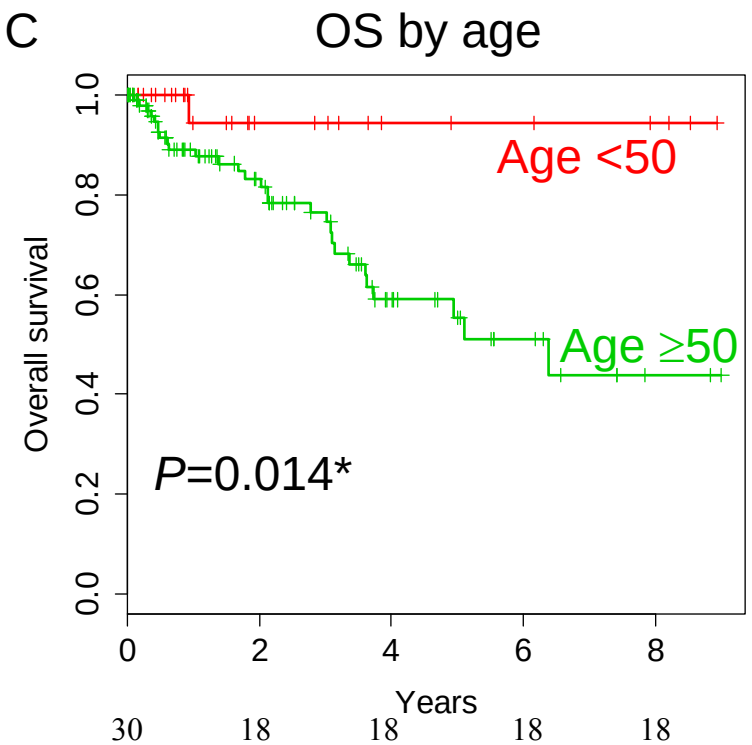
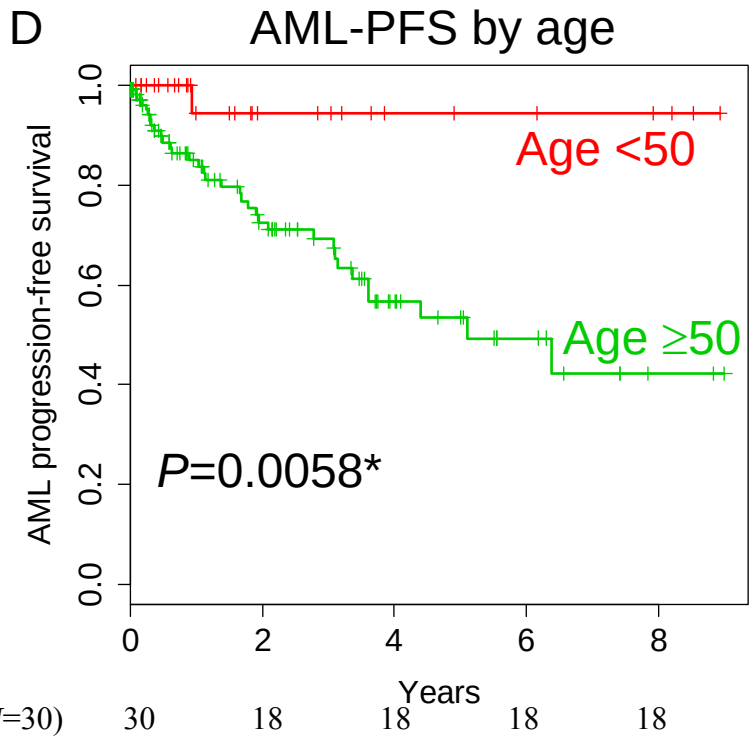


Age <50 (*N*=30)	30	18	18	18	18
Age ≥50 (*N*=113)	113	56	25	13	7



Age <50 (*N*=30)	30	18	18	18	18
Age ≥50 (*N*=112)	112	51	26	13	7

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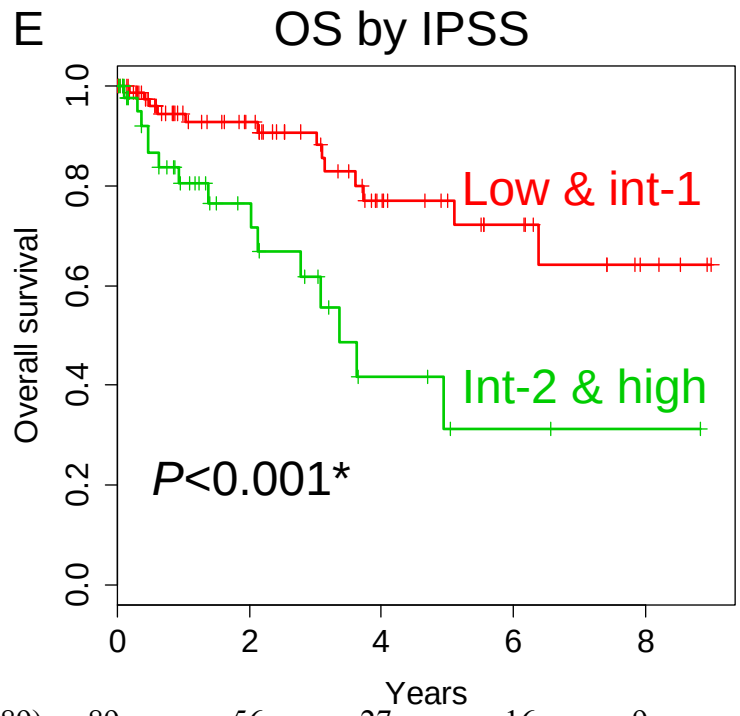
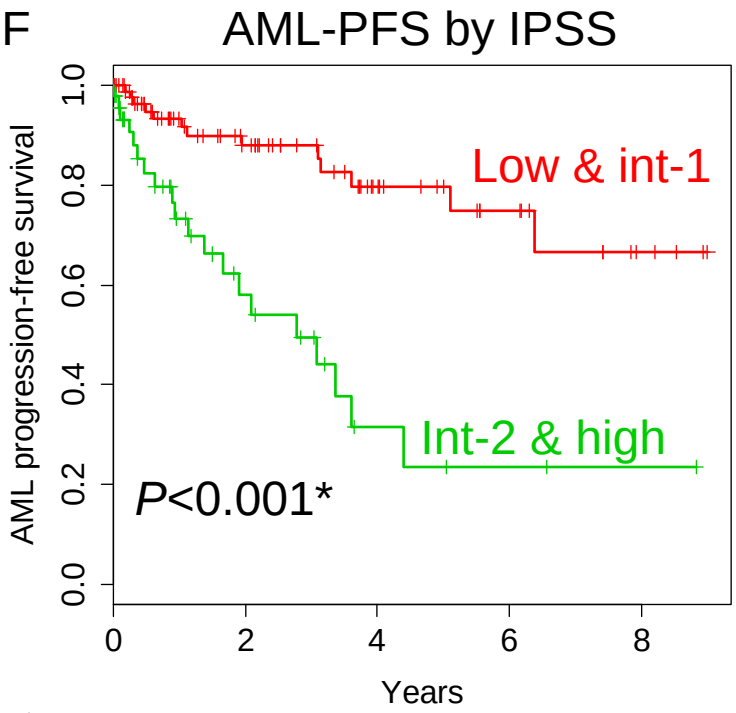


Lower risk (*N*=89)	89	56	27	16	9
Higher risk (*N*=47)	47	26	7	4	4

(7 observations omitted due to missing data.)



Lower risk (*N*=88)	88	46	29	16	9
Higher risk (*N*=47)	47	15	6	4	4

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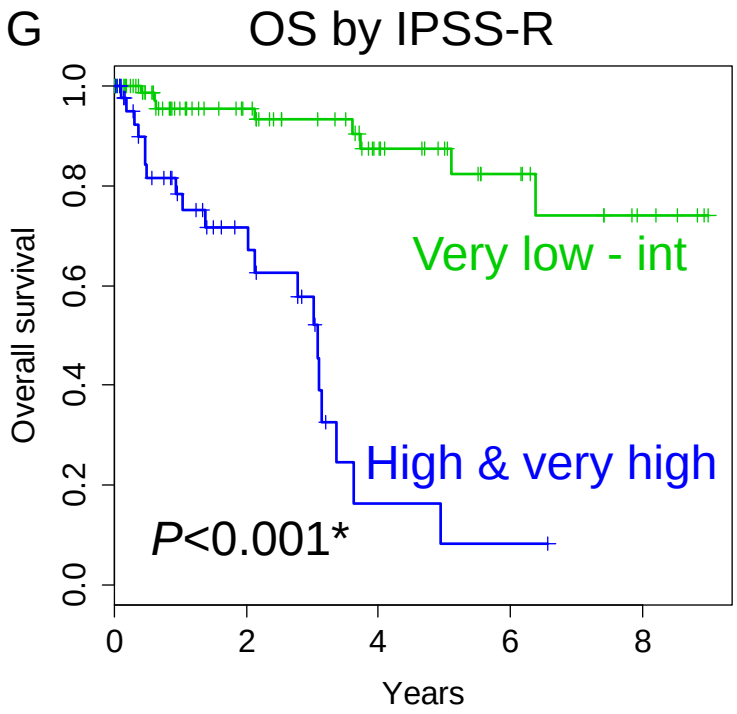
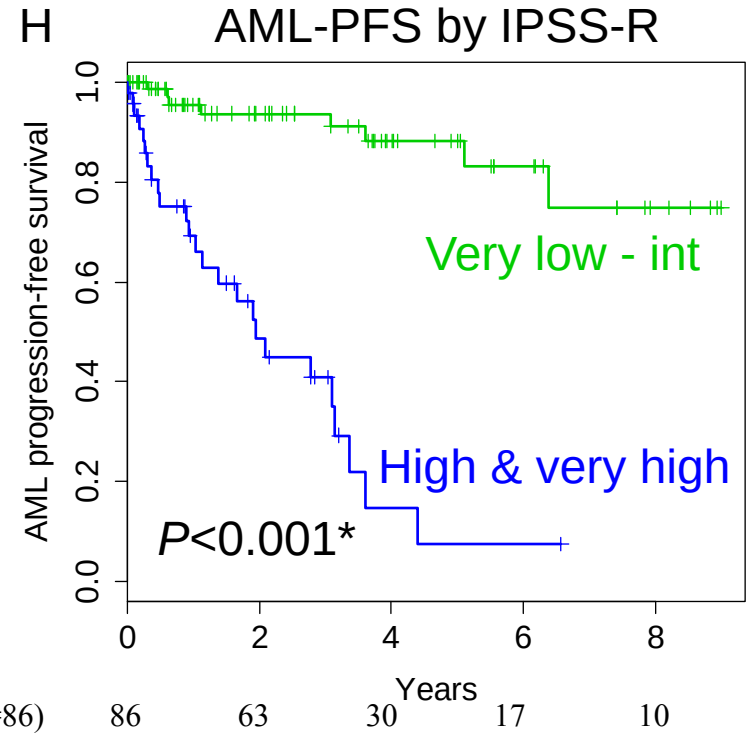


Lower risk (*N*=86)	86	63	30	17	10
Higher risk (*N*=47)	47	21	3	2	2

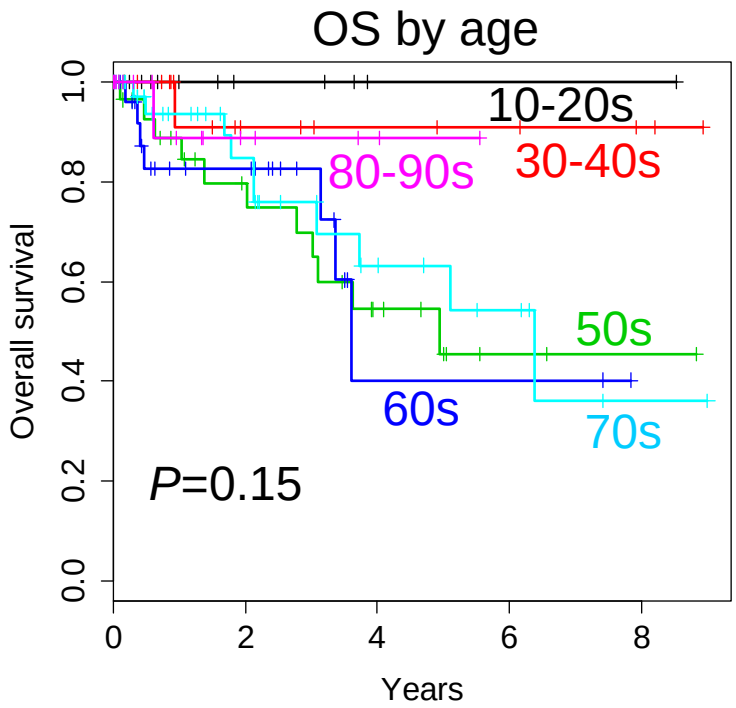
(10 observations omitted due to missing data.)



Lower risk (*N*=86)	86	63	30	17	10
Higher risk (*N*=47)	47	21	3	2	2

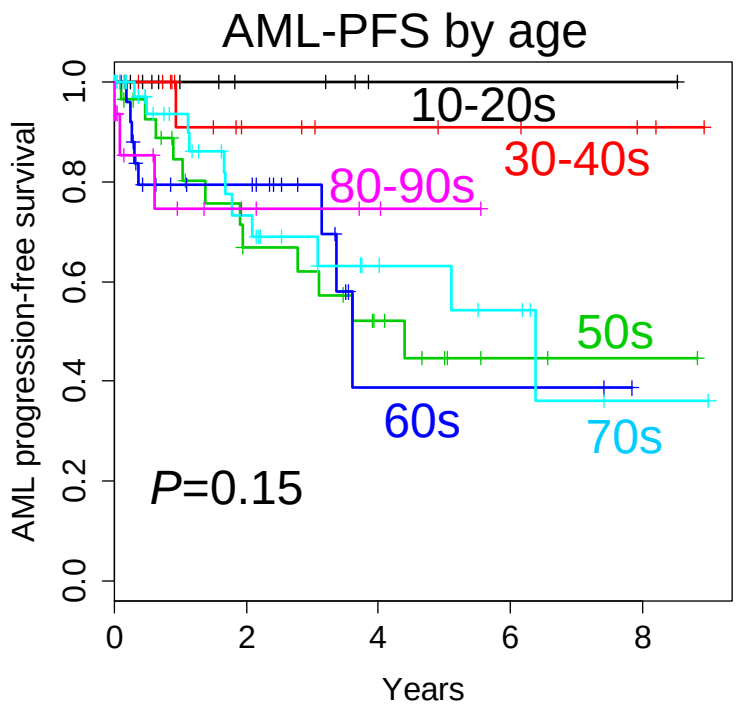
(10 observations omitted due to missing data.)

I



10-20s (*N*=12)	12	12	12	12	12
30-40s (*N*=18)	18	11	11	11	11
50s (*N*=28)	28	18	11	6	6
60s (*N*=26)	26	19	3	3	3
70s (*N*=42)	42	20	11	7	3
80-90s (*N*=17)	17	9	9	9	9

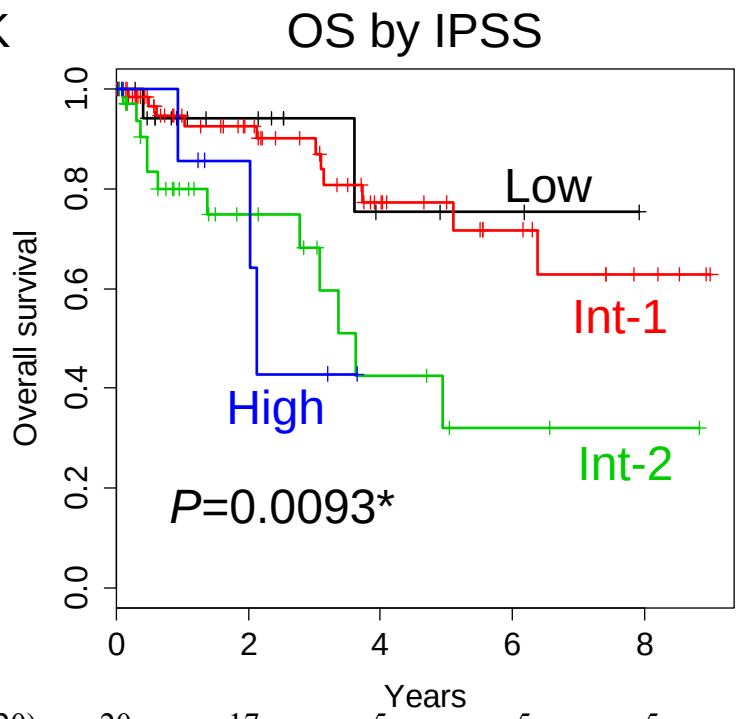
J



10-20s (*N*=12)	12	12	12	12	12
30-40s (*N*=18)	18	11	11	11	11
50s (*N*=28)	28	16	11	7	7
60s (*N*=26)	26	19	3	3	3
70s (*N*=42)	42	18	12	7	3
80-90s (*N*=16)	16	8	8	8	8

(1 observation omitted due to missing data.)

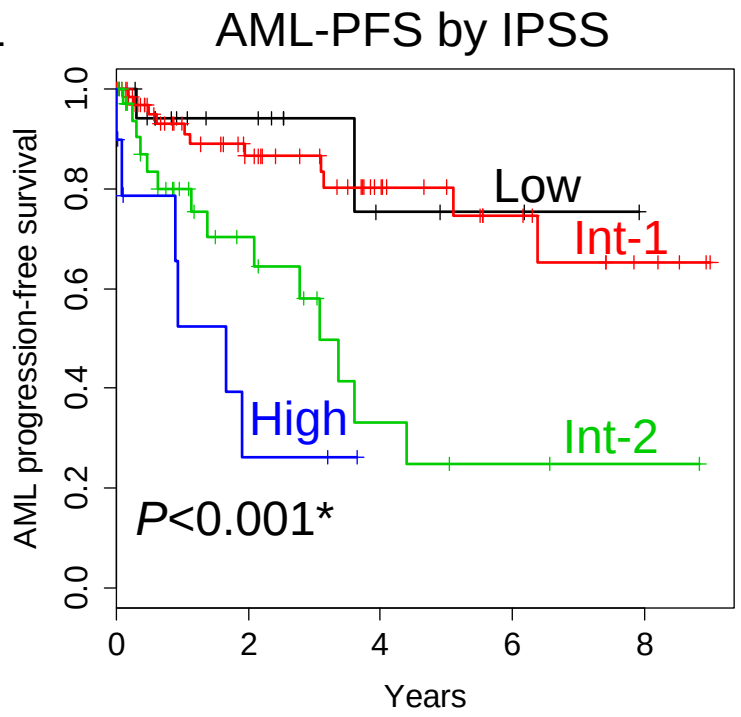
K



Low (*N*=20)	20	17	5	5	5
Int-1 (*N*=69)	69	45	23	14	8
Int-2 (*N*=37)	37	16	6	4	4
High (*N*=10)	10	7	3	3	3

(7 observations omitted due to missing data.)

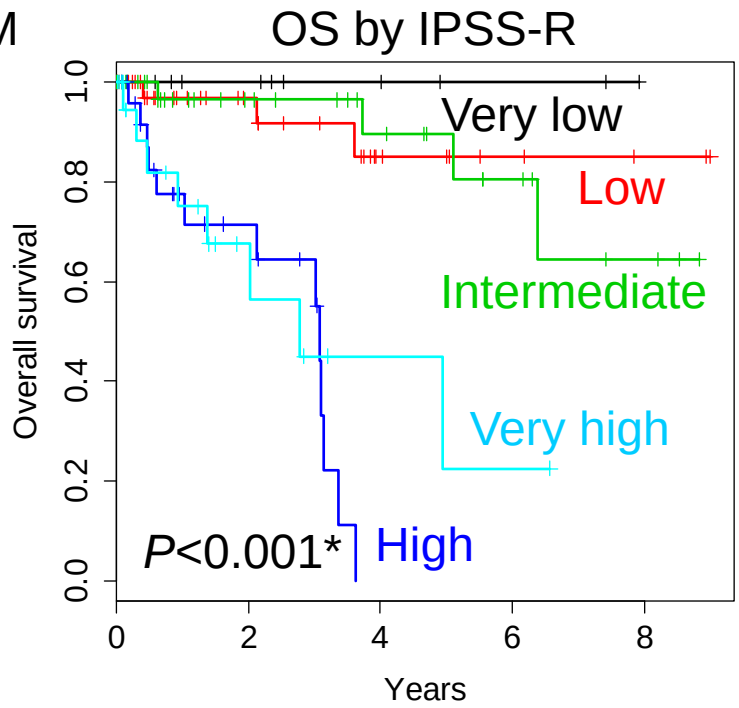
L



Low (*N*=20)	20	17	5	5	5
Int-1 (*N*=68)	68	37	27	14	8
Int-2 (*N*=37)	37	15	5	4	4
High (*N*=10)	10	3	3	3	3

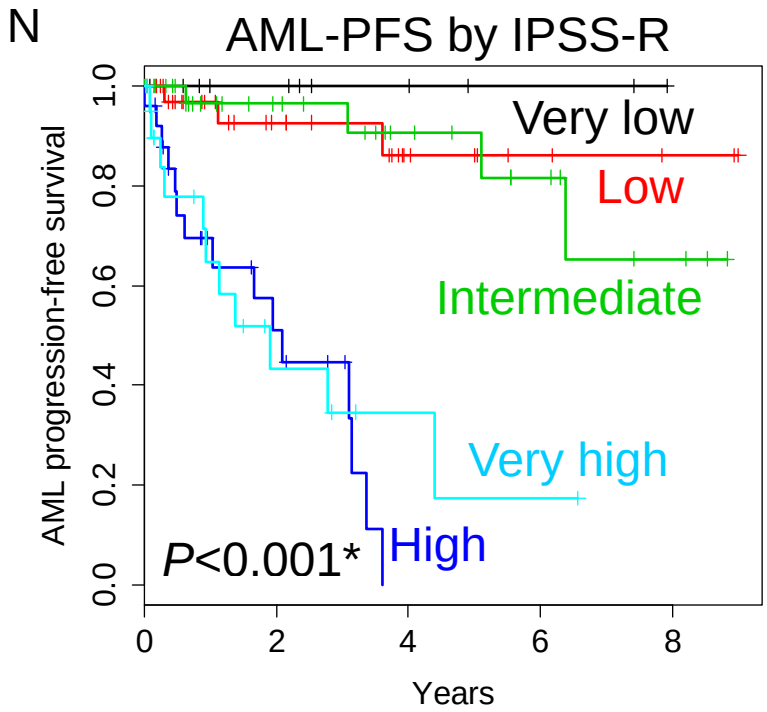
(8 observations omitted due to missing data.)

M



Very low (*N*=11)	11	11	11	11	11
Low (*N*=38)	38	31	14	14	14
Intermediate (*N*=36)	36	28	14	10	5
High (*N*=26)	26	13	7	7	7
Very high (*N*=22)	22	10	5	2	2

(10 observations omitted due to missing data.)



Very low (*N*=11)	11	11	11	11	11
Low (*N*=38)	38	23	14	14	14
Intermediate (*N*=36)	36	28	17	10	5
High (*N*=26)	26	9	1	1	1
Very high (*N*=22)	22	6	5	2	2

(10 observations omitted due to missing data.)

Figure 2. The OS and the AML-PFS of hMDS. OS: overall survival. AML-PFS: acute myeloid leukemia progression-free survival. hMDS: hypoplastic myelodysplastic syndrome. The numbers below the figures are the numbers of patients at risk in the even-numbered years from the beginning of the observations for these groups. A. OS of hMDS patients; 5-year OS = 62%. B. AML-PFS of hMDS patients; 5-year AML-PFS = 61%. C. OS of hMDS patients by age, younger group (age <50) and older group (age ≥50). *: statistically significant. D. AML-PFS of hMDS patients by age, younger group (age <50) and older group (age ≥50). E. OS of hMDS patients by IPSS, lower risk group (low and int-1) and higher risk group (int-2 and high). IPSS: International Prognostic Scoring System. int: intermediate. F. AML-PFS of hMDS patients by IPSS, lower risk group (low and int-1) and higher risk group (int-2 and high). G. OS of hMDS patients by IPSS-R, lower risk group (very low, low and intermediate) and higher risk group (high and very high). IPSS-R: revised IPSS. H. AML-PFS of hMDS patients by IPSS-R, lower risk group (very low, low and intermediate) and higher risk group (high and very high). I. OS of hMDS patients by age. J. AML-PFS of hMDS patients by age. K. OS of hMDS patients by IPSS. *: statistically significant. L. AML-PFS of hMDS patients by IPSS. M. OS of hMDS patients by IPSS-R. N. AML-PFS of hMDS patients by IPSS-R.

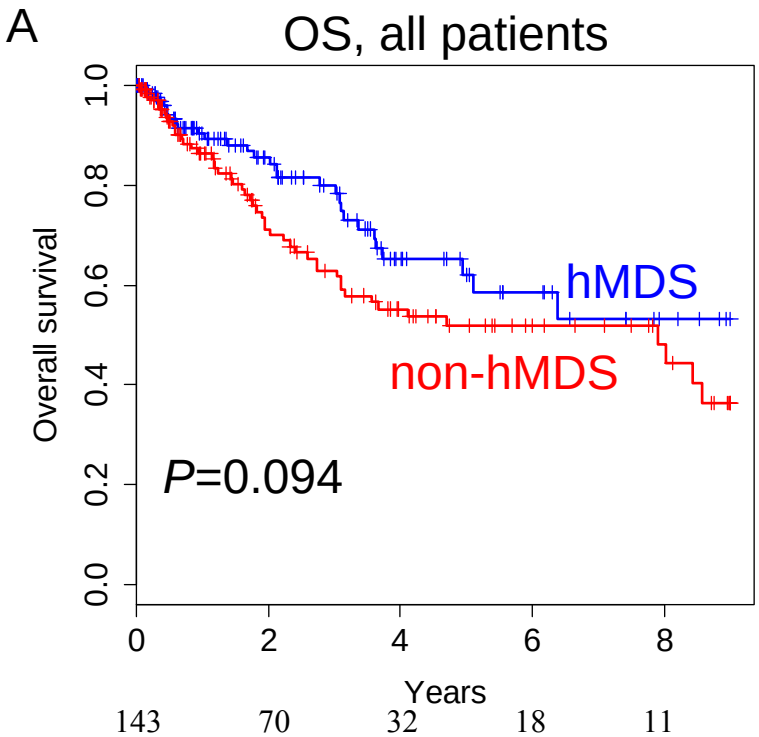
high, respectively.

The 5-year OS and the 5-year AML-PFS of hMDS differ by only 1 % (Figure 2A, 2B). This is due to the fact that most of the hMDS patients who had progressed to AML eventually died; 35 of the 143 hMDS patients progressed to AML (25%), and 29 of these 35 hMDS patients were observed until their deaths (83%), and only 5 of them were alive and observed for more than 5 years (3.4%); the other 6 patients were censored within 5 years before their deaths.

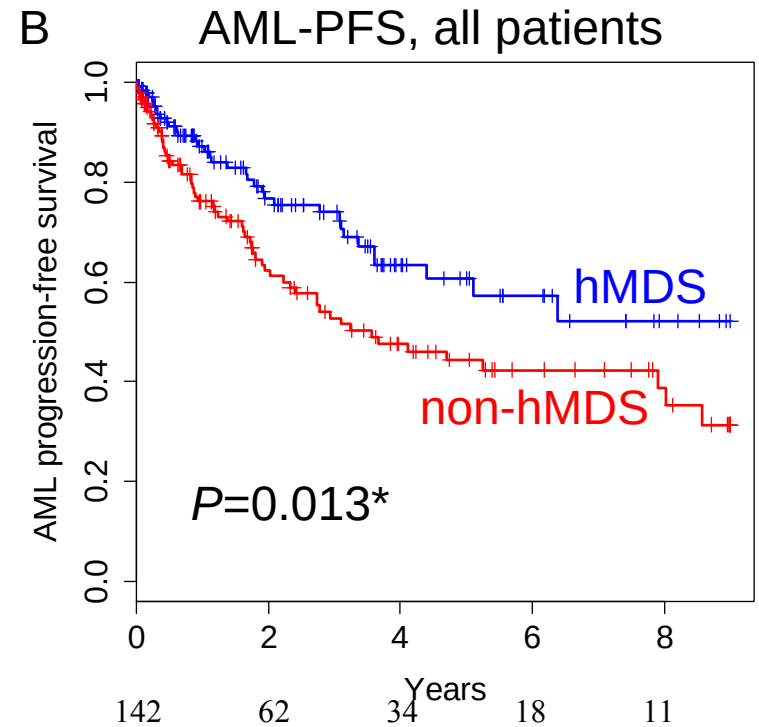
3.5. The OS and the AML-PFS, hMDS versus non-hMDS

The OS and the AML-PFS of hMDS were compared with those of non-hMDS (Figure 3). The difference in the OS between hMDS and non-hMDS was not statistically significant (P=0.094), and their 5-year rates of OS were 62% and 52%, respectively (Figure 3A). The difference in the AML-PFS between them was statistically significant (P=0.013), with their 5-year rates being 61% and 44%, respectively (Figure 3B). Medians of OS for hMDS and non-hMDS were 593 days and 610 days (P=0.12), and medians of AML-PFS for them were 583.5 days and 502 days (P=0.33), respectively. Based on the findings in Figure 2, hMDS and non-hMDS patients were divided into two groups by age, IPSS, and IPSS-R. For age <50, the rates of 5-year OS and AML-PFS of hMDS patients were higher than those of non-hMDS

Figure 3. OS and AML-PFS, hMDS versus non-hMDS



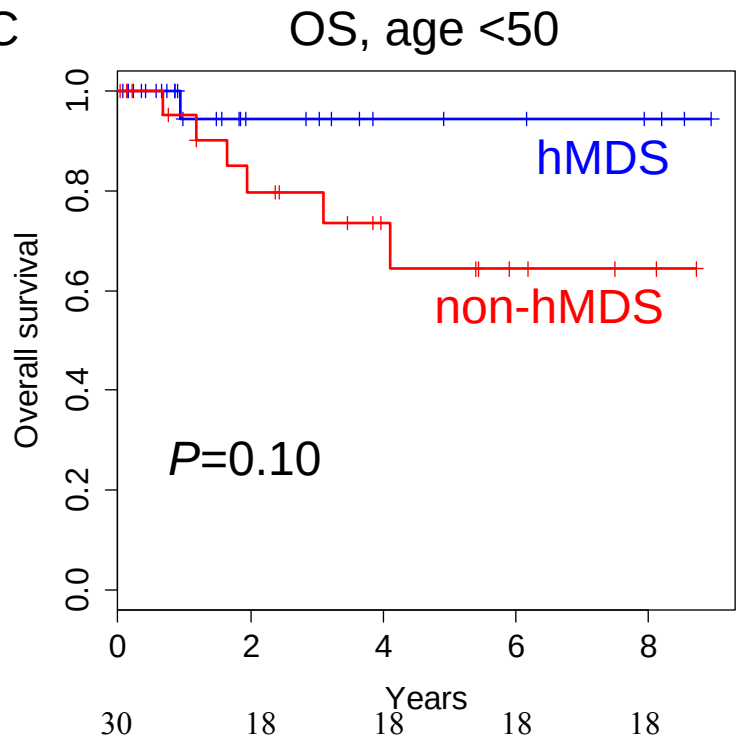
hMDS (*N*=143)	143	70	32	18	11
non-hMDS (*N*=143)	143	63	42	29	14



hMDS (*N*=142)	142	62	34	18	11
non-hMDS (*N*=143)	143	56	36	23	12

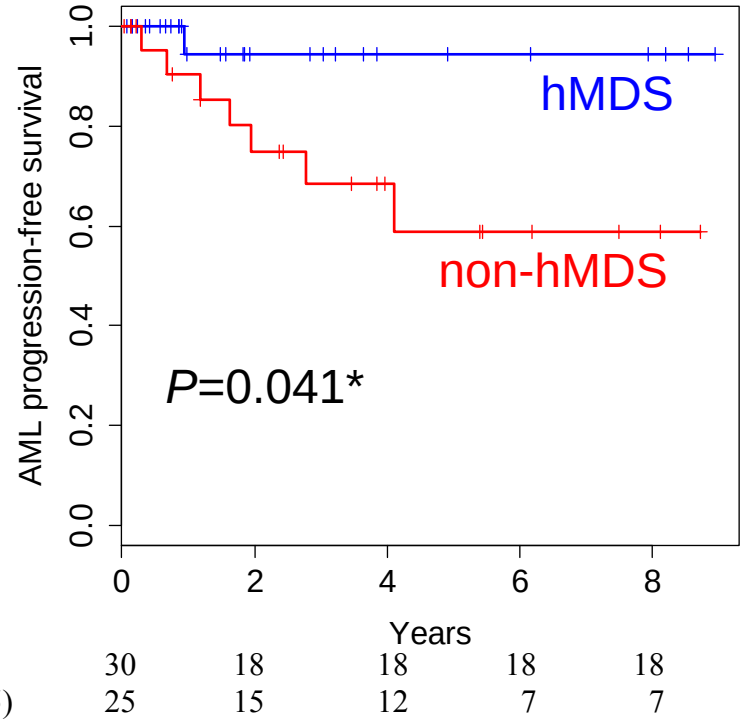
(1 observation omitted due to missing data.)

C

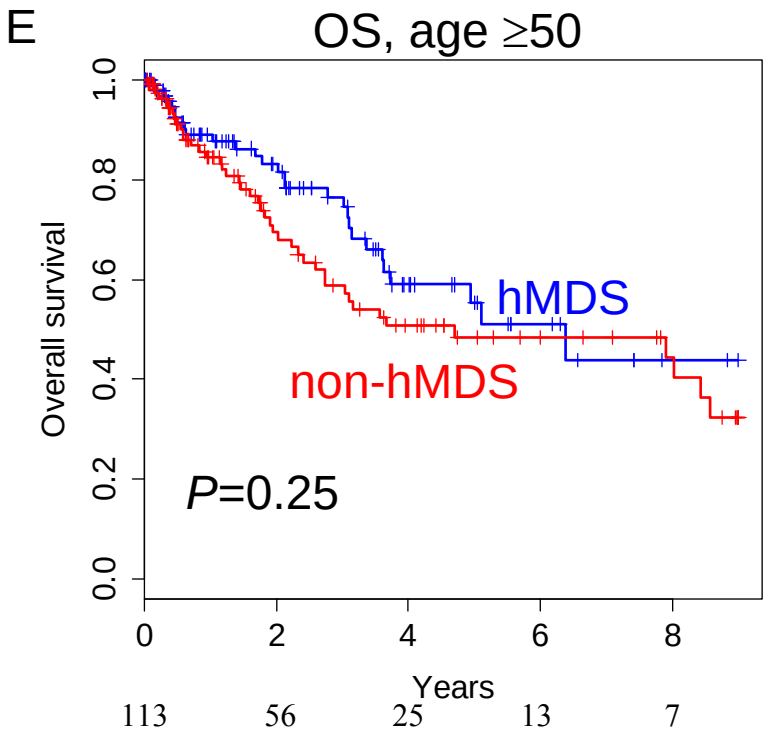


hMDS (*N*=30)	30	18	18	18	18
non-hMDS (*N*=25)	25	16	13	8	8

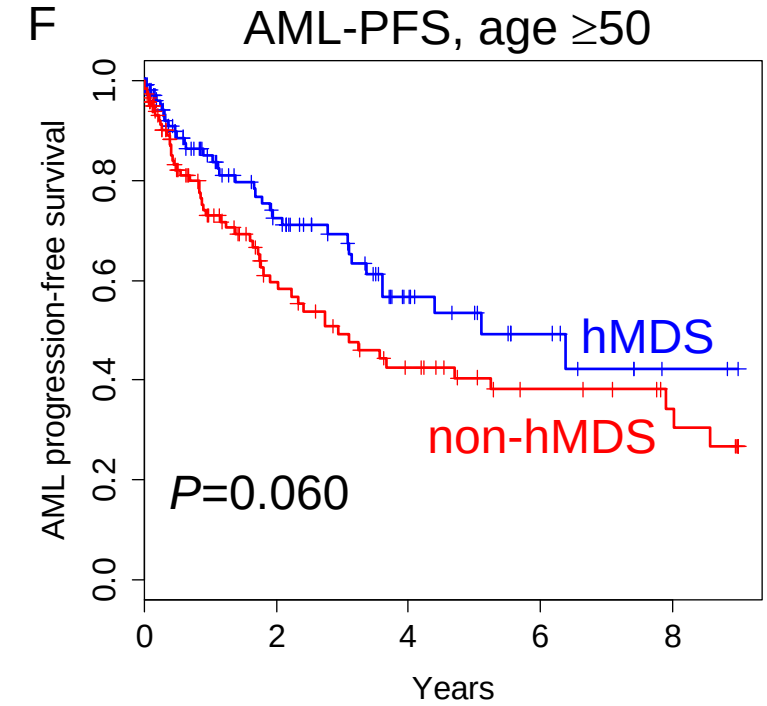
D



hMDS (*N*=30)	30	18	18	18	18
non-hMDS (*N*=25)	25	15	12	7	7



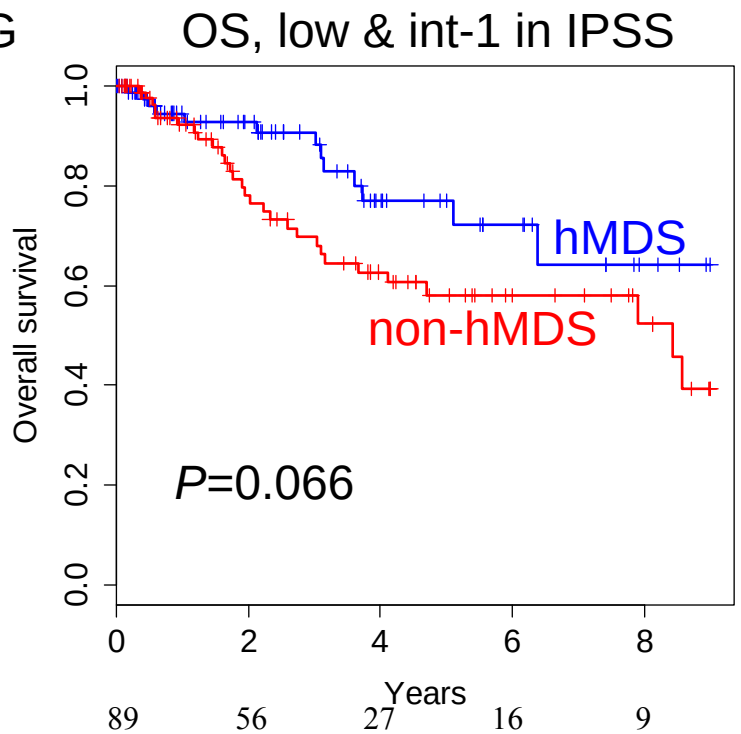
hMDS (*N*=113)	113	56	25	13	7
non-hMDS (*N*=118)	118	48	31	22	12



hMDS (*N*=112)	112	51	26	13	7
non-hMDS (*N*=118)	118	42	26	17	10

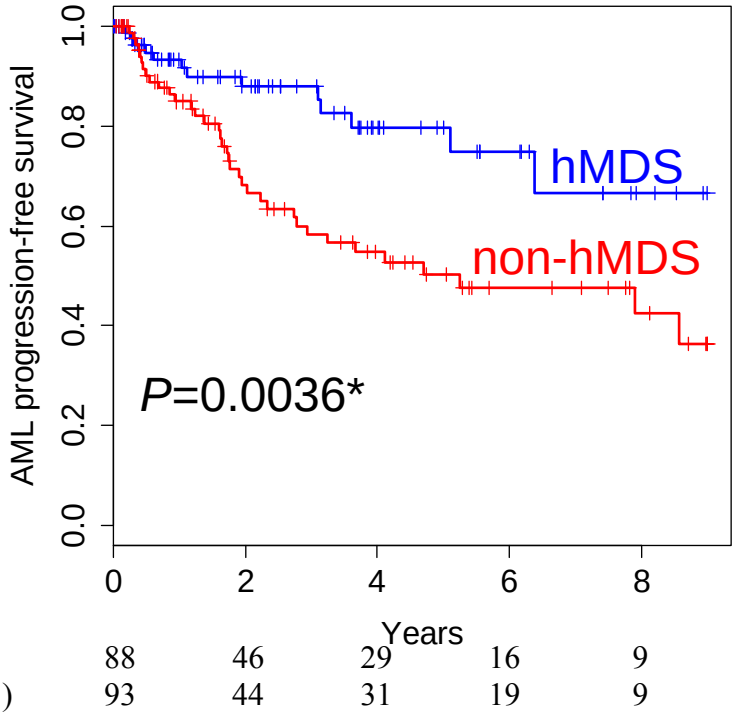
(1 observation omitted due to missing data.)

G



hMDS (*N*=89)	89	56	27	16	9
non-hMDS (*N*=93)	93	49	35	24	10

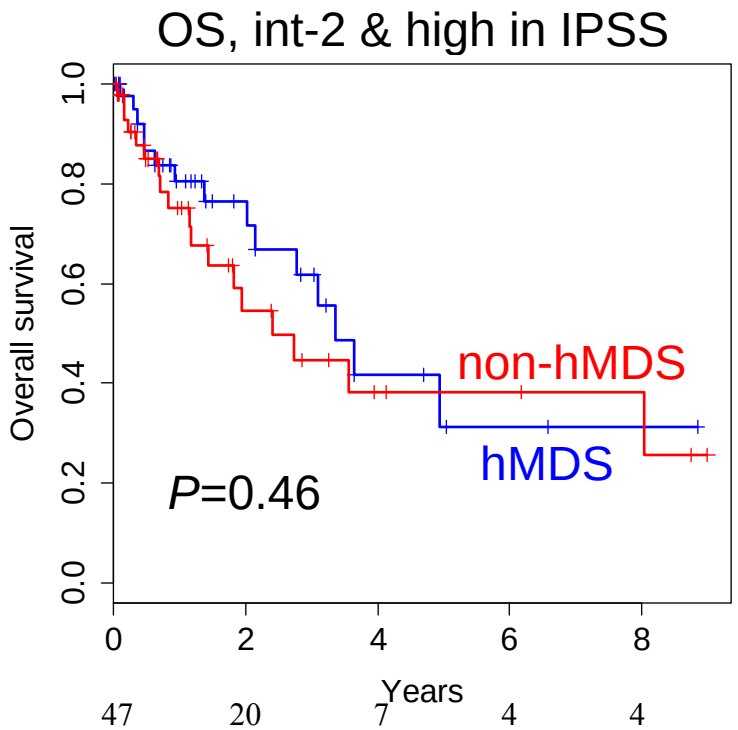
H



hMDS (*N*=88)	88	46	29	16	9
non-hMDS (*N*=93)	93	44	31	19	9

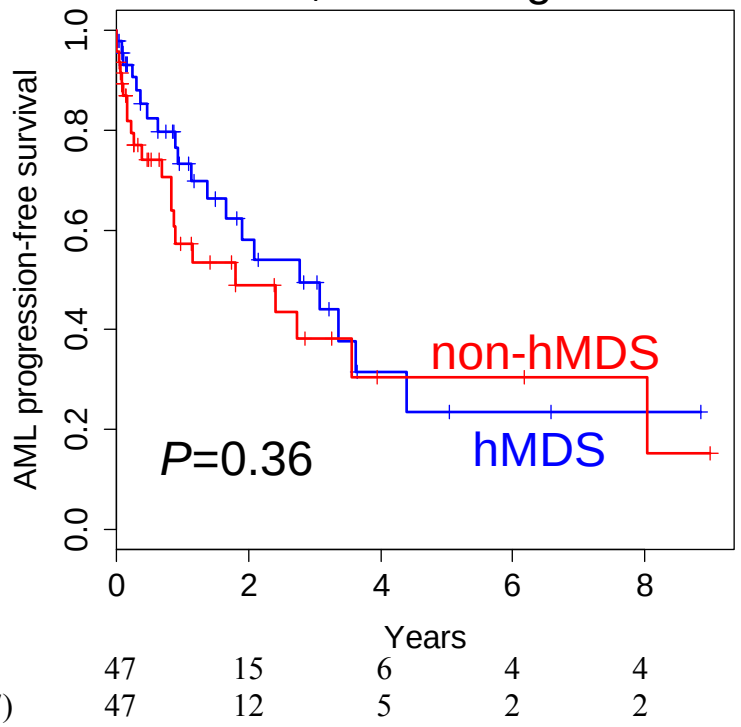
(1 observation omitted due to missing data.)

I



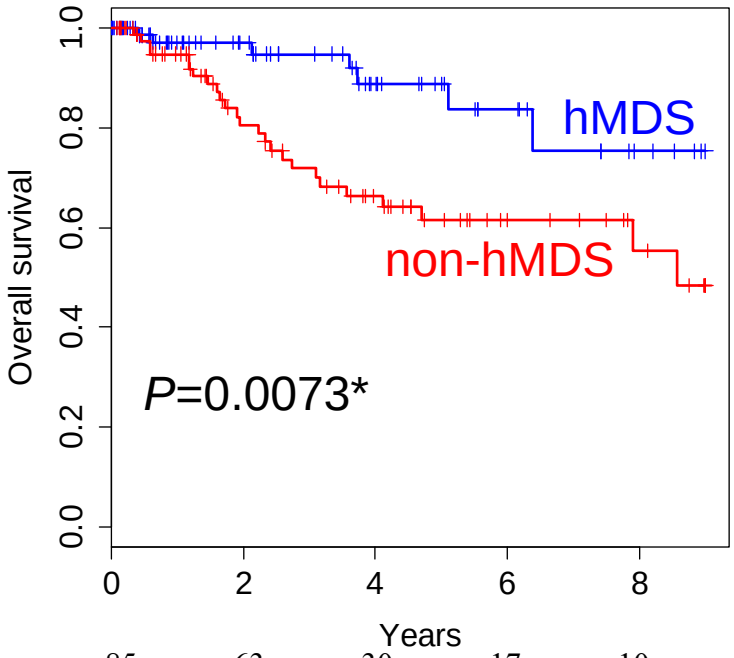
hMDS (*N*=47)	47	20	7	4	4
non-hMDS (*N*=47)	47	13	7	7	7

J



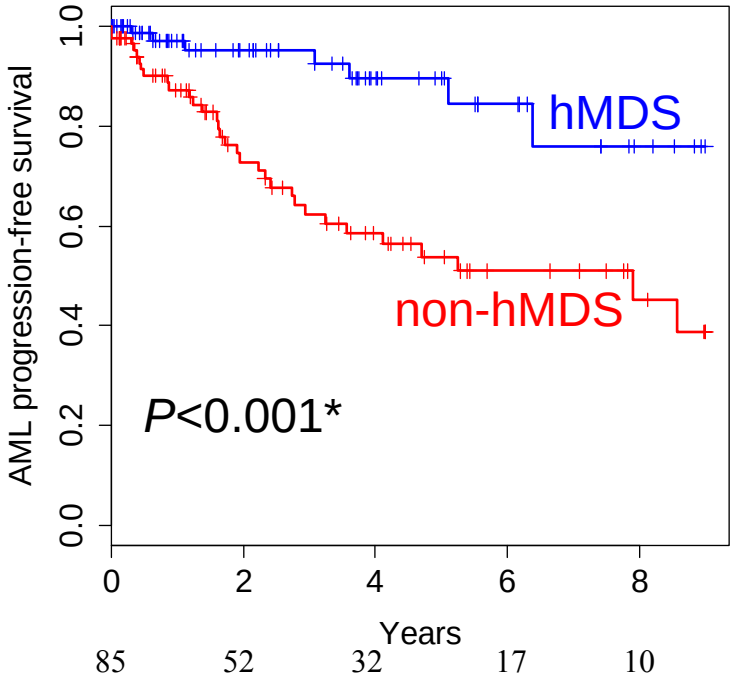
hMDS (*N*=47)	47	15	6	4	4
non-hMDS (*N*=47)	47	12	5	2	2

K OS, very low - int in IPSS-R



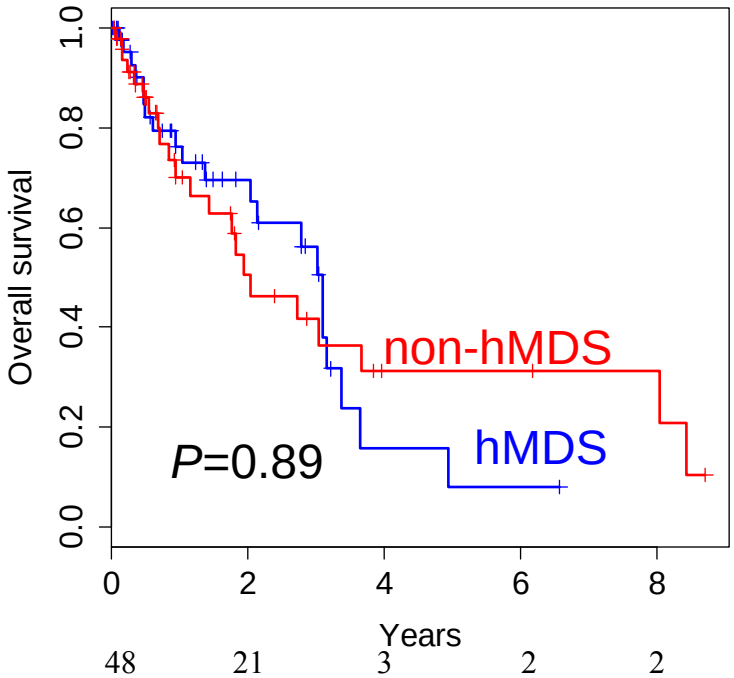
hMDS (*N*=85)	85	63	30	17	10
non-hMDS (*N*=88)	88	49	36	24	10

L AML-PFS, very low - int in IPSS-R



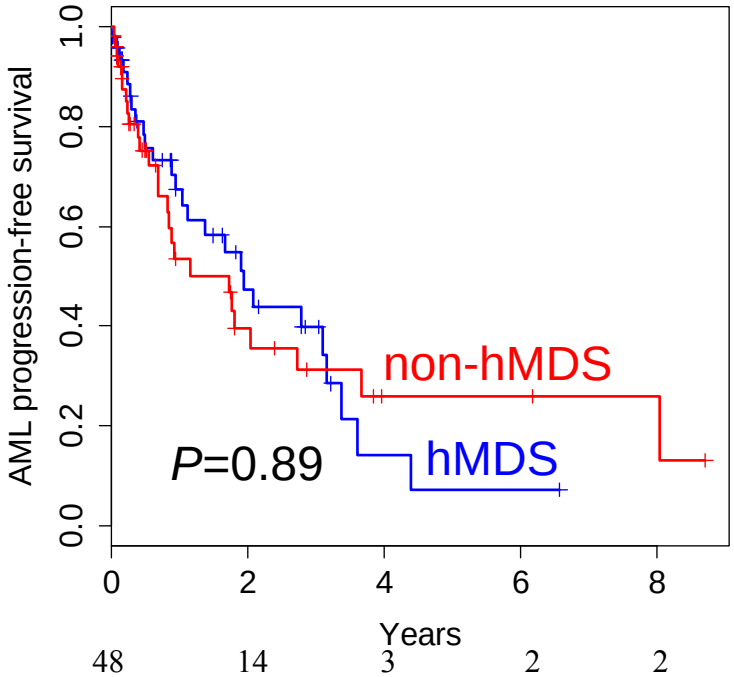
hMDS (*N*=85)	85	52	32	17	10
non-hMDS (*N*=88)	88	44	31	19	9

M OS, high & very high in IPSS-R



hMDS (N=48)	48	21	3	2	2
non-hMDS (N=52)	52	13	7	7	7

N AML-PFS, high & very high in IPSS-R



hMDS (*N*=48)	48	14	3	2	2
non-hMDS (*N*=52)	52	12	6	2	2

Figure 3. The OS and the AML-PFS, hMDS versus non-hMDS. OS: overall survival. AML-PFS: acute myeloid leukemia progression-free survival. hMDS: hypoplastic myelodysplastic syndrome. The numbers below the figures are the numbers of patients at risk in the even-numbered years from the beginning of the observations for these groups. A. OS, all patients. B. AML-PFS, all patients. *: statistically significant. C. OS, age <50. D. AML-PFS, age <50. E. OS, age ≥50. F. AML-PFS, age ≥50. G. OS, low and int-1 risk groups in IPSS. int: intermediate. IPSS: International Prognostic Scoring System. H. AML-PFS, low and int-1 risk groups in IPSS. I. OS, int-2 and high risk groups in IPSS. J. AML-PFS, int-2 and high risk groups in IPSS. K. OS, lower-risk group (very low, low and intermediate) in IPSS-R. IPSS-R: revised IPSS. L. AML-PFS, lower-risk group in IPSS-R. M. OS, higher-risk group (high and very high) in IPSS-R. N. AML-PFS, higher-risk group in IPSS-R.

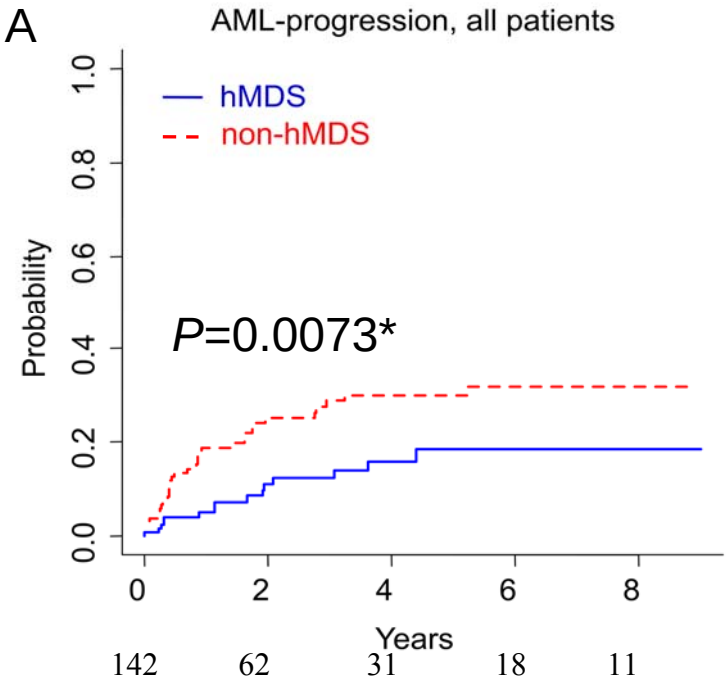
patients (94% versus 64% (P=0.10), and 94% versus 59% (P=0.041), respectively) (Figure 3C, 3D). For age ≥50, OS and AML-PFS did not exhibit statistically significant differences (55% versus 48% (P=0.25), and 53% versus 41% (P=0.060), respectively) (Figure 3E, 3F). The OS and AML-PFS of patients in low and intermediate-1 risk groups of IPSS and those in intermediate-2 and high risk groups were also analyzed separately (Figure 3G – 3J). For low and intermediate-1, the 5-year OS and AML-PFS of hMDS patients were higher than those of non-hMDS patients, especially for AML-PFS with a statistically significant difference (77% versus 58% (P=0.066), and 80% versus 50% (P=0.0036), respectively) (Figure 3G, 3H), whereas the OS and the AML-PFS of patients in intermediate-2 and high risk groups of IPSS did not exhibit statistically significant differences between hMDS and non-hMDS (31% versus 38% (P=0.46), and 23% versus 30% (P=0.36), respectively) (Figure 3I, 3J). Likewise, the OS and the AML-PFS of patients in very low, low and intermediate risk groups of IPSS-R and those in high and very high risk groups of IPSS-R were analyzed separately (Figure 3K – 3N). The 5-year OS and AML-PFS of hMDS patients in very low, low and intermediate risk groups were significantly higher than those of non-hMDS patients (89% versus 62% (P=0.0073), and 90% versus 54% (P<0.001), respectively) (Figure 3K, 3L), whereas the OS and AML-PFS in high and very high risk groups were low for

both hMDS and non-hMDS without significant differences between them (7.9% versus 31% (P=0.89), and 7.1% versus 26% (P=0.89), respectively) (Figure 3M, 3N). To summarize, the higher OS and AML-PFS of hMDS patients compared with those of non-hMDS patients were attributed to the favorable outcomes of younger and lower-risk hMDS patients.

3.6. Competing risks analysis of AML-progression and death from BMF

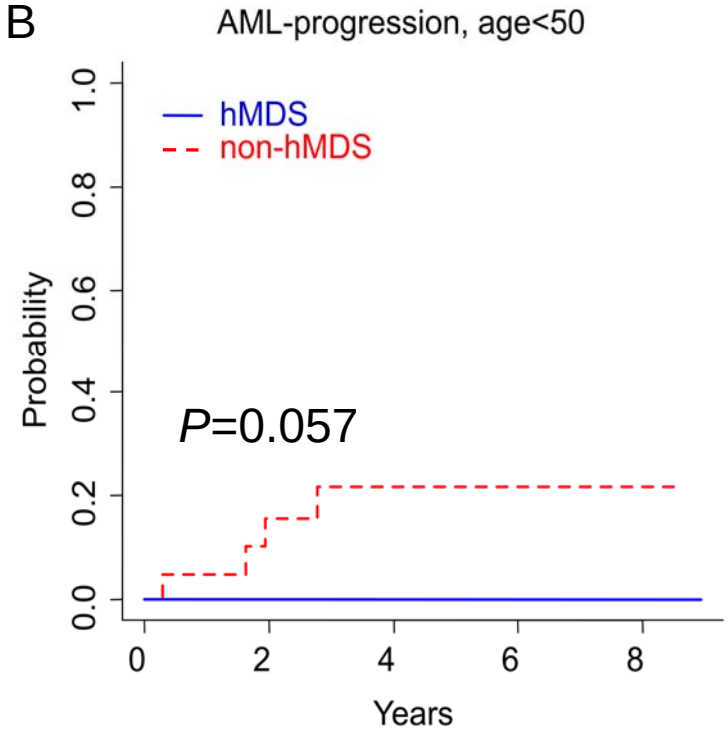
The risks of progression to AML and death from BMF were investigated by competing risks analysis (Figure 4). The difference in the risk of AML-progression between hMDS and non-hMDS was statistically significant (P=0.0074), with the 5-year cumulative incidence of 18% and 30%, respectively (Figure 4A). Therefore, hMDS patients face lower risk to progress to AML than non-hMDS patients. By dividing the patients into two groups by age, IPSS, and IPSS-R, it was revealed further that no hMDS patient at age <50 progressed to AML. Also, statistically significant differences between hMDS and non-hMDS were exhibited in the AML-progression of low and intermediate-1 risk groups in IPSS (5-year cumulative incidence = 6.2% versus 27% (P=0.0027)) (Figure 4D), and AML-progression of very low, low and intermediate risk groups in IPSS-R (5-year cumulative incidence = 5.9% versus 25% (P=0.0025)) (Figure 4F). As given earlier, the criterion of death caused by cytopenia of at least two lineages

Figure 4. Competing risks analysis



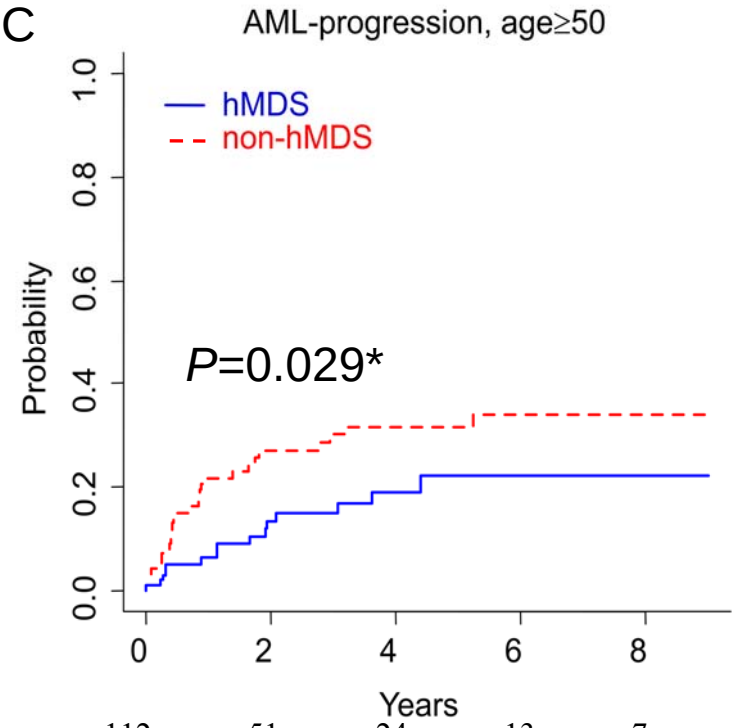
hMDS (*N*=142)	142	62	31	18	11
non-hMDS (*N*=143)	143	56	36	23	12

(1 observation omitted due to missing data.)



hMDS (*N*=30)	30	18	18	18	18
non-hMDS (*N*=25)	25	15	12	7	7

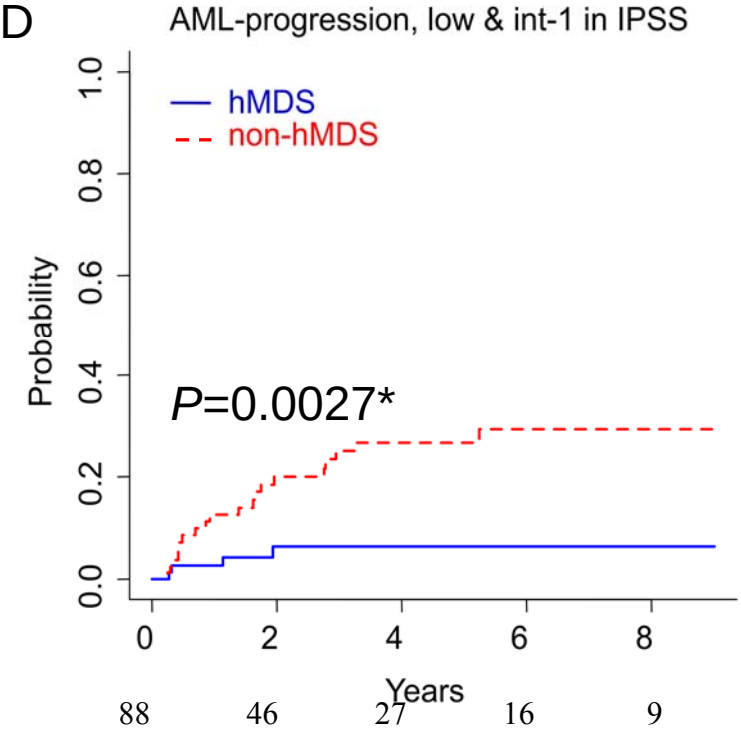
C



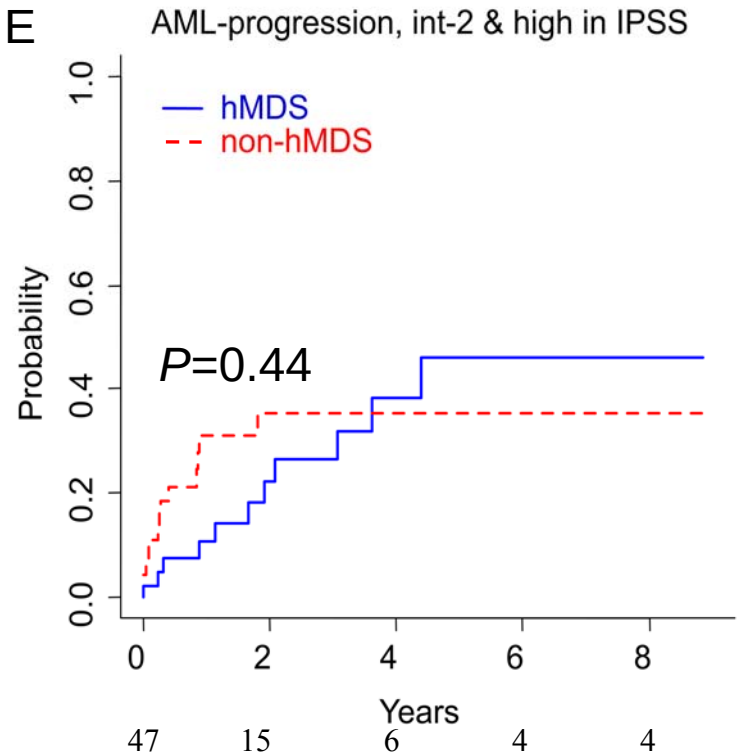
hMDS (N=112)	112	51	24	13	7
non-hMDS (N=118)	118	42	26	17	10

(1 observation omitted due to missing data.)

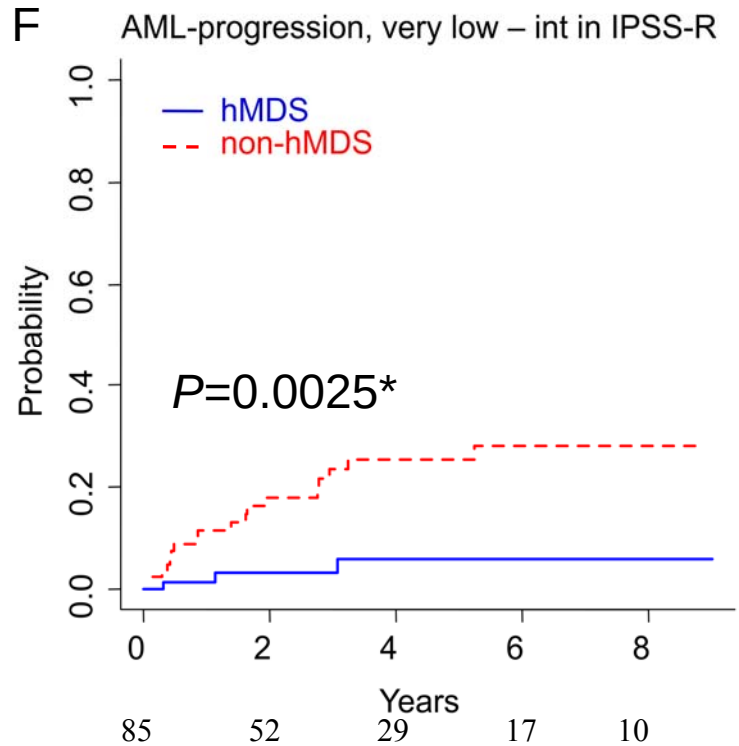
D



hMDS (*N*=88)	88	46	27	16	9
non-hMDS (*N*=93)	93	44	31	19	9

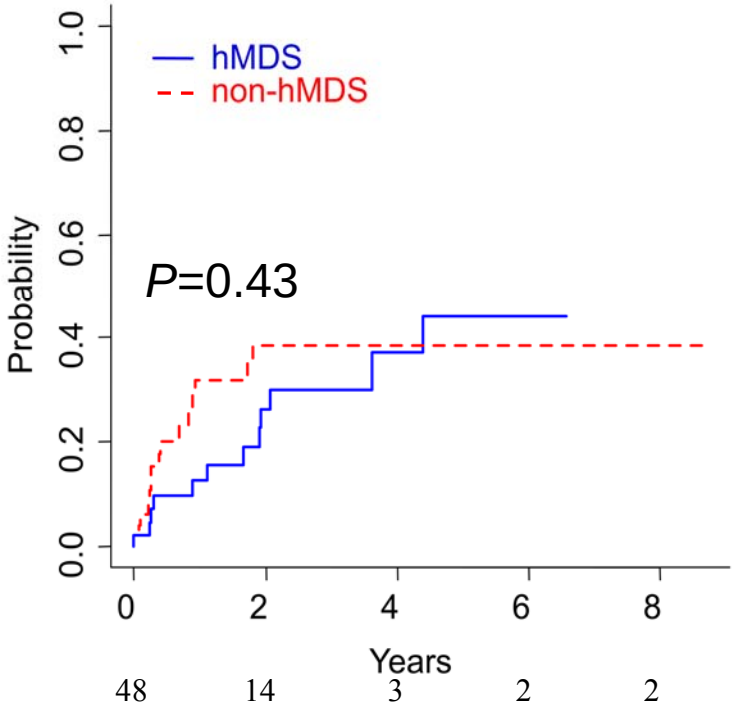


hMDS (*N*=47)	47	15	6	4	4
non-hMDS (*N*=47)	47	12	5	5	5



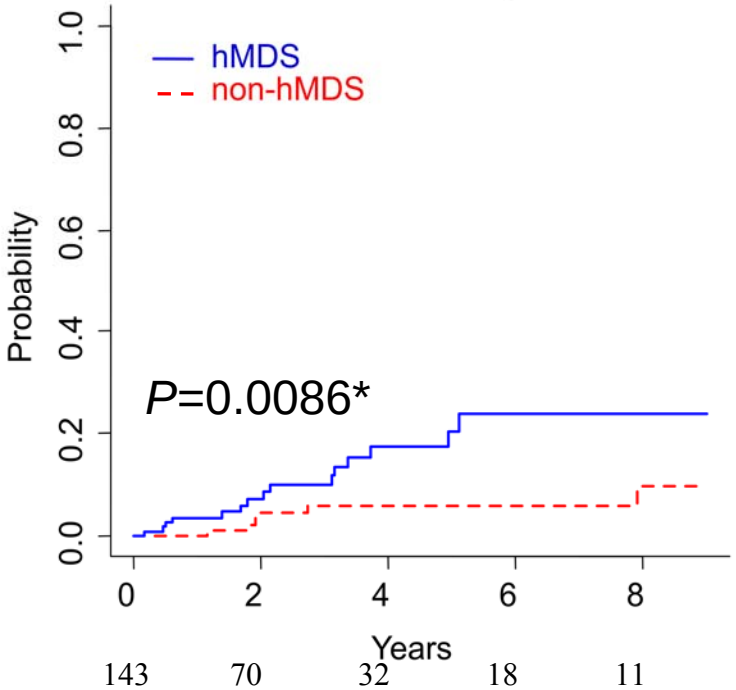
hMDS (N=85)	85	52	29	17	10
non-hMDS (N=88)	88	44	31	19	9

G AML-progression, high & very high in IPSS-R



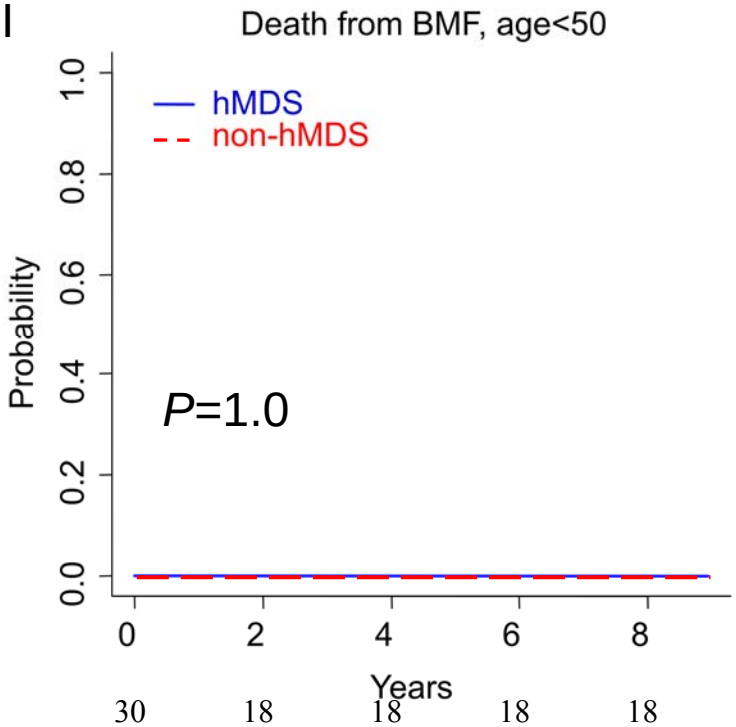
hMDS (*N*=48)	48	14	3	2	2
non-hMDS (*N*=52)	52	12	6	2	2

H Death from BMF, all patients



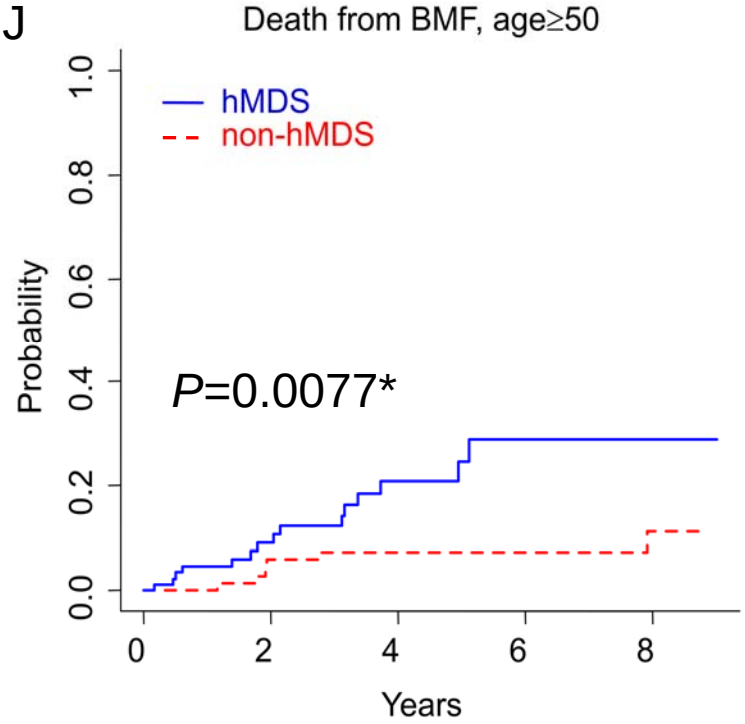
hMDS (*N*=143)	143	70	32	18	11
non-hMDS (*N*=143)	143	63	42	29	14

I



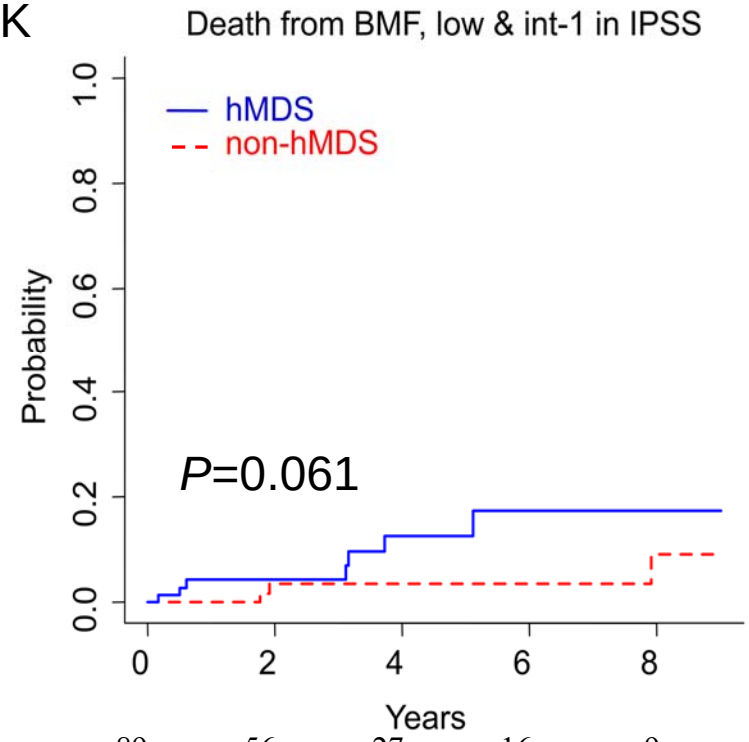
hMDS (*N*=30)	30	18	18	18	18
non-hMDS (*N*=25)	25	16	13	8	8

J



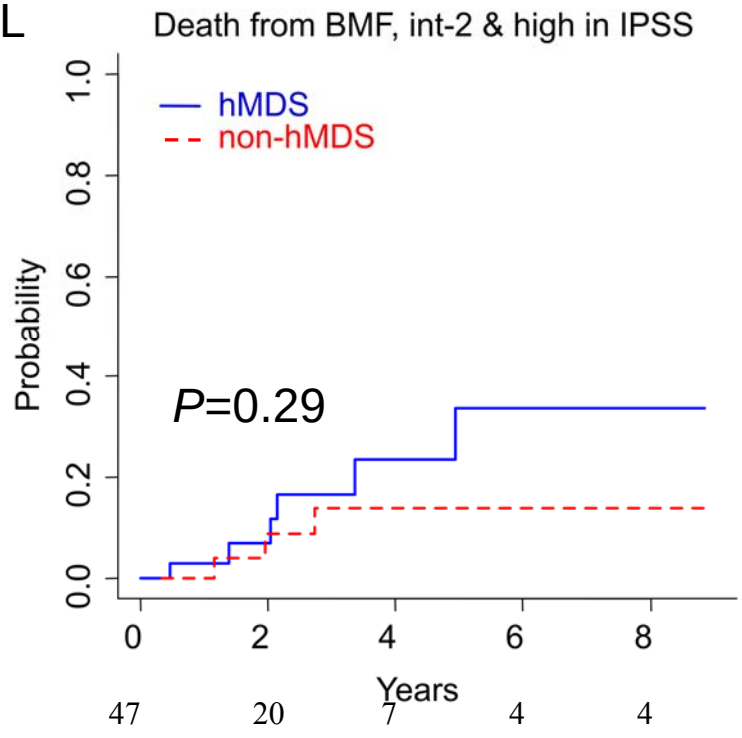
hMDS (*N*=113)	113	56	25	13	7
non-hMDS (*N*=118)	118	48	31	22	12

K



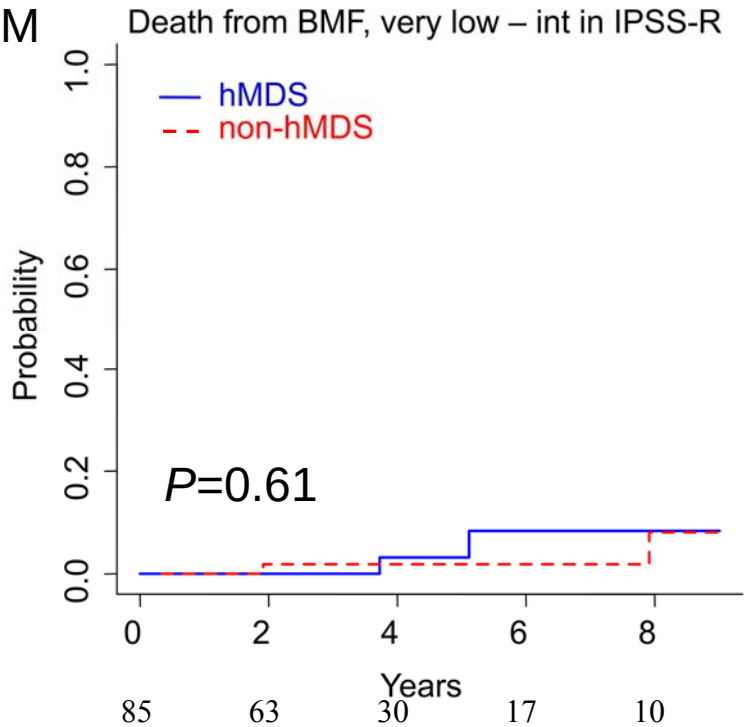
hMDS (*N*=89)	89	56	27	16	9
non-hMDS (*N*=93)	93	49	35	24	10

L



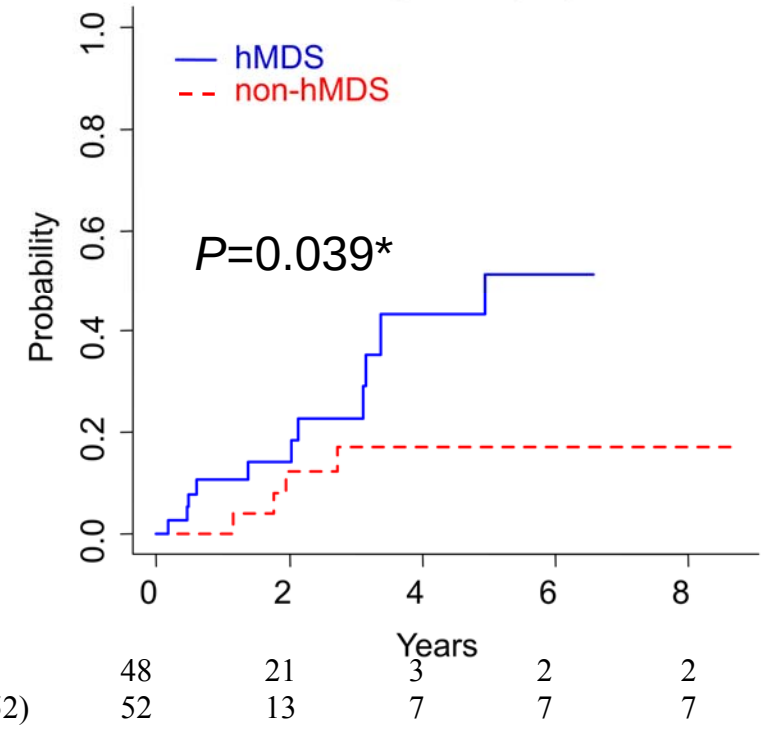
hMDS (*N*=47)	47	20	7	4	4
non-hMDS (*N*=47)	47	13	7	7	7

M



hMDS (*N*=85)	85	63	30	17	10
non-hMDS (*N*=88)	88	49	36	24	10

N



hMDS (*N*=48)	48	21	3	2	2
non-hMDS (*N*=52)	52	13	7	7	7

Figure 4. Competing risks analysis of AML-progression and death from BMF for hMDS and non-hMDS. AML: acute myeloid leukemia. BMF: bone marrow failure. hMDS: hypoplastic myelodysplastic syndrome. The numbers below the figures are the numbers of patients at risk in the even-numbered years from the beginning of the observations for these groups. A. AML-progression, all patients. B. AML-progression, age <50. C. AML-progression, age ≥50. D. AML-progression, low and int-1 risk groups in IPSS. int: intermediate. IPSS: International Prognostic Scoring System. E. AML-progression, int-2 and high risk groups in IPSS. F. AML-progression, very low, low and intermediate risk groups in IPSS-R. IPSS-R: revised IPSS. G. AML-progression, high and very high risk groups in IPSS-R. H. Death from BMF, all patients. I. Death from bone marrow failure, age <50. J. Death from bone marrow failure, age ≥50. K. Death from BMF, low and int-1 risk groups in IPSS. L. Death from BMF, intermediate-2 and high risk groups in IPSS.M. Death from BMF, very low, low and intermediate risk groups in IPSS-R. N. Death from BMF, high and very high risk groups in IPSS-R. Death from BMF is defined as the death caused by cytopenia of at least two lineages.

Table 3. Actual causes of death from BMF, hMDS patients.

Cause of death	Patients (*N*=15)
Pneumonia	8 (60%)
Infection of other/unknown foci	2 (13%)
Severe transfusion dependence (detail unknown)	2 (13%)
Heart failure and intestinal hemorrhage	1 (6.7%)
Multiple organ failure	1 (6.7%)
Cerebral hemorrhage	1 (6.7%)

Death from BMF was defined as the death caused by cytopenia of at least two lineages. The actual adverse events that caused the 15 hMDS patients (10%) to die from BMF are listed above. BMF: bone marrow failure.

was used for the death from BMF. Applying this criterion to the analysis, the 5-year cumulative incidence of hMDS patients to die from BMF was significantly higher than that of non-hMDS patients (20% versus 5.7% (P=0.0086)), implying that hMDS patients face higher risk of death from BMF than non-hMDS patients (Figure 4H). It was revealed further that none of both hMDS and non-hMDS patients at age <50 died from BMF (Figure 4I). Also, statistically significant differences between hMDS and non-hMDS were exhibited in death from BMF at age ≥50 (5-year cumulative incidence = 23% versus 7.2% (P=0.011)) (Figure 4J), and hMDS patients' higher risk of death from BMF was attributed to high and very high risk groups in IPSS-R (5-year cumulative incidence = 51% versus 17% (P=0.039)) (Figure 4N). Therefore, hMDS patients at younger age and in lower risk groups face lower risks for AML-progression, and hMDS patients at older age and in higher risk groups face higher risks for death from BMF.

The actual adverse events that caused the hMDS patients to die from BMF are listed in Table 3. Most of these 15 patients (10% of the 143 hMDS patients) died from infection; 10 of them (73%) died from pneumonia or infections of other/unknown foci. There were some other adverse events, such as cerebral/intestinal hemorrhage and multiple organ failure.

3.7. Analysis of risk factors by Cox proportional hazards models

The univariate and multivariate Cox proportional hazards models were used to analyze which characteristics of patients served as the risk factors to affect the rates of OS and AML-PFS (Table 4). In the univariate proportional hazards analysis, statistically significant factors that increased the risks of death and AML-progression with the hazard ratios >1 for hMDS patients, non-hMDS patients, and all patients were sex (male=1, female=0), PS (≥2) and karyotype risks in IPSS-R (poor and very poor risk groups) (Table 4A – 4C). For hMDS patients, past illnesses of malignancies and/or hematological diseases and smoking habits were also the significantly significant risk factors of death and AML-progression with the hazard ratios >1 (Table 4A), although these background variables were not statistically significant for non-hMDS and all patients (Table 4B, 4C). Statistically significant risk factors in the univariate analysis were chosen for the multivariate analysis, which exhibited high scores of PS (≥2) and high karyotype risks (poor and very poor risk groups) as the significant risk factors of death and AML-progression for hMDS in multivariate analysis, and the male gender as the significant risk factor of death for hMDS as well (Table 4A).

Table 4. Cox proportional hazards analysis

Table 4A. Cox proportional hazards models for hMDS patients (*N*=143)

Univariate	Overall survival			AML progression-free survival		
hMDS	Hazard ratio	95% C. I.	P-value	Hazard ratio	95% C. I.	P-value
Sex	4.8	1.7-14	0.0038*	3.5	1.5-8.5	0.050*
Age	1.0	1.0-1.0	0.10	1.0	1.0-1.1	0.018*
Past illness†	2.3	1.1-4.8	0.021*	1.9	0.98-3.7	0.058*
Family history†	0.90	0.34-2.4	0.83	0.78	0.30-2.0	0.62*
Smoking	2.6	1.1-6.3	0.028*	2.6	1.2-5.8	0.017*
Hemoglobin	0.90	0.78-1.0	0.18	0.92	0.80-1.1	0.23
Platelet count	0.92	0.86-1.0	0.039*	0.96	0.91-1.0	0.13
Neutrophil count	1.0	1.0-1.0	0.011*	1.0	1.0-1.0	0.041*
PB blast	0.96	0.79-1.2	0.66	0.97	0.82-1.1	0.72
BM blast	1.1	1.0-1.1	0.048*	1.1	1.1-1.2	<0.001*
Performance status	5.0	1.8-13	0.0015*	4.8	2.1-11	<0.001*
Karyotype risks in IPSS-R	3.6	1.6-8.2	0.0024*	3.9	1.9-8.2	<0.001*
Multivariate	Overall survival			AML progression-free survival		
hMDS	Hazard ratio	95% C. I.	P-value	Hazard ratio	95% C. I.	P-value
Sex	5.4	1.3-23	0.024*			
Age				1.0	1.0-1.1	0.032*
Platelet count	0.92	0.82-1.0	0.14			
Neutrophil count	1.0	1.0-1.0	0.054			
BM blast	1.1	1.0-1.1	0.024*	1.1	1.1-1.2	<0.001*
Performance status	3.9	1.3-12	0.018*	6.1	2.3-16	<0.001*
Karyotype risks in IPSS-R	4.7	1.7-13	0.0034*	7.9	3.1-20	<0.001*

Table 4B. Cox proportional hazards models for non-hMDS patients (*N*=143)

Univariate	Overall survival			AML progression-free survival		
non-hMDS	Hazard ratio	95% C. I.	P-value	Hazard ratio	95% C. I.	P-value
Sex	1.9	1.0-3.7	0.052*	1.9	1.1-3.5	0.028*
Age	1.1	1.0-1.1	<0.001*	1.0	1.0-1.1	<0.001*
Past illness†	1.2	0.64-2.4	0.52	1.1	0.61-2.0	0.73
Family history†	1.2	0.67-2.2	0.52	1.2	0.69-2.0	0.55
Smoking	0.99	0.96-1.0	0.60	1.0	1.0-1.0	0.98
Hemoglobin	0.89	0.78-1.0	0.066	0.91	0.82-1.0	0.11
Platelet count	0.98	0.96-1.0	0.21	1.0	0.98-1.0	0.90
Neutrophil count	1.0	1.0-1.0	0.88	1.0	1.0-1.0	0.67
PB blast	1.1	1.0-1.2	0.025*	1.1	1.1-1.2	<0.001*
BM blast	1.0	0.98-1.1	0.26	1.1	1.0-1.1	0.0087*
Performance status	4.2	1.9-9.1	<0.001*	4.1	2.0-8.7	<0.001*
Karyotype risks in IPSS-R	3.8	2.0-7.2	<0.001*	2.7	1.5-4.7	<0.001*
Multivariate	Overall survival			AML progression-free survival		
non-hMDS	Hazard ratio	95% C. I.	P-value	Hazard ratio	95% C. I.	P-value
Age	1.1	1.0-1.1	0.0040*	1.1	1.0-1.1	<0.001*
PB blast	1.1	0.99-1.2	0.084	1.1	1.0-1.2	0.020*
BM blast				1.1	1.0-1.1	0.032*
Performance status	3.5	1.5-8.5	0.0054*	3.7	1.6-8.4	0.0018*
Karyotype risks in IPSS-R	2.4	1.1-5.3	0.029*			

Table 4C. Cox proportional hazards models for all patients (*N*=286)

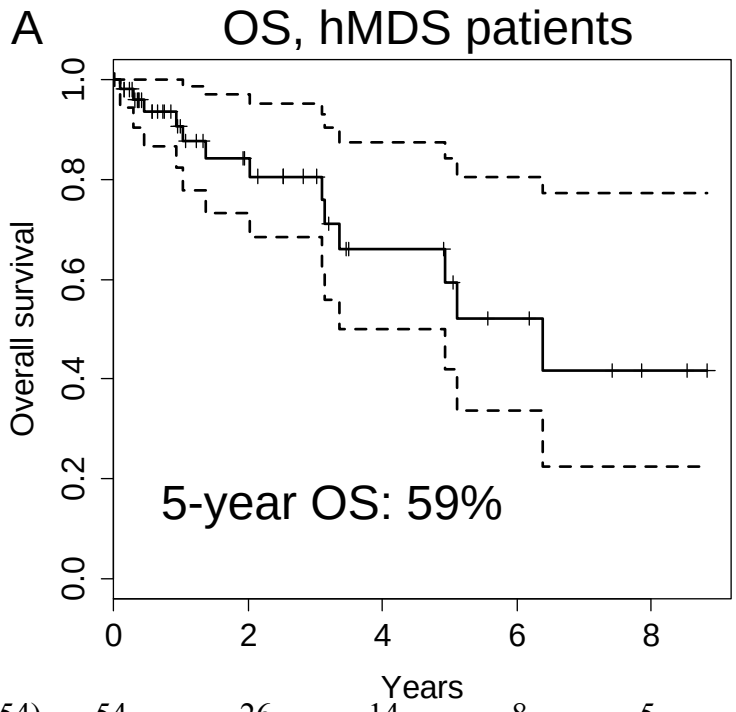
Univariate	Overall survival			AML progression-free survival		
All patients	Hazard ratio	95% C. I.	P-value	Hazard ratio	95% C. I.	P-value
Sex	2.7	1.5-4.6	<0.001*	2.5	1.5-4.0	<0.001*
Age	1.0	1.0-1.1	<0.001*	1.0	1.0-1.1	<0.001*
Past illness†	1.6	0.98-2.5	0.059	1.4	0.87-2.1	0.18
Family history†	1.2	0.75-2.0	0.40	1.2	0.78-1.9	0.39
Smoking	0.99	0.97-1.0	0.52	1.0	1.0-1.0	0.81
Hemoglobin	0.89	0.81-0.99	0.026*	0.91	0.84-1.0	0.041*
Platelet count	0.98	0.95-1.0	0.08	1.0	0.98-1.0	0.80
Neutrophil count	1.0	1.0-1.0	0.81	1.0	1.0-1.0	0.73
PB blast	1.0	0.98-1.1	0.19	1.1	1.0-1.1	0.014*
BM blast	1.0	1.0-1.1	0.018*	1.1	1.1-1.1	<0.001*
Performance status	4.6	2.5-8.3	<0.001*	4.5	2.7-7.7	<0.001*
Karyotype risks in IPSS-R	3.6	2.2-6.0	<0.001*	3.1	2.0-4.8	<0.001*
Multivariate	Overall survival			AML progression-free survival		
All patients	Hazard ratio	95% C.I.	P-value	Hazard ratio	95% C. I.	P-value
Sex	6.3	1.5-27	0.014*			
Age				1.0	1.0-1.1	0.035*
BM blast	1.1	1.0-1.1	0.029*	1.2	1.1-1.2	<0.001*
Performance status	5.2	1.8-15	0.0022*	6.2	2.4-16	<0.001*
Karyotype risks in IPSS-R	5.0	1.8-14	0.0019*	8.0	3.2-20	<0.001*

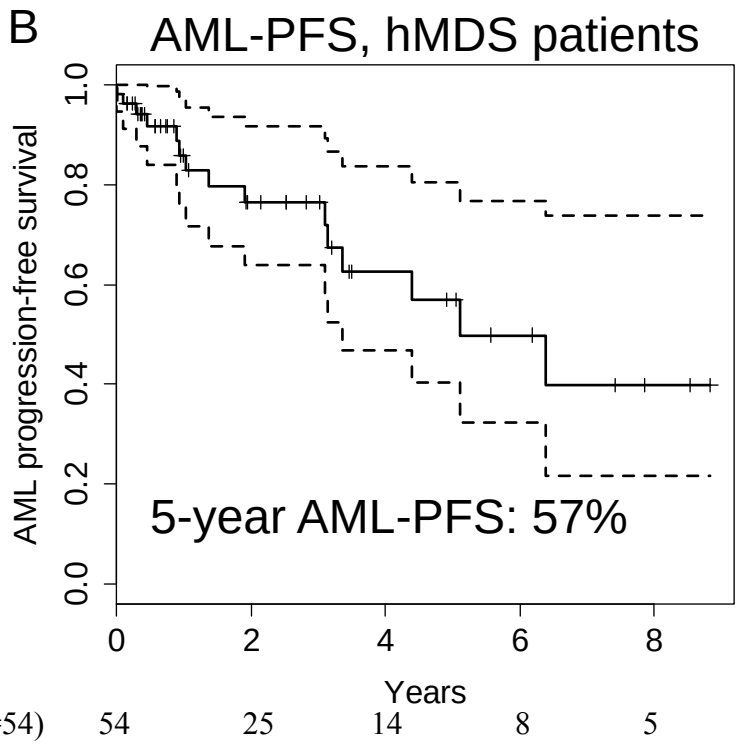
Table 3. Cox proportional hazards models for the analysis of risk factors of death and AML-progression. C.I.: confidence interval. *: statistically significant. Sex: 1 for male, 0 for female. † : past illness/family history of malignancy/hematological disease. PB: peripheral blood. BM: bone marrow. PS: performance status; 1 for score ≥2, and 0 for score ≤1. Karyotype risks in IPSS-R: 1 for poor and very poor risk groups, 0 for very good, good and intermediate risk groups. IPSS-R: revised international prognostic scoring system.

3.8. Subset analysis of the histology-proven MDS

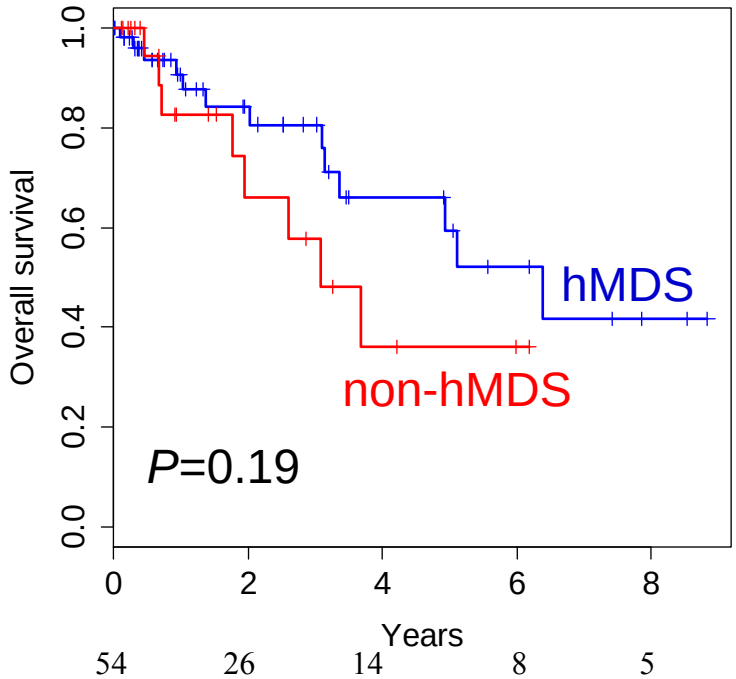
In order to confirm that the results of the study with MDS patients diagnosed without BM biopsy represent the true characteristics of hMDS and non-hMDS based on the diagnosis by BM biopsy, the subset analysis of the histology-proven patients was performed (Figure 5). The rates of OS and AML-PFS for this subpopulation exhibited similar results as those for the entire population including patients who were diagnosed by bone marrow aspiration alone; 5-year OS and AML-PFS for histology-proven hMDS were 59% (95% C. I. = 42 to 84 %) and 57% (95% C. I. = 40 to 80 %), respectively (Figure 5A, 5B). Although the differences were not statistically significant due to the limited size of population, the hMDS patients exhibited trends for higher rates of OS and AML-PFS than the non-hMDS patients (5-year OS = 59% versus 36% (P=0.19), and 5-year AML-PFS = 57% versus 33% (P=0.054), respectively) (Figure 5C, 5D), and likewise the hMDS patients at age <50 exhibited trends for higher rates of OS and AML-PFS than non-hMDS patients of the same age group (Figure 5E, 5F). Statistically significant differences in OS and AML-PFS between hMDS and non-hMDS were observed in the lower risk groups of IPSS and IPSS-R (Figure 5I, 5J, 5M, 5N), whereas the OS and AML-PFS of hMDS and non-hMDS in the higher risk groups did not exhibit significant differences (Figure 5K, 5L, 5O, 5P).

Figure 5. Subset analysis, histology-proven MDS



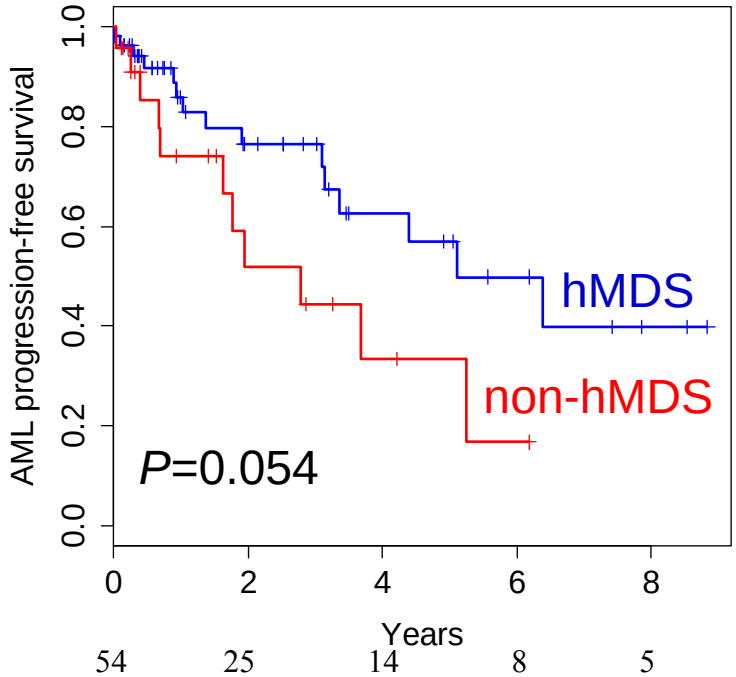


C OS, hMDS & non-hMDS

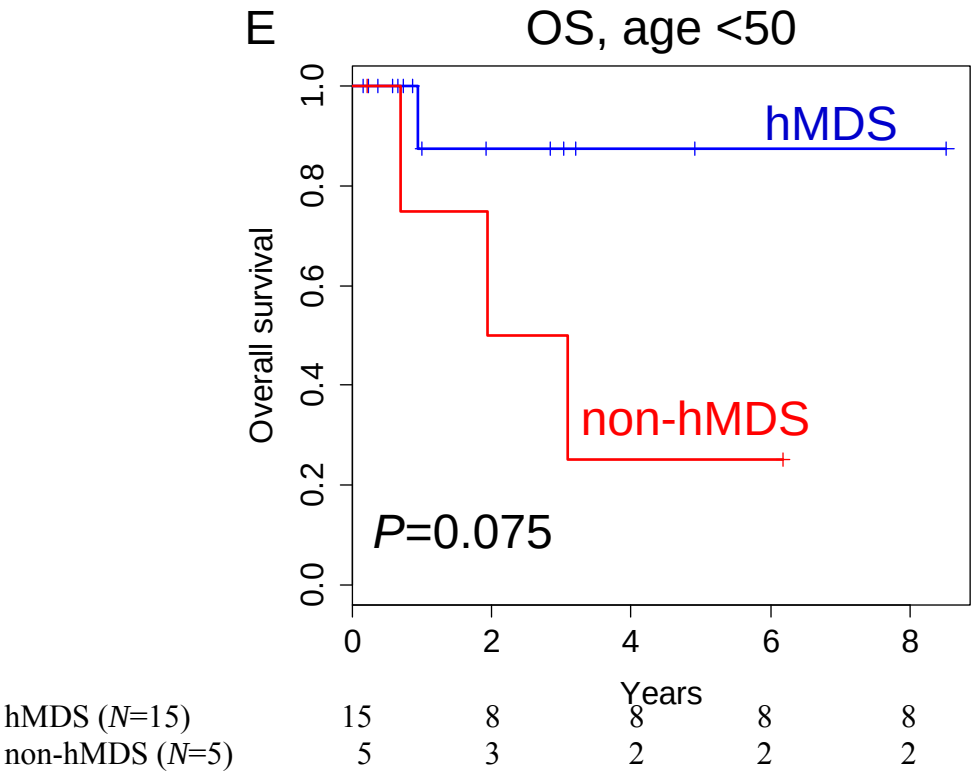


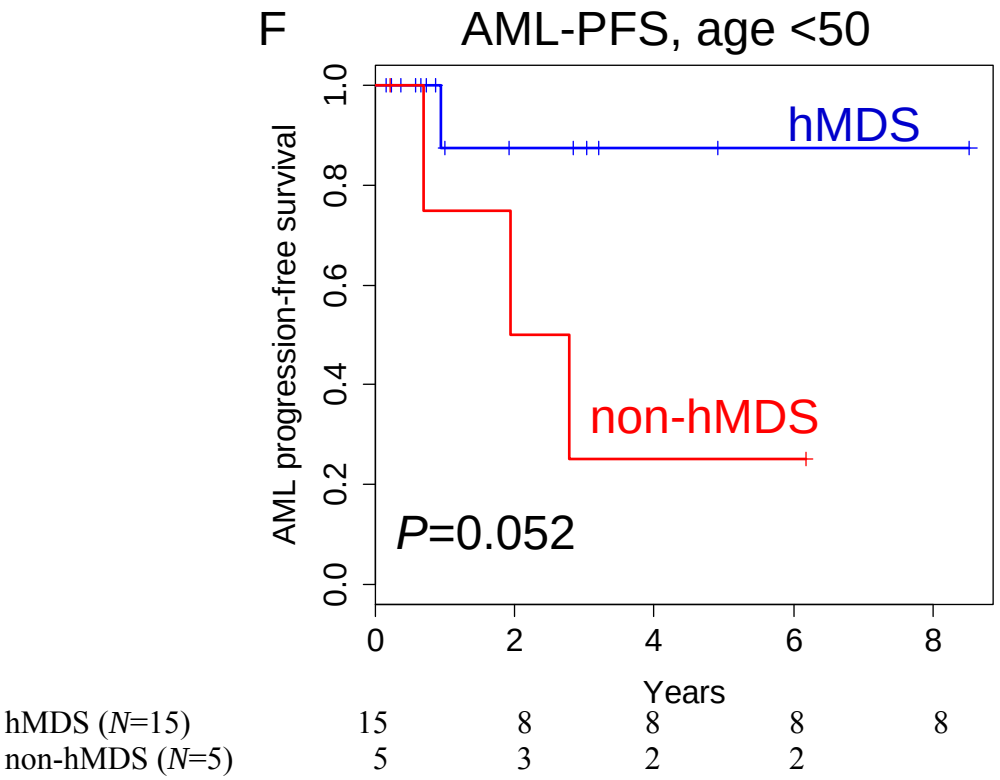
hMDS (*N*=54)	54	26	14	8	5
non-hMDS (*N*=24)	24	9	4	4	4

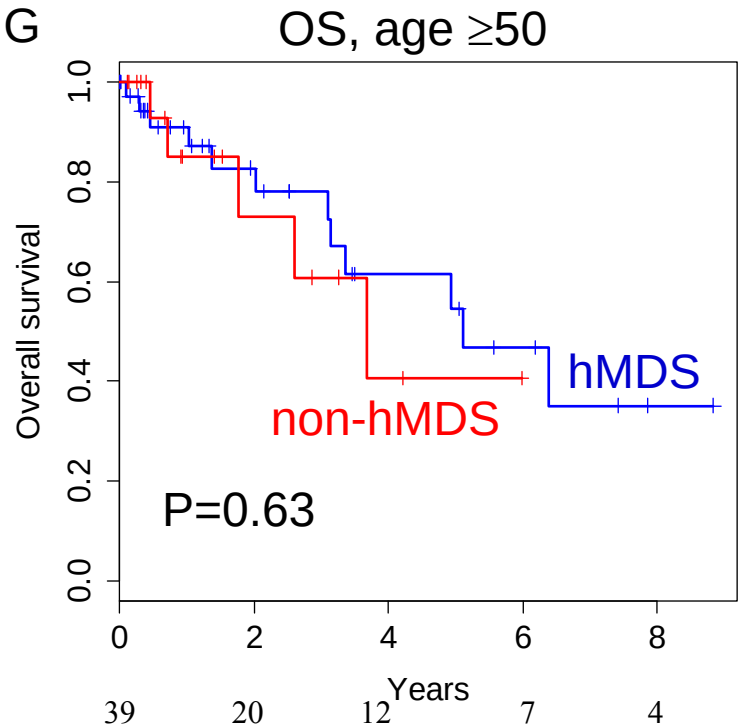
D AML-PFS, hMDS & non-hMDS



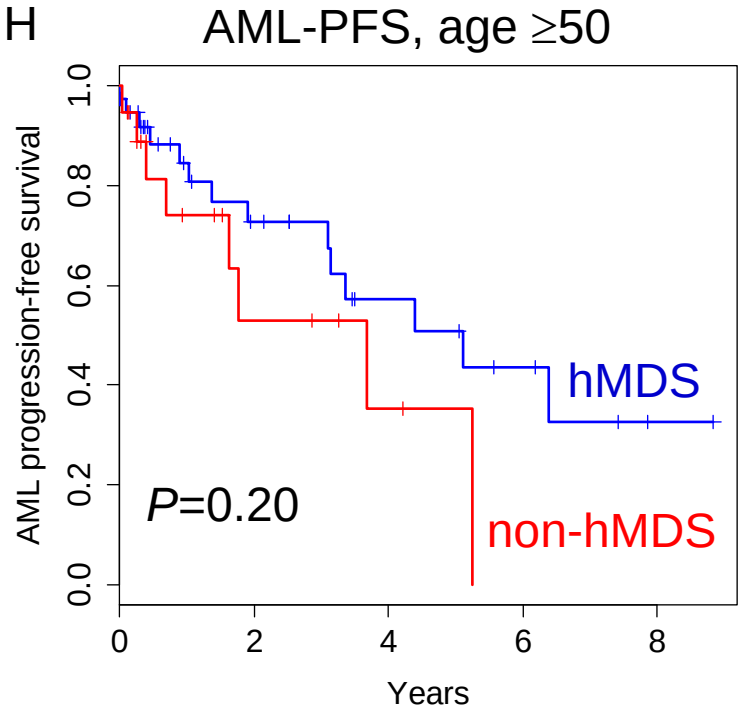
hMDS (*N*=54)	54	25	14	8	5
non-hMDS (*N*=24)	24	8	4	2	2


E
OS, age <50
hMDS
non-hMDS
P=0.075
Overall survival
0.0
0.2
0.4
0.6
0.8
1.0
0
2
4
6
8
Years
hMDS (N=15) 15 8 8 8 8
non-hMDS (N=5) 5 3 2 2 2


F
AML-PFS, age <50
hMDS
non-hMDS
P=0.052
AML progression-free survival
0.0
0.2
0.4
0.6
0.8
1.0
0
2
4
6
8
Years
hMDS (N=15) 15 8 8 8 8
non-hMDS (N=5) 5 3 2 2

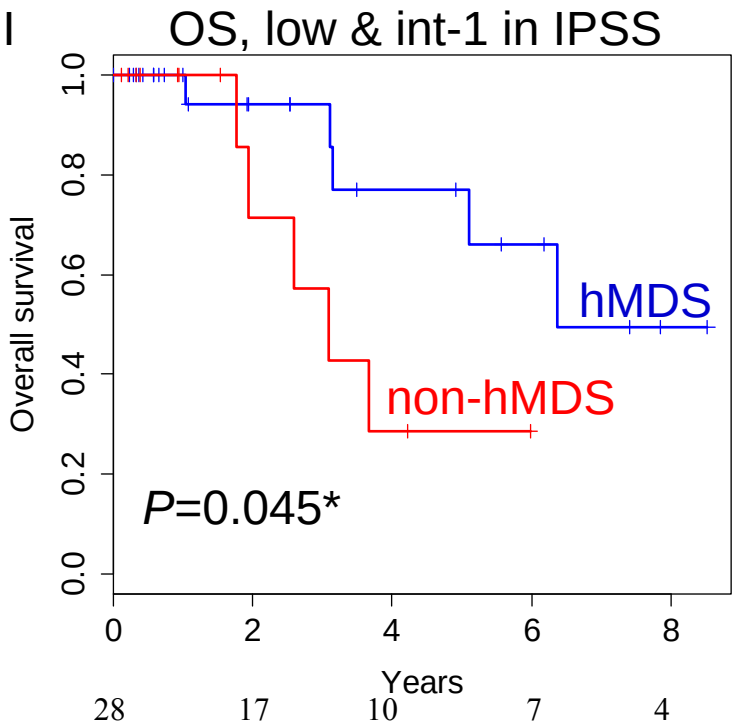


hMDS (*N*=39)	39	20	12	7	4
non-hMDS (*N*=19)	19	7	3	3	3



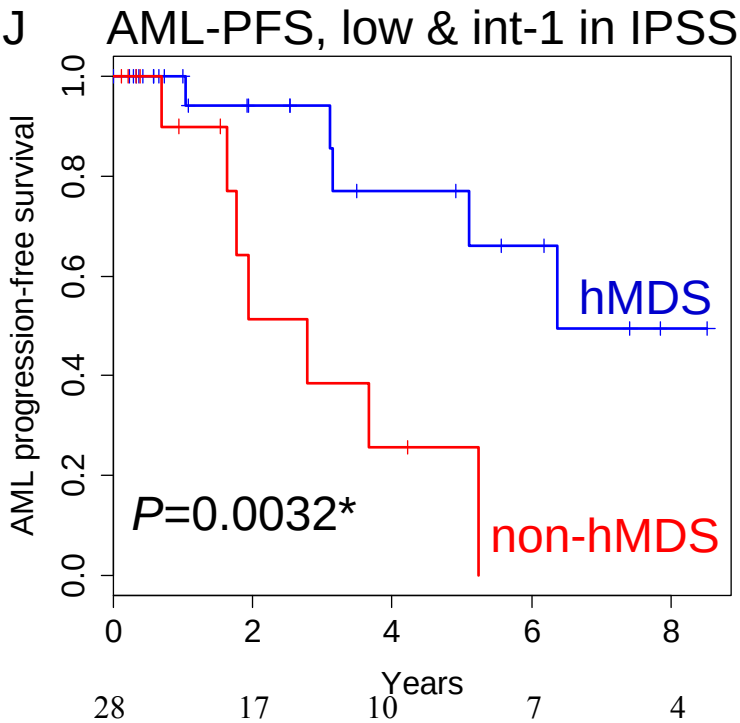
hMDS (*N*=39)	39	19	12	7	4
non-hMDS (*N*=19)	19	6	3	1	1

I



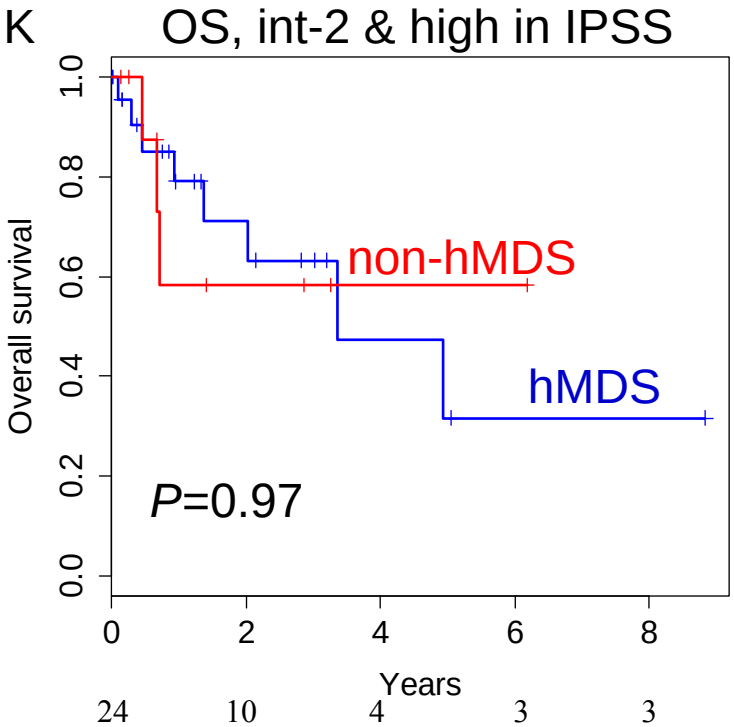
hMDS (*N*=28)	28	17	10	7	4
non-hMDS (*N*=14)	14	6	3	3	3

J



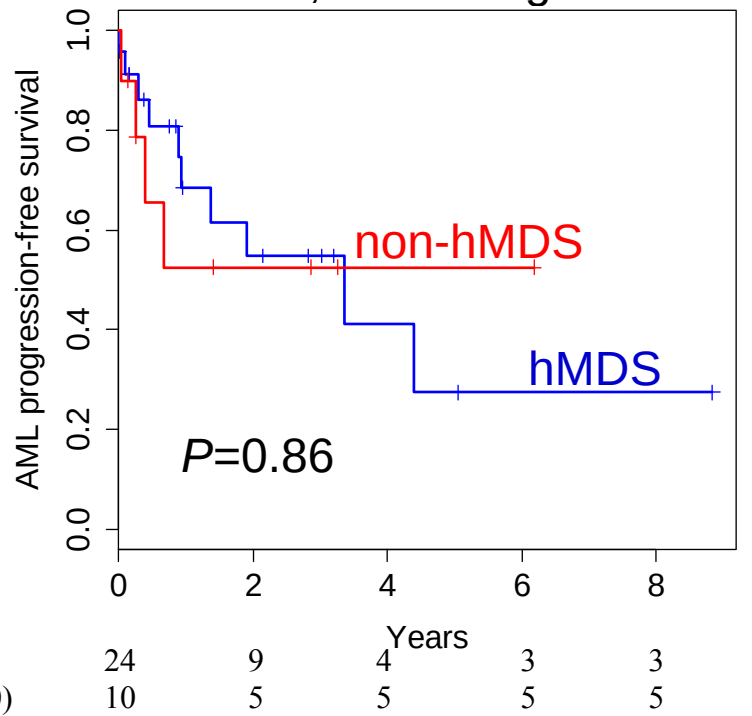
hMDS (*N*=28)	28	17	10	7	4
non-hMDS (*N*=14)	14	5	3	1	1

K



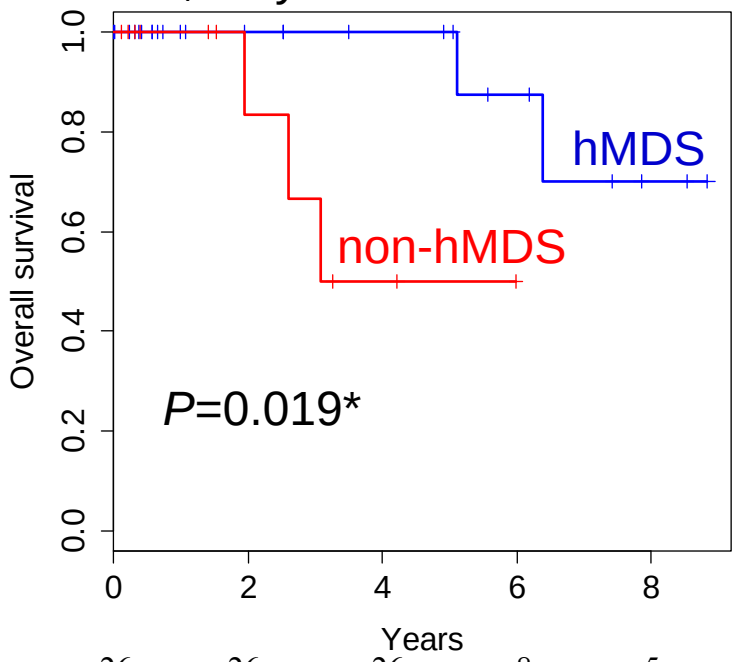
hMDS (*N*=24)	24	10	4	3	3
non-hMDS (*N*=10)	10	5	5	5	5

L



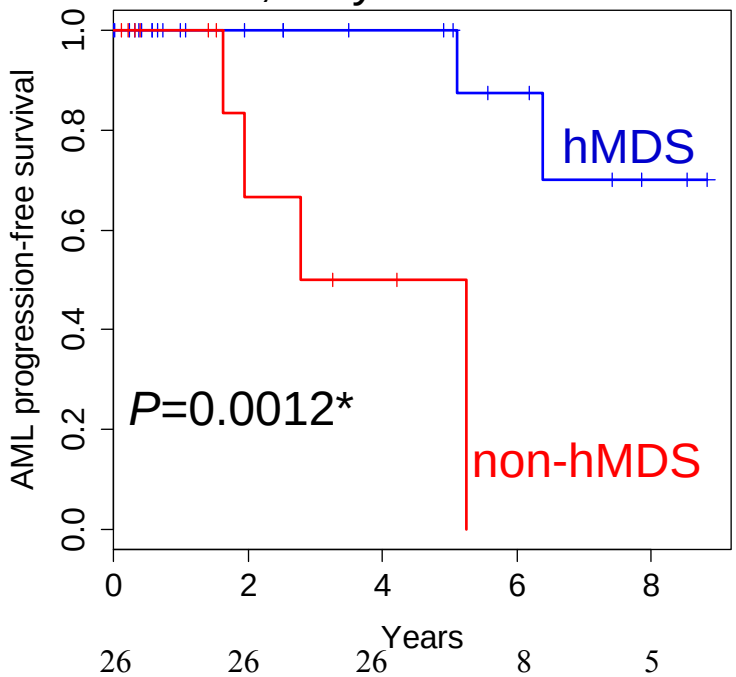
hMDS (*N*=24)	24	9	4	3	3
non-hMDS (*N*=10)	10	5	5	5	5

M OS, very low – int in IPSS-R



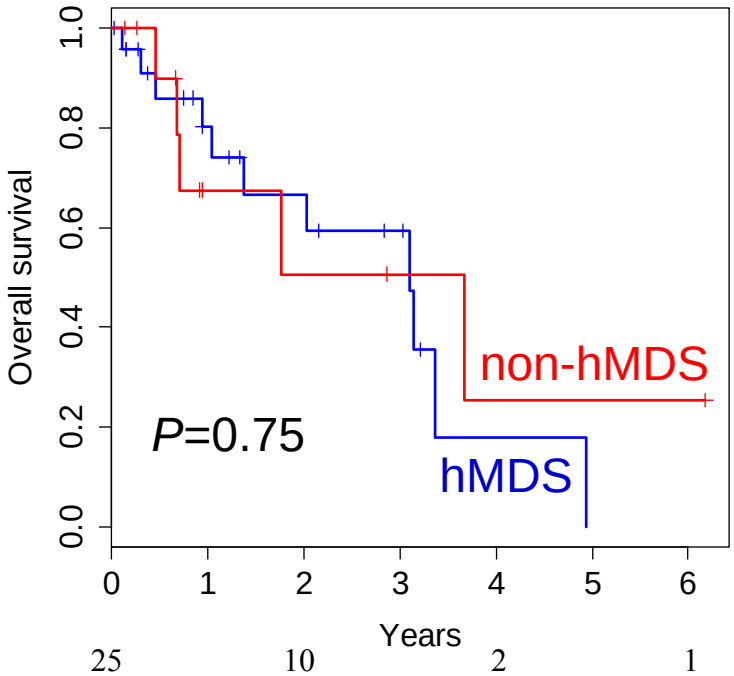
hMDS (*N*=26)	26	26	26	8	5
non-hMDS (*N*=12)	12	6	4	4	4

N AML-PFS, very low – int in IPSS-R



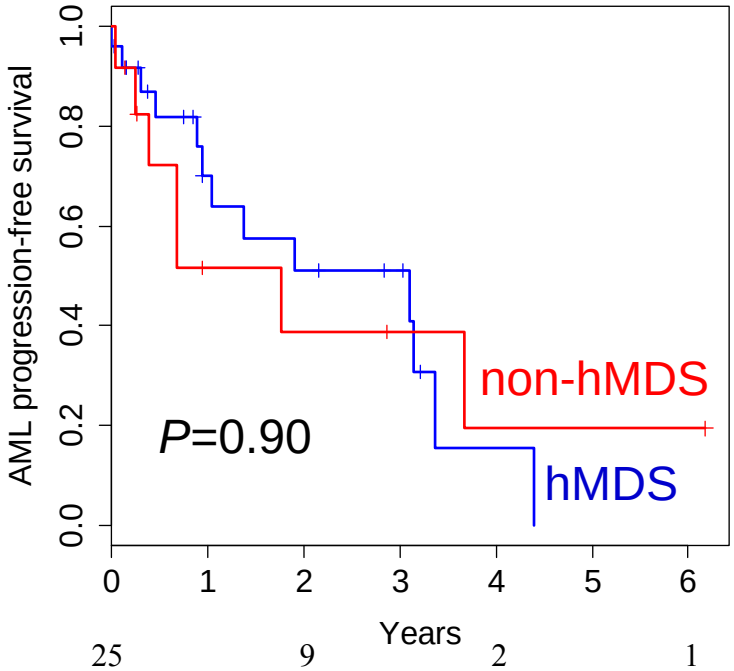
hMDS (*N*=26)	26	26	26	8	5
non-hMDS (*N*=12)	12	5	4	1	1

O OS, high & very high in IPSS-R



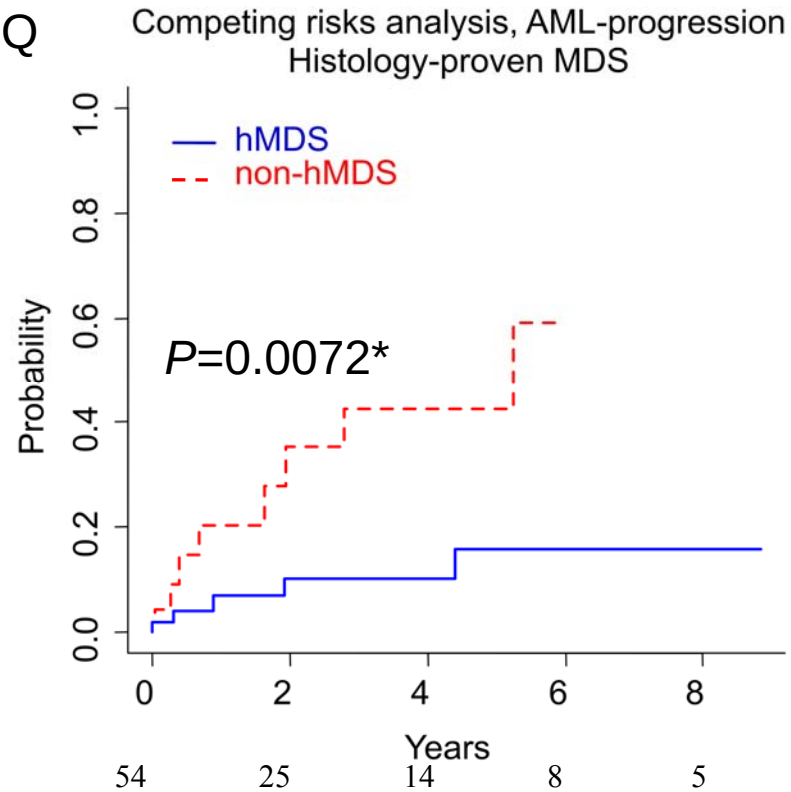
hMDS (*N*=25)	25	10	2	1
non-hMDS (*N*=12)	12	4	2	2

P AML-PFS, high & very high in IPSS-R



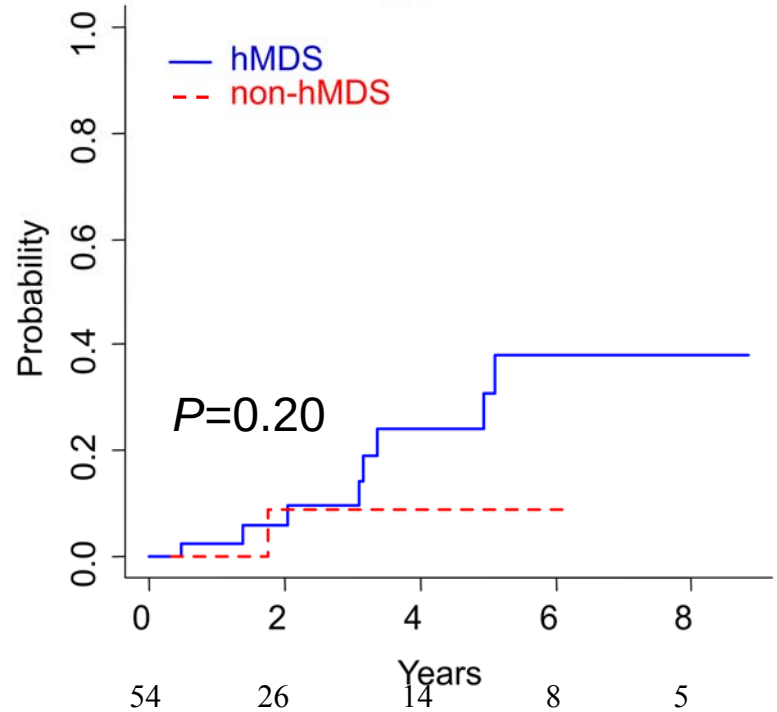
hMDS (*N*=25)	25	9	2	1
non-hMDS (*N*=12)	12	4	2	2

Q



hMDS (*N*=54)	54	25	14	8	5
non-hMDS (*N*=24)	24	8	4	2	2

R



hMDS (*N*=54)	54	26	14	8	5
non-hMDS (*N*=24)	24	9	4	4	4

Figure 5. Subset analysis of the histology-proven MDS. MDS: myelodysplastic syndrome. The numbers below the figures are the numbers of patients at risk in the even-numbered years from the beginning of the observations for these groups. A. OS of the histology-proven hMDS. OS: overall survival. hMDS: hypoplastic MDS. B. AML-PFS of the histology-proven hMDS. AML-PFS: acute myeloid leukemia progression-free survival. C. OS, histology-proven hMDS versus non-hMDS. D. AML-PFS, histology-proven hMDS versus non-hMDS. E. OS, histology-proven hMDS versus non-hMDS; age <50. F. AML-PFS, histology-proven hMDS versus non-hMDS; age <50. G. OS, histology-proven hMDS versus non-hMDS; age ≥50. H. AML-PFS, histology-proven hMDS versus non-hMDS; age ≥50. I. OS, histology-proven hMDS versus non-hMDS; low and int-1 risk groups in IPSS. int: intermediate. IPSS: International Prognostic Scoring System. J. AML-PFS, histology-proven hMDS versus non-hMDS; low and int-1 risk groups in IPSS. K. OS, histology-proven hMDS versus non-hMDS; int-2 and high risk groups in IPSS. L. AML-PFS, histology-proven hMDS versus non-hMDS; int-2 and high risk groups in IPSS. M. OS, histology-proven hMDS versus non-hMDS; very low, low and intermediate risk groups in IPSS-R. IPSS-R: revised IPSS. N. AML-PFS, histology-proven hMDS versus non-hMDS; very low, low and intermediate risk groups in IPSS-R. O. OS, histology-proven hMDS versus non-hMDS; high and very high risk groups in IPSS-R. P. AML-PFS, histology-proven hMDS versus non-hMDS; high and very high risk groups in IPSS-R. Q. Competing risks analysis of AML-progression, histology-proven hMDS versus non-hMDS. R. Competing risks analysis of death from bone marrow failure (BMF), histology-proven hMDS versus non-hMDS. Death from BMF is defined as the death caused by cytopenia of at least two lineages.

Competing risks analysis for histology-proven patients also exhibited similar results as those for all patients; 5-year cumulative incidences of AML-progression for hMDS and non-hMDS were 16% versus 42% (P=0.0072), and 5-year cumulative incidences of death from BMF for hMDS and non-hMDS were 31% versus 8.8% (P=0.20), respectively (Figure 5Q, 5R). The result of the death from BMF did not exhibit statistically significant difference, because of the limited sample size of 54 hMDS and 24 non-hMDS patients.

3.9. Distributions of histology-proven MDS and MDS without BM biopsy

In order to investigate further whether the subset of histology-proven MDS patients represents the characteristics of the entire population including the MDS patients diagnosed without BM biopsy, two-sample Kolmogorov-Smirnov test was applied to the subpopulations of histology-proven patients and the other patients (Table 5). It was confirmed that all of the background continuous variables of the histology-proven patients follow the same distributions as those of the other patients, except for the neutrophil count which may be biased by the data of CMMoL patients for whom BM biopsy was not performed. It can be interpreted, therefore, that the data of all patients, including the data of those who were diagnosed by BM aspiration alone, can be

interpreted to represent the clinical characteristics of hMDS patients, even though the importance of diagnosing by BM biopsy cannot be overemphasized.

Table 5. Two-sample Kolmogorov-Smirnov test for MDS with and without biopsy

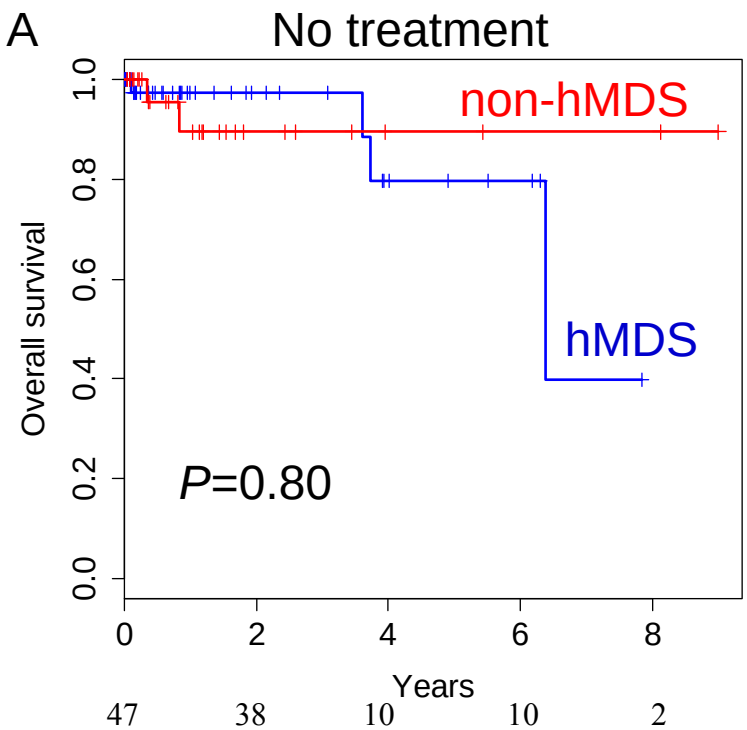
Variables	Kolmogorov-Smirnov	
	D-value	*P*-value
Age	0.16	0.10
Hemoglobin	0.14	0.21
Platelet count	0.13	0.28
Neutrophil count	0.22	0.0070*
PB Blast	0.054	1.0
BM blast	0.14	0.30

Testing the equality of the distributions of the histology-proven MDS patients (both hMDS and non-hMDS) and those of the MDS patients diagnosed without BM biopsy (both hMDS and non-hMDS). The numbers of the histology-proven MDS patients and the MDS patients diagnosed without BM biopsy are 78 and 208, respectively ($n = 78$ and $m = 208$ for the formulae in 2.11.5.), and the null hypothesis that the two one-dimensional probability distributions are the same is rejected if *D*-value exceeds 0.18. In all of these continuous background variables, two populations proved to be from the same distribution by Kolmogorov-Smirnov test in all of the background variables except the neutrophil count. MDS: myelodysplastic syndrome. *: statistically significant. hMDS: hypoplastic MDS. PB: peripheral blood. BM: bone marrow.

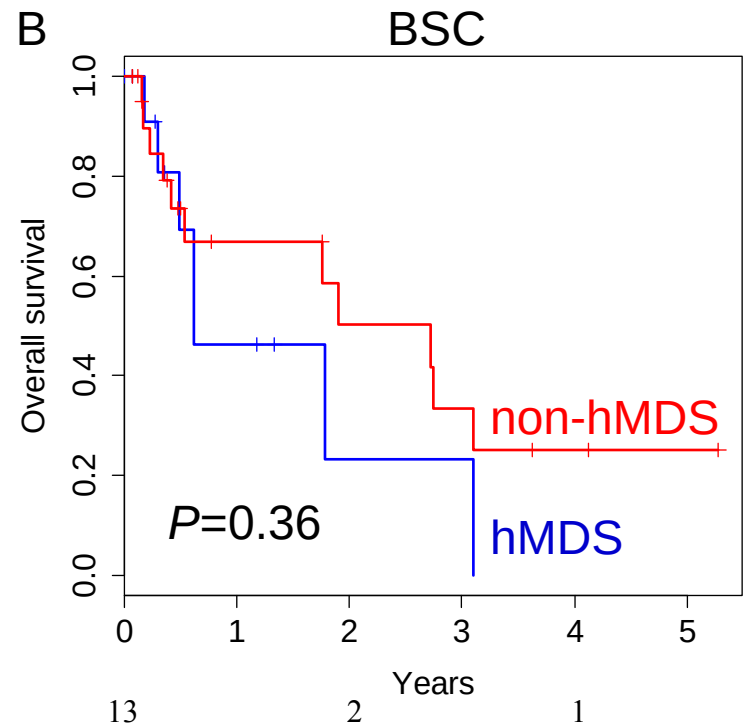
3.10. The OS of MDS patients by initial treatments

The OS of patients according to their initial treatments were also analyzed (Figure 6), but the OS between hMDS and non-hMDS did not exhibit statistically significant differences in any treatment, partly due to the limited sample sizes.

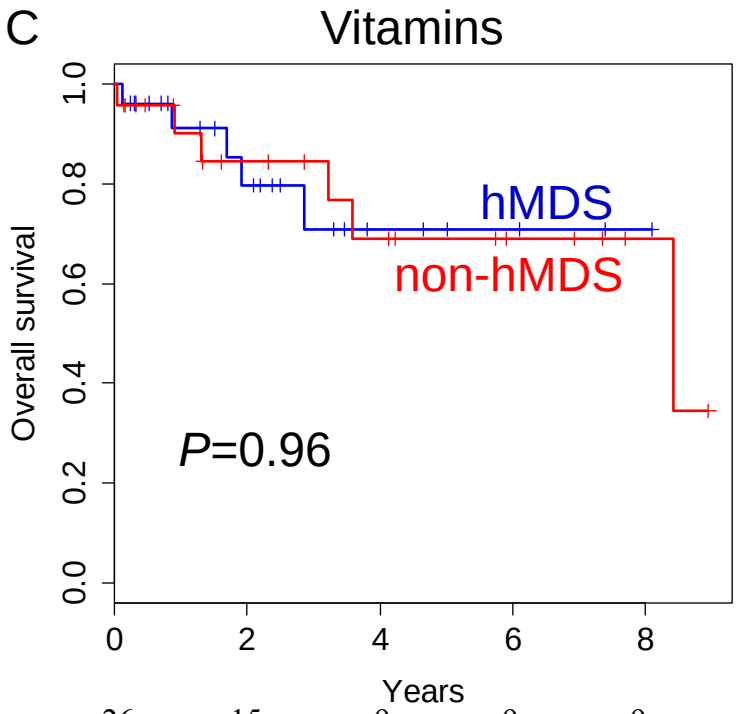
Figure 6. Overall survival by initial treatment



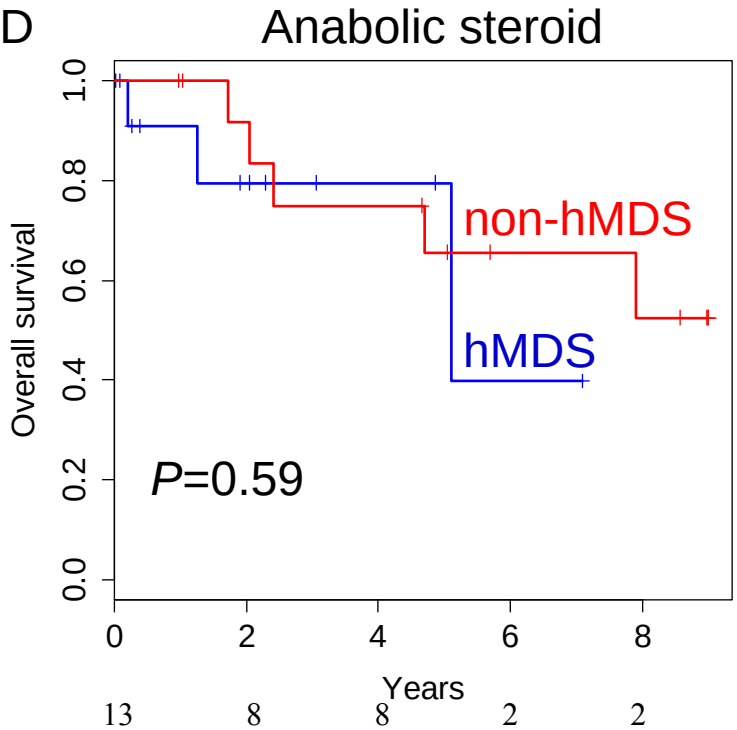
hMDS (*N*=47)	47	38	10	10	2
non-hMDS (*N*=31)	31	16	16	16	16



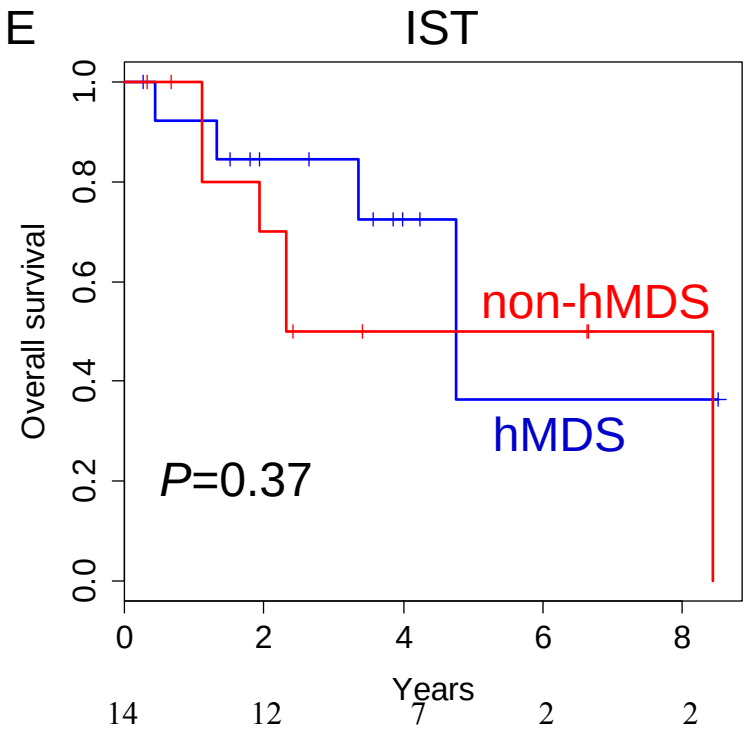
hMDS (*N*=13)	13	2	1
non-hMDS (*N*=23)	23	7	4



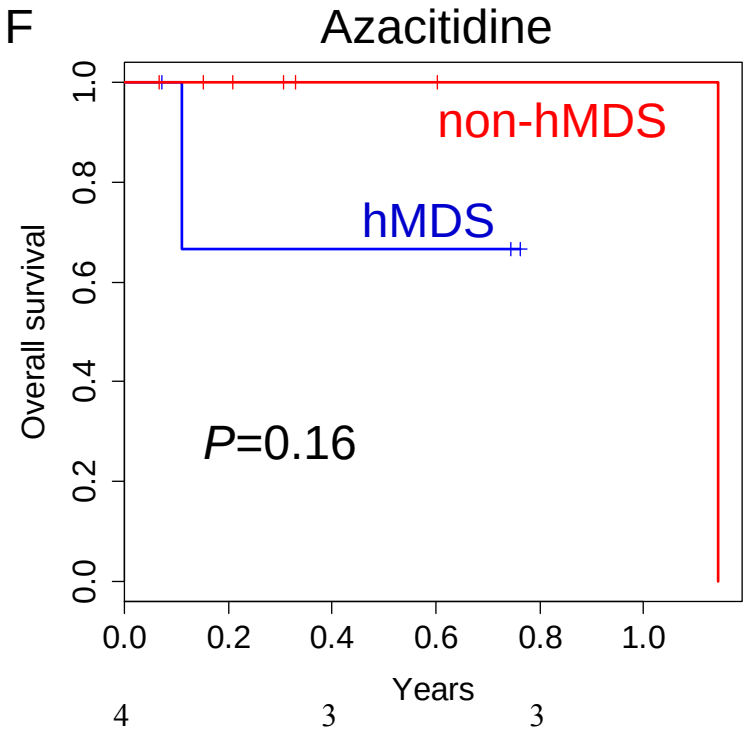
hMDS (*N*=26)	26	15	9	9	9
non-hMDS (*N*=23)	23	16	10	10	10



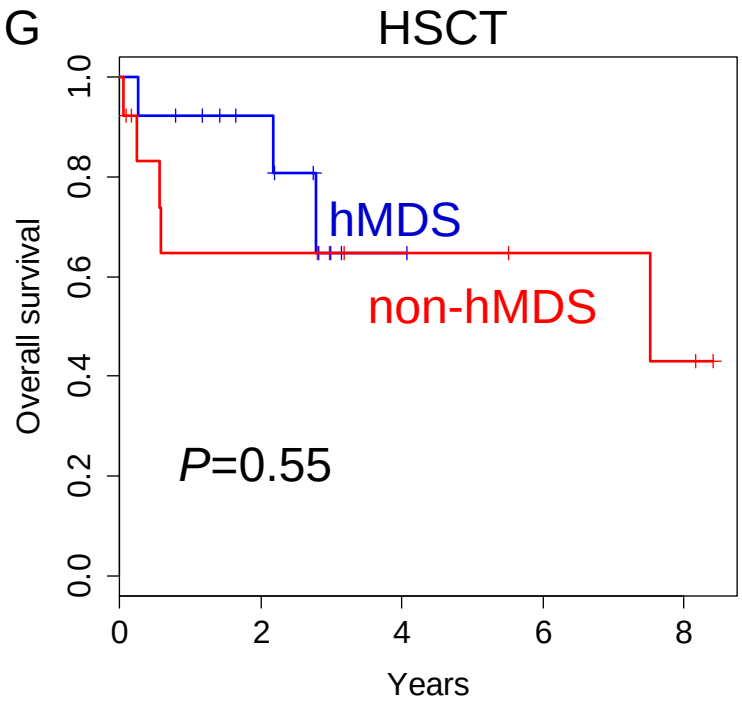
hMDS (*N*=13)	13	8	8	2	2
non-hMDS (*N*=14)	14	12	10	8	5



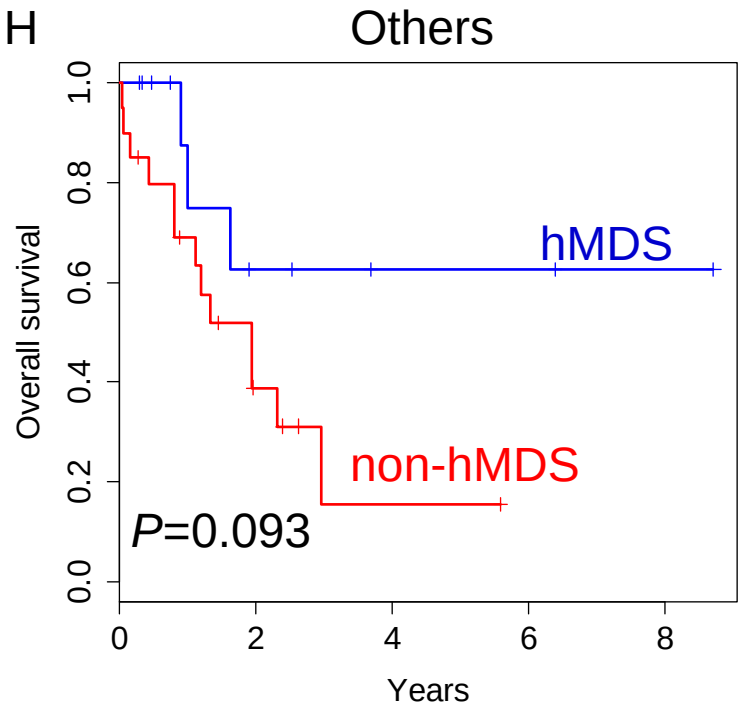
hMDS (*N*=14)	14	12	7	2	2
non-hMDS (*N*=12)	12	8	7	7	7



hMDS (*N*=4)	4	3	3
non-hMDS (*N*=7)	7	7	7



hMDS (*N*=13)	13	13	5	5	5
non-hMDS (*N*=13)	13	8	8	8	3



hMDS (*N*=12)	12	6	6	6	6
non-hMDS (*N*=20)	20	7	2	2	2

Figure 5. The overall survival (OS) of MDS patients by their initial treatments. A. OS of patients with no treatment. B. OS of patients treated with best supportive care (BSC). C. OS of patients treated with vitamins. D. OS of patients treated with anabolic steroid. E. OS of patients treated with immuosuppressive therapy (IST). F. OS of patients treated with azacitidine or decitabine. G. OS of patients treated with HSCT. H. OS of patients treated with other treatments.

Table 6. Treatments for hMDS patients

1st treatment	hMDS patients (*N*=143)
No treatment	39 (30%)
BSC	12 (9.1%)
Vitamins	26 (20%)
Anabolic steroid	11 (8.3%)
IST	14 (11%)
Azacitidine	4 (3%)
HSCT	14 (11%)
Others	11 (8.3%)

2nd treatment	hMDS patients (*N*=143)
Vitamins	1 (0.76%)
Anabolic steroid	4 (3.0%)
IST	4 (3.0%)
Azacitidine	3 (2.3%)
HSCT	5 (3.8%)
Others	11 (8.3%)

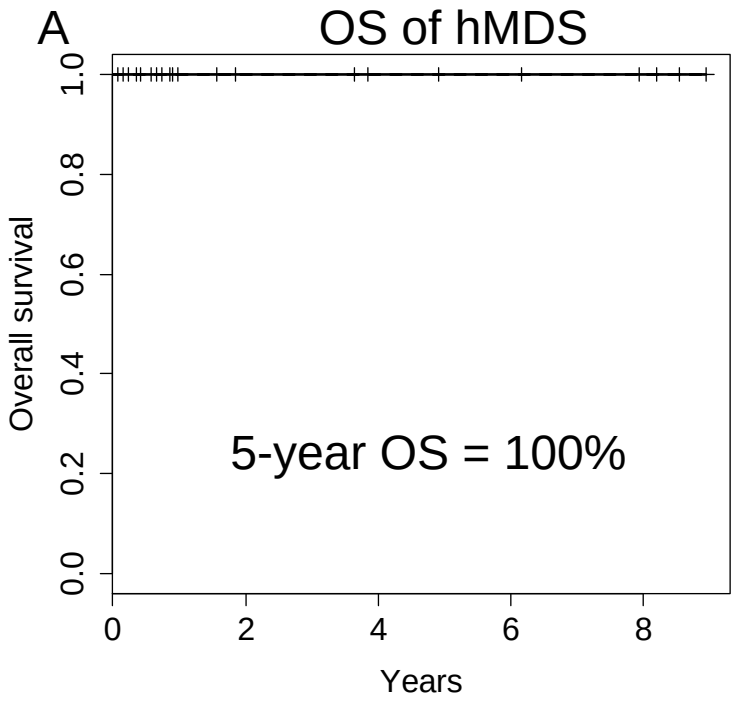
The patients with "no treatment" and "BSC" were without 2nd treatments. In case multiple therapies were administered simultaneously, the patients were categorized in the lower column of categories, e.g., the hMDS patients treated with anabolic steroid and vitamins were categorized in "anabolic steroid." BSC: best supportive care; blood transfusion, antibiotics, etc. Vitamins: vitamin D_3, vitamin K_2, and/or vitamin B_6. Anabolic steroid: metenolone acetate, danazol, etc. IST: immunosuppressive therapy: cyclosporin A (CsA), antithymocyte globulin (ATG), prednisolone, etc. Azacitidine: one patient treated with decitabine is included. HSCT: hematopoietic stem cell transplantation; either allogeneic bone marrow/peripheral stem cell transplantation or cord blood transplantation. Others: myelosuppressive chemotherapies such as citarabine (Ara-C), hydroxyurea (HU), etc., and a few patients treated with other agents such as erythropoietin alone and granulocyte colony-stimulating factor (G-CSF) alone were included.

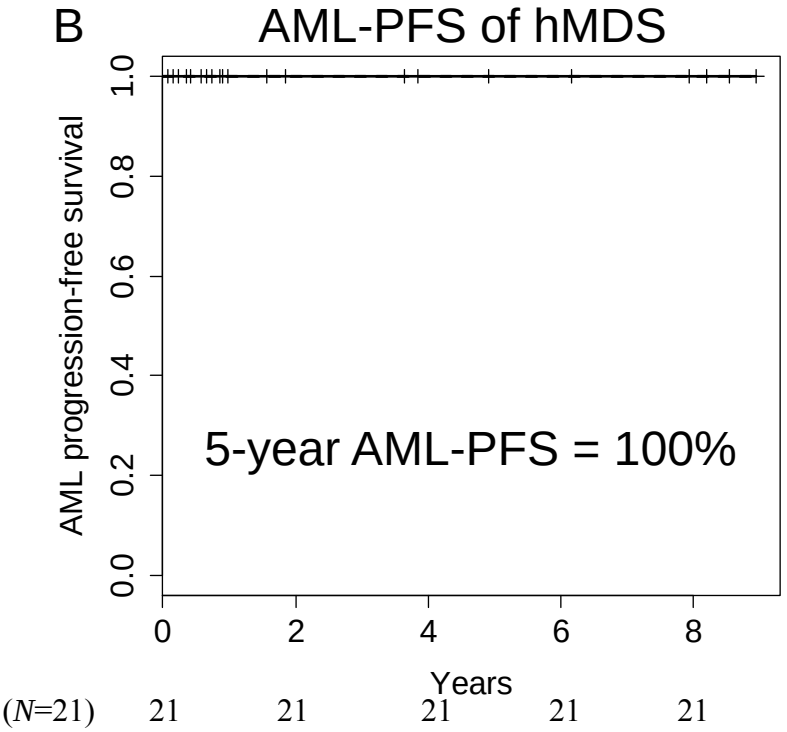
Nearly 60% of the 143 hMDS patients received treatments other than BSC, but 30% of the hMDS patients received no treatments and 9.1% of the hMDS patients were followed up with BSC alone throughout the entire clinical courses, 20% were administered vitamins as their first treatment, and 11% underwent hematopoietic stem cell transplantation (HSCT) as their initial treatment (Table 6).

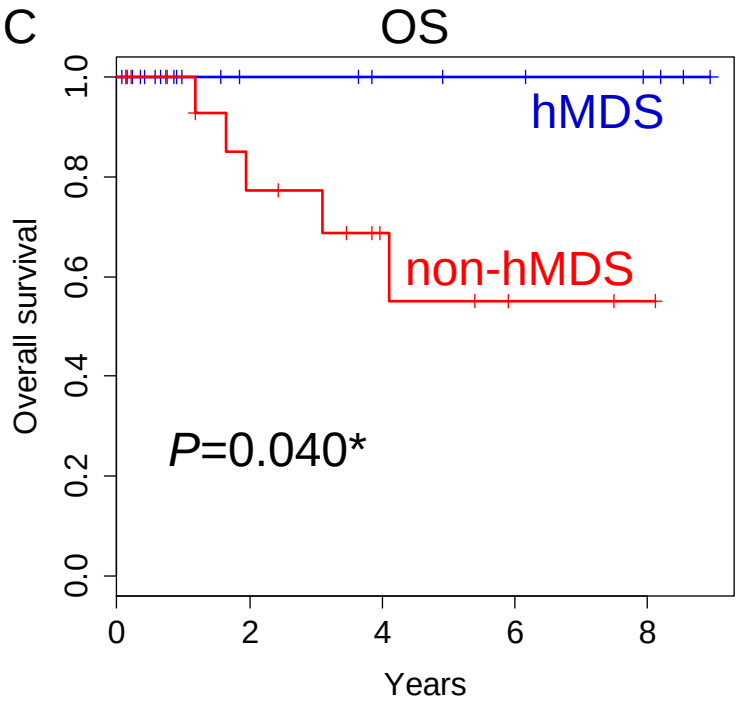
3.11. The subset analysis of MDS patients at age <50 and of lower risks in IPSS-R

As exhibited earlier, higher rates of OS and AML-PFS of hMDS patients were attributed to age <50 and lower risk groups. Therefore, subset analysis was performed for patients who were both at age <50 and of lower risk groups (very low, low and intermediate risk groups of IPSS-R) (21 hMDS and 18 non-hMDS patients) (Figure 7). Significant differences in OS and AML-PFS between hMDS and non-hMDS of this subgroup were exhibited; the 5-year rates of OS for hMDS and non-hMDS were 100% and 55% (P=0.040), and those of AML-PFS were 100% and 46% (P=0.014), respectively. The hMDS patients of this subpopulation neither died nor progressed to AML, whereas some non-hMDS patients either died or progressed to AML. Furthermore, none of them in both hMDS and non-hMDS died from BMF. As for the OS by initial treatments, significant difference was observed in patients treated with IST (P=0.018), where none of the hMDS patients died but some non-hMDS patients died.

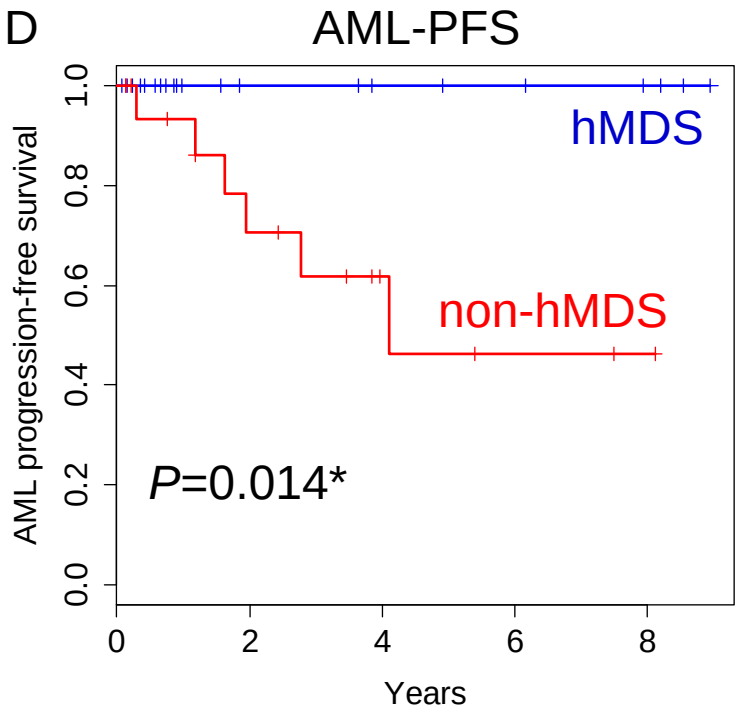
Figure 7. Subset analysis, age <50 and very low – intermediate risk groups of IPSS-R





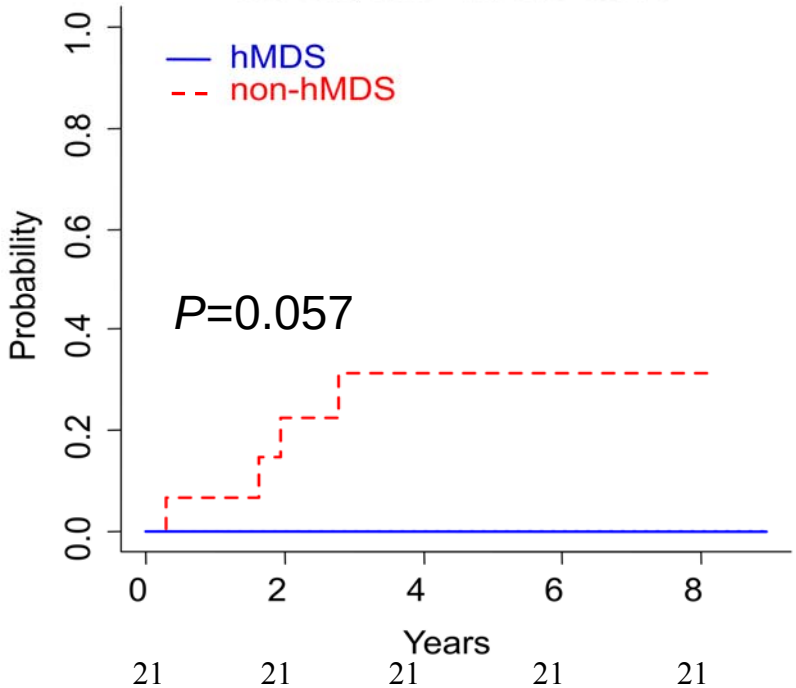


hMDS (*N*=21)	21	21	21	21	21
non-hMDS (*N*=18)	18	11	9	5	5



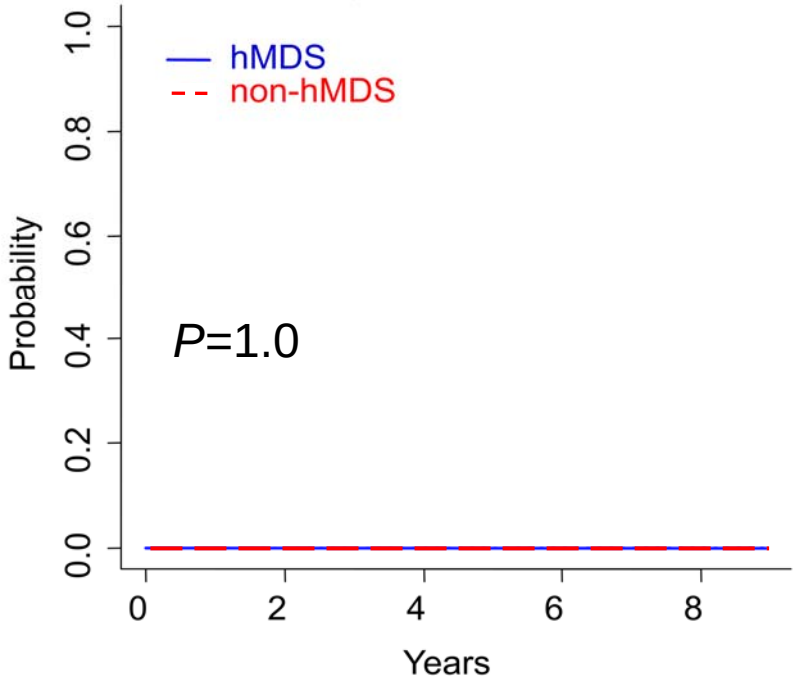
hMDS (*N*=21)	21	21	21	21	21
non-hMDS (*N*=18)	18	10	8	4	4

E



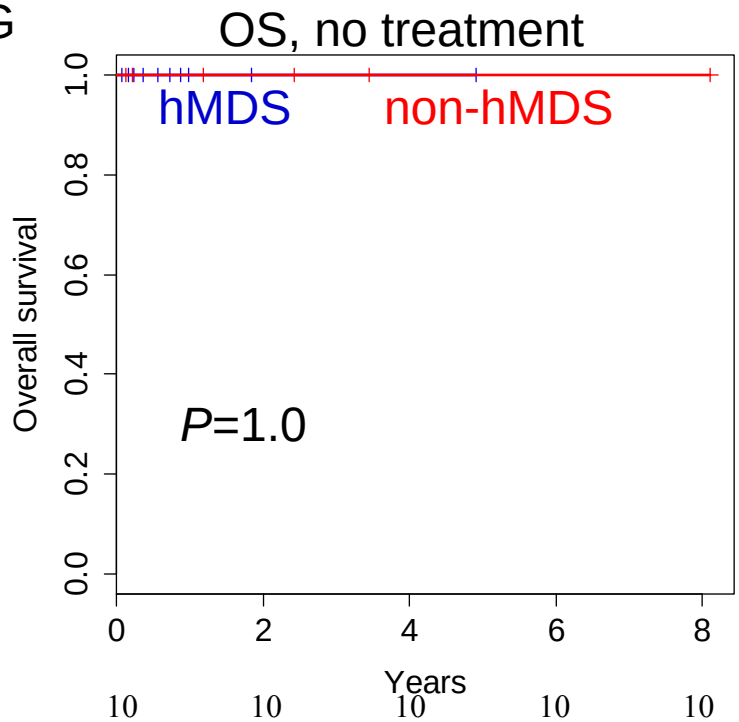
hMDS (*N*=21)	21	21	21	21	21
non-hMDS (*N*=18)	18	10	8	4	4

F



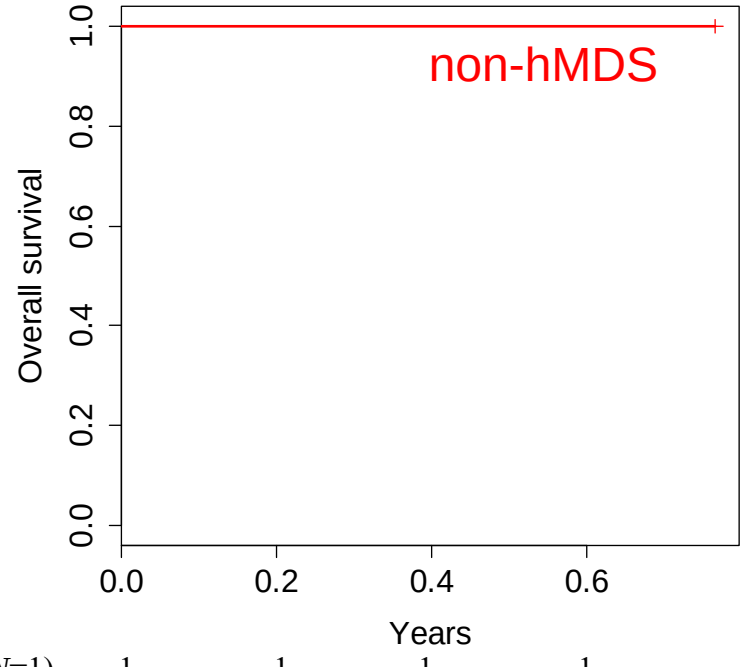
hMDS (*N*=21)	21	21	21	21	21
non-hMDS (*N*=18)	18	11	9	5	5

G



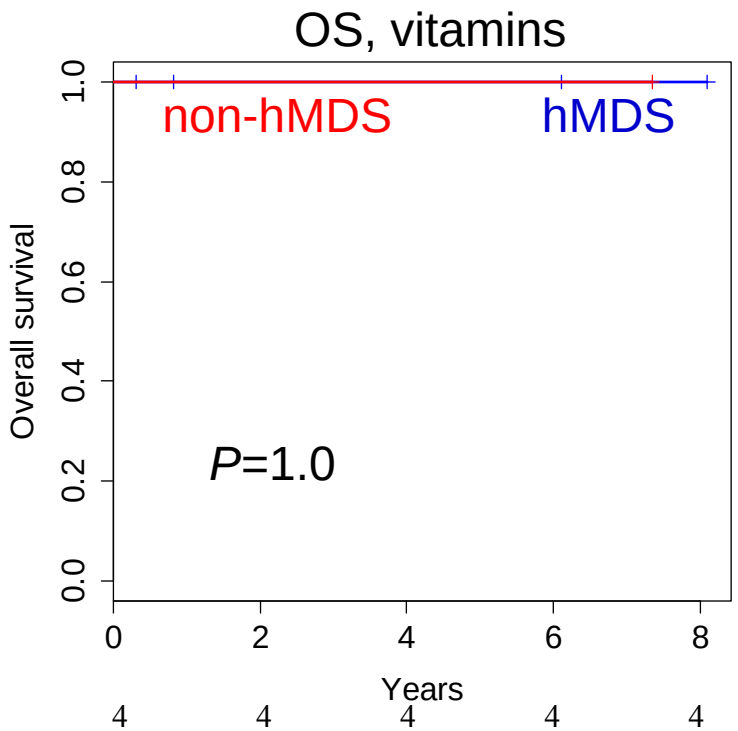
hMDS (*N*=10)	10	10	10	10	10
non-hMDS (*N*=6)	6	6	6	6	6

H



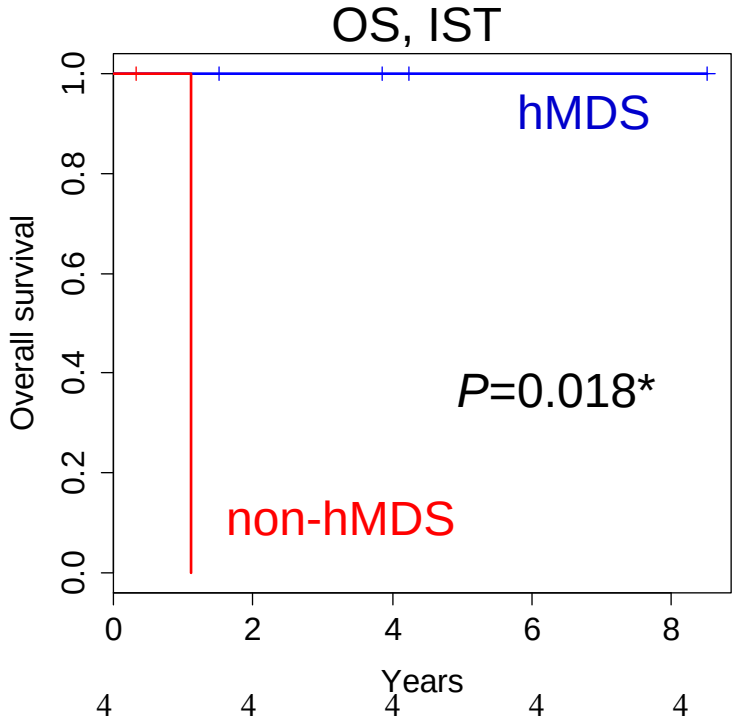
non-hMDS (*N*=1)	1	1	1	1

I

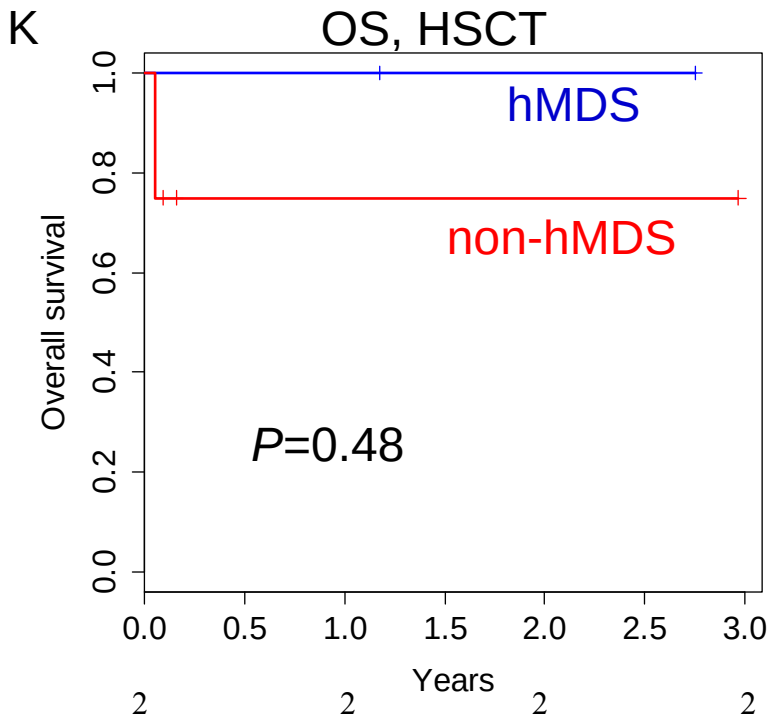


hMDS (*N*=4)	4	4	4	4	4
non-hMDS (*N*=1)	1	1	1	1	1

J

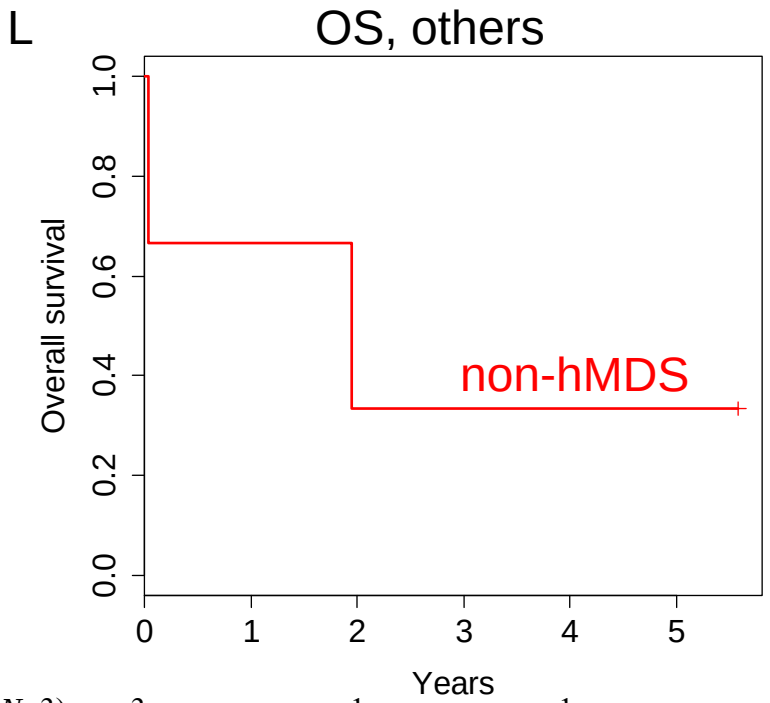


hMDS (*N*=4)	4	4	4	4	4
non-hMDS (*N*=3)	3	1	1	1	1



hMDS (*N*=2)	2	2	2	2
non-hMDS (*N*=4)	4	4	4	4

(1 non-hMDS patient was censored in 50 days.)



non-hMDS (*N*=3)	3	1	1

Figure 7. Subset analysis of MDS patients both at age <50 and in lower risk groups (very low, low and intermediate in IPSS-R). The numbers below the figures are the numbers of patients at risk in the even-numbered years from the beginning of the observations for these groups. IPSS: International Prognostic Scoring System. IPSS-R: revised IPSS. A. overall survival (OS) of hMDS patients. B. AML progression-free survival (AML-PFS) of hMDS patients. AML: acute myeloid leukemia. C. OS, hMDS and non-hMDS. *: statistically significant. D. AML-PFS, hMDS and non-hMDS. E. competing risks analysis of AML-progression. F. competing risks analysis of death from bone marrow failure (BMF). G. OS of patients without any treatments. H. OS of patients treated with best supportive care (BSC); none of the hMDS patients of this subgroup was treated with BSC. I. OS of patients treated with vitamins. J. OS of patients treated with immunosuppressive therapy (IST). K. OS of patients treated with hematopoietic stem cell transplantation (HSCT). H. OS of patients treated with other therapies; none of the hMDS patients of this subgroup was treated with other therapies.

4. Discussion

The hMDS patients for this study consisted approximately 6.3% of the entire MDS patients from the participating institutions. This percentage coincides with the widely acknowledged evidence of hMDS consisting 5-10% of the MDS in the previously published literature [34, 45, 49].

There have been a few reports of single-center clinical study in hMDS, which exhibited poorer prognosis of hMDS than AA and better prognosis than non-hMDS, but they dealt with a limited number of hMDS patients, and a study with a larger sample size is desirable. [55, 64] The prognosis has been discussed according to the risk groups of IPSS in the previously published literature, [55] but since IPSS-R has already been acknowledged worldwide, the prognosis of hMDS needs to be discussed according to IPSS-R. [15] This study is the first multicenter study with the data of >100 hMDS patients, and the first study on hMDS that dealt with IPSS-R.

The characteristics of patients in Table 1 exhibited that more than half of the hMDS patients were classified as RA in FAB classification, which coincides with the previously reported literature. [55] The WHO classification composition of hMDS had hardly been discussed, and as exhibited in this study, there were significant differences between hMDS and non-hMDS in WHO classification, where nearly 30% of hMDS

patients were categorized as RCUD while nearly half of the non-hMDS patients were categorized as RCMD, and more MDS-U patients were found in hMDS than in non-hMDS, but the percentage of RAEB-1/2 patients with hMDS and of those with non-hMDS were nearly the same. A recent study suggests that RCUD exhibits higher rates of OS than RCMD, [96] but the OS of the hMDS patients of this current study according to WHO classification did not exhibit statistically significant difference between RCUD and RCMD (data and graph not shown).

The result in Figure 2, that hMDS patients in low and intermediate-1 risk groups exhibited higher rates of OS and AML-PFS than non-hMDS patients with statistically significant differences whereas the differences in OS and AML-PFS of intermediate-2 and high risk groups were not statistically significant, is the finding that coincides with Huang TC et al. [55] Investigating further, the very low – intermediate risk groups of hMDS patients exhibited higher OS and AML-PFS than those of non-hMDS patients with statistically significant differences, whereas high and very high risk groups of hMDS did not exhibit statistically significant differences in OS and AML-PFS from those of non-hMDS, which implies that the treatments for hMDS patients in very low – intermediate risk groups of IPSS-R should be considered separately from those for non-hMDS in the same risk groups. Therefore, the better

prognosis of hMDS compared with that of non-hMDS can be attributed to the prognosis of hMDS patients in lower risk groups. The hMDS patients of age <50 and lower risk groups were extremely risk-free from death and AML-progression, and the adequate treatment strategies for them should be investigated separately from the strategies for the other hMDS patients.

Risk analysis by the Cox proportional hazards models exhibited high hazard ratios in PS and karyotype risks for both OS and AML-PFS of hMDS patients as well as the other patients. This result coincides with the previously published literature, [97, 98] but it was shown further in univariate Cox proportional hazards analysis that other factors such as past illnesses and smoking habits can also be the risk factors of death and AML-progression for hMDS patients.

Competing risks analysis of this study revealed that hMDS patients are less likely to progress to AML than non-hMDS patients, as Huang et al. exhibited. [55] However, the anticipation that hMDS may have higher risk of death from BMF had never been confirmed before, partly because there had been no numerical criteria for BMF. By applying a criterion of death from BMF for the purpose of this study, it was confirmed that hMDS patients have higher risk of death from BMF. Therefore, there may be some hMDS patients for whom myelo-suppressing therapies are not indicated.

The cytogenetic abnormalities of hMDS patients in this study were summarized into karyotype risk groups of IPSS-R. Koh Y et al. exhibited the AML-PFS of hMDS patients with and without cytogenetic abnormalities, which were not statistically significant. [64] According to IPSS-R, some chromosomal abnormalities are classified into the same risk group as the normal karyotype, and there exist some hMDS patients with chromosomal abnormalities that have more favorable outcomes than those without. Therefore, survival analyses by IPSS-R exhibited earlier may give more adequate assessments for the prognoses of hMDS.

The abnormalities in fluorescent in situ hybridization (FISH) were not dealt with in this study. It has been reported that AA positive of trisomy 1q by FISH progressed to acute leukemia more frequently, whereas no single karyotype or FISH abnormality in hMDS predicted leukemic progression, [64] and therefore, it is likely that FISH analysis for the data of hMDS patients in this study would not have yielded statistically significant outcomes.

The subset analysis of histology-proven patients revealed that hMDS and non-hMDS patients exhibited similar results in OS and AML-PFS compared with the entire population. It is confirmed further by Kolmogorov-Smirnov test that both the patients diagnosed with biopsy and those without are from the same distribution.

Therefore, inclusion of MDS patients diagnosed by bone marrow aspiration alone can be allowed for, although bone marrow biopsy cannot be overemphasized for the proper diagnosis of hMDS.

Comparison of OS between hMDS and non-hMDS according to the initial treatments did not exhibit statistically significant differences between hMDS and non-hMDS. This finding coincides with the fact that hMDS includes both low-risk and high-risk patients, and therapies for hMDS patients should be considered according to their risk groups as well as the risk of death from BMF for elderly hMDS patients. In order to investigate adequate treatment choices for hMDS, however, a study with even a larger size of population is required.

5. Conclusion

The nationwide retrospective study of the 143 hMDS patients in comparison with the 143 non-hMDS patients yielded the following results:

1. The background variables of the hMDS exhibited fewer patients with family histories of malignancies/hematological diseases and smoking habits and severer cytopenia of platelets, neutrophils and blasts in PB.
2. Morphological dysplasia of the hMDS patients were less complex than that of the non-hMDS patients, and the majority of the hMDS patients were categorized as RA in FAB classification and RCUD in WHO classification. Also, more MDS-U patients were found in hMDS than in non-hMDS, and more RAEB-t and CMMoL were found in non-hMDS than in hMDS. On the other hand, the BM blast percentage was not significantly different between hMDS and non-hMDS, and the compositions of IPSS and IPSS-R were not of significant difference, which implies that the clinical outcomes of hMDS may differ from those of non-hMDS because of morphological dysplasia rather than the BM blast percentage.
3. The 5-year OS and AML-PFS of hMDS differ by only 1%, which came from the fact that nearly all of the hMDS patients who had progressed to AML were refractory to treatments and ended up with deaths. The hMDS patients could be

divided into two groups in terms of survival: age <50 and age ≥50, low – int-1 and int-2 – high in IPSS, and very low – int and high – very high in IPSS-R.

4. The rates of OS and AML-PFS of hMDS were higher than those of non-hMDS (especially with statistical significance for AML-PFS), and remarkably significant differences between hMDS and non-hMDS were found in the AML-PFS at age <50 and of lower risk groups in IPSS (low – int-1), and in both the OS and the AML-PFS of lower risk groups in IPSS-R (very low – int).

5. In competing risks analysis, hMDS exhibited lower risk of AML-progression and higher risk of death from BMF than non-hMDS. Although the risk of hMDS to progress to AML was lower than that of non-hMDS for all ages, it was significantly lower than that of non-hMDS in the lower risk groups of IPSS and IPSS-R. The risk of hMDS to die from BMF was significantly higher than that of non-hMDS at age ≥50 and in the higher risk groups of IPSS-R. Therefore, low risk of hMDS to progress to AML was attributed to the lower risk groups, and high risk of hMDS to die from BMF was attributed to age ≥50 and higher risk groups.

6. The univariate and multivariate Cox proportional hazards models exhibited male gender, higher PS (≥2), and higher karyotype risk (poor – very poor risk groups of IPSS-R) as the significant risk factors of death and AML-progression for hMDS.

Also, past illnesses of malignancies/hematological diseases and smoking habits were also exhibited as the risk factors of hMDS in the univariate Cox proportional hazards model.

7. The subset analysis of histology-proven MDS, as well as the two-sample Kolmogorov-Smirnov test for the distributions of the background variables of histology-proven MDS and MDS without BM biopsy, confirmed that the study including MDS patients without BM biopsy still represents the true characteristics of hMDS in comparison with non-hMDS to a large extent; in particular, the OS and the AML-PFS of hMDS in the lower risk groups of IPSS and IPSS-R were significantly lower than those of non-hMDS in the same risk groups, and the risk of hMDS to progress to AML was significantly lower than that of non-hMDS, even with a much smaller sample size.

8. The survival analysis by the initial treatments and the subset analysis of MDS both at age <50 and of lower risks in IPSS-R did not yield satisfactory results, mainly due to the limited sample size. A study with a much larger population is required to investigate the adequate treatment strategies for hMDS.

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Appendix: the documents submitted to the Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo

様式第１－１号

研　究　倫　理　審　査　申　請　書

平成　　年　　月　　日

東京大学医学系研究科長・医学部長　殿

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下記の研究について、倫理審査を申請いたします。

記

研究課題	hypoplastic MDS に関する全国調査（多施設共同後方視的研究）
キーワード（５つ程度）	調査研究、多施設共同研究、hypoplastic MDS、骨髄異形成症候群、侵襲性無
研究従事者の 氏名・所属・職名等	（氏名）　（所属）　（職名）　（研究倫理セミナー受講 No 及び年月日） 南谷　泰仁　血液・腫瘍内科　特任講師　H23-26-537，平成 23 年 5 月 24 日 黒川　峰夫　血液・腫瘍内科　教授　H23-26-756，平成 23 年 5 月 24 日 市川　幹　血液・腫瘍内科　講師　H22-23-305，平成 22 年 6 月　1 日 小林　隆　血液・腫瘍内科　大学院生　H24-1-2473，平成 24 年 6 月 13 日 特発性造血障害に関する調査研究班 研究代表者 黒川 峰夫（東京大学医学部附属病院 血液・腫瘍内科） 参加施設リスト(資料 4)
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添付書類一覧	資料 1：研究計画書 資料 2-1：予備 調査シート 資料 2-2：本調査シート 資料 3：研究公示のホームページ掲載文章 資料 4：参加施設リスト 別紙 1：研究倫理審査申請書チェックリスト 別紙 2：倫理セミナー受講証（南谷，コピー） 別紙 3：利益相反自己申告書 (南谷)

a)研究責任者は常勤教職員に限る。大学院生・研究生は研究責任者になることはできない。
b)研究責任者は研究倫理セミナー受講証の写を必ず添付すること（研究責任者は受講していない場合、審査を受けられない。また学内研究従事者も原則として研究開始前までに受講する必要がある)。
尚、外部施設所属の者は除く。

研　究　計　画　書

資料１

１．研究課題　　hypoplastic MDS（低形成性骨髄異形成症候群)に関する全国調査（多施設共同後方視的研究）

２．研究の概要

２．１　背景及び目的

骨髄異形成症候群(MDS)の新たなentityとして、hypoplastic MDS(hMDS; 低形成性骨髄異形成症候群)という概念が提唱されるようになった。MDSのうち5～20%を占めるこのhMDSは、再生不良性貧血との鑑別が困難である他、低形成骨髄ゆえに汎血球減少が顕著であるため、白血病化よりもむしろ骨髄不全によって死に至ることが懸念される。それゆえ、他のMDSに対して行われているような骨髄抑制を伴う治療の妥当性が不明であり、hMDSに対する適切な治療法や治療効果などは未だ解明されていない。

そこで、本邦におけるhMDSの患者背景、臨床像、治療反応性、予後などを調査することにより、hMDSに対する最適な治療選択を解明することが、本研究の目的である。

近年、造血幹細胞移植以外の治療としてDNA脱メチル化剤であるアザシチジンによる治療の有効性が議論されるようになったが、hMDSはその顕著な汎血球減少ゆえに同薬剤の投与による骨髄抑制の遷延や骨髄不全が懸念される。本調査により、hMDSの臨床像や予後、また患者背景に応じてアザシチジンを含むあらゆる治療法の中でいずれが選択されるべきかについても、理解を深めることができると予想される。

本研究は、東京大学が主導になって行われ、全国の協力施設が参加する多施設共同研究である。

２．２　方法

調査対象と調査データ

本研究は、東京大学が主導になって行われる。全国の協力施設から300例の登録を得ることを目標とする。調査対象疾患および対象期間は、各施設で診断されたMDS患者のうち、診断時に骨髄のcellularityが30%に満たなかった(60歳以上の場合は骨髄のcellularityが20%に満たなかった)hMDS患者を、2003年4月1日から2012年3月31日まで観察する。これまでの治療法の種類や年齢、性別などは問わない。調査対象となるデータは治療経過に関する既存の臨床データと予後に関するデータであり、新たな検体収集や測定は行わない。

本調査のデータは患者の診断日、末梢血の血算値や骨髄穿刺・生検所見、選択された治療法やその治療効果などから成る(資料2-2)。

調査方法

研究総括施設(東京大学)から郵送または電子メールでアンケートを各施設に送付し、当院で集計する。アンケートは二段階に分けて行われる。予備調査は各施設におけるMDS患者数とhMDS患者数のみを把握するために行われ、本研究承認後に各施設へ送付する。本調査は各hMDS患者の詳細な情報を得るため、詳細な調査票を用いて各患者につき一回行われる。

調査期間中の対象疾患各症例に対して、患者の診断日や患者背景、治療内容等の詳細を調査する。資料2の調査用紙に調査項目が明示されている(2. 3　2)①)。データは全て後方視的に収集する。

統計解析としては、行われた治療によって対象患者を分け、t検定を用いて患者背景を群間比較する。生存時間解析として全生存をKaplan-Meier法で評価し、群間比較にlog-rank検定を用いる。全生存時間(OS; overall survival)を本研究のprimary endpointとし、OSに影響を及ぼす因子を比例ハザードモデルで多変量解析する。染色体異常の消失、輸血依存度の軽減、および白血病化をsecondary endpointsとし、これらに及ぼす因子の多変量解析を比例ハザードモデルまたは回帰分析により実施する。P値は0.05未満を有意とする。

実施期間	2003年4月1日から2012年3月31日まで	研究期間	承認後5年間

２．３　対象及び資料等

１）対象

・選択基準

2003年4月1日から2012年3月31日までの間に当院および協力施設で診断された成人hMDS患者

人数：　合計約300名(当院では約25名)　　除外基準：　なし

２）資料

①予備調査シート（資料2-1）

内容は次の通りである。調査依頼文書、アンケート内容説明文、予備調査票（調査研究協力の可否、上記選択基準に該当するMDS患者の人数、およびhMDS患者の人数。

②本調査シート（資料2-2）

内容は次の通りである。患者ID(各医療機関のIDおよび本研究における医療機関毎の通し番号)、診断確定日、診断時年齢、性別・生年月、既往歴・家族歴・生活歴、診断時分類、診断時・治療前後の検査データ、診断時臨床症状・PS、治療の種類とその投与量・期間、治療前の輸血依存度、治療効果、治療終了/変更/中止の理由、最終観察日と転帰。

体細胞のゲノム情報は含まない。

２．４　研究参加者（被験者・研究対象者）の実体験

調査研究であり、研究参加者の実体験はない。

３．研究を実施する施設とその役割

１）該当する本学および学外施設名とその役割

①インフォームド・コンセントを受ける施設：ホームページで開示する

②個人情報及び資料などを収集または所有する施設：東京大学医学部附属病院血液・腫瘍内科
A14 階北病棟検査室

③資料などを匿名化する施設：東京大学医学部附属病院血液・腫瘍内科（ゲノム研究室）

④資料等の解析を行う施設：東京大学医学部附属病院血液・腫瘍内科（ゲノム研究室）

⑤資料等を保存する施設：東京大学医学部附属病院血液・腫瘍内科（ゲノム研究室）

２）学外施設での対応とその状況

本研究は、厚生労働科学研究費補助金 難治性疾患克服研究事業　特発性造血障害に関する調査研究班の事業として計画された調査研究である。当院および全国の協力施設で行う（資料 4)。

下記の手順でデータを収集する。

①予備 調査で参加を表明した施設に本研究事務局から本調査票を送る。

②協力各施設で症例毎に症例番号を付与して連結可能匿名化を行い、対応表を施設の責任者が管理する。

③協力各施設の責任者が、連結可能匿名化された本調査票を本研究事務局に郵送する。

④参加協力施設では資料保存責任者(資料 4-4)が承認後 5 年間、下記 4. 2 と同じ方法で保存し、研究期間終了後に破棄する。

４．研究における倫理的配慮

４．１　インフォームド・コンセント

１）実施方法

本研究は「文部科学省・厚生労働省 疫学研究に関する倫理指針」の第3－1－(2)－[2]イ「人体から採取された資料を用いない場合」に位置づけられるため、研究対象者からインフォームドコンセント(IC)を受けることを必ずしも要さないとされている。ただしICを受けることを必ずしも要しないため、本研究の目的を含む研究の実施について必要な情報を特発性造血障害に関する調査研究班および東京大学医学部附属病院血液・腫瘍内科のホームページに公開し(資料3)、必要に応じて研究への参加を拒否できるようにする。

２）　特に倫理的な配慮を必要とする研究参加者への配慮の有無と対応策　→あり（内容を記入）　☑なし

ありの場合は、該当項目の番号を○で囲み、対処する方法を記入すること。

１．未成年者　２．成人で十分な判断能力のない場合　３．成人で意識のない場合　４．その他　例えば病名に対する配慮が必要な場合

４．２　個人情報保護

１）　本学における個人情報の有無とその種類　→　□あり　☑なし

２）個人情報保護の方法

患者の氏名や患者 ID は記載せず、当院・協力施設毎に対象各患者に対して付与した症例番号を用いて連結可能匿名化を行い、調査票には個人を特定できる情報を記載しない。したがって収集されたデータには個人情報が含まれないが、研究が完遂次第データファイルは廃棄することで情報の漏洩を防ぐ。連結可能匿名化に用いる対応表は、研究責任者（南谷）が東京大学医学部附属病院血液・腫瘍内科ゲノム研究室の鍵付きロッカーで保管し、研究期間終了後 5 年を経過した時点で破棄する。また研究結果の発表においても、被験者を特定できないようにした上で学会や学術雑誌で公表される。

３）研究期間終了後：個人情報の保存／廃棄方法

保存場所：東京大学医学部附属病院 血液・腫瘍内科 ゲノム研究室

保存責任者：東京大学大学院医学系研究科　血液腫瘍内科　特任講師　南谷泰仁

廃棄方法：研究終了後 5 年を経過した段階ですべての資料をシュレッダーにかけ破棄する。

4．3　資料等の取扱

保存：研究終了時から 5 年間を保存期間とし、血液・腫瘍内科ゲノム研究室において研究責任者（南谷）の管理の下、鍵付きロッカーで適切に保管する。

廃棄：保存期間終了後、シュレッダーにかけ廃棄する。

なお、当該研究で発生した資料等は当該研究の目的以外には使用せず、また当該研究の研究従事者以外は使用しないものとする。

5．安全の確保

1）研究によって研究参加者に生じうる危険や不快等

本研究はカルテの調査研究であり、被験者に直接の危険・不快は生じない。

2）危険や不快等への対応策

上記の理由により新たな危険や不快は生じない。

3）研究参加者に対する研究結果の開示

研究結果については、集計結果を論文として公表する予定である。当然ながらその際には被験者を特定できないようにした形で行う。また、研究対象者や代理人から、研究結果の開示を求められた場合、他の研究対象者の個人情報保護などに差し障りのない範囲内で、研究結果を開示する。ただし、研究成果が公表されていない時点では、研究結果の開示を研究成果の公表後まで待って頂くこととする。

6．　備　考

本研究に係る研究資金は厚生労働科学研究費補助金により拠出する。なお、研究参加者に対する謝金はない。

診療科長または教室責任者　　氏名

（自署に限る。捺印省略可）

病院長　　氏名　　印

（附属病院でおこなわれる研究の場合）

資料１

hypoplastic MDS（低形成性骨髄異形成症候群）に関する全国調査（多施設共同後方視的研究）

研究計画書

研究事務局
東京大学医学部附属病院血液・腫瘍内科
(特発性造血障害に関する調査研究班)
TEL：03-3815-5411 内線 35609, FAX：03-5804-6261
担当　南谷 泰仁　ynanya-tky@umin.ac.jp

1. 研究背景と目的

骨髄異形成症候群(MDS)の一つのentityとして、hypoplastic MDS(hMDS; 低形成性骨髄異形成症候群)という概念が提唱されている[1]。 hMDSはMDSのうち5～20%を占めると考えられている。再生不良性貧血との鑑別が困難であるほか、低形成骨髄ゆえに汎血球減少が顕著であるため、白血病化よりもむしろ骨髄不全によって死に至ることが懸念される。そのため、他のMDSに対して行われているような骨髄抑制を伴う治療の妥当性が不明であり、hMDSに対する適切な治療法やその効果などは未だ解明されていない。

そこで、本邦におけるhMDSの患者背景、臨床像、治療反応性、予後などを調査することにより、hMDSに対する最適な治療選択を解明することが、本研究の目的である。

近年、造血幹細胞移植以外の治療としてDNA脱メチル化剤であるアザシチジンによる治療の有効性が示されるようになったが､hMDSはもともと骨髄が低形成であるために同薬剤の投与による血球減少の遷延が懸念される。本調査により、hMDSの臨床像や予後、また患者背景に応じてさまざまな治療法の中でいずれが選択されるべきかについても、新たな知見を得ることができると期待される[2]。

2. 調査対象と調査データ

調査対象疾患は、各参加施設で診断されたMDS患者のうち、診断時に骨髄のcellularity(細胞密度)が30%未満(60歳以上の場合は20%未満)の、hMDSである[2]。 2003年4月1日から2012年3月31日に診断された症例を対象とする。これまでの治療法の種類や、年齢・性別などは問わない。調査対象となるデータは治療経過に関する既存の臨床データと予後に関するデータであり、新たな検体収集や測定は行わない。

本調査で収集するデータは患者の診断日、末梢血の血算値や骨髄穿刺・生検所見、選択された治療法やその治療効果などからなる。

3. 調査方法

各参加施設に対し、郵送または電子メールでアンケートを行う。アンケートは二段階に分けて行う。一次調査は研究参加の可否と、各施設におけるMDS患者数とhMDS患者数を把握するために行い、二次調査は個人調査票を用いて、各hMDS患者の詳細なデータを得るために行う。

個人調査票では対象症例に対して、診断日や患者背景、治療内容等の詳細を調査する。別紙添付の「hypoplastic MDSに関する全国調査 二次調査票」に調査項目が示されている。データは全て後方視的に収集する。

統計解析としては、hMDSの診断方法で層別化を行い、行われた治療によって対象患者を群分けして、患者背景を群間比較する。生存時間解析として全生存をKaplan-Meier法で評価し、群間比較にlog-rank検定を用いる。全生存時間(OS; overall survival)を本研究のprimary endpointとし、OSに影響を及ぼす因子を比例ハザードモデルで多変量解析する。

染色体異常の消失、輸血依存度の軽減、および白血病化をsecondary endpointsとし、これらに影響を及ぼす因子の解析を比例ハザードモデルまたは回帰分析により実施する。

4. 参加者への説明同意について

本研究は「文部科学省・厚生労働省 疫学研究に関する倫理指針」の第3-1-(2)-[2]イ「人体から採取された資料を用いない場合」に位置づけられるため、研究対象者からインフォームドコンセント(IC)を受けることを必ずしも要さないとされている。

①本研究が対象者に被害を及ぼす危険性がないこと、②調査には匿名化されている既存の資料を用い、アンケート調査でもその番号で調査されるため個人情報が漏洩する危険性がないこと、③後方視的臨床研究であるため個別のIC取得が現実的には困難であること、④新たな検査や薬剤の使用を伴わないこと、などから本調査研究には説明・同意文書は必要ないと考えられる。但し、本研究の目的を含む研究の実施内容については、必要な情報をホームページに公開し、必要に応じて研究への参加を拒否できるようにする。

5. 収集されたデータの管理について

患者氏名や患者IDは除去して、参加施設毎に対象各患者に対して付与した症例番号を用いて連結可能匿名化を行い、調査票には個人を特定できる情報を記載しない。したがって収集されたデータには個人情報が含まれないが、研究が完遂して一定期間経過後にデータファイルを廃棄することにより、情報の漏洩を防ぐ。また、研究結果の発表においても、被験者を特定できないようにした上で学会や学術雑誌に公表する。

6. 倫理審査

本研究は各施設での倫理委員会での承認を要する。各施設の倫理審査委員会における審査を踏まえて施設長の許可を得た上で調査を行うものとする。これは「疫学研究に関する倫理指針」第4-3-(2)に規定された要件を満たすためである。

7. 調査および結果の公表

研究結果については、集計結果を論文として公表する予定である。当然ながらその際には被験者を特定できないようにした形で行う。

8. 備考

本研究に係る研究資金は厚生労働科学研究費補助金により拠出する。なお、研究参加者に対する謝金はない。

9. 研究組織

特発性造血障害に関する調査研究班

研究代表者: 〒113-8655 東京都文京区本郷7-3-1
東京大学医学部附属病院 血液・腫瘍内科
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hypoplastic MDS (低形成性骨髄異形成症候群)に関する全国調査研究

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10. 参考文献

[1] Nand S and Godwin JE. Hypoplastic myelodysplastic syndrome. *Cancer* 1988 Sep 1;62(5):958-64.

[2] Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al., Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol* 2009;10:223-32.

[3] Orazi A and Czader MB, Myelodysplastic syndromes. *Am J Clin Pathol* 2009;132:290-305.

hypoplastic MDSに関する全国調査　本調査票

記入日	西暦　　年　月　日
貴施設名	
連絡御担当者	
連絡先	e-mail: Tel: FAX:

各患者毎に、下記の各項目にご記入ください。

匿名化ID(患者毎に1から順に)	
貴施設診断確定日	西暦　　年　月　日
診断時年齢・患者性別・生年月	歳 1. 男　2. 女　西暦　　年　月生
既往歴(ある場合のみ)	1. 血液疾患(　　(西暦　　年　月頃)) 2. その他の腫瘍(　　(西暦　　年　月頃)) 3. 放射線治療歴　部位(　　) 線量(　　Gy) 4. 化学療法歴　(　　)
家族歴(ある場合のみ)	(　　)
生活歴	喫煙:　1.＿＿＿＿ 本/日 × ＿＿＿＿ 年間　2. 吸わない 飲酒:　1.＿＿＿＿ 合/日 × ＿＿＿＿ 日/(週・月) 2. 機会飲酒　3. 飲まない 化学物質曝露(　　) 放射線曝露(　　)
診断時分類(FAB)	1. RA　2. RARS　3. RAEB　4. CMMoL　5. RAEB-t 6. その他(　　)
診断時分類(WHO2008)	1. RCUD(1.1 RA; 1.2 RN; 1.3 RT)(1.1～1.3のどれかに○) 2. RARS　3. RCMD　4. RAEB-1　5. RAEB-2　6. MDS-U 7. MDS associated with isolated del(5q) 8. その他(　　)
診断時における末梢血の血算値	検査日: 西暦　　年　月　日 Hb ＿＿＿＿ g/dl　Plt ＿＿＿＿ ×10^4/μl Neu ＿＿＿＿ /μl (WBC ＿＿＿＿ /μl中 ＿＿＿＿ %) Blasts ＿＿＿＿ %
血清EPO値(測定した場合のみ)	mIU/ml　(検査日:西暦　　年　月　日)
PNH血球(測定した場合のみ)	1. 陽性　2. 陰性　(検査日:西暦　　年　月　日) (赤血球(CD235a(+))(　　)%, 顆粒球(CD11b(+))(　　)%)
血清TPO値(測定した場合のみ)	A.U./ml　(検査日:西暦　　年　月　日)
MRI所見(検査した場合のみ)	検査日: 西暦　　年　月　日 所見:(　　)
診断時骨髄穿刺所見(List 1から複数選択可) ※List 1から選択("その他"は具体的に記入)→	検査日: 西暦　　年　月　日 有核細胞数(NCC) ＿＿＿＿ ×10^4/μl 巨核球数 ＿＿＿＿ /μl　芽球 ＿＿＿＿ % (過・正・低)形成骨髄(いずれかに○) 脂肪/細胞(Fat/Cell)比 ＿＿＿＿ Cellularity ＿＿＿＿ % 形態異常 (　　)
診断時骨髄生検所見(List 1から複数選択可) ※List 1から選択("その他"は具体的に記入)→	1. 所見:　(過・正・低)形成骨髄(いずれかに○) 脂肪/細胞(Fat/Cell)比: ＿＿＿＿ Cellularity: ＿＿＿＿ % 形態異常: ＿＿＿＿ 線維化　1. 有　2. 無　3. 記載なし 2. 未施行
診断時染色体検査所見(List 2から複数選択可) ("その他"は具体的に記載)	1. 所見: (　　) 2. 未施行
診断時IPSS ※List 3を参照して計算→	1. Low　2. Intermediate-1　3. Intermediate-2　4. High (Score Value:　　)
診断時WPSS(Point totalはList 4を参照して計算) ※染色体異常の分類はIPSSと同じ→	WHO-subtype: ＿＿＿＿ 輸血依存: ＿＿＿＿ 染色体異常:　Point total:
診断時臨床症状	0. なし　1. 貧血　2. 易感染性　3. 出血傾向　4. 脾腫 5. その他(　　)
診断時Performance Status (0～4)	PS(　　)　(西暦　　年　月　日)

治療①(初回治療; List 5から選択)	治療の種類: (　　) 投与量: (　　) 施行日: 西暦　　年　月　日～ 1. 西暦　　年　月　日まで 2. 現在に至る
治療①開始前の末梢血血算値	1. 検査日: 西暦　　年　月　日 Hb ＿＿＿＿ g/dl Plt ＿＿＿＿ ×10^4/μl Neu ＿＿＿＿ /μl Blasts ＿＿＿＿ % 2. 診断時と同じ
治療①開始前に要した輸血単位・頻度	1. 赤血球LR　　治療①開始前の8週間に(　　)単位 2. 血小板LR　　治療①開始前の8週間に(　　)単位 3. 輸血依存なし
治療①開始前の骨髄穿刺所見 ※List 1から選択("その他"は具体的に記入)→	1. 所見:　NCC: ＿＿＿＿ /μl　Cellularity: ＿＿＿＿ % MgK: ＿＿＿＿ /μl　Blasts: ＿＿＿＿ % 形態異常: (　　) 2. 診断時と同じ
治療①開始前の骨髄生検所見 ※List 1から選択("その他"は具体的に記入)→	1. 所見:　(過・正・低)形成骨髄(いずれかに○) 脂肪/細胞(Fat/Cell)比: ＿＿＿＿ Cellularity: ＿＿＿＿ % 形態異常 (　　) 線維化　1. 有　2. 無　3. 記載なし 2. 診断時と同じ
治療①開始前の骨髄染色体検査所見 ※List 2から選択("その他"は具体的に記入)→	1. 所見:　(　　) (　　) 2. 診断時と同じ
治療①の治療効果(List 6から選択)	(　　)
治療①後の骨髄穿刺所見 ※List 1から選択("その他"は具体的に記入)→	1. 検査日: 西暦　　年　月　日 NCC: ＿＿＿＿ /μl　Cellularity: ＿＿＿＿ % MgK: ＿＿＿＿ /μl　Blasts: ＿＿＿＿ % 形態異常: (　　) 2. 未施行
治療①後の骨髄生検所見 ※List 1から選択("その他"は具体的に記入)→	1. 所見:　(過・正・低)形成骨髄(いずれかに○) F/C比: ＿＿＿＿ Cellularity: ＿＿＿＿ % 形態異常: (　　) 線維化　1. 有　2. 無　3. 記載なし 2. 未施行
治療①後の染色体検査所見	1. 検査日: 西暦　　年　月　日 1. 染色体異常消失、かつ新たな異常の出現なし 2. 染色体異常が50%以上減少 3. その他(　　) 2. 未施行
治療①を終了/中止/変更した理由(List 7参照)	1. 終了　2. 中止　3. 変更　理由: (　　)

最終確認日と転帰 (2012年3月31日以前の最終診療日)	西暦　　年　月　日 転帰:　1. 無病生存　2. 有病生存　3. 死亡
理由	上記2.で観察終了の場合:　1. 転院　2. その他(　　) 上記3.の場合: 死因 (　　) 観察期間中における白血病化・骨髄不全の有無: 白血病化 1. あり　2. なし　骨髄不全 1. あり　2. なし

治療②(初回治療; List 5から選択)	治療の種類: (　　) 投与量:　(　　) 施行日: 西暦　　年　月　日～ 1. 西暦　　年　月　日まで 2. 現在に至る
治療②開始前の末梢血血算値	1. 検査日: 西暦　　年　月　日 Hb _____ g/dl Plt _____ ×10^4/μl Neu _____ /μl Blasts _____ % 2. 治療①後と同じ
治療②開始前に要した輸血単位・頻度	1. 赤血球LR　　治療①開始前の8週間に(　　)単位 2. 血小板LR　　治療①開始前の8週間に(　　)単位 3. 輸血依存なし
治療②開始前の骨髄穿刺所見 ※List 1から選択("その他"は具体的に記入)→	1. 検査日: 西暦　　年　月　日(診断時と異なる場合) NCC: _____ /μl　Cellularity: _____ % MgK: _____ /μl　Blasts: _____ % 形態異常: (　　) 2. 治療①後と同じ
治療②開始前の骨髄生検所見 ※List 1から選択("その他"は具体的に記入)→	1. 所見:　(過・正・低)形成骨髄(いずれかに〇) 脂肪/細胞(Fat/Cell)比: _____ Cellularity: _____ % 形態異常 (　　) 線維化　1. 有　2. 無　3. 記載なし 2. 治療①後と同じ
治療②開始前の骨髄染色体検査所見 ※List 2から選択("その他"は具体的に記入)→	1. 所見:　(　　) (　　) 2. 治療①後と同じ
治療②の治療効果(List 6から選択)	(　　)
治療②後の骨髄穿刺所見 ※List 1から選択("その他"は具体的に記入)→	1. 検査日: 西暦　　年　月　日(診断時と異なる場合) NCC: _____ /μl　Cellularity: _____ % MgK: _____ /μl　Blasts: _____ % 形態異常: (　　) 2. 未施行
治療②後の骨髄生検所見 ※List 1から選択("その他"は具体的に記入)→	1. 所見:　F/C比: _____ Cellularity: _____ % 形態異常: (　　) 2. 未施行
治療②後の染色体検査所見	1. 所見:　1. 染色体異常消失、かつ新たな異常の出現なし 2. 染色体異常が50%以上減少 3. その他 (　　) 2. 未施行
治療②を終了/中止/変更した理由(List 7参照)	1. 終了　2. 中止　3. 変更　理由: (　　)

治療②以後における造血幹細胞移植の有無	1. 有　2. 無

List 1: 形態異常

E. 赤芽球系形態異常
- E1. 環状鉄芽球(RS)
- E2. 核辺縁不整
- E3. 核間(染色質)架橋
- E4. 核崩壊像
- E5. 多核赤芽球
- E6. 過分葉核赤芽球
- E7. 巨赤芽球様変化
- E8. 赤血球系細胞質空胞化
- E9. 赤血球系PAS陽性
- E10. その他

G. 顆粒球系形態異常
- G1. 低分葉好中球(Pelger核異常)
- G2. 脱顆粒(a-Gr/hypo-Gr)
- G3. 小型または大型好中球
- G4. 過分葉核好中球
- G5. 偽Chédiak-Higashi顆粒
- G6. その他

M. 巨核球系形態異常
- M1. 微小巨核球(mMgk)
- M2. 非分葉核
- M3. 分離多核
- M4. その他

List 2: 染色体異常

1. +8	7. −13 or del(13q)	13. t(3;21)(q26.2;q22.1)
2. −7 or del(7q)	8. del(11q)	14. t(1;3)(p36.3;q21.2)
3. −5 or del(5q)	9. del(12p) or t(12p)	15. t(2;11)(p21;q23)
4. del(20q)	10. del(9q)	16. inv(3)(q21q26.2)
5. −Y	11. idic(X)(q13)	17. t(6;9)(p23;p34)
6. i(17q) or t(17p)	12. t(11;16)(q23;p13.3)	18. その他

List 3: IPSS(International Prognostic Scoring System)***

	Score value				
	0	0.5	1	1.5	2
BM blast(%)	<5	5～10	−	11～20	21～30
Karyotype*	Good	Intermediate	Poor		
Cytopenias**	0, 1	2, 3			

Scores for risk groups
- Low: 0
- Intermediate-1: 0.5～1.0
- Intermediate-2: 1.5～2.0
- High: ≧2.5

Karyotype*
- Good: normal, −Y, del(5q), del(20q)
- Poor: complex(≧3 abnormalities) or chromosome 7 anomalies
- Intermediate: other abnormalities

Cytopenias**
- Hb＜10g/dl, Neu＜1800/μl, Plt＜100000/μl

***白血球数12000/μlのCMMoLは除外

List 4: WPSS(WHO-based Prognostic Scoring System)

Point	0	1	2	3
WHO-subtype	RA, RARS, del(5q)	RCMD, RCMD-RS	RAEB-1	RAEB-2
輸血依存	無	有		
染色体異常	good	intermediate	poor	

Points total: 0: very low　1: low　2: intermediate　3: high　4: very high

List 5: 治療(輸血以外)

1. G-CSF (グラン、ノイトロジン、ノイアップ	13. キロサイド皮下注
2. エリスロポエチン	14. スタラシド内服
3. ビタミンK2(グラケー)	15. ラステット点滴
4. ビタミンD3(アルファロール等)	16. キロサイド点滴
5. ビタミンB6(ピドキサール)	17. ハイドレア内服
6. ATG	18. ベプシド内服
7. シクロスポリン(CsA)(ネオーラル等)	19. IDR + Ara-C
8. 副腎皮質ホルモン	20. CA(G)
9. 蛋白同化ホルモン(プリモボラン等)	21. その他
10. レナリドミド(レブラミド)	
11. アザシチジン(ビダーザ)	
12. 造血幹細胞移植(骨髄、末梢血幹細胞、臍帯血)	

List 6: International Working Group (IWG) Response Criteria for MDS
1.～7.: Altering natural history; 4週間以上の持続を必要とする。
1. CR (complete remission)
骨髄: 芽球≤5%かつ3系統の成熟(異形成残存は許容)
末梢血: 芽球0%, Hb≥11g/dl, Plt≥10万/μl, Neu≥1000/μl
2. PR (partial remission)
骨髄: 芽球が治療前の≥50%減少するが、5%よりも多く残存
骨髄細胞密度と細胞形態の異常あり
その他はCRと同じ
3. Marrow CR
骨髄: 芽球が5%以下、かつ治療前に比べて50%以上減少
末梢血: CRの条件を満たさないが、HI(後述)があれば明記
4. Stable disease
PRに達しないが、>8週間増悪の徴候がない
5. Failure
治療中の死亡、または次のいずれかを伴うDP(後述):
・血球減少の悪化　・骨髄中の芽球増加　・治療前よりもFAB subtype増悪
6. Relapse after CR or PR: 次の3項目のうち1項目以上を満たす。
・骨髄中の芽球が治療前の比率に戻る
・顆粒球または血小板が寛解時最大値から≥50%減少
・Hbが≥1.5g/dl減少または輸血依存
7. DP (disease progression)
a) 芽球5%以下: ≥50%増加し、>5%
b) 5%<芽球≤10%; ≥50%増加し、>10%
c) 10%<芽球≤20%; ≥50%増加し、>20%
d) 20%<芽球≤30%; ≥50%増加し、>30%
上記a)～d)のいずれかに該当し、かつ 次の1項目以上を満たす:
・ 顆粒球または血小板が寛解時最大値から≥50%減少
・ Hbが≥2g/dl減少
・ 輸血依存へ移行
8.～9.: Hematologic improvement; 8週間以上の持続を必要とする。
8. Hematological improvement
8-1. HI-E: 治療前がHb<11g/dl, 治療後1.5g/dl以上のHb上昇
治療前に比べ、8週間あたり8単位以上の赤血球輸血回数減(Hb≤9.0g/dlに対して)
8-2. HI-P: 治療前が2万/μl<Plt<10万/μlの場合、治療後30000/μl以上のPlt増加
治療前がPlt≤2万/μlの場合、≥100%増加かつ>2万/μlに増加
8-3. HI-N: 治療前Neu<1000/μl, 治療後100%以上の上昇率かつNeu>500/μlの増加量
9. Progression/Relapse after hematological improvement: 次のうち1項目以上を満たす。
・顆粒球または血小板が治療後の最大値から50%以上減少
・1.5g/dl以上のHb減少
・輸血依存

List 7: 治療を終了・中止・変更した理由
1. ガイドライン等が定める最多コース数に達した。
2. 十分な治療効果を得ることができた。
3. 予算や保険の制約による。
4. 患者からの要求(治療拒否を含む)。
5. 十分な治療効果が得られなかった。
6. 副作用・有害事象の発生:
6.1. 感染症
6.2. 出血傾向
6.3. 貧血
6.4. 心機能異常
6.5. 肝機能異常
6.6. 腎機能異常
6.7. 神経系異常
6.8. 薬疹等
6.9. その他(具体的に記載)
7. 併存する他の疾患の増悪(具体的に記載)

資料 3

当院において骨髄異形成症候群と診断された方へ

「hypoplastic MDS に関する調査研究」（全国多施設共同研究）のご案内

当科では2003年4月から2012年3月までの間に当院で診療された骨髄異形成症候群の患者さんに対して、治療効果を調査する研究を行っています。

【対象となる方】

2003年4月1日～2012年3月31日に東京大学医学部附属病院血液・腫瘍内科および協力施設で診断されたhypoplastic MDS（低形成性骨髄異形成症候群; 診断確定時の骨髄中細胞比率が、60歳未満の方は30%未満、60歳以上の方は20%未満)の患者さん

【研究の目的と意義】

骨髄異形成症候群に対しては従来の輸血や免疫抑制療法、幹細胞移植に加え、新たな治療法としてDNA脱メチル化剤(アザシチジン(ビダーザ®))が、2011年3月から我が国でも使用できるようになり、GVHD等の移植合併症やドナー不在、年齢等の理由で移植ができない方々にも使用でき、予後を改善し得る新たな治療法として、注目されています。しかしながら、特にhypoplastic MDSの患者さんには、骨髄抑制の問題ゆえにこの薬剤や他の薬剤による治療が行いにくく、それゆえに輸血以外の治療についての情報が不十分であり、治療効果を比較し解析する必要が生じています。

そこで、我が国におけるhypoplastic MDSの患者さんがどのような治療を受け、それらによってどのような治療効果を得ているのか、全国規模で実態を調査することにしました。この研究は、各治療によって予後がどれくらい改善するか、また、輸血頻度の減少、染色体異常の消失、白血病化の有無も、併せて明らかにすることを目的としています。

【研究の方法】

この研究は東京大学医学部倫理委員会に承認された上で実施されます。なお、すべて過去の検査データを用いるため、新たに患者さんにご負担頂くことは全くありません。

研究結果は学会や専門誌において公表されることがあります。当研究において研究結果は統計的に処理されますので、個人の特定に至る可能性のある情報は公表されません。収集したデータは厳重な管理のもとで、研究終了後5年間保存されます。ご要望があれば、患者さんとそのご家族がお読みになるという目的に限り、この研究の実施計画書をご覧いただくことができます。研究の実施計画書は一般公開されていないため、担当医師にご依頼ください。また、この研究の結果は、ご希望があれば担当医師からお伝えいたします。

この研究のためにご自分のデータを使用されたくない場合は、主治医にお伝えいただくか、下記の事務局までご連絡ください。ご連絡いただかなかった場合、ご了解いただいたものとします。

平成 24 年 10 月

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資料 4

hypoplastic MDS に関する全国調査 参加施設リスト
(平成 24 年 11 月 12 日現在)

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札幌医科大学 第四内科（小船 雅義）
和歌山県立医科大学医学部 血液内科学講座（花岡 伸佳）
三重大学医学部附属病院 血液内科（桝屋 正浩）
NTT 東日本関東病院 血液内科（臼杵 憲祐）
近畿大学医学部 血液・膠原病内科（森田 泰慶）
聖路加国際病院 小児科（真鍋 淳）
岩手医科大学 血液・腫瘍内科（伊藤薫樹）
筑波大学 血液内科（小原 直）
名古屋医療センター 血液内科（大橋 春彦）
大阪大学医学部附属病院 血液・腫瘍内科（金倉 譲）
大阪市立大学医学部附属病院 血液内科（寺田 芳樹）
順天堂大学医学部附属順天堂医院 血液内科（高久 智生）
防衛医科大学校病院 血液内科（佐藤 謙）
京都大学医学部附属病院 血液・腫瘍内科（川端 浩）
新潟大学医歯学総合病院 血液内科(第一内科)（森山 雅人）
名古屋大学医学部附属病院 血液内科（冨田 章裕）
東北大学病院 血液・免疫科（勝岡 優奈）
宮崎大学医学部附属病院 第二内科（北中 明）
福島県立医科大学附属病院 血液内科（野地 秀義）
福島県立会津総合病院 血液内科（大田 雅嗣）
自治医科大学附属病院 血液科（鈴木 隆浩）
済生会横浜市南部病院 血液内科（藤田 浩之） ←2012 年 3 月以前はなし、不参加。
香川大学第一内科（松永 卓也）

hypoplastic MDS に関する全国調査　参加施設リスト

(平成 25 年 9 月 7 日現在)	hMDS (人)	全 MDS (人)
東京大学	35	178
大阪大学	28	234
名古屋大学	11	116
札幌医科大学	10	37
広島大学	10	213
central review	8	82
旭川医科大学	7	80
熊本大学	6	30
和歌山県立医科大学	5	100
聖路加国際病院小児科	3	
秋田大学	2	55
岡山大学	2	80
近畿大学	2	260
埼玉医科大学国際医療センター	2	56
三重大学	2	31
名古屋医療センター	2	50
大阪市立大学	2	50
防衛医科大学校	2	62
筑波大学	1	120
NTT 東日本関東病院	1	140
福島県立医科大学会津医療センター	1	40
香川大学	1	
順天堂大学	0	80
宮崎大学	0	99
京都大学小児科	0	7
計	143	2200

研究倫理審査申請書チェックリスト

《新規申請のみ提出必須（軽微な変更の場合には提出不要)》

研究課題名：hypoplastic MDS に関する全国調査

研究責任者氏名　黒川 峰夫
記入者氏名　南谷 泰仁
電話　03-3815-5411(内線35609) E-mail ynanya-tky@umin.net

【注意】
■原則的に受付順に審議を行うことをご了承ください。審議まで時間がかかる点に配慮し、時間的余裕をもって申請書類を提出してください。
■以前に倫理委員会等にて承認された研究に関連する研究については、以前に提出した申請書の写しを必ず添付してください。また、双方の研究の類似点、相違点を箇条書きにした資料を添付してください。承認済みの研究の内容変更・追加の場合についても同様です。
■類似の内容の研究について同時に複数の申請書を提出する場合は、それらの研究の類似点、相違点をわかりやすく箇条書きにした資料を添付して下さい。
以下の項目が記載されているかをチェックし、提出する際は本チェックリスト及び研究責任者の研究倫理セミナー受講証の写し、申請書の添付書類一覧に記載されている書類をすべて添付してください。

☑申請書の提出先が医学部倫理委員会であることを再度確認しました。
※倫理委員会ホームページに掲載されている「研究の分類と申請先」を再度ご参照ください。

一般的な事項
● すでに医学系研究科長・医学部長が承認した研究計画の変更で……
☑ない。新規計画の申請です。
☐ある。→☐以前提出した申請書等の写し・研究変更申請書を添付しました。

表書　欄
☑申請者（研究責任者）の氏名・所属・職名・電話・E-mail を記しました。
☑審査番号及び日付欄は空欄のままにしました。
☑キーワード（５つ以内）を記しました。
☑研究従事者記載欄の一番上に申請者（研究責任者）の氏名・所属・職名を記しました。
☑研究従事者の氏名・所属・職名・研究倫理セミナー受講 NO.及び年月日等を記しました。
☑連絡担当者の氏名・所属・職名・電話（内線）・E-mail を記しました。
☑添付書類一覧：すべての添付書類名を記しました。

１．研究課題　欄
☑表書（１頁）と研究計画書（２頁)、(必要に応じ）説明文書及び同意文書の課題名を一致させました。

２．研究の概要　欄
２・１　目的
☑学術的背景：専門外の方にも理解しやすいよう記しました。

２・２　方法
☑研究の大まかな流れ：専門外の方にも理解しやすいよう記しました。
☑研究期間：「承認後＊年間」と記しました（最長５年間)。

２・３　対象及び資料等
☑研究参加者：選択基準・(必要に応じ）除外基準を記しました。
● 研究参加者に特に倫理的な配慮を必要とする方（未成年者・高齢者等）を……
☑含まない。
☐含む。
☑研究参加者（被験者・研究協力者）の人数・例数（１年あたり及び総計例数）を記しました。

☑資料等の内容を記しました。

２・４　研究参加者の実体験

● 研究参加者の体験内容が……
　☑ない。
　□ある。→□研究の進行に沿う形で受動的に箇条書きしました。
　　□研究参加者が検査・試験等１回で拘束される時間及び必要回数を記しました。

３．研究を実施する施設とその役割　欄

☑該当する本学及び学外施設名とその役割を記入しました。
☑本学施設名は実施する部屋の名前まで詳細に記しました。

● 研究の実施施設に学外施設を……
　□含まない。
　☑含む（多施設共同研究）。→☑学外施設での対応とその状況を記しました。
　　● 多施設共同研究：学外の主たる施設の倫理審査委員会が承認して……
　　☑いない（必要に応じ、当該施設の長による研究倫理審査依頼状を添付）。
　　□いる（必要に応じ、当該施設の長等による承認通知書等を添付）。

４．研究における倫理的配慮　欄

４・１　インフォームド・コンセント

☑説明を行う方法等を記入しました。
　● 説明文書が……
　　□ない。
　　☑ある。→（説明文書を添付）

☑同意を受ける方法等を記しました。
　● 同意書（必要に応じ、同意撤回書）が……
　　☑ない。
　　□ある。→（同意書・同意撤回書を添付）

　● 特に倫理的な配慮を必要とする者（未成年者・高齢者等）に配慮して……
　　☑いない。
　　□いる。→□配慮の内容を記しました。

４・２　個人情報保護

● 個人情報を……
　□含まない。
　☑含む。→☑個人情報の種類を記しました。
　　☑個人情報保護の方法を記しました。
　　☑研究期間終了後：個人情報の保存／廃棄方法を記しました。

４・３　個人情報の含まれていない資料（試料）等の取扱

● 研究期間終了後に資料（試料）等を保存……
　☑しない。→☑廃棄方法を記しました。
　□する。→□保存方法を記しました。

５．安全の確保　欄

● 研究によって研究参加者に生じうる危険や不快等は…
　☑ない。
　□ある。→□その対応策を記しました。

６．備考　欄

● 企業等から資金・装置等の供与を受けて……
　☑いない。→☑公的な研究費の名称（東京大学医学部研究費・科研費等）を記しました。
　□いる。→□研究形態・企業名等の名称を記しました。

● 謝金の支払いは……

☑ない。
☐ある。→☐金額を記しました。

必要書類の詳細に関するチェックリスト

A．申請書、附属書類の添付方法（説明文書、同意書、同意撤回書、チェックリストその他資料）

☑ 用紙の大きさはＡ４版で、両面印刷で作成しました。
（必ずＡ４版で作成して下さい。なお、場合によっては片面印刷でも結構です。）

☑ まとめて一箇所のみをダブルクリップまたはゼムクリップで止めました。
（ホッチキスは使用しないで下さい。また、それぞれの書類を止めることはせず、一つの申請案件につき一か所を止めるのみとして下さい。また、付箋は外れることがあるので付けないで下さい。）

B．「申請者（研究代表者)」の印（初回申請時から必要です）

☑ 押印を確認しました。

C．「診療科長または教室責任者」の自署

☑ 自署を確認しました。
（フォーマットチェック終了後すなわち個別審査直前からは自署のある申請書が必要です。）

D．「病院長の氏名・公印」を確認

☑ 附属病院で行われる研究の場合→個別審査終了後すなわち倫理委員会全体会議直前に、氏名・公印を押印して下さい。

☐ 該当しません。

E．研究倫理審査依頼状（様式第４号）及び相手方からの公文書原本の添付と保管

☑ コピーを添付しました（原本は申請者が保管して下さい）（申請書再提出の都度、添付して下さい)。

☐ 該当しません。

※研究協力係使用欄

研究倫理ｾﾐﾅｰ受講証
利益相反自己申告書

F．「東大研究倫理セミナー受講証」の写しの添付《申請書類の最後に添付して下さい》

☑ 添付を確認しました（添付は、申請者（研究責任者）のみで結構です）
（尚、不備が無ければ申請書の再提出の際は添付の必要はありません)。

G．「臨床研究に係る利益相反自己申告書」の添付《申請書類の最後に添付して下さい》

☑ 申請者氏名を署名し、添付を確認しました（様式は、倫理委員会ホームページからダウンロードできます)（尚、不備が無ければ申請書の再提出の際は添付の必要はありません)。

☐ 該当者を確認しました。
（企業との共同研究又は委託された研究の場合は、申請者（研究責任者）以外に、共同研究者全員分を提出する必要があります。）

H．資料等の表示

☑ 資料の右上の部分に、「資料１（例：説明文書)」、「別紙２（例：倫理ｾﾐﾅｰ受講証)」等の表示を記載しました。

I．申請者用

☑提出する申請書、附属書類のコピーを申請者用控としてとりました。

別紙2

第 23 回 東大研究倫理セミナー受講証

以下のとおり、東大研究倫理セミナーを受講したことを証明します。

受講年月日　　平成２２年６月１日（火）

受　講　番　号	H22－23－487
所属（教室名）	血液・腫瘍内科
職　名（身分）	特任講師
氏　　名	南谷　泰仁

平成２２年６月１日

東京大学大学院医学系研究科長・医学部長
清水　孝雄

■この受講証の有効期間は、平成２５年３月３１日までです。
■この受講証は、治験申請、研究倫理申請に必要となりますので、紛失しないように大切に保管してください。

別紙3

臨床研究に係る利益相反自己申告書

大学院医学系研究科・医学部及び医学部附属病院
利益相反アドバイザリー機関長　殿

該当する委員会　■倫理委員会　□ヒトゲノム・遺伝子解析研究倫理審査委員会
□治験審査委員会

申請番号：　　申請代表者：南谷　泰仁
共同研究者（当研究科の者のみ）：黒川峰夫、市川幹、小林隆

研究課題：hypoplastic MDSに関する全国調査（多施設共同後方視的研究）
この研究に係る経費について、次のとおり申告致します。
（1又は2に○をつけ、該当する項目を選んで下さい。1及び2の両方に該当する場合は、両方に○をつけて、該当する項目を記載してください。）

① この研究が一般的な学術研究又は自主臨床試験である場合
■ 科学研究費補助金（厚生労働省）
□ 委任経理金
□ その他（　　）

2．この研究が、治験或いは、特定企業との共同研究又は委託された研究の場合（民間等から受託研究契約又は共同研究契約を結ばないで経費の支払いを受けること、また現物の支給を受けることは出来ませんので注意して下さい。）
□ 治験（企業或いは医師主導）（東大側研究代表者名:　　相手先名称:　　）
□ 受託研究費　（東大側研究代表者名:　　相手先名称:　　）
□ 民間等との共同研究（東大側研究代表者名:　　相手先名称:　　）
□ その他（具体的に記載：　　）

（2に該当する場合、以下にお答え下さい。）
2の企業等に関連した活動（兼業規程による診療活動を含む）の有無、あるいは、2の企業等からの奨学寄附金の授受の有無　有／無

（有の場合にのみ、企業・団体ごとに記載して下さい。記載欄が不足する場合は適宜追加して下さい。⑤～⑧は、100万円を超えるものについて記入して下さい。）
①企業・団体名 ＿＿＿＿＿＿＿＿　②①におけるご自分の役割 ＿＿＿＿＿＿
③活動内容 ＿＿＿＿＿＿＿＿　④活動時間 ＿＿＿＿時間／月
⑤報酬・給与 ＿＿＿＿＿＿万円／年　⑥ロイヤリティ＿＿＿＿万円／年
⑦原稿・講演料等＿＿＿＿＿＿万円／年　⑧奨学寄附金 ＿＿＿＿＿＿万円／年
⑨公開・未公開の株式、出資金、ストックオプション、受益権等の保有の有無
有／無　（有の場合、その種類と数量等を記載願います）
有の場合 ＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿
⑩その他産学官連携活動（実施許諾、権利譲渡、技術研修、委員等の委嘱等）に関わる活動を行っている場合は具体的に記載して下さい。

注1：申告日より起算して、1年間の活動・報酬について記載する。
注2：2に該当する場合は、当研究科内の共同研究者全員について申告すること。

申告日　平成　24年　9月　11日
所属教室、診療科等 血液・腫瘍内科
職名・連絡先内線　特任講師　35609
申告者氏名（自署に限る）　南谷泰仁

様式第 2 号

回答書

平成 24 年 10 月 10 日

東京大学大学院医学系研究科・医学部
倫理委員会委員長　殿

申請者(研究責任者)　氏名　　南谷泰仁
血液・腫瘍内科　特任講師
電話：37537、　E-mail ynanya-tky@umin.ac.jp

受付番号：**3949**
個別審査日：2012/10/9
研究課題　：　hypoplastic MDS に関する全国調査（多施設共同後方視的研究）

平成 24 年 4 月 6 日の倫理委員会（B チーム）における指摘事項の訂正等を、下記のとおり行いました。

記

１．研究倫理審査申請書
添付書類一覧：資料 2-1 を 予備 調査シートとしました。
資料 2-2 を本調査シートとしました。

２．研究計画書
2.2 方法: 調査方法 2 行目　一次調査 → 予備 調査 としました。
3 行目　二次調査 → 本調査 としました。
2.3 対象および資料等 2) 資料 ①一次調査シート → 予備調査シート としました。
②二次調査シート → 本調査シート としました。
3. 研究を実施する施設とその役割 2) 学外施設での対応とその状況
「①予備 調査で参加を表明した施設に本研究事務局から本調査票を送る」としました。
「③協力各施設の責任者が、連結可能匿名化された本調査票を」としました。
4. 研究における倫理的配慮 4.1 インフォームド・コンセント 4 行目
「必要な情報を 特発性造血障害に関する調査研究班および東京大学医学部附属病院 血液・腫瘍内科の ホームページに公開し(資料 3)」としました。

以上となります。

様式第２号

倫　理　委　員　会
審 査 結 果 報 告 書

平成２４年１０月２９日

申請者
　血液・腫瘍内科
　特任講師
　南谷　泰仁　殿

東京大学大学院医学系研究科長・医学部長
宮園　浩平　　印

審査番号　3949
研究課題　hypoplastic MDS に関する全国調査　（多施設共同後方視的研究）

上記研究計画を平成２４年１０月２９日の委員会で審査し下記のとおり判定しました。
ここに通知します。

判　定 ○承認する。　　承認しない。 条件付きで承認する。　　該当しない。 変更を勧告する。
条件あるいは変更勧告の理由（細則第３条第２項）